A QUICK GLANCE AT PAEDIATRICS

16 Authors

Edited By
Beckie Nnenna TAGBO and
Bertilla Uzoma EZEONWU

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FOREWORD

Fundamental to the practice of paediatrics is the impact of growth and development on the epidemiology and clinical presentations of diseases, the choice of drugs to administer, the doses of drugs, and indeed the type of rehabilitation needed for the child with social, mental or physical challenges. The changing size and maturity of a child from newborn to adolescence underscore the need for the individualization of interventions. A quick reference book is a common need in child healthcare.

A Quick Glance at Paediatrics is a reference book written and compiled by teachers of paediatrics and clinicians who know the needs to support appropriate clinical paediatric practice. It is a useful tool for medical students, resident doctors, paediatricians and nurses. The contents cover a wide scope of child healthcare and are presented in a reader-friendly succinct manner to save the reader's time and yet maintain interest in further reading. The changing trends in the practice of this field are also captured to stimulate interest in updates in the subjects and stimulate research and innovations.

The lead author, Beckie Tagbo, is an experienced paediatric clinician, researcher and teacher who, with the other authors, knows first-hand the common needs for quick references in child healthcare. The authors are all specialists in the various fields of paediatrics and practise in settings with resource challenges where there may not be access to paediatricians and to a reference library.

The book focuses on child healthcare in the developing world, addressing the persisting challenges of infectious diseases, the emerging infections and the growing problems of non-communicable diseases in children. Social paediatrics, arguably less addressed in the developing world by governments and other stakeholders, is also included in a stimulating manner. The book should be an accessible handbook for all stakeholders in paediatric practice as it will help to further narrow the knowledge gap in child healthcare.

Dorothy Omono Esangbedo MBBS, FMCPaed, FWACP
President, Union of National African Paediatric Societies and Associations (UNAPSA)
Former President, Paediatric Association of Nigeria (PAN)

PREFACE

Medical students, resident doctors, general practitioners, family physicians and paediatricians frequently require quick reference textbooks to give them concise information on specific topics in paediatrics and child health. This could be for the purpose of examination preparation, teaching, or practical, on-the-spot management of patients. This is the purpose of this book. It essentially covers major systems and disease conditions. Each chapter is presented in a few pages for ease of reference. The authors hope that the book will fill the observed gap and so contribute to the improved care of children.

ACKNOWLEDGEMENT

We acknowledge our teachers, our students and our patients. They all contributed to our wealth of knowledge and experience. Our acknowledgement also goes to Colleges of Medicine and Postgraduate Medical Colleges in the West African sub-region. My husband, Dr Moses Tagbo, deserves special mention for his immense and invaluable suggestions. Above all, we acknowledge God without whom we can do nothing.

CHIEF EDITOR

Beckie Nnenna Tagbo (JP) MBBS, FWACP (Paed), FCAI, PhD

Dr Beckie Tagbo is a Fellow of the Royal Society of Medicine London, and Chief Consultant Paediatrician and Vaccinologist in the ICH and Paediatrics Department at the University of Nigeria Teaching Hospital. She is a Visiting Scholar at the Chukwuemeka Odumegwu Ojukwu University, Nigeria. She has many years' experience in clinical and field practice and in teaching medical students and resident doctors. She is a consultant to the WHO Geneva, AFRO Nigeria Offices and consults for organizations and governments. She is a member of the Brighton Collaboration and a member of 5 Brighton Case-Definition Working Groups as co-author. She has authored books and publications in high impact-factor journals including 5 chapters in *Paediatrics and Child Health in a Tropical Region*. She has pioneered researches, established research sites, and trained and mentored research teams and sites. She is an editorial board member and a recognized outstanding peer reviewer for many journals.

Associate Editor

Bertilla Ezeonwu; MBBS, FMCPaed; Consultant Paediatrician; Federal Medical Center, Asaba, Delta State, Nigeria

CONTRIBUTORS

Opara, Hyginus Ikechukwu Okezie; MBBS, FWACP (Paed); Consultant Paediatric Haematologist; Federal Medical Centre, Asaba, Delta State

Josephat Maduabuchi Chinawa; MBBS, FMCPaed, FPaedCard, DipTheol; Senior Lecturer and Consultant Paediatrician; Department of Paediatrics, UNN and UNTH

Francis Oji Ekumankama; FWACS; Consultant Orthopaedic Surgeon; Department of Surgery, Federal Teaching Hospital Abakaliki

MaryAnn Ugochi Ibekwe; MBBS (Nig) FWACP; Paediatrician/Paediatric Endocrinologist
Federal Teaching Hospital Abakaliki; Associate Professor; Ebonyi State University Abakaliki, Nigeria

Chuka P. N. Manyike; MBBS (Nig), FWACP; Senior Lecturer; Department of Paediatrics,
Ebonyi State University, Abakaliki

Ikenna Ndu; FWACP (Paed); Consultant Paediatrician; Department of Paediatrics, Enugu State, University Teaching Hospital, Park-Lane, Enugu

Uche Rowland Ojinmah; MBBS, FMCP; Consultant Dermatologist/Senior Lecturer; College of Medicine, University of Nigeria, Enugu Campus; Department of Dermatology, University of Nigeria Teaching Hospital, Ituku-Ozalla, Enugu State

Ngozi Patricia Udechukwu; MBBS, FWACP (Paed); Chief Consultant Paediatrician and Consultant Lecturer; Dept of Paediatrics, (FETHA) Federal Teaching Hospital Abakaliki; College of Health Sciences Ebonyi State University, Abakaliki

Ifeyinwa Bernadette Okeke; MBBS, FWACP; Lecturer/Consultant, Enugu State University of Science and Technology/ESUT Teaching Hospital

Chinwe Laura Charity Onyekonwu; MBBS (Nig), FMCP, MPH (Liverpool); Consultant Physician/Dermatologist/Senior Lecturer; University of Nigeria, Ituku-Ozalla/University of Nigeria Teaching Hospital, Ituku-Ozalla

Leonard Emeka Abonyi; MBBS (Nig) FWACP (Paed); Consultant Paediatrician
Head Children Emergency Unit; Federal Medical Center Asaba, Delta State, South-South Nigeria

Wilson Chukwuneke Igwe; MBBS, FWACP (Paed); Senior Lecturer/Senior Consultant Pediatrician & Child Neurologist; Department of Paediatrics, Faculty of Medicine, College of Health Sciences, Nnamdi Azikiwe University Nnewi Campus/Nnamdi Azikiwe University Teaching Hospital Nnewi

Chikaodili Adaeze Ibeneme; MBBS, FMCPaed; Paediatrician, Consultant Special Grade II; Federal Medical Centre, Umuahia, Abia State Nigeria

Ijeoma Jane Nnodim; MBBS, FWACP (Paed); Lecturer/Consultant Paediatrician, Imo State University/Imo State University Teaching Hospital, Orlu, Imo State, Nigeria

SECTION 1:

INTRODUCTORY PAEDIATRICS

1.1 History Taking (Okeke, I. B.)

History taking in paediatrics must be adapted to the child's age (as regards relevant areas of emphasis) and level of ability (ability to complain).

- Talk to the child and get him/her on your side.
- Document the following;
  - Child's age and sex;
  - Child's domicile;
  - Source of history/informant–e.g. father, mother, child (if > 8 yrs), others.
- Presenting complaint;
  - This is the symptom that brought the child to the hospital. If more than one symptom, document them and their duration sequentially, e.g. fever 1/52, vomiting–4/7, etc.
- History of presenting complaint;
  - This is the sequential documentation of the character of the symptoms and its evolvement since the onset of illness.
  - Treatment interventions should be documented because subsequent symptoms, after the intervention, may result from such interventions.
  - Pay attention to duration of symptoms, frequency of occurrence, severity, relieving/aggravating factors, and diurnal/seasonal variation.
- Past medical history;
  - Document illnesses or symptoms in the past, hospital admissions, surgery, etc.
  - Allergies–any known allergy to drugs, food, etc.
- Prenatal/natal/postnatal history;
  - This is especially important in neonates and infants. Also, children with congenital abnormalities or developmental

problems. Note–antenatal problems, birth history, problems in early neonatal period (first 2 weeks of life).

- Nutritional history;
  - Lay emphasis on this in neonates, infants, malnourished patients, failure to thrive.
  - Know the limitations of dietary recalls (usually the diet of the child during illness does not reflect the normal diet of the child or the family menu).
  - In children old enough to be on the family menu, estimate the adequacy of family meals by asking how much the family spends daily on feeding.
- Developmental history;
  - Document important developmental milestones e.g., gross motor milestones–holds head steady 2-3 months, sits without support 4-6 months, stands without support 9-11 months, walks at 12-14 months.
  - Fine motor milestones–thumb-finger grasp 8 months.
  - Communication/language–inhibits to "no" 7 months, Mama, dada 10 months, first real word 12 months.
  - Social– smiles to face at 6 weeks.
  - Mental–reaches for objects at 4 months, hand transfer at 6 months.
- Immunization history;
  - Know current immunization schedule in the country.
  - If any immunization has been omitted–ask why
  - Ask for documented evidence of immunization.
- Family/Social history;
  - Enter the family through your patient e.g. birth order of the patient in the family.
  - Physical/mental health of siblings.
  - Relevant genetic/inheritable disorder.
  - Physical environment–housing, waste disposal, source of water.
  - Social environment–family structure e.g. polygamous/ monogamous, single parent, etc.
  - Care giver to under-5 children.
  - Socioeconomic status of parents–educational qualification and occupation.
- Systems review;
  - This is an inventory of body systems obtained by verbal history, with the signs and/or symptoms which the patient is experiencing or had.

- General screen e.g. weight loss, level of activity.
- Digestive–vomiting, abdominal pain, appetite, bowel habit, diarrhoea/constipation, blood in stool, swallowing difficulties.
- Cardiovascular–breathless on exertion, slow to feed, sweaty on feeding, cyanotic episodes, chest pain, palpitation, squatting, dizzy spells or faints.
- Respiratory–sore throat, earache, cough (nocturnal), breathlessness compared with peers during games, haemoptysis, aspiration, wheezing.
- Genitourinary–urine stream, enuresis (primary/secondary), dysuria, incontinence, haematuria, flank pain, suprapubic pain, frequency of urination, menstrual history.
- Neurological–headache, faints, visual disturbances, anosmia, deafness, paraesthesia, weakness, frequent falls.
- Musculoskeletal–joint pain or swelling, limp, skin rash, alopecia, muscular pains.

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1.2 Physical Examination

1.2.1 General Examination (Chinawa, J.)

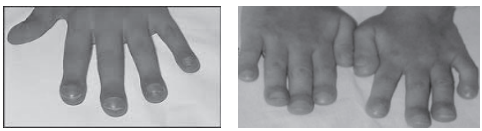
- The order of the examination should conform to the age and temperament of the child. For example, many infants under 6 months are easily managed on the examining table, but from 8 months to 3 years you will usually have more success examining on the mother's lap.
- Certain parts of the exam can sometimes be done more easily with the child in the prone position or held against the mother. After 4 years, they are often cooperative enough for you to perform the examination on the table again.
- Wash your hands with water before the examination begins. You will impress your patient's mother.
- Exam checklist: WIPE:
  - Wash your hands [thus warming them];
  - Introduce yourself to the patient; explain what you are going to do;
  - Position the patient on the couch or the parent's lap;
  - Expose the area as needed [parent to undress the patient].

Striking features

- State of health (acutely ill looking such as evidence of respiratory distress, painful distress, toxaemia OR chronically ill looking such as presence of bony prominences, generalized body swelling, muscle wasting);
- Head (size, shape, circumference, asymmetry, cephalhaematoma, bosses, craniotabes, control, molding, bruit) fontanel (size, tension, number, abnormally late or early closure), sutures, dilated veins, scalp, hair (texture, distribution);
- Facie (coarse as in congenital hypothyroidism, elfin as in William’s syndrome, wizened old man’s, moon facie, downs, etc.);
- Posture (limpy, decorticate: flexing upper and extension of lower limbs depicting cortical lesion, and decerebrate which involve extension of both limbs with opisthotonus showing pontine lesion, other posture could be cardiac position and antalgic posture)
- Crying (high-pitched vs. normal).

Inspection

- *Pallor*: Palpebral conjunctiva (remember that crying and conjunctivitis can affect results), buccal mucosa, tongue, nail bed, palms (remember shock, fever, low temperatures could affect the results at palm and nail beds). The bulbar conjunctiva can also be hyperaemic as in heart disease or any condition that may cause polycythaemia.
- *Cyanosis*: nail beds, tongue, buccal mucosa.
  - Tongue and buccal mucosa (peripheral cyanosis) others are central. Remember to warm your hands.
- *Jaundice*: Bulbar conjunctiva. Should be done in good lighting.
  - Lemon yellow: Haemolysis;
  - Greenish yellow: hepatobiliary obstruction.
- *Finger clubbing*:
  - Three possible pathogenesis: escape of unfiltered platelets from the lungs and their eventual deposition at end arteries. Oestrogen theory and theory of prostaglandins.
  - 5 grades (some merge grades 4 and 5 into one), see figures 1a and 1b.
  - Grade 1: Fluctuation (increased ballotability) and softening of the nail bed (no visible clubbing).
  - Grade 2: Loss of (obliteration) normal angle (Lovibond angle) between the nailbed and the proximal nail fold (cuticula).
  - Grade 3: Increased convexity of the nail.
  - Grade 4: Clubbed appearance of the fingertip (drumstick appearance).
  - Grade 5: Shiny or glossy nail and adjacent skin with longitudinal striations.



Figures 1a and 1b: Finger clubbing
https://clinicalgate.com/history-and-examination-5/
Sheikh et al. Bronchiectasis in paediatric AIDS. Chest 1997; 112:1202-07

- *Skin*: Look out for skin lesions such as erythema, macule, papules, patch, plaques, nodules, vesicle, bulla, pustule, cyst, erosion, and wheal.

Palpation

- *Lymph Nodes:* Location, size, sensitivity, mobility, consistency. One should routinely attempt to palpate sub occipital, pre-auricular, anterior cervical, posterior cervical, sub maxillary, sublingual, axillary, epi-trochlear, and inguinal lymph nodes.
- Occipital, cervical, submandibular and sub mental lymph nodes are palpated from behind the child.
- Axillary lymph node: left hand of clinician to left hand of the child.
- If lymph nodes are present; check for the site, shape, size, consistency, discreteness, fluctuancy (measured in 2 planes), warmth and tenderness.
- Remember: generalized palpable lymph nodes: involvement of 2 or more non-contiguous sites.
- Significant palpable lymph nodes: lymph nodes more than 1 cm at all sites except inguinal which is more than 2 cm.
- *Oedema*: check if pitting (most common systemic diseases associated with oedema involve the heart, liver, and kidneys) or non-pitting (disorders of the lymphatic system such as lymphoedema, which is a disturbance of the lymphatic circulation, lymph node surgery, or congenitally, pretibial myxoedema, which is a swelling over the shin that occurs in some patients with hyperthyroidism. Non-pitting oedema of the legs is difficult to treat).
- Pitting oedema could be graded as:
  1. Up to the ankle joint;
  2. Midpoint of the leg;
  3. Knee involvement;
  4. Beyond the knee.

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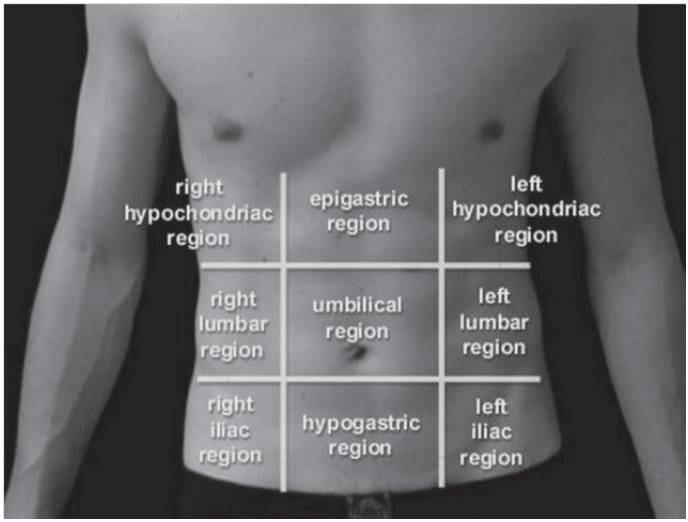
1.2.2 Examination of the digestive system (Okeke, I. B.)

- This system is made up of the whole gastrointestinal tract with its attached organs necessary for its complete function; it involves examination of the mouth, throat, abdomen and anal regions.
- Examination of the patient is done with the doctor standing on the right side of the patient's bed unless otherwise stated.

Inspection;

- The mouth, inspect;
- The lips and the angles of the mouth for fissures or cracks.
- The buccal mucosa and gum for ulcers and blisters.
- White patches on the buccal mucosa or tongue may be milk curds or oral candidiasis.
- The teeth for dental caries, discolouration, hypoplasia, supernumerary.
- The hard and soft palate for ulcers, patches and cleft.
- The throat for tonsillitis or pharyngitis.
- The abdomen is anatomically divided into nine regions. These are made use of in reporting the examination findings.
- Expose the abdomen from above the xyphi-sternum to mid-thigh.
- Inspect the abdomen from the foot of the bed (stooping down in order that the abdomen is at the same level with the examiner's eye). Note the fullness, contour and symmetry.
- From the right side of the bed, inspect for scars (surgical, scarification), movement with respiration, distended veins, visible peristalses, hernias (umbilical, inguinal, incisional).



Palpation;

- The neck–with the patient sitting on the bed, palpate for the submental, submandibular, and cervical lymph nodes from behind the patient.
- Then in supine position–do superficial (light) palpation of the abdomen checking for areas of tenderness or guarding.
- Deep palpation (with the hand flat on the abdomen and the radial edge of the index finger used to define the edge of enlarged organs. Avoid poking with finger tips). Palpate for abdominal organs and masses and note the texture (soft, firm, hard), surface (smooth, lobulated), edge (sharp, blunt), and tenderness.

Percussion;

- The normal abdominal percussion note described as tympanitic is heard over all the abdominal wall.
- Enlarged organs, masses and fluid in the peritoneal cavity will produce a dull percussion note over the organs, masses or at the flanks respectively. Shifting dullness indicates free peritoneal fluid (ascites).
- Massive ascites is demonstrated by fluid thrill (an assistant places the side of his hand firmly in the midline of the abdomen, the

examiner places one hand flat over the lumbar region of one side, then taps the opposite lumbar region).

- A definite impulse felt in the hand held flat demonstrates fluid thrill.
- Hypertympanitic denotes air in the stomach or intestines.

Auscultation;

- Listen for bowel sounds with the diaphragm and for bruits with the bell.
- Place the stethoscope on one site on the abdomen and listen for an intermittent low to medium pitched gurgling sound that normally occurs every 15-30 seconds. Must listen for at least two minutes at a site before documenting absent bowel sounds.
- Increased bowel sounds are heard in mechanical intestinal obstruction.
- Absent bowel sounds occur in paralytic ileus, generalized peritonitis, post abdominal surgery and when strangulation and gangrene supervene in mechanical obstruction.

Anal examination;

- With the patient in the left lateral decubitus position with the right leg flexed at the hip and knee joints, inspect the anal region for fissure, anal tag, rectal prolapse or haemorrhoid.
- The gloved and lubricated index or little finger is gently introduced into the rectum.
- Note the tone of the anal sphincter, the degree of fullness of the rectum, the consistency and colour of faeces on the examining finger.

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1.2.3 Physical examination-Respiratory system (Ibeneme, C. A.)

- The respiratory system comprises the airway passages (anterior nares, air passages in the nose, the nasopharynx, larynx, trachea, bronchi and bronchioles) and the alveolar sacs. An examination of the respiratory system is incomplete without a simultaneous relevant general examination.

General examination/Inspection of the chest

- Cyanosis: the lips and tongue are inspected for central cyanosis which almost always indicates poor oxygenation of the blood by the lungs. Peripheral cyanosis alone is usually due to poor peripheral perfusion.
- Use of accessory respiratory muscles–indicates breathlessness.
- Pallor: anaemia may be a cause of tachypnoea.
- Ears and pharynx: these are anatomically related to the respiratory tract.
- Digital clubbing: gross degrees of clubbing are seen in chronic suppuration within the chest such as lung abscess, bronchiectasis, empyema; lesser degrees are found in carcinoma of the lungs, pulmonary tuberculosis.
- Finger staining by tobacco.
- Listen to the patient: Is the voice hoarse? Any audible wheeze or stridor?
- Are there any obvious scars, lumps or skin lesions on the chest?
- Shape and symmetry: Is the chest bilaterally symmetrical? Chest symmetry may be distorted by:
    - Diseases of the ribs or spinal vertebrae such as kyphosis, scoliosis.
    - Underlying lung disease: unilateral apical fibrosis secondary to tuberculosis may cause flattening of the affected side; severe chronic airflow limitation may lead to overinflated and barrel-shaped chest.
- Movements of the chest: Are they symmetrical? Diminished movement on one side may be due to abnormalities on the ipsilateral side such as pleural effusion, pneumothorax, extensive consolidation, collapse or fibrosis.
- Rate of respiration.

- Rhythm/pattern of respiration: fast and deep (acidosis), fast and shallow (hypoxic), prolonged expiratory phase (lower airway obstruction).

Palpation (Anterior and Posterior)

- Lymph nodes: supraclavicular, cervical and axillary lymph node enlargement may be secondary to the spread of malignant disease from the chest.
- Position of the trachea: the trachea may be deviated to the contralateral side in pleural effusions or pneumothorax. Fibrosis or collapse of the lungs will pull it to the affected side.
- Tenderness/swellings.
- Chest movement/expansion: best done at the back and in those 5 years and above.
- Tactile fremitus: increased over an area of consolidation, decreased in pleural effusion and pneumothorax.

Percussion (Anterior and Posterior)

- Percuss 3 or 4 areas on the anterior chest wall, comparing left with right; percuss the axilla, then 3 or 4 areas on the back of the chest.
- Percussion note is resonant over a normal lung, dull over a consolidation, stony dull in pleural effusion, hyperresonant unilaterally in pneumothorax or emphysema and bilaterally in states of hyperinflation.
- Ensure proper hand and finger positioning, finger alignment to intercostal spaces, symmetrical progression of percussion and coverage of the lung zones.

Auscultation (Anterior and Posterior)

- Neck and trachea.
- Breath sounds for intensity and quality
  - Intensity may be normal, reduced or increased. It is reduced when there is localized airway narrowing, pneumothorax or pleural effusion. It may be increased in very thin subjects.
  - Quality/character of breath sounds can be vesicular in normal lungs beyond 3 months of age, bronchovesicular in normal lungs below 3 months or bronchial in consolidation.
- Vocal resonance as in tactile fremitus.

- Added sounds: crackles, wheezes, stridor, pleural rub.

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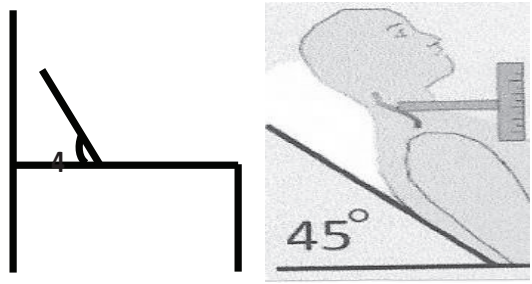
1.2.4 Physical examination-Cardiovascular system (Manyike, C.)

- The physical examination of the cardiovascular system begins as the patient is brought or walks into the consulting room and follows the normal convention of IPPA–Inspection, Palpation, Percussion and Auscultation.
- Before this, is IPPEC which stands for Introduction, Permission, Positioning, Expose, and Comfortable.
- Introduce yourself to the caregiver/patient.
- Ask permission (establish rapport) of the caregiver/patient.
- Position the patient properly at 45^{o}.
- Expose the patient decently.
- Ensure the patient is comfortable.

Inspection

- Evaluate the patient for pallor, conjunctival hyperaemia, cyanosis, diaphoresis, dyspnoea–flaring of the ala nasi, intercostal, subcostal and suprasternal recessions; then finger and toe clubbing, sacral and pedal oedema as well as evidence of failure to thrive.
- In patients with congestive heart failure, there will be dyspnoea on exertion (walking, playing; and even sucking at the breast and sweating in the neonate) and difficulty in lying flat (orthopnoea).
- The jugular venous pressure is inspected by positioning the patient in the cardiac position at an angle of 45^{o}. The jugular vein shows the pressure changes in the right atrium and is not visible above the clavicle except in congestive cardiac failure when it is engorged and visible. When there is doubt as to whether it is engorged, hepato-jugular reflux is done by applying gentle pressure over the liver.
- The jugular venous pressure (JVP) is measured by having the patient in the cardiac position with the head of the bed at an angle of 45^{o}. The upper level of the engorged vein is noted and the manubrium sterni–sternal angle is identified.
- Then a wooden metre rule is placed perpendicular to the manubrium sterni and another metre rule or any suitable object is placed above the upper border of the engorged vein, horizontally across the perpendicular metre rule.
- The point of intersection between the horizontal and perpendicular metre rules gives the value in mmHg.



- *Precordium***:** This is the area overlying the heart. The precordium may be quiet, which is normal or active or hyperactive in carditis, rheumatic heart disease and congestive cardiac failure. A precordial bulge to the left of the sternum with increased precordial activity suggests cardiac enlargement. A substernal thrust indicates the presence of right ventricular enlargement, while an apical heave is noted with left ventricular hypertrophy. A hyperdynamic precordium suggests a volume load such as that found with a large left to right shunt e.g. VSD.
- A silent precordium with a barely detectable apical impulse suggests pericardial effusion or severe cardiomyopathy.

Palpation:

Pulse:

- The pulses–radial, femoral, popliteal, the posterior tibial and dorsalis pedis pulses are palpated. The pulse should be counted for one full minute.
- The radial pulse is used to check the pulse rate, volume (normal, small, medium or full volume); whether the pulse is bounding as in truncus arteriosus and coarctation of the aorta or collapsing as in Patent Ductus Arteriosus, aortic incompetence, arterio-venous malformations and other run-offs. The rate is generally <60 in bradycardia and higher than 100 in tachycardia, depending on age.
- It is small volume, thready or impalpable in congestive cardiac failure and cardiac tamponade; and medium volume in moderate to severe dehydration.
- It is thready and fast in shock. Small volume pulse is also seen in aortic stenosis.
- Large volume pulse is obtained in fever, anaemia, patent ductus arteriosus, aortic regurgitation and thyrotoxicosis.

- Simultaneous palpation of the femoral and radial pulses gives nearly the same pulses, but the femoral pulse is felt slightly before the radial artery pulse except in coarctation of the aorta where there is radio-femoral delay.
- The pulse is normally regular. It is irregular in ectopic beats and irregularly irregular in atrial fibrillation. A regularly irregular pulse is characterized by an extra beat and/or missed beats at regular intervals.
- Sinus arrhythmia is an example of a regularly irregular pulse and characterized by a rapid pulse during inspiration and slowing down during expiration. This is normal.
- A regularly irregular pulse may also be observed when there are extra systoles at fixed intervals (every fifth or tenth beat).
- Pulsus paradoxus occurs when the pulse volume gets lower and even disappears at the end of inspiration.
- The presence of pulsus paradoxus is best confirmed by listening to the Korotkoff sounds while measuring blood pressure during inspiration and expiration.
- A difference of over 10 mmHg between systolic pressure obtained during inspiration and systolic pressure obtained during expiration indicates the presence of pulsus paradoxus.
- Conditions associated with pulsus paradoxus are pericardial effusion, cardiac tamponade, pericarditis and severe airway obstruction as seen in bronchial asthma.

Blood pressure:

- This is the pressure exerted by blood on the walls of the blood vessel (artery). It is measured with a sphygmomanometer and a stethoscope. There are 5 cuff sizes to cover the varied spectrum of the paediatric age group. These are 3, 5, 7(8) 12 and 18 cm cuffs. The appropriate cuff size must always be used.
- The cuff bladder must cover three-quarters of the arm's circumference, while the cuff itself will cover two-thirds of the length of the arm, measured from the acromion to the olecranon process.
- Large cuffs give lower BP values whereas small cuffs give higher values.
- The right arm is preferable because of coarctation of the aorta which almost always occurs on the left arm. Tight clothes should be removed.

- Having made the patient relax, the cuff is loosely applied round the right arm. Using the palpatory method, the cuff is inflated gradually with the fingers on the radial pulse.
- Once the radial pulse is no longer felt, the point at which this happens is read off from the sphygmomanometer and this gives a rough idea of the systolic pressure.
- The cuff is deflated and inflated by 10-20 mmHg above the value obtained at palpation.
- The diaphragm of the stethoscope is then applied on the cubital fossa over the brachial artery with the ear pieces to the ears.
- The cuff is then gradually deflated. The first sound represents the systolic blood pressure. The sound will increase in intensity, muffles and finally disappears.
- There is a controversy whether the muffling or disappearance represents the diastolic blood pressure. The point at which it disappears is mostly favoured.
- These sounds are the Korotkoff sounds and there are five (5) phases:
    - Phase 1–the first appearance of the sounds marking systolic blood pressure;
    - Phases 2 and 3–increasingly loud sounds;
    - Phase 4–abrupt muffling of the sounds;
    - Phase 5–disappearance of the sounds.

Apex beat:

This is defined as the lowermost and outermost point of maximal cardiac impulse.

- This represents the area of the mitral valve.
- The location is always done in relation to the mid clavicular line.
- How to locate the apex beat*:*
    - Let the patient lie supine with the chest exposed. Apply the right palm over the precordium and feel for the cardiac impulse;
    - Having felt it, identify the point with the right index finger. Then with the finger still in place, run down the left index finger along the manubrium sterni to identify the sternal angle;
    - The adjacent costochondral junction is that of the second rib. Above this costochondral junction is the 1st intercostal space and below it is the 2nd, then 3^{rd,} etc., until the space that corresponds with the point where the right index finger is, and that represents the apex beat.

Oedema:

- The oedema of cardiac origin is pitting. It could be sacral or leg oedema. Leg oedema is graded from 1 to 4.
  1. Below the ankle joint;
  2. Above the ankle joint;
  3. Up to the knee joint;
  4. Above the knee joint up to the groin.

Percussion:

- The value of percussion in cardiovascular examination is limited. However, it helps in delineating the area of cardiac dullness which is increased in cardiomegaly.

Auscultation:

- Auscultation has to do with heart sounds and murmurs. It is done with the stethoscope.
- There are 4 auscultatory windows on the chest walls. These are the apex, left lower sternal border (LLSB), left upper sternal border (LUSB) and right upper sternal border (RUSB), representing the mitral, the tricuspid, the pulmonary and the aortic valves respectively.
- *Heart sounds:* There are 4 heart sounds–1^{st}, 2^{nd}, 3^{rd}, and 4^{th}. The 1^{st} heart sound is produced by the closure of the mitral and tricuspid valves while the 2^{nd} heart sound is produced by the closure of the aortic and pulmonary valves.
- The 3^{rd} and 4^{th} heart sounds occur early and late in diastole respectively. They give the characteristic gallop to the cardiac rhythm.
- The third heart sound is as a result of the opening of atrioventricular valves early in diastole. It can occur in high output states like anaemia, fever and thyrotoxicosis while the 4^{th} heart sound is as a result of vigorous atrial contraction late in diastole and occurs in elderly hypertensive patients; those with aortic stenosis and hypertrophic cardiomyopathy.
- *Murmurs*: These are caused by turbulent flow within the heart and great vessels. They may indicate valve disease or abnormal communication between the left and right sides of the heart, e.g. ventricular septal defect (VSD).

- Occasionally, the turbulence is caused by increased flow through a normal valve e.g., aortic or pulmonary valves producing innocent murmurs also referred to as functional, normal or insignificant murmurs.
- Innocent murmurs unrelated to heart disease are always mid-systolic in timing and caused by turbulent flow in the left sometimes right ventricular outflow tract.
- They usually reflect a hyperkinetic circulation in conditions such as anaemia (haemic murmurs), fever and thyrotoxicosis. They are rarely louder than grade 3 with no thrill and do not radiate to the back.
- Heart murmurs are defined by 4 characteristics–loudness, quality, location and timing.
- Loudness: This is graded on a scale of 1-6.
  - Grade 1–soft, not heard in all positions. It is heard by trained ears. No thrill;
  - Grade 2–soft, heard in all positions, no thrill;
  - Grade 3–loud, no thrill;
  - Grade 4–loud, thrill present;
  - Grade 5–louder with thrill; can be heard with the stethoscope at an angle on the chest wall;
  - Grade 6–louder, thrill present. Heard with the stethoscope a little above the chest wall.
- Quality: this relates to the frequency and is described as–low-, medium- or high-pitched.
- Location: this corresponds to the 4 auscultatory sites. Some radiate e.g., pansystolic murmur of mitral regurgitation that radiates to the axilla, and that of aortic stenosis to the neck.
- Timing: this is in relation to the cardiac cycle e.g., systolic and diastolic. It is timed with the carotid artery. If the murmur coincides with the pulsation of the carotid artery, it is systolic otherwise it is diastolic.
- It is also timed with the heart sounds. If it starts with or immediately after the first heart sound, it is systolic, if it is after the 2nd heart sound, it is diastolic.
- Diastolic murmurs are almost always pathologic.
- Systolic murmurs can be mid systolic also known as ejection systolic murmurs as in aortic or pulmonary stenosis.
- Innocent murmurs are ejection systolic murmurs.

- Pansystolic murmurs are audible throughout systole, from the 1st to the 2nd heart sound. Defects that give pansystolic murmurs are VSD, tricuspid and mitral regurgitation.
- Continuous murmurs: they are heard during systole and diastole. They are also known as machinery murmur. Patent Ductus Arteriosus gives a continuous murmur.
- End diastolic murmurs: these are produced by regurgitation through incompetent aortic and pulmonary valves. They are high-pitched and soft and are heard immediately after the second heart sound.
- Mid diastolic murmurs: these are caused by turbulent flow through arterio-venous valves. Mitral stenosis produces mid diastolic murmur.
- Thrill: this is a palpable murmur. It corresponds to the valve that produces it and the lesion. It could be systolic or diastolic. It is elicited through palpation.
- *Systolic clicks:* in aortic stenosis, valve opening produces a click.
- *Opening snap:* this occurs in mitral stenosis because of the elevated left atrial pressure causing the forceful opening of the thickened mitral valve leaflets.

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1.2.5 Physical examination-Urogenital system (Ezeonwu, B.)

- This involves general physical examination, abdominal, perineal and bedside urine examinations.

General physical examination

- *Inspect* for
  - Pallor–anaemia of chronic kidney disease (CKD);
  - Oedema (periorbital and leg oedema): fluid retention;
  - Abdominal size: fluid retention and nephromegaly;
  - Hair changes: malnutrition of CKD;
  - Skin changes: uraemic frost, sallow complexion of end stage renal disease (ESRD).
- *Measure* the:
  - Height/length: stunting of CKD;
  - Weight: malnutrition of CKD;
  - Mid arm circumference: malnutrition of CKD;
  - Occipitofrontal circumference: malnutrition of CKD;
  - Pulse: variable; bounding in anaemia and small volume in intravascular contraction due to oedema;
  - Blood pressure: hypertension as a cause or sequalae of nephropathy.

Abdominal examination

- *Inspect* for uniform distension from fluid or flank fullness from nephromegaly.
- *Palpation*: ask for areas of tenderness viz. generalized in peritonitis, epigastric in uraemic gastritis, suprapubic in urinary tract infection (UTI), renal angle in acute pyelonephritis (APN).
- Looking at the patient's face, do light palpation in all the 9 quadrants to feel for masses.
- Deep palpation for the liver, spleen, bladder and any delineated masses on light palpation.
- Ballot for the kidneys: ballotable in polycystic kidney disease, obstructive uropathy.
- *Percussion*: shifting dullness, fluid thrill (ascites), percuss the bladder for retention, fist percussion of the loin for renal angle tenderness.

- *Auscultation*: absent bowel sound in spontaneous bacterial peritonitis (SBP) of nephrotic syndrome.

Perineum examination (courtesy to patient)

- Genitalia inspection: size (Congenital Adrenal Hyperplasia), oedema (Nephrotic Syndrome, hydrocele), site of urethral opening (hypo/Epispadias).
- Genital palpation: testes in the scrotal sac.

Bedside urine examination

- Ask for urine specimen.
- Inspect: for colour, cloudiness, odour.
- Dipstick testing: pH, blood, protein, urobilinogen, specific gravity, nitrite, leucocyte esterase, glucose, ascorbic acid, bilirubin.

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1.2.6 Examination of the central nervous system (Igwe, W.)

Steps in the neurologic examination

- For the purpose of simplicity, the neurologic examination is divided into several steps even though the steps are not always necessarily performed in the same order.
- These steps include the following: Conscious level and higher cerebral functions, Skull (size & shape, fontanels–size and tension while patient is calm and in a sitting position, sutures, scalp and hair), Meningeal signs, Cranial nerves, Motor system, Sensory system and Reflexes.

Consciousness

- The child's age and developmental level are important in evaluation.
- The state of awareness of self and the environment. Consists of wakefulness and awareness.
- ***Impaired consciousness*** implies a significant impairment in the awareness of self and the environment, with a variable degree of wakefulness.
- ***Coma*** is the total absence of arousal and awareness. Coma is typically a transitional state, and evolves towards recovery of consciousness, vegetative state or brain death.
- ***Vegetative state*** is a condition of complete unawareness of self and environment but preservation of sleep wake cycles.
- ***Brain death*** is the permanent absence of all brain functions including those of the brainstem.

Assessing the level of Consciousness

- Inspect for–spontaneous body position, activity, eye opening or vocalization.
- Observe the response to stimuli–verbal commands, tactile cues, and painful stimuli.
- Look for evidence of interaction with the environment–e.g., following commands, appropriate smiles/cries, reaching for objects, fixation and following.

- Record the level of consciousness in the form of an objective scale such as the Glasgow Coma Scale (GCS), for children >5 years, verbal component modified for children <5 years (Table 1).
- *Interpretation of scores in GCS:*
  15 = normal level of consciousness;
  13-14 = mild impairment;
  9-12 = moderate impairment;
  <8 = severe impairment.

Table 1: Glasgow Coma Scale (GCS)

GCS	MODIFIED GCS
Eye opening	
Spontaneous 4	**4**
To sound 3	**3**
To pain 2	**2**
No response 1	**1**
Best motor response	
Spontaneous 6	**6**
Localizes pain 5	**5**
Withdraws to pain 4	**4**
Abnormal flexion 3	**3**
Abnormal extension 2	**2**
No response 1	**1**
Best verbal response	
Oriented 5	Smiles, oriented to sound, follows objects, interacts **5**
Confused 4	Crying, inappropriate interactions **4**
Inappropriate words 3	Inconsistently consolable, moaning **3**
Incomprehensible sounds 2	Inconsolable cry, irritable and restless **2**
No response 1	No response **1**

Higher mental functions

- A detailed assessment is not feasible in all patients; however it is necessary in children who present with cognitive decline, stroke, language and memory deficits.
  1. General behaviour and appearance–is the child interested in the surroundings, hyperactive, anxious, indifferent, or making good eye contact?

2. Orientation–to time, place, and person (appropriate to the developmental level). For infants, familiarity with parents and stranger anxiety (orientation to person).
3. Attention span (ability to attend to a specific stimulus without being distracted by extraneous stimuli)–assess using the digit repetition test. Say the digits in a normal tone of voice at a rate of one digit per second and ask the child to repeat after you.
4. Speech and language–assess the child for articulation and volume of speech. Identify the first/native language and test for understanding by asking simple questions e.g., what is your name? Assess for fluency, naming and repetition.
5. Memory–immediate memory (recall after an interval of a few seconds), recent memory (recall day-to-day events), remote memory (recall events that occurred months/years ago).
6. Intelligence (higher cognitive function)–e.g., calculation, abstract thinking (e.g. explain known proverbs; explain the difference between a pair of objects).
7. Spatial perception and constructional ability (tests parietal and occipital lobe functions)–e.g., draw a clock and fill in the numbers.

Examination of the skull

- Head circumference (occipito-frontal circumference–OFC), measured in those younger than 3 years.
- Measured over the most prominent parts of the head (occiput) and supra-orbital ridges with a flexible, non-stretchable tape and read to the nearest 0.1 cm.
- The tape should be pulled snugly to compress the hair and underlying soft tissue.
- Three measurements are taken with the measurements agreeing within 0.2 cm. The average of the two measurements in closest agreement is taken as the OCF.
- The fontanels provide a window into what may be occurring in the brain, examined with the infant in both upright and supine positions.
- The normal anterior fontanel is diamond shaped and measures 4 cm in anterior-posterior and 2.5 cm in transverse diameter. The posterior fontanel is normally less than 1 cm at the time of birth and is no longer palpable by 8 weeks.

- Examining the skull shape and size will identify underlying problems that require further evaluation or intervention. The skull should be examined for:
  - Microcephaly, macrocephaly, flattening of the occiput;
  - Prominence of scalp veins = increased ICP;
  - Prominence of the occiput (Dandy-Walker syndrome);
  - Ridging of the cranial sutures (sign of craniosynostosis);
  - Macewen (cracked pot) sign = sutures are separated, may indicate increased ICP.

Signs of meningeal irritation

- Clinical signs of meningeal irritation: may be due to meningitis or subarachnoid haemorrhage.
- ***Nuchal rigidity or neck stiffness:*** elicitation
  - Place a hand under the patient's head;
  - Ask the patient to flex the neck or the examiner should gently try to flex the neck.

  Positive test:
  - Patient cannot flex the neck to place the chin on the chest;
  - Muscle spasms limit passive neck flexion.
- Unreliable in children under 18 months due to underdevelopment of the neck musculature.
- ***Brudzinski sign*** (flexing the patient's neck causes flexion of his hips and knees): elicitation
- Place the patient supine, immobilize the trunk against the bed, flex the neck, chin to the chest.
  - Positive test: involuntary hip flexion.
- ***Kernig sign:*** elicitation:
- Place the patient in supine position, flex the hip and knee to 90 degrees.
- Immobilize the hip and extend the knee.
  - Positive test: resistance to knee extension due to pain in hamstring muscles.

Examination of the cranial nerves

- Helps localize a brainstem lesion. All, except 1 and 12, originate from the brainstem.

Olfactory (1st) nerve

- Olfactory discrimination can be tested objectively from the age of 5 years.
- Use non-irritant familiar substances and test each nostril separately with the eyes closed.

Optic (2nd nerve): Functions: vision and afferent for papillary constriction.

- Tests: Visual acuity, Colour vision, Visual field, Pupillary reactions and Fundoscopy.
- An ability to follow moving light or an object is an indication of intact cortical vision.
- A consistent blink response to a menace suggests intact cortical vision.
- *Visual acuity:* finger counting and perception of light shone in front of the eyes. In newborns and infants: behavioural responses to light and faces can be observed (blinking, turning the eyes or head towards light, fixation on an object), menacing response: the child blinks to avoid a menacing stimulus.
- *Colour vision:* difficult in those less than 3 years. The Ishihara colour vision chart is used.
- *Visual field:* use the confrontation test.
- *Pupillary reactions:* Light and Accommodation
    1. Light reflex: Shine bright light on the bridge of the nose; inspect the pupils for constriction (direct); repeat and look at the other eye (consensual). In cortical blindness, the pupils will be normal in size, with normal reactions to light. In optic lesions, the pupil on the affected side will neither react to direct light nor elicit a consensual response but will constrict if light is shown in the normal eye.
    2. Accommodation: ask the patient to look into the far distance and then at the examiner's finger. Look at the pupils for constriction.
- *Fundoscopy*: appearance, of the optic disk, macula and retina.

Eye movements (cranial nerves 3, 4, 6; oculomotor, trochlear, abducens):

- Ask the patient to follow the examiner's finger in all directions. If weakness is present, test each eye separately.

Cranial nerve 5:

- Look for the wasting of temporalis and masseter muscles with the teeth clenched. Palpate to feel the bulk. Ask the patient to clench his teeth.

- The muscles do not contract on the paralyzed side. Ask the patient to open his mouth. The jaw deviates to the paralyzed side. The patient cannot also move his jaw from side to side.
    - *Corneal reflex:* (efferent is carried by CN 7). Touch the limbus of the cornea with a strand of cotton from the side. Observe the reflex blink of both eyes. In CN 5 lesion, there will be no response from both eyelids when the abnormal side is stimulated and a normal response from both lids if the normal side is stimulated.
    - With a wisp of cotton wool and eyes closed, test light touch sensation in all the 3 divisions.
    - *Jaw jerk*: ask the child to open the mouth a little. Strike your finger, placed on the child's chin, with a tendon hammer. In normal response, there is no appreciable movement.
    - It is exaggerated when jaw movement is clearly visible (closure), indicating a supra nuclear lesion. It is absent in nuclear and infranuclear lesions.

Cranial nerve 7

- Examine for facial symmetry at rest and during movements (talking, crying and smiling).
- Ask the patient to wrinkle his forehead, close his eyes, show his teeth.
- In the complete paralysis of the facial nerve the patient will not able to close the affected eye.
- In upper motor neuron lesion only the movements of the lower part of the face are affected because the corticonuclear fibres concerned with movements of the upper part of the face are bilateral whereas those of the lower part of the face are unilateral.

Cranial nerve 8: *Hearing and equilibrium*

- Hearing: call the patient's name, make a loud noise, if impaired, do the Rhinne and Weber's tests.
- Principle–air conduction is better than bone conduction but in defects of conduction, sound is better heard through bone.
- Rhinne's test–put the turning fork near the ear until it cannot be heard, then put it on the mastoid process. If still audible, the test is negative (the ear with a negative test is abnormal).
- Weber's test–place the turning fork in the centre of the forehead.
- The sound is heard in both ears but is clearer in the ear with a conduction defect.

Cranial nerves 9 (glossopharyngeal) and 10 (vagus)

- Ask the patient to say "aah" and observe the movement of the soft palate. In a normal person, the soft palate is elevated.
- In unilateral paralysis, the palate is pulled towards the normal side. In bilateral paralysis, the soft palate does not move.
- Gag reflex–touching the pharyngeal mucosa causes symmetrical retraction of the soft palate. Cranial N 9 is the afferent while cranial N 10 is the efferent pathway.
- If injury occurs on one side the palate retracts to the normal side. Bilateral paralysis manifests as stridor, hoarse voice, drooling and nasal regurgitation.

Cranial nerve 11 (accessory)

- Ask the patient to shrug his shoulders against the examiner's resistance. In paralysis, the movement will be weak in the paralyzed side.
- Ask the patient to turn and face the opposite side (against the resistance offered by your hand). In paralysis, the movement will be weak on the affected side.

Cranial nerve 12 (hypoglossal)

- Ask the patient to stick out his tongue and look to see whether there is atrophy, fasciculation (suggests a lower motor neuron lesion), or deviation to one side.
- In unilateral lesions the tongue deviates to the paralyzed side while in bilateral lesions the tongue is motionless and swallowing is difficult.

Examination of the motor system

- Five areas are to be examined in the upper and lower limbs: Muscle bulk, Tone, Power, Deep tendon reflexes, coordination and Gait

Upper and Lower limbs

- Look for deformities, wasting, abnormal postures and movements, skin abnormalities in both upper and lower limbs respectively.
- Compare the left and right limbs and also the upper and lower limbs. Note any differences if present.

Power

- Muscle power can be judged either by observing the child's activities or by the manual testing of individual muscles.
- Power is assessed in various muscle groups e.g., shoulder abductors, knee extensors, elbow flexors, etc. Detailed power is not possible in infants and very young children.
- In such cases the power can be judged by observation of the limb movements.
- Grading of power
  0. No movement;
  1. Flicker of movement;
  2. Movement with gravity removed;
  3. Movement against gravity;
  4. Movement against resistance;
  5. Normal power.
- Patterns of muscle weakness
  1. UMN lesion–weaker extensors than flexors with increased tone;
  2. LMN lesions–global weakness with flaccidity and wasting;
  3. Peripheral neuropathy–distal weakness with wasting;
  4. Mononeuropathy–local muscle wasting or weakness.

Tone

- Observe the spontaneous posture of the patient when lying supine. Put the major joints of the limbs through their full range of movement and note the resistance encountered during this passive movement. Compare both sides and both upper and lower limbs.

Deep tendon reflexes (DTR)

- Important deep tendon reflexes include: Biceps, Triceps, Patella (knee) and Ankle jerks
- Determine if the DTR is present or absent. If it is present, is it normal or abnormal? If it is abnormal, is it unilateral or bilateral?
- Biceps (root: C5). Test: support the child's forearm by resting it on the examiner's forearm. The child's arm should be held midway between flexion and extension. Place your thumb over the biceps tendon and tap over the thumb. Normal response: contraction of the biceps and flexion of the forearm at the elbow.

- Triceps (root: C6, 7). Test: with the arm flexed 90 degrees at the elbow, the forearm supported by the examiner's forearm, tap over the triceps tendon. Normal response: contraction of the triceps with extension of the elbow joint.
- Knees/patella (root: L3, 4). Test: with the patient lying supine, knees relaxed and flexed at 40 degrees and supported by the examiner's hands, tap the patellar tendon. Normal response: visible contraction of the quadriceps with extension of the knee.
- Ankle jerk (root: S1). Test: with the patient lying supine, the hip is flexed and rotated externally; the knee is flexed with mild dorsiflexion at the ankle, the tendoachilles is tapped. Normal response: plantar flexion at the ankle.
- Abnormalities of DTR:
  1. Absent or reduced reflexes–seen in LMN lesions and peripheral neuropathy;
  2. Brisk reflexes–UMN lesions. Brisk reflexes are of pathologic significance if other features of UMN lesions are present (such as spasticity and plantar);
  3. Pendular reflexes–lesions of cerebellum and basal ganglia;
  4. Clonus–a stretched muscle goes into clonic contractions until the stretch is relieved.
- Ankle clonus–while in supine position, the hips flexed; with the knee and ankle in moderate flexion. Support the leg under the knee and quickly dorsiflex the foot.
- In clonus, there is a series of contractions. If it is sustained (more than 5 repeated contractions), it indicates a UMN lesion.
- To classify the reflexes as normal or abnormal you must be familiar with the standard of normal for the various reflexes.

Coordination

- The cerebellum and its connections are responsible for the coordination of voluntary movements and these movements depend on normal power and joint position sense.
- An abnormality of joint position sense invalidates tests for coordination.
- Cerebellar abnormalities are characterized by incoordination of speech, limbs and gait that occurs on the same side of the cerebellar lesion.
- Other signs of cerebellar disease include nystagmus that worsens on looking to the side of the lesion, dysarthria and hypotonia.

- The tests of incoordination in the upper limbs are, the finger to nose test and alternating hand movements (dysdiadochokinesia) while in the lower limbs they consist of the heel to shin test and gait.
- The finger to nose test is performed with the patient sitting and observes for intention tremor. The heel to shin test is performed with the patient lying supine.

Gait

- Ask the patient to walk normally with his hands hanging loosely by his sides and observe his gait for: movement, balance, posture, arm swing, turning and symmetry.
- Note whether the patient's gait is unsteady and he is able to walk in a straight line. The main types of gait abnormalities include hemiplegic, waddling, paraplegic, cerebellar, parkinsonian, sensory ataxic and antalgic gaits.
- The gait in cerebellar disease is wide-based and ataxic and worse on walking in a straight line with a tendency to fall to the side of the lesion.
- Romberg test: the test is done by requesting the patient to keep his feet firmly together, arms by the side and the eyes open at first.
- The balance of the patient is noted. Now the patient is asked to close both eyes and the balance is now noted for around 1 minute. Interpretation:
  1) If the patient cannot maintain balance with his eyes open, there may be a problem with the cerebellum (cerebellar ataxia);
  2) If closing his eyes causes much worse balance then the test is said to be positive (Romberg test positive).
- It indicates that the patient is excessively reliant on his vision to maintain balance. The problem may lie in the vestibular or proprioceptive systems.

Sensory system

1. Superficial–touch, pain, temperature;
2. Deep sensations–pressure, joint position, vibration;
3. Cortical–stereognosis, two-point discrimination, texture and tactile extinction;
4. Special sensory: smell, taste, hearing, vision.

- The sensory system is difficult to examine in children because it requires the patient's cooperation and attention. It aims at detecting any loss of sensation and the pattern of loss.

Reflexes

- Superficial, Deep, Developmental, Autonomic.

Superficial (cutaneous) reflexes:

- These are involuntary contractions of muscles following skin stimulation.
- Plantar (L4-5, S-1)–stimulation of the sole of the foot starting from the heel along the lateral border to the base of the metatarsals, ending near the base of the big toe.
  - Normal response is plantar flexion of the big toe with adduction and flexion of the other toes.
  - Abnormal response is dorsiflexion of the big toe with fanning of the other toes. It is seen in pyramidal lesions.
- Cremasteric–scratching the upper medial aspect of the thigh in males leads to contraction of the cremaster muscle with the elevation of the scrotum on the same side. This reflex is lost in lesions above L-2.
- Abdominal–stroking the four quadrants of the abdominal wall results in the contraction of the stimulated quadrant. This reflex is lost in lesions above T-8.
- Anocutaneous–stimulation of perianal skin with a sterile object leads to the contraction of the external anal sphincter with resultant in-drawing of the anal opening. This reflex is lost in lesions involving S-2, S-3 and S4.

Deep tendon reflexes

- These are involuntary contractions of muscles caused by a brisk stretch of the muscles. These reflexes include biceps, triceps, brachioradialis, knee and ankle (discussed in examination of the motor system above).
- Exaggerated deep reflexes are seen in pyramidal lesions while these are decreased or absent in peripheral nerve lesions.

- Clonus is the rapid movement of a joint due to alternating contractions of its agonists and antagonists' muscles. This is seen in pyramidal lesions.

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1.2.7 Physical examination-Musculoskeletal system (Igwe W)

- Competent history taking and examination is the key to making an accurate diagnosis and assessment of diseases of the musculoskeletal system. History taking aims at identifying patterns that may help in the diagnosis, involvement of other systems and the impact of the disease process on the patient.

Symptoms

- Diseases of musculoskeletal system manifest mainly in the form of the following:
- *Pain:* Pain is a very common complaint in the diseases of musculoskeletal system. It may originate from the bone or periosteum, the synovia of the joints, tendons, ligaments or muscles.
- Enquiry must therefore be made about its onset (acute/insidious), site (may be localized accurately in muscle/joints or may be radiating from adjacent organ), character (dull aching/throbbing), relieving and aggravating factors.
- *Impaired movement:* In diseases of the musculoskeletal system movement may be limited by pain and stiffness. Note the timing of stiffness and its duration. Inflammatory arthritis is associated with early morning stiffness.
- *Swelling:* The site of the swelling and its relationship with activities are very important.

Signs

- Physical examination should first consist of a general inspection of the patient with special attention to stance, gait, posture and performance of simple activities.
- Start with visual inspection of exposed areas at rest. Examine the skull, jaw, rib cage spinal column and each limb in turn, comparing one side with the other and noting any abnormality in structure or function of the joints and adjacent structures. Look for any skin changes and the muscle bulk.
- ***Inspection*** will reveal gross deformities, displacement, enlargement or wasting. Check for swelling, discoloration and deformities in the joints. Observe the range of active movements. Note the distribution of joint changes throughout the body.

- Assess the gait by asking the child to walk bare footed on a flat surface. A wide based gait is normal in infancy. Any abnormalities in gait should be noted.
- ***Palpation****:* Using the back of the hand, feel the skin temperature over the area and at relevant neighboring sites. Any swellings should be assessed for fluctuation and mobility.
- Palpation is used to elicit tenderness, determine the anatomic origin and consistency of any swelling, to assess the range and power of movement of limb/joint and also to note crepitus or abnormal mobility.
- Assess full range of movements in flexion/extension, abduction/adduction and rotation.
- Assess each muscle groups for strength and grade them from zero (no motion) to 5 (normal strength). Note the pattern of muscle weakness if present.
- This may be proximal or distal, symmetric or asymmetric.
- Measurement of the length and circumference of the affected limb is very important. Compare one side with the other. Note the dimensions of any swollen joints/limbs.
- Assess active movements (patient moves the limb) and passive movements (the examiner moves the limb).
- Loss of active movement with preservation of passive movement may suggest problems with the muscles, tendons or nerves rather than the joint.

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1.3 Clinical reasoning (Chinawa, J. and Tagbo, B. N.)

- This is an important aspect of paediatrics which involves the following:
- Identifying the important and valid information in history taking.
- Identifying the important and valid information on the review of the system.
- Identifying the important and valid information in physical examination.
- Identifying pathological processes
  - Inflammatory;
  - Neoplasm;
  - Trauma;
  - Immune mediated, etc.
- Identifying functional and structural abnormalities.
- It is a thinking and decision-making process used in the evaluation and management of patients.

Objectives

- Mastery of the sequence in history taking.
- Exactness and aptness in eliciting each aspect of history taking.
- Concise but accurate documentation of the history taken.
- Sequential and gentle flow in the examination.
- Thoroughness and aptness in performing each section of the examination.
- Courtesy and respect for patients.
- Informed consent for the examination performed.
- Using the signs and symptoms obtained to detect precisely the abnormality in the organ or system function.
- Using the signs and symptoms obtained to detect precisely the abnormality in the organ or system structure.

Clerkship

The following should be noted:

- Clerking, apart from passing exams is vital in managing your patient and generating data.
- Do not be fixed but be free to think and to be endowed with the pathophysiology of all paediatric diseases and beyond.

- Then apply this pathophysiology when taking history and eliciting signs.
- History must be in tandem with timing and events arranged in a chronological sequence.
- Candidates should be able to characterize every symptom and elicit every sign and then in a moment know if it is a structural or functional problem and to which system it belongs.

Sequence

- Biodata: name, age, sex, tribe, place of residence with parents (high or low density), religion (child will naturally adopt the religion of the parents till the age of accountability).
- Presenting complaint: exactly what the child came with, however when examining a child and a very important sign is picked, say pyrexia, the candidate is free to return to the history and document fever as a presenting complaint if this information was not given before. Usually, one or more presenting complaints and fewer than six may be worthwhile.
- History of the presenting complaint: sequence and chronology in terms of time and event are paramount
- Past medical history: any significant illnesses in the past like diarrhoea, cough, fever, jaundice, convulsions; history of similar complaints in the past. Note that if the patient had similar complaints in the recent past, establish that there was a complete resolution before the current illness; otherwise it should be part of the present illness. Also ask for previous hospitalizations, previous trauma/accidents and previous surgeries.
- Prenatal, natal and postnatal history: follow the sequence.
- Nutrition history: remember FADU (frequency, adequacy, density and utility). Remember 3 scoops or spoonfuls of BMS in 90 ml (or 100 ml) of water (or pap) as the case may be.
- One can of Nan or SMA gold is approximately 67 Kcals.
- One tin of BMS (Nan) should last for at least 3-4 days; find out how much the father gives the mother to prepare each meal.
- Developmental History: apart from gross motor, remember fine motor milestones, social, cognitive, vegetative and even SMR (sexual maturation rating) and time of menarche, adrenachy, etc.
- Immunization history: follow the current national routine immunization schedule and remember pentavalent vaccines. Ask for the immunization card and look for the scar if the mother does

not remember if the child is immunized. Remember to always request to see the immunization card as evidence of the immunization history. Tell the caregiver to always come to hospital with the immunization card whenever the child is ill.

- Family and social: father's and mother's education and occupation, age of parents, do they live together, number of rooms, how many live in a room, any cross ventilation, any overcrowding, is the mother a single parent and why, how many children, all alive, if not why, any history of sickle cell, diabetes mellitus, epilepsy, hypertension? This should be used judiciously and not as a routine.
- Summary of history: name, age, sex, presenting complaint, important information in history and striking interventions, patient's present condition.
- Review of system: endeavour to know at least 10 symptoms from each system (Table 1.3.1)

Table 1.3.1. Types of Clinical Reasoning (pediatricapta.org)

Type of Reasoning	Definition	Primary Users
Hypothetico-deductive (deductive reasoning)	Generation of a hypothesis based upon results of tests and measures, followed by testing this hypothesis.	Frequently used by novices in all situations and by experts during challenging or unfamiliar cases. Used by experts when pattern recognition isn't working.
Pattern recognition (inductive reasoning)	Quick retrieval of information from well-structured knowledge based upon previous clinical experience.[9]	Frequently used by experts during familiar situations as they recognize patterns or "scripts" that they have previously heard or experienced.

Examination

- General: IMENH (Inspection, Mental status, Emotional status, Nutritional status, Hydration status), pale? icteric? febrile? Any oedema (grade), any palpable peripheral lymph nodes? (Please characterize: size, shape, location, consistency, fluctuancy, etc., is it generalized, significant); anthropometry (please comment if normal or not).
- *Systemic examination:* start from the system implicated in the history. See section 2 on physical examination.
- *Diagnosis:* this is based on logical and analytical synthesis of both positive and relevant negative findings in the history and physical examination. A number of likely diagnoses are then listed in order of priority; the first being the tentative diagnosis while the rest are differential diagnoses.

- This list is reviewed (and/or the diagnosis confirmed) as laboratory investigation results are obtained and as the disease process evolves. Finally, there is a discharge diagnosis which may be the same or different from the admitting diagnosis.
- *In clinical reasoning;*
  - You synthesize a problematic representation comprising salient details from the history and physical examination.
  - Identify epidemiological/predisposing factors for the possible diagnosis.
  - What are the pathophysiologic processes contributing to the disease process?
  - What clinical features/consequences (symptoms and signs) are likely to result from the predisposing epidemiological factors and the pathophysiological process?
  - What diagnosis best matches the patient's presentation?
- Clinical reasoning is based on deductive and inductive reasoning (Table 1.3.2).
- By deductive reasoning, you are able to produce multiple clinical scripts (over time) in your clinical memory using semantic qualifiers (like acute vs. chronic; mild vs. severe) to make a clinical representation with the clear structure of;
  - Predisposing/epidemiological factors;
  - Pathophysiologic process/insult; and
  - Clinical consequences.
- When non-analytical methods are used, they often leave the inexperienced at a loss on the diagnosis.

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SECTION 2:

INFECTIOUS DISEASES

2.1 Malaria (Ibeneme, C. A.)

- Malaria is an infectious disease caused by the protozoan Plasmodium.
- Human malaria is caused by *P. falciparum, P. vivax, P. ovale, P. malariae* and *P. knowlesi* (a zoonotic infection).
- *P. falciparum* accounts for up to 98% of the cases in most parts of Africa where malaria has remained a major public health problem.

Epidemiology

- **Transmission:** Malaria can be transmitted through (i) Bites of infected female anopheles mosquitos (ii) Accidental: from blood transfusion and needle stick injury (iii) Congenital: from the mother to the foetus.
- **Distribution:** Malaria occurs in about 99 countries mainly in Africa, Asia, Latin America and parts of the Caribbean islands which are between latitudes 45°N and 40°S.
- **Burden:** The WHO estimates that 3.3 billion people were at risk of malaria in 2010 worldwide; 81% of malaria cases and 91% of malaria deaths occurred in Africa; 86% of 655 000 deaths were in children <5 years.
- **Endemicity:** Malaria endemicity is classified based on the spleen rate in children aged 2-9 years as:
  - **Hypoendemic**–Spleen and parasite rates 0–10%;
  - **Mesoendemic**–Spleen and parasite rates 11–50%;
  - **Hyperendemic–**Spleen and parasite rates persistently >50% but <70%;
  - **Holoendemic–**Spleen and parasite rates persistently >70%.

Pathophysiology

- The life cycle of malaria parasites consists of asexual and sexual cycles.
- The asexual cycle (in the human body) consists of the tissue and erythrocytic phases.
- In tissue schizogony, inoculated sporozoites invade the liver cells and multiply. The liver cells rupture and release merozoites into the bloodstream.
- Some *P. vivax* and *P. ovale* sporozoites transform into hypnozoites which may cause a clinical relapse months or years later.
- In erythrocytic schizogony, released merozoites enter the red cells, divide and develop into trophozoites which divide and form more merozoites that invade fresh erythrocytes.
- Some merozoites transform into male and female gametocytes which enter the mosquito during a bite. In the sexual cycle in the mosquito, the male and female gametes fuse and form a zygote which transforms into an ookinete and penetrates the gut wall to become an oocyst.
- This divides asexually into numerous sporozoites which reach the salivary gland of the mosquito waiting for the next blood meal.
- The pathogenetic factors involved in the development of severe malaria include parasite biomass, cytokines, microvascular obstruction (due to cytoadherence, sequestration and rosetting) and red cell membrane rigidity and reduced deformability.

Clinical presentation

- **Uncomplicated malaria**: There is no evidence of vital organ dysfunction. The patient may have non-specific symptoms including fever, chills, rigours, headaches, body pains, malaise, nausea, vomiting, abdominal pain and diarrhoea. Examination may reveal hepatosplenomegaly.
- **Severe malaria**: Malaria with any clinical or laboratory evidence of vital organ dysfunction, majorly caused by *P. falciparum* infection.
- The features include:
  - Impaired consciousness (including unarousable coma);
  - Prostration: extreme weakness; unable to stand without support;
  - Multiple convulsions: more than two episodes within 24 hours;
  - Deep breathing and respiratory distress (acidotic breathing);

- Acute pulmonary oedema and acute respiratory distress syndrome;
- Circulatory collapse or shock, systolic BP <50 mmHg in children;
- Acute kidney injury;
- Clinical jaundice;
- Abnormal bleeding;
- Hypoglycaemia (<2.2 mmol/l or <40 mg/dl);
- Metabolic acidosis (plasma bicarbonate <15 mmol/l);
- Severe anaemia (haemoglobin <5 g/dl, packed cell volume <15%);
- Haemoglobinuria;
- Hyperlactataemia (lactate >5 mmol/l);
- Renal impairment (serum creatinine >265 μmol/l);
- Hyperparasitaemia: *parasite density >250,000/μl of blood;*
- Pulmonary oedema (radiological).

Diagnosis

- Clinical diagnosis requires a high index of suspicion especially in severe cases with any of the features listed above.
- Laboratory diagnosis: involves 2 types of tests: microscopic and non-microscopic tests.

Microscopic tests:

- Peripheral blood smear for malaria parasite using a thick or thin smear. This is the gold standard.
- Quantitative buffy coat (QBC) test: blood is mixed with acridine orange, centrifuged and read directly with a fluorescent microscope.

Non-microscopic tests:

- Employ the identification of the parasite antigen, antiplasmodial antibodies or parasite metabolic products.
- Rapid Diagnostic Tests (RDTs):
  - ParaSight-F test: detects the histidine rich protein (HRP-2) antigen of *P. falciparum.*
  - OptiMAL (pLDH): detects the LDH of viable *P. vivax* and *P. falciparum*.
- Polymerase chain reaction (PCR).
- Antibody detection by radio immunoassay, immunofluorescence or enzyme immunoassay.

Treatment

Uncomplicated malaria:

- The goal of treatment is to eliminate the parasites. The WHO recommends the use of Artemisinin Combination Therapy (ACT):
  - Artemether/lumefantrine: 1.4-4/10-16 mg/kg twice a day for 3 days.
  - Artesunate/Amodiaquine: 4 mg/10 mg/kg daily for 3 days.
  - Artesunate/Mefloquine: 4 mg/8.3 mg/kg daily for 3 days.
  - Artesunate/sulfadoxine-pyrimethamine: 4 mg/kg/day artesunate daily for 3 days and a single administration of 25/1.25 mg/kg sulfadoxine-pyrimethamine.
  - Dihydroartemisinin/piperaquine: 4/18 mg/kg/daily for 3 days.

Severe malaria: A medical emergency. The goal of treatment is to prevent death.

- The recommended treatment for severe malaria:
  - Artesunate Injection 2.4 mg/kg IV bolus at times 0, 12 hours, 24 hours, then daily until the patient can tolerate oral medication. Other alternatives are:
  - Intramuscular Artemether 3.2 mg/kg on the first day and then 1.6 mg/kg daily (for a maximum of 3 days) until the patient can take oral treatment;
  - Intravenous quinine (in 10 mls/kg of dextrose infusion), give 20 mg/kg as a loading dose, then 10 mg/kg 8 hourly until the patient is able to take it orally.
- Each of the above treatments should be followed by a full course of ACT for 3 days.
- Supportive treatment/treatment of complications.

Prevention

- Malaria control program: the Roll Back Malaria initiative comprising of:
  - Early detection through health education and surveillance;
  - Rapid diagnosis and Effective Treatment;
  - Multiple prevention through insecticide treated nets (ITNs) environmental management and prevention in pregnancy;
  - Focused research (vaccines);
  - Well-coordinated actions (technical support);
  - Dynamic movement (collaboration).

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2.2 Polio/Poliomyelitis (Tagbo, B. N.)

Epidemiology

- Polio, an abbreviation of poliomyelitis; Greek words polio (grey) and myelon (marrow, indicating the spinal cord). The Latin suffix itis refers to inflammatory diseases; meaning "inflammation of the gray matter of the spinal cord."
- ***Definition:*** A highly infectious viral disease that mainly affects children, causes inflammation of motor neurons of the spinal cord and brainstem, could result in paralysis, muscular atrophy, and deformity.


- Occurred globally and in all ages but mostly in children less than five years old. Severity increases with increasing age of infection. Eradication efforts since 1988 have reduced the disease burden by more than 99% with only 3 endemic countries by 2013 (Pakistan, Afghanistan and Nigeria). However, re-infection by importation still affects several countries.
- An enterovirus of the Picornaviruses family, a single stranded RNA virus. Three serotypes (P1, P2, and P3). P1 is most likely to cause outbreaks; P2 is the easiest to eradicate followed by P3. Minimal heterotypic immunity between serotypes (i.e., immunity against a type does not confer significant immunity against other serotypes). Rapidly inactivated by heat, formaldehyde, chlorine, and ultraviolet light but acid resistant.
- Man is the only reservoir. ***Transmission***–faeco-oral and contact with pharyngeal secretions. Incubation period is 7-10 days (4-35 days). Most infectious immediately before and 1-2 weeks after the onset of symptoms. High infectivity–90-100% among susceptible household contacts.

Pathogenesis/Pathophysiology

- The virus enters through the mouth, multiplies in the pharynx, GI tract and local lymph nodes; haematologic spread to lymphatic and CNS; viral spread along nerve fibres; destruction of motor neurons (nerve cells); loss of function of corresponding muscles; acute flaccid paralysis (AFP).

- Attack of motor neurons of the brain stem by polioviruses; respiratory/swallowing/speech difficulties (***bulbar polio***) and without respiratory support, respiratory failure can lead to death.

Clinical features

- ***Inapparent/asymptomatic*** (90-95%). The estimated ratio of paralytic to inapparent illness is about 1:200 (1:50 to 1:1,000). Infected asymptomatic persons shed virus in the stool and are therefore infectious.
- ***Abortive Polio or Minor Illness*** (4-8%), complete recovery in less than 1 week. No evidence (lab or clinical) of CNS involvement. Three syndromes are usually observed with this form of poliovirus infection: (1) Upper respiratory tract infection (sore throat and fever), (2) Gastrointestinal disturbances (nausea, vomiting, abdominal pain, constipation or, rarely, diarrhoea), and (3) Influenza-like illness. These syndromes are indistinguishable from other viral illnesses.
- ***Non-paralytic polio/aseptic meningitis*** (1%-2%). Symptoms of stiffness of the neck, back, and/or legs, increased or abnormal sensations, usually following several days after a prodrome similar to that of minor illness. Symptoms last 2 to 10 days, with complete recovery.
- ***Paralytic polio*** [<1% (0.1-2%)]: Paralysis begins 1 to 10 days after prodromal symptoms and progresses for 2 to 3 days. Other prodromal signs and symptoms can include loss of superficial reflexes, ***initially*** increased deep tendon reflexes and severe muscle aches and spasms in the limbs or back. Then ***progression*** to flaccid paralysis with diminished deep tendon reflexes, reaching a ***plateau*** without change for days to weeks, and this is usually ***asymmetrical***. Strength then begins to return. ***No sensory losses or changes in cognition.*** Complete recovery or a measure of return of muscle function occurs in some cases. Persisting weakness or paralysis 12 months after onset is likely to be permanent. Paralytic polio could be ***spinal***, ***bulbar*** or ***bulbospinal***. Recovery from an infection confers serospecific immunity.

Diagnosis

- Virus isolation from stool, pharynx and rarely, CSF. Serology-neutralising antibodies are usually high at presentation making a four-fold rise difficult to demonstrate. Raised CSF, WBC and mildly elevated protein.

Differential diagnosis

- Guillain-Barre Syndrome, Spinal cord lesions, Meningitis, Encephalitis, myopathies, trauma with spinal cord injury, peripheral neuropathies, transverse myelitis.

Treatment

- No specific treatment. The goal is to control the symptoms while the infection runs its course. Mostly supportive: bed rest, analgesia, prevention of bed sores and constipation, urinary catheterization with prophylactic antibiotics.

Complications/Prognosis

- Paralysis, respiratory failure, pneumonia, UTI, Cor pulmonale, Pulmonary oedema, Post-polio syndrome (occurs about 30-40 years later in some patients characterized by neurologic, musculoskeletal and other manifestations such as malnutrition, dehydration, pneumonia, osteoporosis, and respiratory failure).
- Prognosis depends on the type of polio; usually complete recovery in non-paralytic polio. Only about 0.1-2% of infected people have paralytic polio out of which 5-10% die of respiratory failure, usually in the first 2 weeks. Survivors have disabilities.

Prevention/Control

- Immunization (close to eradication) using oral polio vaccine (OPV) and inactivated polio vaccine (IPV), Aggressive acute flaccid paralysis (AFP) surveillance, environmental/sewage sampling, environmental and personal hygiene, good sewage disposal.

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2.3 Viral Hepatitis (Ezeonwu, B.)

Introduction

- Major health problems in both developing and developed countries.
- Hepatotropic viruses are hepatitis A, B, C, D, E and G. Other viruses can also cause hepatic inflammation in their course.
- HBV is a DNA virus while others are RNA. HAV and HEV do not cause chronic illness, HGV causes mild chronic illness while HBV, HCV and HDV cause serious chronic illness.

Features	HAV	HBV	HCV	HDV	HEV	HGV
Incubation period (weeks)	2-6	4-26	7-9	4-7	2-8	unknown
Percutaneous transmission	Rare	common	common	common	No	common
Faeco-oral	common	No	No	No	Common	No
Sexual	Rare	Common	Rare	Rare	Rare	Rare
Trans placental	No	Common	Rare	No	No	Rare
Carrier state	None	Yes	Yes	Yes	Unknown	None
Chronic infection	No	Yes	Yes	Yes	No	Yes
Fulminant hepatitis	Rare	Yes	Rare	Yes	Rare	No

Hepatitis A Virus

- Non-enveloped single-stranded picornavirus. No chronicity and no carrier state, rarely fulminant except if superimposed on chronic hepatitis caused by HBV, HCV or alcohol.
- Transient viraemia so donated blood is not routinely screened for HAV. Clinically asymptomatic or mild, rare after childhood, causing about 25% of clinically acute hepatitis globally.
- Specific IgM against HAV appears in acute infection and as it rises faecal shedding ends. IgM declines in a few months while IgG anti-HAV appears and remains protective for life against reinfection from all strains of HAV, thus the HAV vaccine is effective.

Hepatitis B Virus

- The mature HBV virion is a 42 nm spherical double-stranded Dane particle with an outer surface envelope and inner core. It remains in blood and is present in all body fluids except the stool.
- The World Health Organization (WHO) estimated that 2 billion people worldwide have evidence of past or recent infection of HBV; about 400 million people are estimated to be chronically infected and are at risk of liver-related disease, while about 600,000 people die each year from HBV-related liver disease or hepatocellular carcinoma (HCC).
- Nigeria has been classified as hyper-endemic (prevalence ≥8%).
- Neonatal infection often leads to the carrier state for life.
- HBV can cause majorly subclinical disease with full recovery, acute hepatitis with 99% resolution and about <1% fulminant disease, persistent infection with 67-90% recovery and 10-33% chronic hepatitis evolving to cirrhosis and hepatocellular carcinoma, about 5-10% become healthy carriers. HBV is also a backdrop for HDV.
- The surface has 2 particles: the hepatitis B surface antigen (HBsAg) comprising 22 nm spherical and tubular particles.
- The inner portion contains the nucleocapsid that encodes the viral DNA: the hepatitis B core antigen and proteolytic self-cleavage of HBcAg is called the hepatitis B e antigen (HBeAg) which is a marker of active HBV replication.
- A noncytopathogenic, hepatocyte injury via an immune-mediated process and the more optimal the immune response, the better the viral clearance but with severe hepatocyte damage. 2 phases of hepatocyte infection: proliferative and integrative.
- ***Proliferative phase:*** new virions are formed and HBsAg and HBcAg appear on the cell surface, combine with class I MHC and activate cytotoxic T lymphocytes which lysis the cell. Circulating immune complexes containing HBsAg occur in patients with membranous or membranoproliferative glomerulonephritis, polyarteritis nodosa, Guillain-Bare syndrome, etc.
- ***Integrative phase:*** in hepatocytes not destroyed, viral DNA integrates into the host genome establishing risk for hepatocellular carcinoma.
- HBsAg appears before symptoms, peaks during the course of the illness and declines to undetectable levels in 3-6 months. HBeAg

(indicating the highly infectious state), HBV-DNA and DNA polymerase appear soon after HBsAg signifying active infection.
- Shortly after the symptoms, IgM to HBcAg (IgM anti-HBc) appear with the onset of the elevation of aminotransferases, and persist for many months, replaced by IgG anti-HBc for years.
- IgM anti-HBc is not present in perinatal HBV infection. Anti-HBc is the most valuable single serologic marker of acute HBV infection because it appears as early as HBsAg and remains longer. It is present with anti-HBsAg in the resolved infection but only anti-HBsAg after the HB vaccine.
- Anti-HBe appears after the disappearance of HBeAg, signalling the waning of infection.
- IgG anti-HBs rises weeks to months after the disappearance of HBsAg, at the end of the infection.
- Anti-HBs may persist for life, conferring immunity and forms the basis of HBsAg vaccination.
- Carrier state: Serum HBsAg >6 months after initial detection. Chronic HBV replication is persistent: HBsAg, HBeAg, HBV DNA, usually anti-HBc and occasionally anti-HBs.

Hepatitis C

- Single-stranded RNA Flaviviridae and the most common cause of liver disease worldwide.
- Acute infection is usually subclinical, with 15% resolution, 85% chronic disease (80% are stable and 20% progress to cirrhosis and hepatocellular carcinoma), the fulminant disease rarely occurs.
- Chronic HCV infection is characterized by episodic elevations in serum transaminases with periods of normal levels in between.
- HCV RNA is detectable in the blood for 1-3 weeks with elevation in serum transaminases.
- Anti-HCV antibodies are detected in symptomatic acute HCV infection. In chronic infection, HCV RNA persists despite the neutralizing Ig. Anti-HCV IgG does not confer effective immunity.

Hepatitis D

- Hepatitis delta virus, replication defective, infective only when encapsulated by HBsAg.

- There could be coinfection with HBV if exposed to serum containing both HBV and HDV, so that HDV infection occurs after HBV infection is established, providing HBsAg.
- There could also be superinfection of a chronic HBV carrier with a new inoculum of HDV and therefore a shorter incubation period.
- Detectable HDV RNA occurs prior to and early in the symptomatic infection. IgM anti-HDV is the most reliable indicator of recent HDV infection. In coinfection IgM to both HDAg and HBcAg appear while in superimposed HDV infection, HBsAg and IgM anti-HDV persists.

Hepatitis E Virus

- Unenveloped single-stranded RNA calciviridae. No chronicity or persistent viraemia. Sporadic and overt illnesses in children are rare.

Hepatitis G Virus

- Single-stranded RNA Flaviviridae. Coinfection with HBV and HCV occurs but does not worsen the clinical course of these infections. Diagnosis is by PCR assay.

Clinical features of viral hepatitis:

- Exposure to the hepatitis virus can lead to acute asymptomatic infection with recovery, acute symptomatic infection with recovery, chronic hepatitis ± progression to cirrhosis or fulminant hepatitis with submassive hepatic necrosis.
- **Acute asymptomatic with recovery**: common with HAV and HBV in childhood with serologic evidence of anti-HAV and HBV in adulthood. HCV too but recovery is uncommon.
- **Acute symptomatic** occurs in all except HCV. 4 phases of incubation period, symptomatic preicteric, symptomatic icteric and convalescence phase.
- ***Preicteric phase*** with malaise, anorexia, easy fatiguability, nausea ± fever, arthralgias, myalgia, diarrhoea, and serum sickness-like syndrome with HBV (fever, rash, arthralgia).
- ***Icteric phase*** (conjugated) in adults with HAV, absent in majority of HBV, HCV and childhood. Symptoms begin to abate and convalescence follows in weeks or months.

- **Chronic viral hepatitis:** symptomatic, biochemical, serologic evidence for >6 months with histologic inflammation and necrosis. A carrier state which may have no adverse clinical or histologic effect, asymptomatic with laboratory or histologic disease or overt clinical disease.
- Risk of carrier state with impaired immunity. Vertical transmission of HBV leads to 90-95% in carriers but 1-10% in adult infection. HCV and HBV + HDV are also involved commonly.
- Fulminant hepatic failure: progression to hepatic encephalopathy within 2-3 weeks of onset.

Differential diagnosis:

- Infections especially in neonates, malaria, HUS, Reye's syndrome, gallstone, Wilson's disease, SLE, acetaminophen overdose, valproate and mushroom toxins.

Treatment and Prevention

- HAV: symptomatic. Inactivated Vaccine for children >2 years.
- HBV: no successful treatment, interferon-α-2b, lamivudine for chronic disease in those >18 years. Infants of a positive mother should receive HB Ig soon after birth with HBsAg vaccine. If post vaccination testing is positive for anti-HBs then the child is immune. If it is positive for only HBsAg, refer to the hepatologist. If negative to both, give another dose of vaccine and retest again for anti-HBs.

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2.4 Pertussis (Chinawa, J.)

- Pertussis is an acute respiratory tract infection caused by *Bordetella pertussis; a gram-negative pleomorphic coccobacillus.*

Epidemiology

- There are 48.5 million cases of pertussis each year worldwide with 295,000 deaths/year.
- It occurs at all ages: more than two-thirds of cases occur in children <5 years but recently, the majority of cases have been noted to occur in persons of 10 years of age and older.
- One-third of the cases, including nearly all deaths, occur in infants <6 months because of the lack of maternal immunity transfer. It is more common in females and in the white race.
- Life-long or complete immunity is not conferred following the disease or the vaccination. Vaccination protects against the disease for 3-5 years and wanes, undetectable after 12 years, therefore booster doses are required.

Pathophysiology

- *Bordetella* organisms are tiny, fastidious, gram-negative coccobacilli that only colonize ciliated epithelium. *Bordetella pertussis* is transmitted from person to person by close contact with aerosolized droplets. The incubation period of pertussis is about 7 to 10 days. Though it has been reported to be as long as 6 weeks.
- **Filamentous haemagglutinin** (FHA), **agglutinogens,** and surface protein called **pertactin** are attached to epithelial cells and trigger the symptoms typical of pertussis.
- Only *B. pertussis* expresses **pertussis toxin** (PT).

Clinical features

- **History and physical findings**
- It is divided into catarrhal, paroxysmal and convalescent stages. It is usually a 6-week disease with each stage lasting 1-2 weeks.
- **Catarrhal stage** (1-2 weeks) begins insidiously after an incubation period ranging from 3 to 12 days with non-distinctive symptoms of congestion, rhinorrhoea, low-grade fever, conjunctival injection, sneezing, and tearing.

- **Paroxysmal stage** (2-6 wks). The cough begins as a dry, intermittent, irritative hack and evolves into the inexorable paroxysms that are the hallmark of pertussis.
- **Convalescent stage** (≥2 wks), the number, severity, and duration of episodes diminish.
- Whoop infrequently occurs in infants <3 months of age who at the end of a paroxysm lack the stature or muscular strength to create sudden negative intrathoracic pressure.
- Findings on physical examination generally are uninformative except if there is superimposed bacterial pneumonia.

Diagnosis

- Clinical case definition of cough of ≥14 days' duration with at least 1 associated symptom of paroxysms, whoop, or post-tussive vomiting has a sensitivity of 81% and a specificity of 58% for culture confirmation.
- Direct fluorescent antibody (DFA) testing of potential isolates is helpful. Polymerase chain reaction (PCR) for nasopharyngeal wash specimens has sensitivity similar to that of cultures.
- However, culture is the hallmark of diagnosis.

Differential diagnosis

- Common cold, Influenza, Cystic fibrosis, interstitial pneumonitis, Bronchiolitis, Croup (Laryngotracheobronchitis), Bronchopneumonia and Tuberculosis.

Treatment

- Children with pertussis are infectious from the beginning of the catarrhal stage through to the third week after the onset of paroxysms (multiple, rapid coughs) or 5 days after the start of effective antimicrobial treatment.
- The recommended antimicrobial agents for treatment or chemoprophylaxis are azithromycin, clarithromycin and erythromycin. Trimethoprim-sulfamethoxazole can also be used.

Complications/Prognosis

- Infants <6 months of age have high mortality and morbidity.
- Infants <2 months of age have the highest reported rates of pertussis-associated hospitalization (82%), pneumonia (25%), seizures (4%), encephalopathy (1%), otitis media, pulmonary hypertension, pneumothorax, conjunctival and scleral haemorrhages, petechiae on the upper body, epistaxis and death (1%).
- Umbilical and inguinal hernias.
- Laceration of the lingual frenulum is not uncommon.

Prevention/Control

- **General health promotion:** Health education, antenatal care.
- **Specific protection:** Immunization with acellular pertussis (aP) vaccine (together with Diphtheria and Tetanus toxoids as DTaP), given at 2, 4, 6 and 15-18 months of age and 4-6 years. A booster is recommended from 19 years of age with Tdap (Tetanus toxoid with a reduced strength of diphtheria toxoid and acellular pertussis vaccine), in adults (to reduce transmission in children) and also before pregnancy or in the third trimester (to provide maternal antibodies to the infant. DTaP is given at 6, 10, and 14 weeks of age in Nigeria.
- **Early diagnosis and treatment:** High index of suspicion and use of antimicrobials.
- **Treatment of debility:** Treat complications: epistaxis, hernia, etc.
- **Rehabilitation:** Physiotherapy for complicated pneumonias.

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2.5 Diphtheria (Chinawa, J.)

- Diphtheria, derived from the Greek meaning a "pair of leather scrolls," is an upper respiratory tract illness caused by *Corynebacterium diphtheriae*, a facultative anaerobic, gram-positive bacterium.

Epidemiology

- The primary modes of spread consist of close contact with infectious material from respiratory secretions (direct or via airborne droplets) or from skin lesions. Humans are believed to be the only known reservoir for C. diphtheriae, although the transmission of C. ulcerans via cow's milk has been observed.
- Diphtheria currently occurs sporadically, mostly among the native population, children of homeless people, lower socioeconomic groups, and alcoholics.
- Mortality is higher in children <5 years, occurs about day 3-4 of the illness and is due to asphyxia or myocarditis.

Pathophysiology

- The toxin is a single polypeptide with an active (A) domain, a binding (B) domain, and a hydrophobic segment known as the T domain, which helps to release the active part of the polypeptide into the cytoplasm.
- The toxin is responsible for many of the clinical manifestations of the disease.
- In most cases, C. diphtheriae infection grows locally and elicits toxin rather than spreading haematogenously.
- The characteristic membrane of diphtheria is thick, leathery, greyish-blue or white and composed of bacteria, necrotic epithelium, macrophages, and fibrin.
- The membrane firmly adheres to the underlying mucosa; forceful removal of this membrane causes bleeding.
- The membrane can spread down the bronchial tree, causing respiratory tract obstruction and dyspnoea (Buffalo neck).
- The primary modes of dissemination are by airborne respiratory droplets, direct contact with droplets, or infected skin lesions.

- Asymptomatic respiratory carrier states are believed to be important in perpetuating both endemic and epidemic disease. Immunization reduces the likelihood of carrier status.

Clinical features

History and physical findings

- Following an incubation period of 2-4 days, patients typically report upper respiratory tract symptoms (e.g., nasal discharge, sore throat).
- The posterior pharynx and tonsillar pillars are most often involved.
- Onset is often sudden, with low-grade fevers, malaise, and membrane development on one or both tonsils. The myocardium may also be infected.
- Neurological symptoms can also occur. Bulbar symptoms generally occur within the first 2 weeks after disease onset.
- Signs of cranial nerve dysfunction can occur within a few days of disease onset, with paralysis of the soft palate and the posterior pharyngeal wall causing dysphagia and regurgitation.

Diagnosis

- The diagnoses of C. diphtheriae infection can be confirmed definitively by culture on blood agar or selective tellurite media, which inhibit the growth of normal oral flora.
- If isolated, the bacillus is tested for toxin production–the Elek test, PCR.
- Moderate leucocytosis, transient proteinuria.
- Serology: antibody to the toxin (low levels do not exclude, high levels of 0.0-0.01 IU can protect against severe disease), serum troponin I level (may predict severity).

Differential diagnosis:

- Amyloidosis, Bacterial pharyngitis, Candidiasis, Viral pharyngitis, dilated cardiomyopathy, Bacterial pneumonia, Infectious mononucleosis, etc.

Treatment

- Ensure the patient's airway.
- The therapy includes antitoxin to neutralize the toxin before entry into the cells so as to deter the progression of symptoms.
- Antibiotic treatment to eradicate the organism, stop toxin production, hasten recovery and prevent spread to others. Many antibiotics are effective, including penicillin, erythromycin, clindamycin, rifampin and tetracycline.
- The disease does not confer immunity therefore treatment is incomplete in infants without immunization.

Complications/Prognosis

- Blocking of the airway, damage to the heart muscle (myocarditis), polyneuropathy, lung infection.

Prevention/Control

- **General health promotion:** Health education on overcrowding, adherence to immunization schedule, antenatal care.
- **Specific protection:** Immunization with DPT vaccine: DTaP, DT, Tdap and Td. The full-strength vaccine DTaP is used for childhood immunization at 2, 4, 6 and 15-18 months, then at 4-6 years of age.
- DT is used for childhood immunization where an adverse reaction to acellular pertussis (aP) was reported.
- The reduced strength: Td and Tdap are used as boosters in adolescents and adults.
- Td is given every 10 years or following exposure. Tdap is used also in the third trimester or soon after delivery to allow for maternal antibodies.
- **Early diagnosis and treatment:** High index of suspicion and use of antimicrobials in exposed individuals, serial ECG to detect cardiac abnormalities.
- **Treatment of debility:** Treat complications.
- **Rehabilitation:** Physiotherapy for neurologic complications, valve replacement in patients with endocarditis.

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2.6 Tetanus (Chinawa, J.)

- Tetanus is caused by a toxin produced by the bacterium *Clostridium tetani*. It is a motile, gram positive, anaerobic rod. The organism may develop a terminal spore that resists stain thus making it look like a racket.

Epidemiology

- Although tetanus affects all ages, the highest prevalence is in newborns and young people.
- Overall, the annual incidence of tetanus is 0.5-1 million cases.
- The incubation period is usually three to 21 days although it may range from one day to several months.
- If it starts immediately after birth, the incubation period could be the age of the child at the time of onset (the period from the time of infection to trismus).

Pathophysiology

- *Clostridium tetani,* an obligate anaerobic gram-positive bacillus, is the pathogen responsible for tetanus.
- The spores from the organism germinate and produce the following 2 toxins:
- Tetanolysin–this substance is a haemolysin with no recognized pathologic activity.
- Tetanospasmin–this toxin is responsible for the clinical manifestations of tetanus. It is one of the most potent toxins known.
- Tetanospasmin has 2 chains: light and heavy chains.
- The Light chain binds to a protein synaptobrevin which is integral to the binding of neurotransmitter containing vesicles to the cell membrane.
- This inhibits the inhibitory neurotransmitters gamma-amino butyric acid (GABA) and glycine.
- There is a loss of inhibitory action on motor and autonomic neurons. This is the basis for the symptoms of tetanus.

Clinical features

History and physical findings

- Tetanus may be categorized into the following 4 clinical types: Generalized, Localized, Cephalic, Neonatal.
- Approximately 50-75% of patients with **generalized** tetanus present with trismus ("lockjaw"), which is the inability to open the mouth secondary to masseter muscle spasm.
- Nuchal rigidity and dysphagia are also early complaints that cause risus sardonicus: the scornful smile of tetanus.
- As the disease progresses, patients have generalized muscle rigidity with intermittent reflex spasms in response to stimuli (e.g. noise, touch).
- Tonic contractions cause opisthotonus (i.e., flexion and adduction of the arms, clenching of the fists and extension of the lower extremities).
- During these episodes, patients have an intact sensorium and feel severe pain.
- **Cephalic** tetanus is uncommon and usually occurs after head trauma or otitis media. Patients with this form present with cranial nerve (CN) palsies.
- **Neonatal** tetanus (tetanus neonatorum) is a major cause of infant mortality in underdeveloped countries.

Diagnosis

- Diagnosis is mainly by thorough history-taking and elaborate clinical examination. No specific lab test is available to determine the diagnosis of tetanus.
- Investigations to rule out meningitis, rabies, strychnine poisoning, and other diseases with similar symptoms may be helpful.

Differential diagnosis

- Strychnine poisoning;
- Hysteria;
- Neoplasms;
- Malignant hyperthermia;
- Stimulant use;
- Intraoral disease;

- Globus hystericus;
- Hepatic encephalopathy;
- Intracranial haemorrhage;
- Dystonic drug reactions;
- Seizure disorder;
- Serotonin syndrome.

Treatment

- Initiating supportive therapy.
- Debriding the wound to eradicate spores and alter the conditions for germination.
- Stopping the production of toxin within the wound: Antibiotic (crystalline penicillin).
- Neutralizing unbound toxin: ATS.
- Controlling disease manifestations.
- Managing complications: sedatives for spasms: chlorpromazine; diazepam.
- Passive immunization with human tetanus immune globulin (TIG) shortens the course of tetanus and may lessen its severity. A dose of 500 U may be as effective as larger doses.

Complications/Prognosis

- Sudden cardiac death (NOT CARDIAC ARREST), pulmonary embolism, aspiration pneumonia, acute kidney failure (from rhabdomyolysis).

Prevention/Control

- **General health promotion:** Health education, antenatal care (where tetanus toxoids are received).
- **Specific protection:** Immunization of women of child-bearing age with 5 doses of Tetanus toxoid vaccine and immunization of infants with TT as a combination vaccine, e.g. the pentavalent vaccine.
- **Early diagnosis and treatment:** High index of suspicion and use of antimicrobials, sedatives, muscle relaxants, ATS and TT.
- **Treatment of debility:** Treat complications.
- **Rehabilitation:** Physiotherapy.

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2.7 Haemophilus Influenzae Infections (Igwe, W.)

- H. Influenzae is a pleomorphic gram-negative coccobacillus. Some strains have a polysaccharide capsule and these are stereotyped into 6 types (a-f).
- The haemophilus influenza type b (Hib) serotype is the most important and most virulent as it causes more than 90% of infections in children.

Epidemiology

- H. Influenzae is a major cause of certain invasive diseases in children, with serotype b being most virulent and accounting for more than 95% of these. Hib infections are seen mainly in children less than 5 years of age.
- Other encapsulated strains occasionally cause invasive disease. Non-encapsulated strains (nontypeable or NTHi) cause mucosal infections and invasive disease in the neonate and immunocompromised.
- Persons at increased risk of invasive disease include those with sickle cell anaemia, asplenia, immune deficiency and malignancy.
- Socioeconomic risk factors for invasive disease include day care attendance, lack of breast feeding and parental smoking.

Pathogenesis

- The nasopharyngeal colonization rate of Hib is 2-5% in unvaccinated children.
- Transmission is by direct contact or inhalation of respiratory droplets. The colonizing bacteria invade mucosa and enter the blood stream.
- The antiphagocytic nature of the Hib capsule leads to increased bacterial proliferation.
- The nasopharyngeal colonization rate of NTHi strains is up to 80%. Infections caused by NTHi strains occur by direct spread.
- Neonatal sepsis due to NTHi strains occurs by vertical transmission via the maternal genital tract.

Clinical features

- Hib accounts for more than 95% of invasive disease (meningitis, cellulitis, epiglottitis, pneumonia, septic arthritis, osteomyelitis, pericarditis and occult bacteraemia).
- Nontypeable strains cause mucosal infections (otitis media, conjunctivitis, sinusitis and pneumonia) and also account for 5% of invasive disease.
- Clinical manifestations are similar irrespective of serotype.
- Features of infections caused by H. influenzae are indistinguishable from those due to other bacteria.
- In all cases a positive culture from CSF, blood or aspirated pus confirms the diagnosis.
- **Meningitis:** features of meningitis in children less than 5 years of age with a direct CSF smear showing gram negative pleomorphic rods.
- **Acute epiglottitis:** high fever, drooling, dysphagia, aphonia and stridor.
- **Septic arthritis:** fever, local redness and swelling, heat and pain with active or passive movement of the affected joint.
- **Cellulitis:** fever with cellulitis often involving the cheek or periorbital area

Diagnosis

- **Gram stain:** shows small gram negative pleomorphic coccobacillus.
- **Culture:** The isolation of the organism from normal sterile sites such as blood, CSF, joints or aspirated pus is the gold standard.
- **Rapid diagnostic test:** detection of Hi antigen in serum, CSF, urine, or other body fluids using CIE, LPA or ELIZA. (It is not affected by prior antibiotic therapy but can give a false positive reaction up to 3 weeks after vaccination.)

Treatment

- Third-generation cephalosporins (Cefotaxime/ceftriaxone) are the initial drugs of choice for suspected Hib meningitis and are given for 7-10 days.

- Dexamethasone, given before or with the commencement of antibiotics is an important adjunct in patients older than 2 months to reduce CNS inflammation and thus prevent complications.
- Cellulitis requires parenteral antibiotics until the swelling subsides. Surgical drainage may be needed.
- In epiglottitis, maintenance of the patient's airway through intubation or tracheostomy is the mainstay. Parenteral antibiotics are given for 7-10 days.
- Septic arthritis: parenteral antibiotics therapy for at least 1 week and then orally for 2-3 weeks.
- In mucosal infections due to NHTi, oral antibiotics (amoxicillin/clavunate or erythromycin) are given.
- In conjunctivitis, topical sulfacetimide or erythromycin is given.
- Invasive disease due to NHTi requires parenteral therapy.

Complications

- Meningitis: subdural effusions in up to 50% of cases, hydrocephalus, focal and sensory deficits and a variety of cranial nerve impairments. Sensorineural hearing loss is seen in about 5-10%.
- Acute epiglottitis: progression to complete airway obstruction, mediastinal emphysema and pneumothorax.
- Cellulitis: may lead to tissue destruction and meningitis.
- Septic arthritis: cartilage destruction and ankylosis.

Prevention/control

- Routine Hib vaccination: This is the most important preventive measure since it reduces the incidence of nasopharyngeal carriage (<1%). Hib vaccine is not protective against NTHi strains.
- Chemoprophylaxis: Given to the index case and close contacts if younger than 4 yrs. (Rifampicin 20 mg/kg/daily for 4 days eradicates potential nasopharyngeal colonization and limits the risk of invasive disease.)

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2.8 Pneumococcal Infections (Igwe, W.)

- Streptococcus pneumoniae is an important pathogen causing invasive diseases such as sepsis, meningitis, and pneumonia in children.

Epidemiology

- Streptococcus pneumoniae is the most common cause of acute purulent otitis media, most cases of community acquired pneumonia, bacteraemia and meningitis in children.
- Among 90 known serotypes, 7 are responsible for 85% of invasive pneumococcal disease.
- Children under 2 years are at greatest risk for invasive disease.
- Children at high risk for pneumococcal disease include those with immune deficiency, sickle cell disease, cerebro-spinal fistula, asplenia, nephrotic syndrome/CRF, and those with cochlear implants. Pneumococcal disease occurs sporadically.

Pathogenesis

- S. pneumoniae invades tissues to cause disease. Infection is spread from person to person by respiratory droplet transmission.
- Pneumococcal disease is preceded by the asymptomatic colonization of the upper respiratory tract, which is especially high in children.
- Most children acquire asymptomatic infections of the nasopharynx by 5 years of age.
- Infection frequently follows a viral respiratory infection that may produce mucosal damage.
- The severity of the disease is related to the virulence and number of organisms and the integrity of host defences.

Clinical features

- The signs and symptoms are related to the site of the infection;
- **Bacteraemia:** high fever (>39.4 C), leukocytosis (>15,000/μL), age 6-24 months.
- **Pneumonia:** fever, leukocytosis, tachypnoea, cough, localized chest pain, crepitation, and chest radiograph may show lobar infiltrates (with effusion).

- **Otitis media:** otalgia, fever, hearing loss, and purulent ear discharge may be present. In infants the symptoms may be less localizing.
- **Meningitis:** fever, leukocytosis, bulging fontanel, neck stiffness, irritability, convulsions.

Diagnosis

- Diagnosis is confirmed by cultures of blood, CSF, pleural fluid or other body fluid.
- Pneumococci can be identified in body fluids as gram-positive, lancet-shaped diplococci.
- The latex particle agglutination test is also useful in partially treated meningitis (the LPA test is negative in localized disease e.g. otitis media).
- Leukocytosis is generally pronounced.

Differential diagnosis

- **Viral pneumonia**: hoarseness, wheezing, rhinorrhoea, CXR shows perihilar infiltrates and increased bronchovascular markings.
- **Staphylococcal pneumonia:** cavitation, empyema, anaemia.
- **Mycoplasma pneumonia:** children >5 years, low grade fever, prominent headache, marked leukocytosis is unusual, striking CXR changes.
- **Meningitis:** culture and gram stain.

Treatment

- **Pneumonia:** for severely ill patients, penicillin G 150,000-200,000 units/kg/day IV in 4-6 divided doses, cefuroxime 50 mg/kg 8 hourly. In mild cases, amoxicillin 80-90 mg/kg/day for 7-10 days. Alternatives include oral macrolides.
- **Otitis media:** oral amoxicillin as first line therapy. Treatment failures may be treated with amoxicillin/clavulanate, oral macrolides or IM cephalosporin.
- **Meningitis:** empirical treatment with IV ceftriaxone/Cefotaxime with dexamethasone. Penicillin G IV is recommended for penicillin-susceptible isolates.

Complications

- Empyema, lung abscess, subdural effusions/brain abscess, osteomyelitis, and hearing impairment/other neurologic complications.

Prognosis

- Case fatality rates of <1% except in meningitis, in which rates of 5-20% can occur.

Prevention

- Universal immunization with heptavalent pneumococcal conjugate vaccine (PCV7) is recommended in children <2 years at 6, 10, and 14 weeks with a booster at 15-18 months of age.
- Vaccination is only recommended for children aged 24-59 months at high risk of invasive disease.
- Vaccination not recommended in healthy children older than 5 years of age.
- Vaccination does not prevent disease caused by serotypes not included in the vaccine.
- Penicillin V prophylaxis is also recommended in children at risk of pneumococcal sepsis especially sickle cell disease (125mg BD for those under 5 years and 250mg BD for those older than 5 years).
- In addition monthly IM benzathine penicillin prevents overwhelming sepsis in children at high risk of pneumococcal disease.

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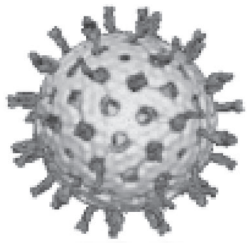
2.9 Rotavirus Disease (Tagbo, B. N.)

Epidemiology

- Health workers' knowledge of rotavirus disease has been suboptimal.
- The most common cause of dehydrating diarrhoea in infants and children worldwide.
- A major cause of **morbidity globally** and **mortality in developing countries.**
- Over 453,000 under-five deaths globally and 232,000 in the African region (>600 per day).
- A ubiquitous organism that causes human disease **independent of socio-economic status**.
- About 85% of deaths occur in Africa and South-East Asia.
- Almost **every child** will suffer at **least one infection** before the age of 3-5 years.
- Slightly affects males more than females. Highly seasonal in many countries.

The Virus

- RNA virus, "rota" is the Latin word meaning "wheel" derived from the wheel-like appearance of the virus.
- Serogroup A is responsible for most human infections.
- It encompasses a viral genome consisting of 11 segments of dRNA.
- Outer capsid proteins VP4 and VP7 define the serotype and genotype of rotaviruses.
- They also elicit protective immunity.



Pathophysiology

- **Transmission** is faeco-oral, person to person, contaminated fomites, toys, food, water? droplet infection.
- **Highly contagious,** a **leading** cause of **nosocomial** infection in hospitalised children.

- Rotaviruses affect the small intestine, multiply in the cytoplasm of enterocytes and damage their transport mechanisms.
- Damaged cells slough into the intestinal lumen releasing large quantities of virus, which appear in stools (up to 10^{10} particles per gram of faeces), known as virus shedding.
- Rotaviruses are shed in very high concentrations (10^{12} particles/gram) and are for many days in the stools and vomitus of infected individuals.
- **Two natural RV infections provide 75% protection against mild RV diarrhoea and 100% protection against moderate to severe RV diarrhoea.**

Clinical features

- **Fever, vomiting,** non-bloody watery **diarrhoea**, abdominal pain (older child), irritability.
- Vomiting is prominent and dehydration is common in severe cases, lethargy and hypovolaemic shock.
- The first rotavirus infection is usually the most severe.

Diagnosis

- The ELISA test on stool samples, PAGE (polyacrylamide gel electrophoresis), PCR, viral culture.
- Most of these tests are not routinely done.
- Diagnosis is largely presumptive in endemic areas.
- In Nigeria prevalence is as high as >50% overall and up to 70-80% during the rotavirus season in some studies.

Differential diagnosis

- Other causes of gastroenteritis–enteroviruses, norovirus, adenoviruses, E. coli, parenteral diarrhoea (Malaria), giardiasis, shigellosis, salmonellosis, amoebiasis, and cholera.

Treatment

- Non-specific, no antiviral therapy, rehydration with ORT/IVF (vomiting often makes ORS and breastfeeding ineffective), continued feeding, Zinc, treatment of co-morbidities.
- Antibiotics not indicated.

Complications/Prognosis

- Severe dehydration.
- Electrolyte imbalance.
- Shock.
- Bacterial superinfection.
- Good prognosis with good access to critical care, but many die when there is no access to IVF therapy.

Prevention/Control

- Personal, environmental and food hygiene, a portable water supply, good sewage disposal.
- Rotavirus vaccination–Rotarix (2 doses at 6 and 10 weeks or 2 and 4 months), RotaTeq (3 doses at 6, 10 and 14 weeks or 2, 4 and 6 months).
- Oral route, the last dose given later than 8 months is associated with increased risk for intussusception.
- Rotavirus vaccination has been demonstrated in many countries to be very effective in preventing rotavirus diarrhoea morbidity and mortality.

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2.10 Measles (Ezeonwu, B.)

- Measles (Rubeola) is highly contagious, an infectious acute viral disease caused by an RNA morbillivirus of the paramyxovirus family, one serotype/strain.
- It is endemic worldwide with seasonal outbreaks (spring).
- Mortality is high especially in the malnourished but infection confers lifelong immunity.
- No sex differences in morbidity and mortality.
- In the tropics, the greatest incidence occurs in children under 2 years of age.
- Spread is by respiratory droplets during the prodromal period (catarrhal stage) and shortly after the rash when the virus is shed in nasopharyngeal secretions, blood and urine.
- The virus can remain viable at room temperature for at least 34 hours.
- Infants acquire passive immunity transplacentally from their mothers (infection or vaccine induced); infants of mothers with vaccine induced immunity lose their antibody at a younger age.

Pathogenesis

- On inhalation, the viruses invade the cells of the respiratory mucosa, multiply, spread to lymphoid tissues and replicate in mononuclear cells.
- The infected cells coalesce into multinucleated giant cells. Interstitial pneumonitis in the form of Hecht giant cell pneumonia occurs.
- By the 10^{th} day (the prodromal phase), cell dysfunction begins and signs of inflammation appear; cilia are paralysed predisposing to secondary bacterial infection (bronchopneumonia).
- By the 12^{th} day, the cells break apart with the release of virions via coughing and sneezing and via the blood stream to all parts of the body.
- Cell fusion, such as in the respiratory mucosa, occurs at the lymphoid tissues (Warthin-Finkeldey reticuloendothelial giant cells especially in the appendix), there is serous exudation and proliferation of mononuclear and a few polymorphonuclear cells around the capillaries e.g., Koplik spots.

- In fatal cases, perivascular demyelination occurs in the brain and spinal cord, there may be degeneration of the cortex and white matter, intranuclear and intracytoplasmic inclusion bodies.
- The essential lesions of measles are seen on the skin, conjunctivae, and mucous membranes of the nasopharynx, bronchi and intestinal tract.
- Viral shedding usually ceases by 48 hours after the onset of the rash.
- Significant antibodies are produced by the 14th day but reach a peak by the 4th to 6th week of infection (not essential for recovery).
- Most children develop T cell-mediated immunity that controls the infection and produces the rash: a hypersensitivity reaction to the viral antigen in the skin, accompanied by a peak of fever, malaise and misery. A sparse rash indicates the failure of the cellular immune response (e.g., HIV) and poor prognosis.

Features

- Measles is rarely subclinical; 3 clinical stages are recognized: Incubation stage, Prodromal stage and the Final stage of the rash.
- **Incubation period** is 10-12 days to the first prodromal symptoms and another 2-4 days to the appearance of the rash.
- **Prodromal stage** with moderate fever, coryza, cough, conjunctivitis (3C's), photophobia, an enanthem (Koplik spot): a greyish dot on the buccal mucosa opposite the lower molar teeth which quickly spreads to the gingival and whole mucosa and it is pathognomonic of measles.
- Severity increases until the rash appears. Lasts 3-5 days. May present with high grade fever, convulsions and pneumonia.
- **The final stage of the rash** is ushered in by an abrupt rise in temperature by the 14th day, at the upper lateral part of the neck, behind the ears, along the hairline on the forehead, reaching the legs by the 3rd day.
- As the maculopapular rash reaches the legs, it starts to fade on the face, fever falls by lysis.
- The rash is confluent on the face in severe illness and rarely appears on the legs in mild illness.
- The maculopapules are so specific for measles that a similar rash is called morbilliform (measles-like).

- **Other features** may include mild splenomegaly, nodal enlargement (angle of the jaw and posterior cervical), abdominal pain from mesenteric adenitis, diarrhoea and appendicitis.

Diagnosis

- It is clinical. Laboratory confirmation is rarely needed. However, measles IgM antibodies are detectable for one month after the illness and therefore can be tested.
- There may be leucopenia with relative lymphocytosis. CSF analysis in encephalitis shows an increase in protein, a small increase in lymphocytes and normal glucose.

Differentials

- Include rubella, roseola infantum, meningococcaemia, scarlet fever, Kawasaki disease, serum sickness, drug rash, infections from echo, adeno and coxsackieviruses.

Treatment

- Majorly supportive: antipyretics, adequate fluid and nutrition, bed rest, antibiotics in secondary bacterial infection, saline nasal drops. No effective antiviral agent.
- Hyporetinemia is present in over 90% of children with measles in Africa therefore Vitamin A supplementation is recommended.

Complications include

- Bronchopneumonia is the most usual single complication which is indistinguishable from interstitial pneumonitis, then otitis media, croup, laryngotracheobronchitis, empyema, surgical emphysema, and the flaring of quiescent primary tuberculosis.
- The second most common complication is bacterial or viral enteritis with lactose intolerance and protein losing enteropathy.
- Malnutrition due to anorexia, stomatitis, enteritis, increased catabolism from high fever, depressed enzyme function, and nasal blockage that interferes with feeding.
- Other complications are corneal ulceration, myocarditis, encephalomyelitis, Noma, SSPE.

Prognosis

- Depends on age, nutritional status and the severity of complications. Death is usually due to pneumonia or secondary bacterial infection.

Prevention

- By active immunization via live attenuated measles vaccine (Attenuated Enders vaccine or further attenuated Schwarz vaccine) given at 9 months of age.
- Due to variability in the duration of transplacentally acquired passive immunity, the inactivated Edmonsten Zagreb vaccine can be given at 6 months of age if available.

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2.11 Yellow Fever (Manyike, C.)

- Yellow fever is an acute infection characterized in its most severe form by fever, jaundice, proteinuria and haemorrhage.
- Yellow fever is a flavivirus that is transmitted by Aedes aegypti and some species of haemagogus.

Epidemiology

- There are 3 types:
  - Urban yellow fever, in which the host is man with the vector as Aedes aegypti.
  - Jungle yellow fever in which the host is forest animals, notably primates, with the vectors as various species of Aedes and Haemagogus mosquitoes.
  - Savannah type in which transmission is from monkeys to humans and humans to humans through mosquito bites.
- The reservoir of infection exists in jungle primates and mosquitoes that bite them in the tree tops.
- Humans are infected when they go to the jungle and then bring the infection to urban areas. Infants are not easily infected probably because of acquired immunity from the mother.
- Yellow fever is found in tropical Africa and parts of South America and none in Asia.

Pathophysiology

- There are non-inflammatory changes in the liver with coagulative degeneration of cytoplasm of the cell with the formation of *Councilman bodies.*
- There are also some inclusion bodies called *Torres bodies* due to changes in the nuclei of the cells.
- Other organs like the kidneys, heart and brain are affected.

Clinical features–history

- The incubation period is between 3 and 10 days.
- Severe headache, fever, conjunctival infection and sometimes epistaxis characterize the disease.
- Sometimes nausea and bilious vomiting are common. Back pain, joint pain is common.

- Epigastric discomfort, bleeding from the mucous membrane of the gut and vomiting of altered blood is noticed.
- There could be oliguria and dark urine.
- There may be meningismus, severe intoxication, prostration and coma.

Clinical features–physical findings.

- Fever of 39.5^0 to 40^0 with rigors is characteristic which falls to normal in 3-4 days.
- There may be varying degrees of alteration in sensorium to coma.
- There may be mild jaundice, conjunctival injection and epigastric tenderness.
- There is body pain–back and joint pain.
- The liver is not always palpable.
- The pulse initially is fast and later declines so that a discrepancy develops between the pulse and the temperature. Occasionally the temperature may rise after onset without much corresponding change in pulse rate. The increasing slowness of the pulse rate relative to the temperature–Faget's sign–is of clinical diagnostic value.
- In severe cases proteinuria, oliguria and renal failure occur.
- Mortality is around 50%.

Diagnosis

- Mild cases–difficult to diagnose.
- Severe cases in endemic area: suspect if the patient presents with fever, conjunctival injection, severe prostration, epigastric discomfort, vomiting and jaundice.
- Leucopenia and heavy proteinuria, hyperbilirubinemia, elevated transaminases and clotting abnormalities.
- Paired acute and convalescent serum specimens show a fourfold or greater rise in antibody level and sometimes an IgM response; IgG antibody levels may be due to previous immunization.
- A postmortem liver biopsy specimen shows mid zone necrosis of hepatic lobules often with eosinophilic Councilman bodies.
- **Confirmation:** isolation of the virus from blood or liver specimens by inoculation of suckling mice or tissue culture cells.

- Polymerase chain reaction may detect the virus in blood or liver specimens.

Differential diagnoses

- Complicated falciparum malaria, typhoid fever, sickle cell crisis, septicaemia, blackwater fever, leptospirosis and relapsing fever.

Treatment

- No specific antiviral treatment is available.
- Careful nursing and symptom control are needed.
- Use antiemetics and paracetamol cautiously.
- Avoid aspirin in view of bleeding tendency.
- Rehydrate with isotonic dextrose fluid.
- Platelet transfusion and fresh frozen plasma if available for bleeding disorder.
- Nurse suspected patients under permethrin-treated bed nets as blood may remain infective for mosquitoes up to 5 days after onset.
- Suspected cases of yellow fever must be notified to national public health authorities who in turn notify the WHO.

Complications/Prognosis

- Severe haemorrhage, liver failure and renal failure.
- Prognosis must be guarded in severe cases
- Mortality is around 50%.

Prevention/Control

- Elimination of breeding sites of Aedes aegypti mosquitoes around homes.
- Sleep under permethrin-treated bed nets.
- Immunization of local population with live attenuated 17D yellow fever vaccine, 0.5 ml subcutaneously.
    - Immunization is effective after 10 days.
    - Not for children <4 months, pregnant women and immunosuppressed individuals.

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2.12 HIV/AIDS (Manyike, C.)

- Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome is a major cause of infant and child morbidity and mortality.

Epidemiology

- Mother to child transmission (vertical) of HIV accounts largely for childhood infections, accounting for >90%.
- It could be in utero, at delivery or during breastfeeding. Prolonged breastfeeding and mixed feeding are key factors responsible for higher transmission rates in Africa.
- In breastfed cohorts from disadvantaged countries, the rates of transmission are 25-45%.
- In older children, sexual contact (forced or consensual), transfusion of blood and blood products and the use of contaminated sharps are other routes.
- Every day, 1150 children under 15 years are infected with the virus globally.
- Nigeria accounts for 30% of the global burden of Maternal-to-Child-Transfer of HIV and 10% of the global paediatric HIV/AIDS burden.
- The 2010 National Sero-prevalence Sentinel Survey estimated that 157,510 new infections occurred in children and only 12% of the total 212,720 HIV positive children eligible for therapy received ARVs.
- AIDS related deaths accounted for 3% of under-5 mortality in 2009.

Pathophysiology

- There are 2 types of HIV–HIV-1 and HIV-2. HIV-1 is the main cause of the worldwide pandemic while HIV-2 is mainly found in West Africa, Mozambique and Angola. Increasing numbers of cases are being reported in Europe and Southern Asia. It causes a similar but less severe illness than HIV-1.
- HIV-1 primarily targets the CD4+ molecule on T-helper and other target cells including macrophages and glial cells.

- The virus uses its gp120 and gp41 to bind CD4+ receptors and chemokine co-receptors (CCR5 and CXCR4 and maybe CCR1 and CCR3) on the host cell membrane.
- This permits the entry of the contents of the viral particle into the host cytoplasm.
- The viral enzymes and the RNA are then released to begin the process of replication while the viral envelope is shed. HIV RNA is now transcribed by reverse transcriptase to a double-stranded DNA.
- It is then integrated into the host DNA by integrase and continues to reside there indefinitely as a provirus.
- On activation, the proviral DNA is transcribed into mRNA by the host enzyme RNA polymerase to begin replication. The mRNA is then translated into viral proteins which assemble and "bud off" from the host cell membrane.
- The binding of the virus on CD4+ leads to the destruction of CD4+ cells and progressive immunosuppression and increased incidence of opportunistic infections.
- The CD4+ cells are eventually overwhelmed and the immune system fails, leading to disease progression to AIDS.

Clinical features–history

- There is persistent or recurrent fever. Poor weight gain or loss. Persistent diarrhoea, chronic cough and pulmonary infections are features of HIV/AIDS. History of HIV infection in one or both parents.

Clinical features-physical findings

- Patients present with growth failure, severe malnutrition, generalized lymphadenopathy, hepatosplenomegaly, pneumonia, including lymphocytic interstitial pneumonitis (LIP), oral thrush and occasionally, skin rash.
- There may also be chronic parotid swelling and recurrent bacterial infections.
- There could be early onset neurological deterioration.

Diagnosis

- **Clinical**–The failure of oral candidiasis to respond to treatment or rapid relapse is a highly specific sign of HIV infection.

STAGING (WHO)

  - Stage 1: Asymptomatic. There may be generalized lymphadenopathy.
  - Stage 2: Mild Disease. May have weight loss of 5-10% plus some signs of HIV e.g. itching rash, herpes zoster, recurrent URTI (suppurative otitis media), etc.
  - Stage 3: Moderate Disease. May have weight loss >10% plus signs like oral thrush and skin rash, diarrhoea, pneumonia, TB, etc.
  - Stage 4: Severe Disease (AIDS). Patient may have HIV wasting syndrome. Oesophageal thrush, herpes simplex, lymphoma, pneumocystis pneumonia, extrapulmonaty TB, HIV encephalopathy, etc.

- **Laboratory**–the simplest lab test is an antibody test done by ELISA. This is useful from 18 months because of maternally acquired IgG present in a child <18 months.
- In those less than 18 months, the diagnosis can be confirmed using assays that detect the virus itself or viral components.
- In exposed children with negative virologic testing at 1-2 days of life, additional testing should be done at 1-2 months of age and at 4-6 months of age; some also favour testing at 14 days as almost 90% of infected infants can be identified and ARV therapy can be started early.
- Breastfed infants should have antibody testing done 12 weeks after cessation of breast feeding to identify those who became infected at the end of lactation by the HIV infected mother.
- These tests include an antigen detection test (PCR), virus culture, amplification techniques and HIV-specific IgA tests. Rapid salivary tests (IgG or IgA) are in limited use.
- Hypergammaglobulinaemia, a low CD4 count or CD4:CD8 ratio and a low total lymphocyte count are also helpful.
- Surrogate markers like neopterin and β_2-microglobin are useful in diagnosis.
- Neopterin is an early marker of HIV infection and its level rises further as the disease progresses to AIDS. β_2-microglobin which is present in blood and urine spikes in the acute phase of the disease,

declines during the asymptomatic phase and rises again as the disease progresses.
- Others are anaemia, thrombocytopenia and lack of thymic shadow on chest X-rays.

Differential diagnosis

- Immunodeficiency conditions, severe malnutrition, and any chronic disease state can be a differential.

Treatment

- **Prophylaxis**
  - Administration of a single oral dose of 200 mg nevirapine to the mother in labour and 2 mg/kg as a single oral dose to the baby within 48-72 hours of birth.
  - Elective caesarean section which reduces the risk by >50% should be done.
  - In the early rupture of membranes, >4 hours, chlorhexidine vaginal disinfection is done.
  - Invasive procedures like forceps delivery, scalp electrodes/ samples and artificial rupture of the membranes should be avoided.
- **Anti-retroviral therapy (ART)**
- The major classes of anti-retroviral drugs are Non-nucleoside reverse transcriptase inhibitors (NNRTIs)–Nevirapine, Efavirenz; Nucleoside reverse transcriptase inhibitors (NRTIs)–Zidovudine, Lamivudine; Protease inhibitors (PIs)–Lopinavir, Ritonavir and Nucleotide reverse transcriptase inhibitors (NtRTIs)–Tenofovir; Fusion inhibitor–enfuvirtide; Integrase inhibitors–raltegravir.
- **Criteria for ART eligibility**
  - Children <24 months of age with confirmed HIV irrespective of clinical or immunological stage;
  - Children ≥24 months of age with confirmed HIV plus: CD4 < 25%;
  - Children >59 months of age with confirmed HIV plus: CD4 count >350 cells/µl.
- **HAAR (cART)**–Highly Active Antiretroviral Therapy is used for treatment: a combination of 3 or more (Antiretrovirals) ARVs from at least two different groups.

- Treatment with appropriate antiretroviral agent may result in immune reconstitution inflammatory syndrome **(IRIS)**. This is characterized by increased inflammatory response from the recovered immune system to subclinical opportunistic infections like tuberculosis, pneumocystis jiroveci or cryptococcal infection.

Complications

- Conditions that can complicate HIV infection are Tuberculosis–use the anti-tuberculous regimen; Pneumocystis carinii (jiroveci) pneumonia–give co-trimoxazole prophylaxis from 6 weeks;
- Failure to thrive–adequate nutritional care;
- Diarrhoea (persistent and chronic)–adequate fluid and electrolyte replacement and antibiotic/antimicrobial therapy;
- Candida (oral thrush)–anti-fungal drug, mycostatin, co-trimazole;
- Other complications like meningitis, HIV encephalopathy, encephalitis, skin infection, chicken pox, varicella zoster, herpes simplex virus, measles, etc., should be treated accordingly.

Immunization

- This follows the Expanded Programme on Immunization scheme with the exception of BCG and yellow fever which should not be given to HIV symptomatic children.

Prognosis

- Prognosis is guarded and depends on early diagnosis, quality of care and ARV therapy.

Prevention/control

- This involves information dissemination about HIV, safe sex (the use of condoms), the screening of blood and blood products, routine HIV screening, universal precautions and avoidance of contaminated sharps, prophylaxis and prompt diagnosis and adequate treatment.

Counselling

- Counselling requires empathy, sympathy and compassion. Psychologically prepare the patient before and after the test. Let them know that HIV is no longer a death sentence. Impress upon them the need to lead a healthy life; to take good care of the HIV positive child.

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2.13 Cholera (Manyike, C.)

- Cholera is a dehydrating disease that can rapidly lead to death if appropriate and prompt measures are not instituted.
- Caused by Vibrio cholerae, a gram negative, non-spore forming, motile, comma-shaped bacillus, with a polar flagellum.
- Vibrio cholerae 01 and 0139 cause disease, but some non-01 and non-0139 V. cholera strains (075 and 0141) can also cause small outbreaks.
- Vibrio cholerae 01 is differentiated as classic and El Tor.
- They are also subdivided into the sero group based on the O antigen.
- Vibrio cholerae 01 has two major antigenic types–Ogawa and Inaba and an unstable intermediate type–Hikojima.
- Vibrio cholerae 0139 is closely related to the El Tor biotype.

Epidemiology

- Cholera exists in sporadic, endemic, epidemic, and pandemic forms.
- Transmission is mainly by the faecal-oral route–contaminated water, food, utensils and houseflies.

Pathophysiology

- Vibrio cholerae elaborates enterotoxin-cholera toxin.
- The toxin causes the production of adenylyl cyclase.
- Adenylyl cyclase causes voluminous loss of fluid and electrolytes through diarrhoea leading to severe dehydration.

Clinical features–history

- History of epidemic or intrafamilial spread.
- Watery diarrhoea and vomiting develop after an incubation period of 6 hours to 5 days.
- There may be low grade fever.
- There is profuse, painless, watery diarrhoea with a rice-water consistency and a fishy odour. Stools may have flecks of mucous but no blood.
- The fluid loss leads to thirst.

Clinical features–physical findings

- There is dehydration, with sunken eye balls and anterior fontanel.
- The patient is irritable; dehydrated with poor skin turgor, reduced urinary output, an absence of tears, dry oral mucosa, shrivelled hands and feet (washerwoman's hands), thready pulse, hypotension, tachycardia and tachypnoea.
- Kussmaul breathing signifies metabolic acidosis.
- There may be progression to circulatory collapse and renal failure.
- Cholera gravis with the loss of 500-1000 ml/hr may occur and can rapidly lead to death if prompt measures are not instituted.

Diagnosis

- Transport specimen on Cary-Blair media.
- Stool culture on TCBS medium is the gold standard for cholera diagnosis.
- Thiosulfate-citrate-bile salt-sucrose agar (TCBS), and tellurite-taurocholate-gelatin agar (TTGA) are the media of choice.
- There is hyponatraemia, hypokalaemia, hypoglycaemia and acidosis.
- Haemoconcentration shown by increased serum protein, elevated haematocrit and increased urine specific gravity is present.
- Few faecal leucocytosis and erythrocytes.
- Dark field microscopy can be done.
- Rapid diagnostic test and PCR and DNA probes are available.

Differential diagnosis

- Acute watery diarrhoea.
- Diarrhoea of any cause.

Treatment

- The mainstay of treatment is fluid and electrolyte replacements. ORS, especially rice-based ORS in mild cases of dehydration and intravenous fluid in severe cases.
- Antibiotics–doxycycline, azithromycin, and ciprofloxacin are the drugs of choice.
- Zinc, 10 to 20 mg daily for 14 days.

Complications/prognosis

- Lethargy, seizures, altered consciousness, fever, hypoglycaemia, hyperglycaemia and death may occur especially in children.
- Acute tubular necrosis may result from inadequate fluid and electrolyte replacement.
- There could be arrhythmia and sudden death in children with acidosis and hypokalaemia.

Prevention/control

- Prolonged breast feeding.
- Safe food and water.
- Good handling of sewage and Vaccination.

Counselling

- Hand washing practice.
- Prolonged breast feeding.
- Safe food and water, and good handling of sewage.
- Prompt hospitalization of victims.
- Vaccination.

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2.14 Typhoid Fever (Ibeneme, C. A.)

- Typhoid fever or enteric fever is a severe systemic disease caused by *Salmonella typhi*, *S. paratyphi* A, *S. paratyphi* B (*S. Schottmuelleri*) and *S. paratyphi* C (*S. Hirschfeldii*).
- Salmonella is a motile, gram-negative rod, in the family Enterobacteriaceae. It possesses 3 antigenic groups: a) the cell wall (O) lipopolysaccharide or somatic antigen; b) the flagellar (H) antigen; c) the virulent (Vi) or capsular K antigen.

Epidemiology

- Typhoid fever remains an important problem in many developing countries.
- Incidence is about 500 cases/100,000 population, with a high mortality rate. In the United States, annual incidence is less than 0.2 cases/100,000 population.
- The global incidence in 2000 was estimated as 21.6 million cases with 216,510 deaths.
- In developing countries, most cases occur in school-age children and young adults with both sexes equally affected.
- Humans are the only reservoir for *S. typhi* and transmission is by the faecal-oral route through contaminated food or water.
- The main human sources of infection are asymptomatic faecal carriers. Congenital infection can occur from a bacteraemic mother to her foetus.
- Cell mediated immunity is important in protecting the human host against typhoid fever.

Pathogenesis

- Following ingestion of S. typhi, the inoculum that survives stomach acid enters the small intestine, penetrates the mucosa and enters the mononuclear phagocytes of ileal Peyer's patches and mesenteric lymph nodes.
- Bacteria proliferate in mononuclear cells and reach the blood (transient bacteraemia) via the thoracic duct to spread to the reticuloendothelial cells of the spleen, liver and bone marrow where further proliferation occurs, following which bacteraemia recurs.

- Inflammatory reactions consisting of mononuclear cell infiltration, hyperplasia and focal necrosis occur in the reticuloendothelial cells with the release of cytokines responsible for the systemic symptoms.
- Intestinal manifestations are caused by hyperplasia of Peyer's patches with ulceration of overlying mucosa resulting in bleeding, or perforation.
- The gallbladder is particularly susceptible to being infected.

Clinical features

- The incubation period is 7-14 days; it may range from 3-30 days depending on the inoculum size.
- Clinical manifestations depend on age. In **school-aged children and adolescents**, onset of symptoms is insidious. Initial symptoms of fever, malaise, anorexia, headache and abdominal pain develop over 2-3 days.
- Diarrhoea may occur initially but constipation becomes more prominent.
- Fever increases in a stepwise fashion, becomes unremitting, reaching 40□C within 1 week.
- During the 2nd week, the high fever is sustained, initial symptoms increase in severity and the patient appears acutely ill, disoriented and lethargic.
- Physical findings include relative bradycardia disproportionate to the high fever, hepatomegaly, splenomegaly, a distended tender abdomen and discrete macular erythematous rash (rose-spots) in 50%.
- Without complications, the symptoms and physical findings gradually resolve within 2-4 weeks.
- In **infants and young children**, the disease is mild and relatively rare.
- **Neonatal** disease via vertical transmission can occur.

Complications

- These include intestinal bleeding and perforation, sepsis, hepatitis, cholecystitis, pancreatitis, pneumonia or bronchitis, toxic myocarditis or cardiogenic shock, neurologic complications (raised ICP, acute cerebellar ataxia, psychosis, transverse myelitis, aphasia, deafness, cerebral thrombosis), pyelonephritis, nephrotic syndrome, meningitis and endocarditis.

- Osteomyelitis and septic arthritis are common in children with haemoglobinopathies.

Diagnosis

- Diagnosis is confirmed by culturing the salmonella organism. Blood cultures are positive in 40-60% early in the course of the disease. Stool and urine cultures are positive after the 1st week. In suspected cases with negative stool cultures, a culture of duodenal string capsule may be helpful in confirming diagnosis.
- Bone marrow culture is the most sensitive test, positive in nearly 90% of cases.
- Direct detection of *S. typhi*-specific antigens has been attempted using monoclonal antibodies.
- PCR enables diagnosis within a few hours.
- The Widal test measures the agglutinating antibodies against the O and H antigens of *S. typhi*. A titre of ≥1:80 or a fourfold rise supports the diagnosis. The Widal test is of limited value because of many false positive and negative results especially with malaria infection.
- Normochromic, normocytic anaemia, leucopenia and thrombocytopenia occur. Abnormal LFT results, proteinuria, faecal leucocytes and faecal blood are common.

Differential diagnosis

- Common possibilities in our environment include malaria, hepatitis, shigellosis, amoebic liver abscess, sepsis with other pathogens, tuberculosis, leukaemia and lymphoma.

Treatment

- Antimicrobial therapy is essential. The choice of drug is limited by increasing antibiotic resistance. Drugs that are used include 3rd generation cephalosporins, chloramphenicol, ampicillin, fluoroquinolones and trimethoprim-sulphamethoxazole. The duration of therapy ranges from 7-14 days.
- Supportive therapy with fluid and electrolytes, blood and platelet transfusion where appropriate.
- Surgical intervention where necessary.

- Eradication of chronic carriage is attempted with 4-6 weeks of high dose antibiotics ± cholecystectomy.

Prognosis

- Mortality is less than 1% in developed countries and higher than 10% in developing countries, due to delays in diagnosis, hospitalization and treatment.
- Disease relapse may occur after antimicrobial therapy.
- 1-5% of patients become chronic carriers.

Prevention/Control

- Health education, improved sanitation, clean running water, a proper sewage disposal system, personal hygiene measures, hand washing, attention to food preparation practices, efforts to eradicate *S. typhi* from chronic carriers as well as preventing carriers from working in food processing activities.
- Typhoid vaccination is available in developed countries.

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2.15 Mumps (Ibeneme, C. A.)

- Mumps is an acute systemic viral illness that is usually self-limiting and clinically characterized by non-suppurative parotitis.
- It is caused by the mumps virus, a paramyxovirus.
- Only one serotype is known and humans are the only known natural host.

Epidemiology

- Before the introduction of the vaccine, mumps was a common childhood disease worldwide. More than 90% of school-aged children will have mumps antibodies by the age of 15.
- Mumps infection is still a significant threat to health in developing countries, and outbreaks still occur sporadically in developed countries.
- It affects both sexes equally and incidence peaks predominantly in late winter and spring, though the disease has been reported throughout the year.
- It has a rapid spread among members living in close quarters through direct contact, airborne droplets and contaminated fomites.
- It is most infectious 1 to 2 days prior to parotid swelling till 5 days after swelling has appeared.

Pathogenesis

- Primary viral replication takes place in epithelial cells of the upper respiratory tract, followed by the spread of the virus to regional lymph nodes with subsequent viraemia and systemic dissemination to many tissues among which the salivary glands are the most susceptible.

Clinical features

- The incubation period ranges from 14-24 days with a peak of 17-18 days.
- About 30-40% of infections are subclinical.
- Non-specific symptoms such as fever, headache, anorexia, and abdominal discomfort may precede parotid swelling by 1-2 days.
- Parotid gland swelling and pain generally develop on the third day of illness. Parotitis occurs in 30 to 40% of infected persons. Pain is elicited especially by tasting sour liquids such as lemon juice.

- Parotid swelling may be unilateral or bilateral (70%). The ear is displaced upward and outward with the obliteration of the mandibular angle.
- The opposite side may be involved 2 to 3 days after onset of the swelling on one side.
- Submandibular glands may be involved.
- Illness is of short duration (7 to 10 days) and resolves spontaneously.
- Anorexia is a frequent complaint. Abdominal pain may represent the involvement of the pancreas or of the ovary in females. Vomiting may be a significant problem in severely ill patients.

Diagnosis

- Diagnosis is usually made on the basis of clinical findings in a child who presents with parotitis.
- Leucopenia is usually present with relative lymphocytosis.
- Diagnosis depends on either the isolation of the virus in culture, detection of viral nucleic acid (PCR) or identifying the mumps-specific IgM antibody.
- The virus can be isolated from a throat swab, 48 hours before to 7 days after parotid swelling begins. The virus can also be isolated from saliva, cerebrospinal fluid (CSF), blood, urine and brain tissues.

Differential diagnosis

- Other viral causes of parotitis include HIV infection, influenza, parainfluenza viruses 1 and 3, cytomegalovirus and coxsackieviruses.
- Salivary calculus obstructing the parotid or submandibular duct causes intermittent swelling.

Treatment

- No specific antiviral therapy.
- Treatment is entirely supportive: antipyretics, bed rest, hydration, light diet with generous fluids; analgesics for severe headaches and discomfort caused by parotitis.
- Treatment of orchitis includes bed rest, scrotal support, analgesics and ice packs.

- The patient should be isolated for 9 days after parotid swelling begins.

Complications

- Meningoencephalitis: most frequent complication in childhood. Incidence is approximately 250/100,000 cases. CSF pleocytosis (predominantly lymphocytes) occurs with elevated protein and normal glucose.
- Orchitis/epididymitis: this is the most feared complication in males, more common (14-35%) in postpubertal males. It usually follows parotitis within 8 days. It is characterized by severe pain, swelling and tenderness. Testicular atrophy may occur after orchitis and if bilateral may result in sterility.
- Oophoritis: occurs in about 7% of postpubertal females.
- Pancreatitis: epigastric pain and tenderness are suggestive.
- Others are arthritis, mastitis, thyroiditis, myocarditis, deafness and ocular complications.

Prevention

- The MMR vaccine is recommended for all preschool-aged children. This provides 80% effective immunity against mumps following a two-dosage schedule (at 12-15 months with a booster at 4-6 years of age).
- A catch-up vaccination can be given at age 11 or 12 years to those children who have not yet received two doses of MMR. The second dose of MMR may be administered as soon as 4 weeks after the first dose.
- Lifelong immunity usually follows clinical or subclinical infection.
- Transplacental antibodies seem to be effective in protecting infants during their first 6-8 months.

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2.16 Rubella (Ibeneme, C. A.)

- Rubella (German or three-day measles) is an acute, highly contagious viral infection caused by rubella virus, an RNA virus from the Togaviridae family.
- The major clinical significance is the transplacental transmission to the embryo and foetus from an infected mother leading to congenital rubella syndrome.

Epidemiology

- It is distributed worldwide and affects both sexes equally.
- Humans are the only natural host.
- Before the introduction of the vaccine, the peak incidence was among children of 5-14 years of age in developed countries, but most cases now occur among susceptible teenagers and young adults.
- The route of infection is either through droplets or transplacentally to the foetus.
- During clinical illness, the virus is shed in nasopharyngeal secretions, blood, faeces and urine.
- The period of infectivity is from 7 days before the rash to 7 days after its disappearance.
- Subclinical cases can be a source of infection.
- Infants with congenitally acquired infections may excrete the virus for months after birth and are contagious during this time.
- Lifelong immunity occurs after initial infection. Subclinical reinfection demonstrated by an increase in IgG serum antibody has been documented.
- IgM response distinguishes primary infection from reinfection.

Pathogenesis

- After the initial invasion of the upper respiratory tract, the virus spreads to local lymphoid tissue, where it multiplies and initiates a viraemia of approximately 7 days' duration.
- The respiratory tract shedding of the virus and the viraemia rise to peak levels until the onset of rash, then the viraemia becomes undetectable, whereas respiratory secretions contain the virus over the succeeding 5 to 15 days.

- Necropsies of foetal and neonatal victims of intrauterine infection have shown a variety of embryonal defects related to developmental arrest involving all three germ layers.
- The virus establishes chronic persistent infections of many tissues with resultant intrauterine growth retardation.
- Delayed and disordered organogenesis produces embryopathic structural defects of the eye, brain, heart and large arteries.
- Continued viral infection during the foetal and postnatal period causes organ and tissue damage, e.g. hepatitis, nephritis, myocarditis, pneumonia, osteitis, meningitis, cochlear degeneration, and pancreatitis with the development of diabetes.

Clinical features

- **Postnatally acquired rubella.**
- Incubation period is 12 to 21 days.
- The prodromal phase of mild catarrhal symptoms is shorter than that of measles and may go unnoticed. Adolescents may complain of malaise, headache, low-grade fever and sore throat.
- A characteristic pattern is that of adenopathy, rash and low-grade fever.
- Enlargement of the posterior auricular, suboccipital and posterior cervical nodes appears about a week prior to the rash.
- The rash, which occurs in 50-80% of cases, is initially small irregular pink macules which begin on the face and neck before progressing down the body, may coalesce and become maculopapular and scarlatiniform, lasting 1-3 days. Desquamation is rare.
- Fever is low grade and pharyngeal mucosa and conjunctivae are slightly inflamed. There is no photophobia.
- An enanthem (Forchheimer spots) may be seen on the soft palate in 20%.

Diagnosis

- Diagnosis may be apparent from the clinical symptom and physical examination but is usually confirmed by serology or viral culture.
- The spleen is often slightly enlarged. White blood cell count is normal or slightly reduced. Thrombocytopenia occurs rarely with or without purpura.

- Rubella antibodies can be demonstrated through latex agglutination, enzyme immunoassay, haemagglutination inhibition and fluorescent immunoassay.
- IgM antibodies are detectable in the first few days of illness and are considered diagnostic. Detection of IgM antibodies, which do not cross the placenta, in the newborn is useful for the diagnosis of congenital rubella syndrome.
- Seroconversion or a fourfold increase in IgG titre is diagnostic.
- The virus can be cultured from the nasopharynx and blood.

Differential diagnosis

- Viral infections causing similar rash include scarlet fever, rubeola, roseola infantum, infectious mononucleosis and enteroviral infections. Drug rashes may be difficult to differentiate from rubella rash.

Treatment

- Treatment is entirely supportive as there is no specific antiviral therapy. Antipyretics are indicated for fever.

Complications

- Transient polyarthralgia or polyarthritis are more common among adolescent females.
- A Meningoencephalitis may occur 1 to 6 days after the appearance of rash and is fatal in about 20% of those affected.
- Progressive rubella panencephalitis, a persistent slowly progressive rubella infection of the central nervous system can occur.
- **Congenital rubella syndrome** is the most important consequence of rubella in a pregnant woman.
- Common manifestations include intrauterine growth retardation, macular blueberry muffin lesions of thrombocytopenic purpura, cataracts, microphthalmia, myocarditis, structural cardiac defects, sensorineural deafness and meningoencephalitis.
- Later sequalae include motor and mental retardation.

Prognosis

- Complete recovery from postnatally acquired rubella is almost invariable. In congenital rubella, mortality is greatest during the first 6 months of life.

Prevention

- The Measles-Mumps-Rubella (MMR) vaccine is recommended at 12-15 months of age, and a second dose at 4-6 years but may be administered at any time during childhood provided at least 4 weeks have elapsed since the first dose. Children who have not previously received the second dose should be immunized by 11 to 12 years of age.
- Pregnant women should not be given live rubella vaccine and should avoid becoming pregnant for 3 months after vaccination.
- Immune globulin administration for postexposure prophylaxis in pregnancy should be considered if termination of pregnancy is not an option.

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2.17 Influenza (Ezeonwu, B.)

Introduction

- Respiratory illness caused by the single-stranded RNA influenza viruses of the orthomyxo family.
- Haemagglutinin (15) and neuraminidase (9) are the two major surface proteins that determine the serotype.
- Three types: A, B and C. Epidemic is caused by A and B strains while C causes sporadic disease.
- Yearly variation in the antigenic composition of the surface protein conferring selective advantage to the new strain, causing a localized epidemic with high mortality in the elderly and those with cardiopulmonary disease.
- Attack rate is highest in children with increased school absenteeism.
- Common in the colder months and spread is by small-particle aerosol.

Pathology

- The virus attaches to the sialic acid residue on the respiratory epithelium via Haemagglutinin, causing lysis with loss of ciliary function, decreased mucous production and desquamation of the epithelial layer.

Incubation period

- This can be as short as 48-72 hours and the immediate and effective response is the production of protective mucosal IgA against the Haemagglutinin.
- Onset is abrupt with coryza, conjunctivitis, pharyngitis, dry cough or localized as croup, bronchiolitis or pneumonia.
- Children may be quite toxic.
- Fever, malaise, myalgia and headache are systemic manifestations, and may be cytokine mediated rather than a systemic spread of the virus.
- Close contacts may have a similar illness.

Differentials

- These are respiratory infections caused by respiratory syncytial virus, parainfluenza viruses and adenoviruses.

Diagnosis

- Clinical especially during an epidemic. Confirmation could be by isolation from a nasopharyngeal specimen early in the illness, antigen capture via enzyme-linked immunosorbent assay or serologically via haemagglutination inhibition.
- A relative leucopenia is frequent otherwise laboratory findings are non-specific.

Treatment

- Antiviral; inhaled or oral neuraminidase inhibitors, for A and B strains.
- Fluid, rest and antipyretics are adjuncts. Recovery within 48-72 hours.
- Recrudescence of fever, prolonged fever or clinical deterioration will suggest bacterial superinfection which is very common: an antibiotic may then be required.

Common complications

- Acute otitis media and pneumonia.
- Also, acute myositis, myocarditis and toxic shock syndrome, with type B strain.

Prognosis

- Quite good. Cough may persist for weeks.

Prevention

- **Primary prevention:** 2 doses of inactivated influenza vaccine given with a 1-month interval, to children ≥6 months of age, adults at higher risk of complications and persons who may infect those at higher risk such as health care workers.

- **Secondary prevention** involves chemoprophylaxis with the antiviral for vaccinated and unvaccinated high-risk persons and their unvaccinated health care providers during an influenza A outbreak.

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2.18 Varicella (Nnodim, I. J.)

- Varicella is the primary infection of DNA varicella-zoster virus (VZV) of the Herpesvirus family.
- VZV causes lifelong latent infection of the sensory ganglion and neurons and reactivation causes herpes zoster.

Epidemiology

- Varicella occurs worldwide. Prevalence in Nigeria is 66.3% with no sex predilection. There is a rising prevalence with increasing age with a peak at 13 to 15 years.

Pathophysiology

- The route of infection is the mucosa of the upper respiratory tract or the conjunctiva.
- An initial replication in regional lymph nodes causes a primary viraemia that spreads the virus and leads to replication in the liver and spleen.
- Secondary viraemia involving infected mononuclear cells carries the virus to the skin where the typical rash develops.
- Swelling of epithelial cells, ballooning degeneration and accumulation of tissue fluid lead to the formation of vesicles.
- Replication and spread of VZV are limited by host humoral and cellular immune responses.

Clinical features

- The incubation period is 10-21 days.
- Prodromal symptoms of fever, malaise, anorexia, headache, and abdominal pain, more common in older children or adolescents, may occur and may be present 24-48 hours before the rash appears.
- Fever and other systemic symptoms persist 2-4 days after the onset of the rash.
- The rash is pruritic and centripetal in distribution; appearing first on the scalp, face or trunk then spreading to other parts of the body.
- Successive fresh vesicles appear in crops so that all stages of macules, papules, vesicles and crusts may be seen simultaneously.
- This is characteristic of varicella.

Diagnosis

- Laboratory diagnosis is not considered necessary for uncomplicated cases.
- VZV can be identified quickly by the direct fluorescent assay of cells.
- Viral culture. The virus can be isolated from vesicle fluid early in the course of the illness using cultures of human cells in 3-7 days.
- Tzanck smear; shows multinucleated giant cells but does not differentiate VZV from the herpes simplex virus.
- VZV IgG antibodies; four-fold rise confirms acute infection.

Differential diagnosis

- Infections by the herpes simplex virus, enterovirus, *Staphylococcus aureus*; drug reactions; contact dermatitis; insect bites.

Treatment

- Usually not required in immunocompetent children. Neonates and immunocompromised children with severe infections should be treated.
- Oral acyclovir (20 mg/kg/dose, maximum 800 mg/dose given as 4 doses/day for 5 days).
- Clinical benefit is uncertain if commenced >72 hours after the onset of rash.
- Intravenous acyclovir is used in severe cases.
- Foscarnet can be used in acyclovir resistant cases.

Complications

- Secondary bacterial infections usually by group A streptococci or *Staphylococcus aureus*.
- Encephalitis and cerebellar ataxia; pneumonia; congenital varicella syndrome in 2% of infants born to women who contract varicella in the first 20 weeks of pregnancy.

Prevention

- Varicella vaccine; varicella-zoster immune globulin for exposed individuals at high risk of severe disease.

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SECTION 3:

GASTROENTEROLOGY

OKEKE, I. B.

3.1 Gastroenteritis

- The WHO defined diarrhoea as the passage of 3 or more loose or liquid stools per day (or more frequent passage than is normal for the individual).
- Diarrhoeal disorders can be infectious or non-infectious.
- Gastroenteritis denotes infections of the gastrointestinal tract caused by bacteria, viruses or parasitic pathogens. It occurs as acute onset of diarrhoea in most cases with vomiting.

Epidemiology

- Approximately one billion episodes in under-fives in less developed countries (Africa, Asia, Latin America).
- Causes more than four million deaths in the same regions of the world.
- It is the most common cause of death in the under-fives.
- Viruses are the most common cause of acute gastroenteritis with rotavirus alone estimated to cause up to 35% of severe watery diarrhoea episodes.
- Common between 6 months and 3 years.
- Occurrence before 6 months is associated with the early introduction of formula feeds.

Pathophysiology

- Infectious organisms affect enterocyte function by either invasion of or adherence to the mucosa with cytopathic effect or stimulation of secretions by the elaboration of toxins.

- The damage caused leads to loss of the normal regulation of salt and fluid absorption. Inflammation (usually caused by invading organisms) leads to high osmotic load within intestinal lumen leading to further loss of fluid.
- Invasive organisms e.g. shigella, enteroinvasive E. coli, salmonella, campylobacter.
- Adherent organisms e.g. Enteroadherent/enteropathogenic E. coli, giardia lamblia, cryptosporidium. Tight adherence leads to effacement of microvilli.
- Stimulation of secretion e.g. Vibrio cholera, enterotoxigenic E. coli.

Clinical features: History

- Onset of diarrhoea (increase in stool frequency with decrease in consistency or increased water content) could be acute or gradual.
- Vomiting is common and may precede diarrhoea by up to 48 hours.
- Prodromal illness with upper respiratory tract symptoms may indicate viral pathogens.
- Fever can occur in both viral and bacterial infections.
- Abdominal cramps and watery diarrhoea are common in enterotoxin-producing bacteria.
- Invasive and shiga toxin-producing organisms produce diarrhoea that can contain blood, faecal leukocytes with abdominal cramps, tenesmus and fever–bacterial dysentery.
- Organisms associated with haemorrhagic diarrhoea can start with non-bloody, watery diarrhoea that later leads to dysentery.
- A history of recent antibiotic administration in a child with fever and diarrhoea raises the possibility of Clostridium difficile infection as the cause.
- In immunocompromised cases or malnutrition remember the risk of unusual organisms e.g. Cryptosporidium.

Clinical features: Physical findings

- Assess the degree of dehydration and acidosis.
- The degree of dehydration is a continuum from mild dehydration to shock.
- Severe dehydration–sunken eyes/fontanelle, loss of skin turgor, absent tears, small volume pulse, no urine made in several hours.

- Shock is evident in the presence of signs of severe dehydration + prolonged capillary refill (>2 seconds) and tachycardia.
- Altered level of consciousness and hypotension are signs of decompensated shock.
- Deep, rapid breathing without other signs of respiratory distress suggests acidosis.
- A sick, well-hydrated child suggests complications: Bacteraemia, electrolyte imbalance, etc.
- Some features of electrolyte imbalance;

Electrolyte	Features
Hypokalaemia	Lethargy, decreased or absent bowel sound, hypotonia
Hyponatraemia	Irritability, convulsion
Hypernatraemia	Doughy skin, irritability, convulsion
Acidosis (decreased HCO3)	Deep rapid breathing, irritability

Diagnosis:

- Detailed history and thorough physical examination to exclude other causes of diarrhoea including parenteral diarrhoea.
- Stool cultures to isolate the causative organism using appropriate culture media e.g. for shigella, salmonella, use MacConkey. E. coli–MacConkey sorbitol. Giardia lamblia–examine stool for cysts or duodenal aspirate for trophozoites, etc.
- Faecal leukocyte: indicative of bacterial invasion of colonic mucosa or cytotoxin production, seen in shigella, Yersinia and enteroinvasive E. coli, enterotoxigenic E. coli.
- Peripheral blood leukocytosis is seen in shigellosis.
- Possibility of clostridium difficile in recent antibiotic use.

Differential diagnoses

- The symptoms of acute gastroenteritis: diarrhoea and vomiting can be symptoms of infection elsewhere e.g. UTI, otitis media, pneumonia, tonsillitis, septicaemia, meningitis.
- Surgical causes include pyloric stenosis, intestinal obstruction, intussusception, appendicitis.
- Food intolerance/hypersensitivity–intolerances are adverse physiologic responses e.g. enzyme deficiencies and irritable bowel

syndrome, while hypersensitivity can be adverse immunologic responses like coeliac disease or allergies e.g., food protein-induced enterocolitis.
- Malabsorption–this may be due to a general mucosal defect or specific nutrient malabsorption e.g. lactose malabsorption.
- Drugs–laxatives, prolonged antibiotic use.

Treatment

- Principle of treatment: rehydration, continued enteral feeding, zinc supplementation (10 mg/day for infants <6 months, 20 mg/day for those >6 month) for 14 days. Other therapies viz. probiotics, antibiotics.
- No anti-diarrhoea, anti-emetic or anti-secretary agents.

Fluid requirement
- Calculate the fluid requirement for rehydration as a multiple of the degree of dehydration and the body weight in grams e.g. a 10 kg child with mild dehydration (4/100 x 10,000 = 400 ml).

Degree of dehydration	Features	Mode of fluid replacement
Mild (<5% loss of body weight)	Normal or increased pulse, decreased urine output, thirsty, normal physical findings.	Oral rehydration using ORS, delivered slowly over 4 hours.
Moderate (5-10% loss of body weight)	Tachycardia, little urine output, sunken eyes and fontanel, dry mucous membrane, mild delay in skin elasticity, delayed capillary refill (>1.5 secs).	Oral rehydration using ORS.
Severe (>10% loss of body weight)	Rapid weak pulse or absent peripheral pulses, decreased blood pressure, sunken eyes and fontanel, parched mucous membrane, delayed capillary refill (>3 secs), depressed consciousness.	Oral rehydration if the patient is able to drink. IV rehydration if the patient is in shock using 0.9% saline (20 ml/kg over 30 mins). Repeat (PRN) x 2 until the peripheral pulse returns. Then ORS.

- ***Indications for I.V. rehydration***: persistent vomiting (>3 times/day), abdominal distension/ileus, profuse watery diarrhoea, significant psychosocial situation, signs of shock.
- ***Oral rehydration solution (ORS)–use of low*** osmolality ORS found more effective in reducing stool output, vomiting and the need for IV fluids. Give 50 ml/kg for mild, 75 ml/kg for moderate and 100 ml/kg for severe dehydration over 3-4 hrs.
- ***Correction of electrolyte imbalance:***
- Use the following formulae to calculate electrolyte replacement:
  Hypokalaemia = deficit (expected–observed) x body weight (kg) x 0.3.
  Hyponatraemia = deficit (expected–observed) x body weight (kg) x 0.6.
  Hypernatraemia – use 0.45% saline. Correct fluid and electrolyte deficit over 48-72 hrs.
  Acidosis (decreased HCO3) = this usually corrects with rehydration but if severe use (base deficit x weight (kg) x 0.3). Note that 8% NaCO3 1 ml =1 mmol.

Complications/prognosis:

- Most cases of acute gastroenteritis, managed appropriately, settle in a few days to one week. Delays in diagnosis and/or the institution of appropriate management lead to complications and poor prognosis.
- Severe dehydration carries with it complications like shock, acute tubular necrosis, and renal vein thrombosis.
- Electrolyte imbalance (especially hypokalaemia, hyponatraemia and hypernatraemia).
- Rapid correction of hypernatraemia can lead to cerebral oedema.
- Bacteraemia with localized or systemic infections e.g. abscess, pyoderma, UTI, pneumonia, and meningitis especially in malnourished and immune-compromised patients.
- Nutritional depletion: macronutrient malnutrition or micronutrient deficiencies.
- Persistent diarrhoea (acute episode lasting ≥14 days) with high mortality (up to 50% of all diarrhoea-related deaths).
- Immunologic/immune complex complications

Complications	Likely organisms
Reactive arthritis	Salmonella, shigella, campylobacter, cryptosporidium, clostridium difficile.
Guillain-Barre syndrome	Campylobacter.
Glomerulonephritis	Shigella, campylobacter, Yersinia.
IgA nephropathy	Campylobacter.
Erythema nodosum	Yersinia, campylobacter, salmonella.
Haemolytic uraemic syndrome	Shigella dysenteriae, E. coli 0157, others.
Haemolytic anaemia	Campylobacter, Yersinia.

Prevention/control

- Most gastroenteritis is spread by the faeco-oral route. Education and behavioural change strategies through the promotion of hand washing.
- Proper sanitation, water supply, personal and environmental hygiene prevent infection and control the spread of disease.
- Improved nutrition viz., exclusive breastfeeding, improved complementary feeding practices, and vitamin A supplementation.
- Vaccination–rotavirus vaccination reduces both the severity and mortality of rotavirus gastroenteritis.
- Children with gastroenteritis should be isolated from the general ward.
- Improved case management of diarrhoea with the use of low osmolality ORS and zinc supplementation with the selective and appropriate use of antibiotics.

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3.2 Malnutrition

Epidemiology

- Malnutrition is a major worldwide problem which cuts across all age groups. Undernutrition, more prevalent in children under 5, is seen more in developing countries while overweight/obesity is more prevalent in developed countries.

Undernutrition

- In developing countries, the prevalence of undernutrition in the year 2000 showed 26.7% of underweight and 32.5% of stunting while 4-5% stunting was noted in developed countries.
- More than 90% of the world's stunted children live in Africa and Asia.
- Today the world is facing a double burden of malnutrition (both undernutrition and overweight co-existing in the same environment, even the same family) especially in developing countries.

Pathophysiology

- Manifestations in undernutrition represent an adaptive response to inadequate energy, protein and/or micronutrient intakes.
- Initial activity and energy expenditure decrease. Fat stores are mobilized to meet the energy requirement.
- Then protein catabolism follows to provide a substrate for basal metabolism.
- Reasons advanced to explain oedematous and non-oedematous malnutrition include;
  - Variability among infants in nutrient requirement and body composition at the time of the dietary deficit;
  - Oedematous children have a slower protein breakdown rate → decreased amino acid for the synthesis of plasma proteins involved in nutrient transport and the acute phase response to infection;
  - Lipogenesis from excess carbohydrate and decreased apolipoprotein synthesis lead to fatty liver.
- Other propositions for oedematous malnutrition–aflatoxin poisoning, free radical damage, decreased Na^+-K^+ ATPase activity,

and impaired renal function, are thought likely to be consequences of already deranged metabolism.

Clinical features–history

- A history of inadequate dietary intake and/or chronic illness or birth defects.
- Inadequate supervision due to maternal illness or death.
- Non-oedematous severe childhood undernutrition (SCU) is characterized by a failure to gain weight, irritability, and weight loss.
- Oedematous SCU has initial vague manifestations with lethargy, irritability, poor growth, anorexia, lack of stamina, and body swelling.

Clinical features–physical findings

- Mild undernutrition mainly presents with low weight for age, height for age and weight-for-height.
- The most severe forms of SCU are marasmus (non-oedematous) and kwashiorkor (oedematous).
- In non-oedematous SCU there are emaciation, wrinkled skin, muscle wasting, prominence of bony structures, hypotonia, a wizened facial appearance (due to loss of fat in the sucking pad), subnormal temperature and slow pulse.
- Oedematous SCU presents with apathy, loss of muscle tissue, sparse thin hair, dermatitis (such as the darkening of skin in irritated areas), nutritional oedema, subnormal temperature and stupor if left untreated.

Diagnosis

- Diagnosis is made in the presence of clinical features with the anthropometric measures of z-scores for weight-for-height, weight-for-age and height-for-age less than -1 to -3 of the median of the WHO standard and/or MAC <11.5 cm.
- Grading of the severity of undernutrition using the z-scores for weight-for-height;
  - <-1–Mild undernutrition;
  - <-2–Moderate undernutrition;
  - <-3–Severe undernutrition.

- Associated low serum levels of proteins and lipoproteins support the diagnosis.

Differential diagnosis

- Short stature–e.g. in growth hormone deficiency (but only stature is affected).
- Genetic thinness–it has been documented that thinness is genetically determined and so these individuals may fall short of expected anthropometric values for age and sex.

Treatment

- Treatment of the most severe forms of primary undernutrition (inadequate food intake) is subdivided into three phases;
  - Stabilization–in the first 1-5 days: check and treat hypoglycaemia, hypothermia, electrolyte imbalance, infections, anaemia, micronutrient deficiencies and initiate feeding;
  - Rehabilitation–in the next 1-6 weeks: catch-up feeding, sensory stimulation, nutritional counselling and prepare for follow-up;
  - Follow-up–periodic monitoring to avoid relapse.
- In secondary undernutrition (increased nutrient need, decreased nutrient absorption, increased nutrient losses)–there is a need to identify and treat the cause while the nutrient deficiencies are being corrected.

Complications/prognosis

- It is estimated that more than 50% of child deaths are caused directly or indirectly by undernutrition.
- It is a major factor in the potentiation of infectious diseases with increased morbidity/mortality in children.
- Childhood undernutrition → deficit in height and weight in adulthood → deficit in frame, muscle circumference and strength → decreased physical work capacity.
- Severe undernutrition also leads to significant intellectual deficits.
- Childhood undernutrition in females may lead to obstetric complications during child-bearing.

Prevention

- For sustainable solutions, the evolution of thought and behaviour of households, communities, clinical workers, program managers and policy-makers about food insecurity and undernutrition is needed for interventions to be effective.
- The role of female education and women empowerment cannot be overemphasized.
- Risk-avoidance and risk-management strategies of poor households are to be addressed to enable them to accept changes in their livelihood, adopting new crop varieties that will improve the family's food security.
- Multiple micronutrient (MMN) supplementation in pregnancy to reduce the incidence of SGA babies.
- Immunization and micronutrient supplementation to break the vicious cycle between infection and undernutrition.
- Provision of balanced school meals for school-aged children.

Overweight/Obesity

- Obesity is defined as excessive body fat or weight-for-height >120% of normal for age and sex.
- Overweight is defined as a weight-for-height of 110-120% of normal for age and sex.

Epidemiology

- Overweight/obesity, seen more among school-aged children and adolescents, was found to have doubled in most developed countries between the late 1970s to 2000.
- It is highest in low income households and minority ethnic groups in developed countries while in less developed countries better-off households especially in urban areas have the highest prevalence.
- Estimates of world prevalence in 2010-2013 showed overweight in 27% and obesity in 9% of Americans and 5% overweight and 1% obesity in Sub-Saharan Africa.

Pathophysiology

- Three critical periods during human development at which physiologic interactions increase the later prevalence of obesity;

  - Foetal life–large for gestational age increases the prevalence of overweight at 5-6 years;
  - Period of adiposity rebound–early onset (before 5.5 years) → longer duration of body fat deposition → persistence of obesity;
  - Adolescence–rapid growth and redistribution of body fat stores have the risk of onset and persistence of overweight.
- Obesogenic environment–normal or increased food intake accompanied by increased physical inactivity.
- A complex interplay between an individual's genetic predispositions and the environment affects an intricate system that controls appetite and energy expenditure.

Clinical feature –history

- Excessive weight may date from birth, infancy, childhood or adolescence.
- There may be a family history of obesity and/or obesity-related illness e.g. diabetes mellitus.
- Note the history of physical activity, diet, and eating patterns. School attendance and attainment.
- Morbidities–e.g. sleep apnoea, orthopedic problems (Blount disease, slipped femoral epiphysis), respiratory difficulties may be present.
- Drug history–steroids.

Clinical features–physical findings

- Weight-for-height plotted on standard charts will indicate the severity of overweight.
- The blood pressure and cardiovascular assessment is important.
- Check for Acanthosis nigricans (a dark velvety appearance at the neck and axillae)–a sign of insulin resistance.
- Features of rare causes of obesity may be present e.g. short stature, delayed puberty, hirsutism.

Diagnosis

- Given changing adiposity during childhood, the BMI percentile is used for the classification of overweight in children instead of absolute numbers. BMI $\geq 95^{th}$ percentile is overweight.
- Waist-hip ratios have poor reproducibility in children.

- Determine if there is a secondary cause of overweight (overweight children <50th percentile for height-for-age should be screened for endocrinologic abnormality).

Differential diagnosis

- Endocrine disorders e.g. hypothyroidism, Cushing's syndrome.
- Genetic disorders e.g. Beckwith-Wiedemann, Prader Willi syndromes and hyperinsulinism. These are associated with a combination of dysmorphic features.

Treatment

- Overweight/obesity is a chronic medical problem and should be managed as such.
- This is done with the family and requires sensitivity and compassion because of the psychosocial issues associated with overweight/obesity e.g. low self-esteem, stigmatization, bullying or being bullied.
- Explore dietary practices, family structure, and habits and alter these factors where necessary.
- Identify and treat co-morbidities e.g. hypertension, type 2 diabetes mellitus.
- In growing children weight maintenance, instead of weight loss is a reasonable initial goal. As children grow in stature, BMI decreases.
- Lifestyle changes that involve increased physical activity are most likely to be successful.
- Pharmacotherapy is reserved for morbidly obese adolescents when conservative approaches have been exhausted.
- Orlistat (pancreatic-lipase inhibitor → impaired digestion and absorption of dietary fat) and Sibutramine (serotonin-noradrenaline reuptake inhibitor → early satiety and increased energy expenditure).

Complications/ prognosis

- Increased prevalence of type 2 diabetes with complications of kidney failure, blindness, and miscarriages as young adults.
- Hyperlipidemia with associated cardiovascular disease.

- Increased risk of hepatic steatosis, gall bladder disease, gastroesophageal reflux.
- Sleep disordered breathing, sleep apnoea, daytime sleepiness, restless sleep and nocturnal enuresis.
- Dyspnoea on exertion manifesting as coughing, respiratory distress, chest pain and pallor with increasing levels of physical activity.
- Social ostracism, emotional and social difficulties can severely affect overweight children through adolescence and into adulthood.
- Early screening in preschool age, counselling and guidance make goals easier to achieve because habits are more malleable and continuing growth with weight maintenance improves the weight-height relationship.

Prevention/Control

- Prevention can begin with advice to parents about breastfeeding, weaning, and healthy eating habits for toddlers.
- Screening using the BMI percentile chart before the age of 2 years and counselling families on how to establish beneficial eating and physical patterns–parents being role models.
- Children are satisfied and will comply when allowed to choose from a number of healthy food options.

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3.3 Liver/Gall Bladder Diseases

Epidemiology

- Prevalence and incidence of liver diseases are lower in children than adults.
- In the USA 15,000 children are hospitalized per year due to liver diseases.
- A growing incidence of non-alcoholic fatty liver disease (NAFLD) parallels an obesity and type II diabetes mellitus epidemic and is 40% more common in boys than girls.
- African American children have substantially lower rates of NAFLD (2-6%) compared to 10-14% in Hispanic and Asian children.

Pathophysiology

Diseases	Pathophysiology
Infections	Inflammatory reaction compromises hepatic function → impaired formation and excretion of bile salt → widespread parenchymal oedema which interferes with bilirubin conjugation and bile excretion → jaundice.
Non-alcoholic fatty liver	Genetic and acquired factors contribute to peripheral resistance to insulin → increased transport of fatty acids from adipose tissue to the liver. Oxidative stress and cytokines (TNFα) → exacerbation of insulin resistance → further oxidative stress and organelle dysfunction within liver cells → inflammatory process.
Autoimmune hepatitis	Thought to be due to imbalance between CD4 and CD8 in individuals who are genetically predisposed.
Drug-induced injury	Direct hepatotoxicity or immune-mediated hepatotoxicity → steatosis, degeneration, necrosis, cholestasis, biliary cirrhosis, or veno-occlusive disease.

Clinical features

- Clinical features of liver disease are variable at presentation and range from asymptomatic to fulminant hepatic failure.
- Most patients with liver diseases present to health facilities with yellowness of the eyes with/without upper abdominal pain.

- In neonates, persistent jaundice beyond the 2nd week of life in an otherwise healthy neonate is usually found to be cholestasis secondary to intra or extra biliary obstruction. Consistent clay-coloured stool with dark urine is in keeping with extra hepatic biliary obstruction.
- A history of contact with a jaundiced person, receipt of blood product, a HBsAg-positive mother, helps in the diagnosis of infections with the hepatotropic viruses.
- The drug history will identify drugs that can lead to medication-associated liver injury e.g. acetaminophen, allopurinol, isoniazid, tetracycline, HAAR drugs, pyrazinamide, rifampicin.
- Autoimmune hepatitis may be accompanied with extrahepatic manifestations of autoimmunity and can present as;
  - Only biochemical evidence of liver dysfunction;
  - Biochemical evidence + stigmata of chronic liver disease;
  - Hepatic failure.
- Hepatoblastoma which make up >65% of hepatic tumours in children present predominantly below 3 years while in infancy harmatomas, haemangioma, and haemangioendotheliomas predominate.

Physical findings

- The patient may present with only jaundice and hepatomegaly ± malaise or may be very ill with encephalopathy, bleeding, hypoglycaemia, renal insufficiency and respiratory failure–signs of hepatic failure.
- In infants with persistent jaundice, an abnormal liver in size and consistency is seen more in biliary atresia while neonatal hepatitis is seen more in premature, small-for-age neonates with an increased incidence of congenital abnormalities.
- Obesity with diabetes mellitus is associated with non-alcoholic fatty liver disease.
- Signs that indicate other diseases with a hepatic component may be present–sickle cell hepatic dysfunction, Wilson's disease, glycogen storage diseases, haemachromatosis, cystic fibrosis.
- Initial presentation may reflect cirrhosis with stigmata of chronic liver disease–ascites, bleeding oesophageal varices, digital clubbing, palmar erythema, splenomegaly and encephalopathy.

Diagnosis

- Investigation: fractionated bilirubin estimation, hepatic transaminases, focused viral assays.
- Asymptomatic mild elevations of liver enzymes (<5 times the upper limit of normal) may be caused by NAFLD, medication-associated liver injury, haemochromatosis, viral hepatitis, autoimmune hepatitis and extra hepatic conditions–thyroid or muscle disorders, haemolysis.
- Autoimmune hepatitis is confirmed by liver-associated serum antibodies (antinuclear or liver-kidney microsomal) and hypergammaglobulinaemia.
- Ultrasound: extra hepatic biliary atresia and tumours while magnetic resonant cholangiogram and transhepatic cholangiography give images of both the intra and extra biliary tree.
- Histology of a liver biopsy will differentiate biliary atresia (hepatic lobular architecture intact) and neonatal hepatitis (distortion of lobular architecture).

Differential diagnoses

- Bacterial sepsis → cholestasis with mild elevation of liver enzymes and conjugated hyperbilirubinaemia**.**
- Thyroid disorders–hypothyroidism affects synthetic and excretory functions of hepatocytes. Antithyroid drugs can → hepatitis, cholestasis or transient subclinical hepatotoxicity.
- Pancreatic diseases–tumour of the head of the pancreas usually → obstruction of the bile duct → cholestasis.
- Congenital hypopituitarism–causes both cholestatic jaundice in neonates and infants and neonatal hepatitis which resolved with the treatment of hypopituitarism.
- Cardiac diseases–acute or chronic CCF → passive congestion and ↓ cardiac output → liver damage.

Treatment

- General treatment is supportive–decrease gut production of ammonia, maintain nutrition, and monitor for signs of ALF. Avoid further insult to the liver (no alcohol, herbal medicines, etc.).

- In chronic active and recent infections with HBV, interferon-α-2b (IFN-α2b) give seroconversion in some cases.
- Acute liver failure (ALF) is managed in an intensive care unit. Treatment is directed at the complications.

Complications	Treatment
Encephalopathy	Restrict enteral/parenteral protein intake + lactulose or neomycin.
Bleeding	Acid suppression, N/G for gastric bleeding, FFT for PT >25 secs.
Hypoglycaemia	Monitor glucose every 1-2 hrs, glucose infusion at 6 mg/kg/minute.
Renal insufficiency	Haemodialysis/haemofiltration.
Altered haemodynamic/ acid-based disturbance	Input/output, diuretics as needed, fluid and electrolyte replacement.
Sepsis	Surveillance cultures, antibiotics when indicated.
Increased ICP	Intravenous mannitol.

- Early arrangement/referral for liver transplantation.
- For biliary atresia–
  - Extrahepatic–early surgery (portoenterostomy);
  - Intrahepatic cholestatic syndromes–treat pruritus with cholestyramin or ursodeoxycholic acid or rifampicin, give supplements of fat-soluble vitamins (A, D, E, K), monitor for the failure of synthetic functions and hepatocellular carcinoma (serum alpha fetoprotein and ultrasound).
- Autoimmune hepatitis–steroids ± azathioprine.
- In NAFLD gradual weight loss is effective improving the hepatic derangement.

Complication/prognosis

- Infections with hepatotropic viruses carry the risk of acute liver failure.
- Infections with HBV, HCV, and some cases of NAFLD progress to cirrhosis with the risk of carcinoma.
- In drug-induced liver injury prognosis depends on the severity and pattern of the insult. Presentation as acute liver failure predicts a poor outcome.

- Cirrhosis, untreated biliary atresia and cases of intrahepatic cholestasis lead to portal hypertension with its complications and decompensation of liver functions by 8-24 months.
- Failure to thrive with eventual short stature complicates intrahepatic cholestatic syndromes.

Prevention/control

- Education of the public on the hepatotoxic effect of OTC drugs, herbal medicines and infectivity and modes of prevention of viral infections.
- Personal hygiene and standard precautions–careful handwashing, safe faecal disposal.
- Vaccination–active and passive (pre/post exposure).
  - Passive immunization indicated during outbreaks, in household/intimate contacts and in infants of HBsAg positive mothers.
  - Active immunization–universal infant vaccination, vaccination of at-risk persons and persons travelling to endemic areas.

Counselling

- Educate care-giver/child on the nature, course and prognosis of the disease.
- A child with chronic liver disease should not be excluded from mainstream education.
- Active immunization of household contacts.
- Avoid further insult to the liver.
- Discuss and refer to transplantation centres in acute liver failure.

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3.4 Peptic Ulcer Disease

Epidemiology

- Peptic ulcer–the end result of inflammation due to an imbalance between cytoprotective and cytotoxic factors in the stomach and duodenum.
- It presents with varying degrees of gastritis or frank ulceration.
- Deep mucosal lesions that disrupt the muscularis mucosa of the gastric or duodenal wall define peptic ulcers.
- Duodenal ulcers are 4 times more common than gastric ulcers.
- Peptic ulcers in children can be primary or secondary.
- Primary ulcers are usually duodenal ulcers associated with helicobacter pylori infection (80-85%).
- H. pylori-negative duodenal ulcers in children who have no history of taking NSAIDs (seen in 15-20% of primary ulcers) are designated as idiopathic ulcers.
- Secondary ulcers are stress-induced or secondary to the intake of NSAID or hypersecretory states.
- Secondary ulcers are usually gastric and can occur in severe sepsis, shock, intracranial lesions (Cushing ulcer), severe burn (Curling ulcer), Zollinger-Ellison syndrome, systemic mastocytosis and short bowel syndrome.
- Anecdotal reports give an incidence of 5-7 children with gastric or duodenal ulcers per 2,500 hospital admissions in large paediatric centres.

Pathophysiology

- The balance between the action of secretagogues that promote acid secretion and mediators that neutralize acid secreted and enhance mucin production plays a crucial role in the development of peptic ulcers.
- Secretagogues include acetylcholine released by the vagus nerve, histamine secreted by enterochromaffin cells, and gastrin released by the G cells of the antrum.
- Mediators that neutralize secreted acid are prostaglandins, prostaglandin E2 stimulates the production and secretion of mucus.
- Helicobacter pylori (a gram-negative S-shaped rod) produces urease, catalase and oxidase which may play a role in the pathogenesis of peptic ulcer.

- Chronic colonization, by H. pylori, of the gastric antrum is associated with significantly increased risk of developing a duodenal ulcer, gastric adenocarcinoma, or MALT lymphoma.

Clinical features

History: Peptic ulcer pain in children may be poorly localized and may be periumbilical.

- Neonates, infants and young children present with feeding difficulties, vomiting, crying episodes, haematemesis or melena.
- Gastric perforation can occur in neonates.
- Epigastric pain and nausea are common in school-age children and adolescents.
- Frequent exacerbations and remissions lasting from weeks to months. Pain episodes can last for minutes to hours.
- Nocturnal pain is common in older children. Typical ulcer pain with prompt relief after antacids is found in less than 33% of children.
- Extensive inflammation and oedema can lead to acute or chronic gastric outlet obstruction.
- Penetration or perforation of the ulcer into the abdominal cavity or adjacent organs produces shock, peritonitis, or pancreatitis.

Findings on examination may be minimal in the absence of complications.

- Mild to moderate epigastric tenderness may be the only sign.
- Complications may give signs of restlessness and/or shock.

Diagnosis

- Oesophagogastroduodenoscopy is the method of choice to establish the diagnosis of peptic ulcer disease.
- Biopsies for histologic assessment and screening for H. pylori infection are taken during the endoscopy.
- Urea breath testing for H. pylori infection–has high sensitivity and specificity for active infection.

Differential diagnosis

- Cholangitis/cholecystitis/cholelithiasis all give epigastric pain but may present with additional jaundice and/or fever.

- Gastroesophageal reflux/oesophagitis–these are differentiated during endoscopy.
- Gastritis–acute or chronic.
- Diverticular disease with gastric mucosa.
- Abdominal aneurysm.

Treatment

- There are two goals in treatment–1. Ulcer healing; and 2. Elimination of the primary cause.
- First line drugs are H2 receptor antagonists e.g. cimetidine, ranitidine, and proton pump inhibitors (more potent in ulcer healing) e.g. omeprazole, esomeprazole.
- Cytoprotective agents as adjuncts in the presence of gastric mucosal lesions e.g. sucralfate.
- Antibiotics (amoxicillin + metronidazole) + PPI in the treatment of H. pylori-associated ulcers.
- PUD requiring surgery has become rare since the recognition and treatment of H. pylori.
- Indications for surgery include uncontrolled bleeding, perforation, and obstruction.

Complications/prognosis

- Bleeding per rectum or vomited (haematemesis).
- Penetration or perforation into surrounding organs/peritoneum.
- Acute or chronic gastric outlet obstruction.
- H. pylori-associated ulcers can lead to gastric cancer (adenocarcinoma) or MALT lymphoma.
- When the underlying cause of PUD is successfully treated, the prognosis is excellent.
- Idiopathic ulcers have a high recurrence rate after discontinuing antiulcer drugs.

Prevention/control

- Frequent hand washing and eating completely cooked food to reduce risk of H. pylori infection.

- Taking steps to reduce the risk of ulcers when taking drugs like NSAIDs, aspirin e.g. take drugs with food, take the lowest dose that gives pain relief.
- In critically ill patients use H2 receptor antagonists or synthetic prostaglandin analogue (misoprostol) to reduce the risk of stress-induced ulcers.

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3.5 Intussusception

Introduction

- Intussusception is the telescoping of a portion of the alimentary tract into an adjacent segment. The upper part of the bowel (the intussusceptum) invaginates into the lower (the intussuscepiens) pulling the mesentery along with it.

Epidemiology

- It is the most common cause of intestinal obstruction in infancy and preschool children.
- Most common between 3 mo. and 6 yrs.
- Eighty per cent of cases occur before 24 mo. of age.
- Rare in neonates.
- Male to female ratio is 4:1.
- Correlation with prior or concurrent respiratory adenovirus infection had been noted.

Pathophysiology

- Most are ileocolic. The origin being the ileocaecal valve. Can also be caecocolic or ileal.
- The oedematous mucosa of the intussusceptum bleeds leading to bloody, mucoid stool.
- Strangulation of the bowel sets in after 24 hours leading eventually to intestinal gangrene.
- Swollen Peyer patches, lymphoid nodular hyperplasia, Merckel diverticulum, intestinal polyp, neurofibroma, and haemangioma had been found to be lead points in intussusceptions. Identifiable causes are more common in children more than 2 yrs. of age.

Clinical features

- Typically, there is sudden onset of severe paroxysmal colicky pain in a previously well child.
- Associated straining efforts with loud cries (the patient may be comfortable and plays between paroxysms).
- Vomiting occurs in the early phases and may become bilious in the later phase.

- Sixty per cent of infants pass stools containing red blood and mucus (the red currant jelly stools).
- Eventually weakness and fever can develop.
- Chronic intussusception in which symptoms exist in milder forms at recurrent intervals may occur with or after acute enteritis.
- Physical findings–in between paroxysms (within few hours of onset), patient may not look ill but may be dehydrated.
- In late presentation patient may be weak, irritable, dehydrated and febrile.
- Abdominal palpation in 70% of cases reveals a tender sausage-shaped mass usually in the right upper abdomen with its long axis cephalocaudal.
- On rectal examination, a mass may be felt in the rectum (especially in caecocolic intussusceptions), and the examining finger stained with bloody mucus.

Diagnosis

- Diagnosis is usually on clinical grounds.
- Confirmation by plain abdominal x-ray shows a density in the area of intussusception or air-fluid levels.
- Abdominal ultrasound detects a tubular mass in longitudinal view and a doughnut or target appearance on transverse images.
- Contrast enema examination will show a filling defect or cupping in the head of the contrast media.
- Serum electrolyte estimation to correct any derangement.

Differential diagnosis

- Difficult to differentiate from enterocolitis (bloody stools and abdominal pain. But the pain is less severe and less regular and the patient is ill between pains).
- Gastroenteritis–particularly dysenteric. Gastroenteritis can precede intussusceptions (note a change in nature of the illness especially the character of pain).
- Henoch-Schonlein purpura (there is associated joint symptoms and purpuric rash and the patient is ill between pains). But ultrasound is needed because intussusception can occur in this condition.

Treatment

- Reduction of an acute intussusception is an emergency procedure.
- This is done either with an air enema or hydrostatic reduction under radiologic or ultrasound guidance, if the history is short (<48 hrs.), it has a 70-90% success rate.
- Manual reduction is done at laparotomy.
- In prolonged intussusception with signs of shock, peritonitis, irritation, intestinal perforation or pneumatosis intestinalis, reduction should not be attempted.
- Recurrent intussusception occurs in approximately 5-8%. It is more common after hydrostatic reduction.

Complications/prognosis

- Shock with electrolyte imbalance, Peritonitis.
- Intestinal perforation. This can be secondary to hydrostatic reduction.
- Gangrene of the intestine.
- Untreated intussusceptions in infants are usually fatal.
- Most recover if reduction is done within 24 hrs.
- Intussusception caused by lesions like lymphosarcoma, Merckel diverticulum and polyp is not successfully treated by radiologic reduction.

Prevention/control

- Early detection and proper treatment of known causes of intussusception e.g. Henoch-Schonlein purpura, Merckel diverticulum.
- Immunization against respiratory adenovirus type C.
- Education of health workers, mothers/public, will help in early presentation and good prognosis.

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3.6 Abdominal pain in children

- Abdominal pain in children can be acute or recurrent.
- In acute abdominal pain the differential diagnoses are wide.
- Recurrent abdominal pain in childhood is described by Apley as three episodes of abdominal pain occurring during a period of three months severe enough to affect daily activities.

Epidemiology

- Recurrent abdominal pain affects 10-15% of children aged 5-14 years and 10-30% of all children.
- In more than 50% of children admitted for acute abdominal pain, no specific cause is found.
- Ten to twenty per cent of adolescents have symptoms suggestive of irritable bowel syndrome.
- In earlier studies, an organic cause was found in 5% of recurrent abdominal pain.
- More recent studies documented an organic cause in 33% of recurrent abdominal pain (this is attributed to advances in endoscopic, radiologic and biochemical investigations).

Pathophysiology

- Recurrent abdominal pain is classified into four subtypes according to ROME 111 criteria:
  - Functional abdominal pain (FAP);
  - Functional dyspepsia;
  - Irritable bowel syndrome (IBS);
  - Abdominal migraine.
- In IBS, physiologic or psychologic stress → altered gastrointestinal motility (cramping or spasm) and intensified sensation described as visceral hypersensitivity.
- FAP is viewed as a response to external factors (physical or psychologic stress) of inherent personality type (particularly anxious temperament) leading to abdominal pain.
- Abdominal migraine is described as a form of FAP in genetically predisposed children with a family history of migraine.

Clinical features–history

- Pain may be specific, well localized, intense ± radiation or may be vague and diffuse.
- Sharp intense localized pain is more likely to originate from the skin and muscle.
- Pain from the viscera and peritoneum is poorly localized and dull ± radiates.
- A change in bowel habit (diarrhoea, constipation with intermittent cramps) suggests IBS.
- A history of excessive ingestion of fruit juice, candy or gum sweetened with sorbitol.
- Clinical features suggestive of an organic cause;
  - Age <5 years, Urinary symptoms;
  - Vomiting–particularly if bilious, Bloody stool;
  - Nocturnal pain that wakes the child;
  - Pain away from umbilicus;
  - Constitutional problems (fever, weight loss, delayed growth, skin rashes, arthralgia);
  - Family history of peptic ulcer disease, migraine, epilepsy.

Clinical features–physical findings

- Check for abdominal distension, localized tenderness, rigidity, palpable mass, presence of bowel sound, faecal loading, enlarged organs ± constitutional signs (fever, jaundice, pallor, rash, respiratory distress, etc.).
- Absence of physical signs including rectal examination suggests functional pain.
- In boys, testicular examination is mandatory.

Diagnosis

- Priority in the assessment of children with recurrent abdominal pain is to exclude serious underlying organic pathology that will require surgical intervention or urgent medical treatment.

Investigations

- Urinalysis, urine m/c/s, CBC (exclude infective, inflammatory, allergic causes), hepatic and pancreatic enzymes in patients with

jaundice, abdominal ultrasound, colonoscopy in IBS (can precede IBD), endoscopy in nocturnal upper abdominal pain.
- The diagnosis of functional abdominal pain is made in the absence of structural and/or metabolic abnormalities.
- Elicit features known to be associated with recurrent abdominal pain e.g. psychological stress and anxiety. Typical adverse social factors include bereavement, altered peer relationships, school problems and illness of family members.

Differential diagnoses

- In acute abdominal pain age, site, type, duration, time of day, associations, presence of nausea, vomiting, urinary symptoms or changes in bowel habit are important factors in differential diagnosis.
- The commonest cause of acute pain in school-aged children is appendicitis.
- Organic causes of acute and recurrent abdominal pain include urinary tract infection, peptic ulcer disease, primary peritonitis, intussusceptions, sickle cell crises, renal colic, hernia, mesenteric adenitis, cholecystitis, testicular torsion, non-abdominal causes e.g. pneumonia.

Treatment

- Reassurance–many non-organic pains will respond to the acknowledgment of symptoms and reassurance regarding the lack of serious underlying organic disease.
- Psychological intervention–use therapeutic modalities like biofeedback, relaxation therapy, behavioural therapy, coping skill training, family therapy.
- Lifestyle and dietary management–healthy eating (plenty of fruit and vegetables), regular meals, plenty of fluids, exercise.
- Relief of stress–use stress management techniques or anxiolytics, decrease the intake of poorly absorbed sugars in fruit juices.
- Pharmacological therapy–avoid medication that can aggravate symptoms e.g. NSAIDs in functional dyspepsia.
    - Pizotifen in abdominal migraine;
    - H2 antagonists and proton pump inhibitors and prokinetics in functional dyspepsia;
    - Peppermint oil is useful in IBS;

- Laxatives in constipation or incomplete rectal evacuation.

Complications/prognosis

- Recurrent abdominal pain in childhood may be the antecedent of IBD in adulthood.
- An increased incidence of psychiatric disorders like anxiety disorders in adulthood is suggested by retrospective studies.
- Acceptance of the biopsychosocial model by patients and families is an important factor in the response to therapy.

Prevention/control

- Identify dietary triggers and avoid them e.g. fatty foods, spicy food and fizzy drinks.
- Avoid medications like NSAIDs, antispasmodics.
- Stop excessive sorbitol ingestion–a non-absorbable sugar in fruit juices.
- In children with an anxious temperament, family therapy will help prevent recurrence.
- Regular exercise helps to relieve constipation and bloating.

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3.7 Paralytic Ileus

Definition

- Failure of intestinal peristalsis without evidence of mechanical obstruction. It is a major cause of acquired intestinal obstruction.

Epidemiology

- It is common in postoperative patients especially abdominal surgery.
- Metabolic abnormalities–hypokalaemia, hypercalcaemia, hypermagnesaemia and acidosis are common causes in children.
- Drugs like opiates, vincristine and loperamide have a depressant effect on the intestines.

Pathogenesis

- Multifactorial and complex;
- The complex interaction between autonomic and CNS function, as well as local and regional subs, may alter the intestinal equilibrium, resulting in disorganized electrical activity and paralysis of intestinal segments.
- This lack of coordinated propulsive action leads to the accumulation of gas and fluids within the bowel.
- Postoperative items may be mediated via the activation of inhibitory spinal reflex arcs. Surgical stress response leads to systemic generation of endocrine and inflammatory mediators that promote the development of items.

Clinical features

- Increasing abdominal distension, vomiting ± abdominal pain, failure to pass stool or flatus, minimal or absent bowel sound.
- Plain abdominal X-ray will show increased air in the small bowel and multiple air-fluid levels.
- CT scan–differentiate the ileus from the mechanical obstruction.

Diagnosis

- The diagnosis of paralytic ileus is made in the presence of the clinical symptoms and signs of intestinal obstruction without mechanical obstruction.

Differential diagnosis

- Mechanical causes of intestinal obstruction–late in presentation with absent sound.

Treatment

- Stop enteral feeding.
- Gastric decompression with a nasogastric tube–to avoid vomiting with the risk of aspiration pneumonia and improve intestinal circulation.
- Withdrawal of any antimotility anticholinergic drugs.
- Replace fluid and electrolytes by the intravenous route.
- Correct the underlying abnormality.
- Drugs–metoclopramide or erythromycin (prokinetic agents).
- Peripherally acting mu-opioid receptor antagonists e.g. methylnaltrexone and alvimopan.

Complications/Prognosis

- Intestinal ischaemia leading to perforation.
- Compartment syndrome (abdominal distension with intra-abdominal pressure >15 mmHg with at least 3 of the following–oliguria or anuria, respiratory decompensation, decreased thoracic compliance with $\uparrow CO_2$ or $\downarrow PaO_2/FIO_2$), hypotension or shock, metabolic acidosis.
- Fluid and electrolyte imbalances.

Prevention

- High level of suspicion in ill patients, patients with gastroenteritis, post OP patients.
- Replacement of on-going loss in children with vomiting and/or diarrhoea.

- Judicious use of anti-motility drugs (especially in post OP patients).

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3.8 Constipation

- Constipation has varied definitions. It is simply infrequent (<3/week), difficult (manual manipulation), painful or incomplete (inadequate) evacuation of hard stool.
- It is a symptom, not a disease. It is classified as:
- Primary (due to disordered regulation of colonic and anorectal neuromuscular and brain-gut neuroenteric functions);
- Secondary (secondary to other conditions e.g. diet, drugs, endocrine, metabolic, neurological, and primary diseases of the colon).

Epidemiology

- It is seen in 3-5% of all paediatric visits and 25% of referrals to the paediatric gastroenterologist, prevalent in children and the elderly.
- Ninety per cent of cases are functional (psychological or psychosomatic causes), and 10% are due to physical (anatomic) or physiological causes (hormonal or other body chemistry).
- Common at the time of toilet training and during the start of school.

Pathophysiology

- Can arise from defects either in the filling or emptying of the rectum.
- Defects in filling lead to colonic stasis leading to excessive drying of stool and a failure to initiate reflexes from the rectum that normally trigger evacuation.
- Lesions involving rectal muscles, sacral spinal cord/fibres, abdominal or pelvic floor muscles, anal sphincter relaxation lead to defects in the defecation reflex arc and so the emptying of the rectum.

Clinical features–history

- Confirm constipation–ask for consistency, frequency, discomfort/ pain on defecation.
- Age at onset–early history of the delayed passage of meconium, constipation in the neonatal period (may indicate anorectal malformation, Hirschsprung disease and hypothyroidism), onset after infancy indicates functional constipation.

- Stool pattern–large diameter stool (functional constipation), small pellets stool.
- Associated symptoms–pain on defecation, soiling (encopresis), haematochezia, abdominal pain, vomiting.
- Diet history–fibre, fluid content, prior medication (e.g. opiates can cause constipation).
- Psychosocial–difficulties with toilet training, the birth of a sibling, other stressors.
- Stool-withholding behaviour: crouching, dancing or walking on tiptoes, crying out in anticipation of pain, hiding quietly, squeezing buttocks together, clinging to an inanimate object, all indicate functional constipation.

Physical examination

- Abdominal distension with a faecal mass in the left lower quadrant in 40% of cases.
- Lumbosacral region–myelodysplasia, sacral deformities e.g. pilonidal dimple.
- Perianal examination–ectopic placement of anus, perianal infections e.g. candida, fissures, trauma (sexual abuse), perianal sensitivity (anal wink).
- Neurological examination–abnormalities of the lower limbs e.g. equine/calcaneo deformities, muscular tone and deep tendon reflexes.
- Rectal digital examination–sphincteric tone, narrowing or dilation of rectal vault (narrowing indicates an empty rectum while dilation indicates accumulation of faeces), stool consistency. An empty rectum in the presence of a palpable faecal abdominal mass is suggestive of Hirschsprung disease.

Diagnosis

- A good history and examination will establish the presence of constipation in the majority of patients.
- In obese or uncooperative patients when abdominal examination is not reliable, plain abdominal x-ray will show faecal impaction ± dilated colon.
- If the history and examination suggest an organic or physiological cause, investigations include;
- Lumbosacral spinal x-ray,

- Motility studies to identify underlying myopathy or neuropathic bowel abnormalities,
- Barium enema to identify structural abnormalities,
- Rectal motility studies for the pattern or paradoxical contraction of the external anal sphincter.
- MRI for intraspinal lesions,
- Thyroid function test, serum calcium indicated in functional refractory cases.

Differential Diagnosis

- Non-functional constipation could be secondary to:
- Anal disorders–imperforate anus, anterior displacement of the anus, perianal fissure, anal stenosis, anal trauma (sexual abuse).
- Colonic strictures–primary or secondary.
- Pelvic masses–neuroblastoma, pre-sacral teratoma, rectal duplication cyst, ovarian tumour and haematocolpos.
- Endocrine/metabolic conditions–hypothyroidism, hypokalaemia, hypercalcaemia, hyperparathyroidism, diabetes mellitus, uraemia, cystic fibrosis.
- Neurogenic conditions–hypotonia (Down syndrome, Prune-belly syndrome), cerebral palsy, spinal cord abnormalities (spina bifida, spinal tumours).
- Neuromuscular conditions–aganglionosis (Hirschsprung-congenital, Chagas-acquired).
- Drugs–antacids, anticholinergics, antidepressants, opiates, phenobarbitones, sympathomimetics.

Treatment

- Education–explain the evacuation mechanism.
- If soiling is present, explain to the care giver that it is not willful or deviant behaviour.
- If disimpaction is necessary (the presence of a large and hard mass in the abdomen or a dilated vault filled with stool on rectal examination + history of overflow incontinence), use either
  - Polyethylene glycol (PEG) 3350 at 1-1.5 g/kg/day x 3 days (maximum dose 100 g/day), or
  - Daily enema x 6 days (as effective as PEG 3350 but less well tolerated), or

  - High-dose mineral oil (note: digital disimpaction is not recommended).
- Maintenance for PEG 3350–0.4-1 g/kg/day.
- Behavioural/Dietary modifications; increase the fibre content of the diet gradually.
  - Drink plenty of water, Exercise regularly, Discontinue any constipation-causing drugs;
  - Allow enough time for the bowel movement, Use laxatives–PEG 3350.

Complication/Prognosis

- Soiling leads to low self-esteem, social isolation and family disruption.
- Recurrent abdominal pain, blood streaks on stool, excessive flatus, anorexia.
- Pelvic floor dysynergia in children with stool withholding can affect urinary voiding dynamics and predispose the child to enuresis or urinary tract infection.
- Functional constipation has an excellent prognosis with education, disimpaction and behavioural modification.
- Others resolve/improve with adequate management of the primary condition.

Prevention/Control

- Good timing of toilet training and make training fun.
- Enough water and fibre in the diet. Encourage active play to increase bowel activity.
- Proper sitting (sitting up straight) with a footstool to support the feet in small children.
- Have regular and enough time for sitting to avoid feeling rushed.
- The reason for stool withholding should be sought and treated.
- Recognition of causes of non-functional constipation and proper treatment.

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3.9 Malabsorption

- Malabsorption disorders constitute a broad spectrum of diseases with multiple etiologies and varied clinical manifestations.
- There is diminished intestinal absorption of one or more dietary nutrients that results from impaired digestion (intraluminal defect) and/or impaired absorption (mucosal defects).
- This can be categorized into;
  - Generalized e.g. food-induced enteropathy, congenital bowel mucosal defect, protein-losing enteropathy, infection-induced enteropathy.
  - Specific e.g. carbohydrate malabsorption, fat malabsorption, amino acid malabsorption.

Epidemiology

- The prevalence of various types of malabsorption disorders varies in different racial, ethnic and geographic areas.
- In the United States of America coeliac disease, common in females, is the most common type of malabsorption disorder (1:300-1:80 in children) followed by cystic fibrosis and acquired milk protein allergies.
- Congenital sucrose-isomaltase deficiency: in Canadian Eskimos and natives of Greenland.
- Adult-onset lactase deficiency (appears after 6-8 yrs.) is most common in persons of Asian, African, or Mediterranean descent.
- Autoimmune enteropathy is an x-linked disorder seen only in males in familial cases.
- Exocrine pancreatic disease is common in tropical Africa.
- Fructose malabsorption is common in African Americans.

Pathophysiology

- Digestive enzyme deficiencies can be primary (congenital) or secondary (acquired) e.g. monosaccharidoses, lipase deficiency.
- Acquired can result from intestinal infections or bowel resection → impaired digestion or absorption.
- Cholestatic liver disease results in fat and fat-soluble vitamin malabsorption due to the non-availability of bile acid in the intestine.

- Bacterial overgrowth in the small bowel, seen in immunodeficiency, the short bowel, the diverticulum, and diabetes mellitus, leads to ineffective processing of dietary fat and steatorrhoea due to bacterial deconjugation of bile salts.
- Loss of more than 50% of the small bowel can result in symptoms of generalized malabsorption disorder or specific nutrient deficiency, depending on the region of bowel resected, due to the loss of absorptive surfaces.
- In protein energy malnutrition and coeliac disease, the intestinal structure is affected (villous atrophy/stunting) and this in turn affects nutrient digestion and absorption.
- Exocrine pancreatic function is impaired in malnutrition and cystic fibrosis → fat and fat-soluble vitamin malabsorption.
- Lymphatic leakage or obstruction e.g. intestinal lymphangiectasia leads to loss of nutrients absorbed through the lymphatics.

Clinical features

- Generally: failure to thrive or weight loss, diarrhoea, vomiting, irritability, anorexia, foul stools, abdominal pain, rectal prolapse, excessive gas, bulky greasy stools that float.
- Examination: muscle wasting, abdominal distension, low weight and height $<25^{th}$ percentile.
- Other specific features that may be associated depend on the aetiology e.g. stupor or neurologic dysfunction in bacterial overgrowth due to D-lactic acidosis, oedema in protein energy malnutrition.

Diagnosis

- Detailed dietary history, age of onset, number and character of stools, relation to dietary intake, growth parameters (a normal growth curve can exclude chronic severe malabsorption).
- Family history to exclude inheritable causes e.g. autoimmune enteropathy.
- Stool analysis and microscopy–volume, appearance, blood, leukocytes, ova of parasites, giardia lamblia.
- Fat stain (free fatty acid or split fat poor absorption, neutral or large droplets–poor digestion), pH and reducing substances (carbohydrate malabsorption).

- Stool α1-antitrypsin measurement (screening test for protein-losing enteropathy).
- Complete blood count–anaemia in B12, folic acid, iron deficiencies, neutropenia in Schwachman syndrome, lymphopenia in lymphangiectasia.
- Serum protein–decrease albumin in protein-losing enteropathy.
- Breathe Hydrogen test–a rise of 20 ppm above baseline is positive (after an oral load of 1-2 g/kg of suspected sugar that is not absorbed).
- Abdominal ultrasound–gall bladder, liver, pancreas, adenopathy.
- Oesophago-gastro-duodenoscopy–biopsies, duodenal fluid aspirate (evaluate bile acid level). From the biopsy–autoimmune gastritis, H. pylori infection. Inflammatory loss of villi in coeliac disease, stunting of villi in chronic malnutrition, analyze for mucosal disaccharidase deficiencies.
- Sweat test for cystic fibrosis.

Differential diagnosis

- Other causes of failure to thrive in infants e.g. congenital immunodeficiency (presents with recurrent infections in addition).
- Irritable bowel syndrome–encompasses chronic nonspecific diarrhoea ("toddler diarrhoea"), and functional abdominal pain.
- Sorbitol and fructose excess (seen in the excessive consumption of fruit juice), inflammatory bowel disease (the altered host's immune response to bacterial flora).

Treatment

- Two basic principles underlie the treatment (1) correction of the nutritional deficiency, and (2) when possible, treatment of the causative disease.

Nutritional support;

- Supplementation of various minerals e.g. calcium, magnesium, iron and vitamins.
- Caloric and protein replacement.
- Medium-chain triglycerides as fat substitute (do not require micelle formation for absorption and transport is portal not lymphatic).
- Parenteral nutrition in severe intestinal disease e.g. massive resection and excessive regional enteritis.

Treatment of causative diseases;

- A gluten-free diet in coeliac disease.
- A lactose-free diet in lactase deficiency.
- Protease and lipase supplements for pancreatic insufficiency.
- Antibiotics for bacterial overgrowth.
- Corticosteroids, anti-inflammatory agents e.g. mesalamine to treat regional enteritis.

Complications/Prognosis

- If not treated early, it leads to lassitude, stunted growth.
- Untreated coeliac disease may lead to bowel adenocarcinoma or lymphoma.
- Vitamin or calcium malabsorption can lead to rickets with bone deformities.
- Early detection and treatment of treatable causes have a good prognosis.
- Cholestatic liver diseases with chronic liver disease has a poor prognosis. Liver transplantation when available has a 77% five-year survival rate.
- Cystic fibrosis: a multisystemic life-limiting disorder, with median cumulative survival of 35 years.

Prevention/control

- Prevention of malnutrition through education and improvement in the standard of living.
- In coeliac disease, exclusive breastfeeding with the introduction of gluten at the age of 4-7 months while still breastfeeding has been noted to reduce the risk of developing gut sensitivity to gluten in susceptible infants.

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3.10 Gastroesophageal Reflux

Definition

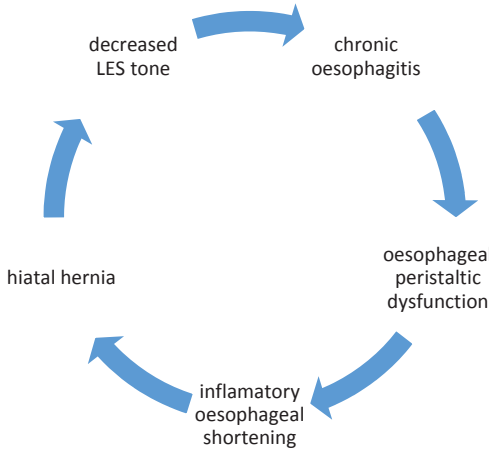
- Gastroesophageal reflux (GER) is the retrograde return of gastric contents across the lower oesophageal sphincter into the oesophagus.
- It is the most common oesophageal disorder in children.
- It can be passive reflux (regurgitation) or forceful reflux (vomiting). Functional or mild reflux means endoscopy-negative reflux.
- When it affects the quality of life, it is termed gastroesophageal reflux disease (GERD).

Epidemiology

- GER affects approximately 50% of infants less than 3 mo. of age.
- It peaks at 4 mo. and decreases to 5-10% at 1 yr.
- The physiologic regurgitation of normal infants is a self-limited effortless postprandial regurgitation which resolves by 12-24 mo. of age.
- Pathologic regurgitation (GERD) is more frequent or persistent episodes of regurgitation leading to oesophagitis or oesophageal symptoms and/or respiratory sequelae.

Pathophysiology

- The lower oesophageal sphincter (LES), the crura of the diaphragm at the gastroesophageal junction (GEJ), the valve-like functions of the GEJ anatomy form the anti-reflux barrier.
- Insufficient LES tone, abnormal frequency of LES relaxation and hiatal herniation increase the frequency of reflux episodes.
- Intra-abdominal pressure is exacerbated by straining or respiratory efforts. Increased gastric pressure → vasovagal reflex, which → transient LES relaxation.
- The duration of reflux episodes is increased by lack of swallowing (during sleep) and by defective oesophageal peristalsis.
- Oesophageal manifestation is determined by the frequency and duration of reflux episodes, the causticity of the refluxate, and the susceptibility of the oesophagus to damage.
- A vicious cycle



Clinical features

- Infant reflux starts a few months after birth, peaks at 4 mo. and resolves by 12-24 mo. Most are self-limited physiologic/functional regurgitations of feeds.
- In infants with frequent regurgitation and associated irritability, choking, gagging, feeding aversion, and arching, indicate oesophagitis. These are usually associated with inadequate weight gain.
- In older children, there may be abdominal/chest pain, and occasionally neck contortions (arching, turning of the head)–designated as Sandifer syndrome.
- Patients may present with respiratory symptoms in infancy–obstructive apnoea, stridor, otitis media, sinusitis, lymphoid hyperplasia, hoarseness, laryngeal oedema.
- In older children, asthma, laryngitis and sinusitis are possible presenting features.
- GER–induced respiratory symptoms can result from the direct aspiration of oesophageal contents or indirect vagally-mediated reflex from oesophageal irritation.

Diagnosis

- Standardized questionnaires are used as an initial tool for diagnosis. The Infant Gastro-oesophageal Reflux Questionnaire (I-GERQ) permits quantitative scores to be evaluated.

- Oesophageal pH monitoring of the distal oesophagus provides quantitative documentation of acidic reflux episodes.
- The intraluminal impedance test (done during an endoscopy) documents non-acid reflux in children with respiratory symptoms.
- An endoscopy allows for the diagnosis of erosive oesophagitis and complications e.g. strictures, Barrett oesophagus.
- Biopsies can diagnose histologic reflux in the absence of erosion.
- Oesophageal manometry evaluates dysmotility.
- In older children, Empirical antireflux therapy–a time-limited trial of high-dose proton pump inhibitors.
- Failure to respond to such treatment mandates formal diagnostic evaluation.

Differential diagnoses

- Milk and food allergies e.g. allergic eosinophilic oesophagitis. This may also present with respiratory symptoms.
- Pyloric stenosis: presents earlier (1^{st} or 2^{nd} week) and usually has a palpable pyloric mass.
- Intestinal obstruction especially malrotation with intermittent volvulus.
- Inborn errors of metabolism. Screening in the neonatal period detects this.
- Increased intracranial pressure, infections, and bulimia.

Treatment

- Thickening of feeds with rice cereal and weight reduction for obese patients.
- Positioning–upright carried position, prone position when patient is awake and observed, for older children elevation of the head of the bed.
- Pharmacotherapy–this is directed at ameliorating the acidity of gastric content or at promoting their arboreal movement.
- Antacids provide transient relief of symptoms.
- Histamine-2 receptor antagonists–anti-secretory agents: cimetidine, ranitidine, nizatidine.
- Proton pump inhibitors (PPIs). They provide the most potent antireflux effect e.g. omeprazole, lansoprazole, esomeprazole.

- Prokinetic agents: increase LES pressure, some improve gastric emptying or oesophageal clearance: clopromide, bethanechol and erythromycin (motilin receptor agonist).
- Surgery–usually fundoplication is effective for intractable GERD in children.
- Complications of this surgery ("too tight" or "too loose" wrap) shift the practice to long-term pharmacotherapy.

Complications/prognosis

- Prolonged and severe oesophagitis leads to formation of strictures.
- Metaplastic transformation of oesophageal mucosa to columnar epithelium (Barrett oesophagus). Adenocarcinoma. The last two occur in prolonged severe reflux and are uncommon in childhood.
- Failure to thrive is secondary to severe oesophagitis and regurgitation.
- Aspiration pneumonia.
- Refractory otolaryngologic and respiratory complaints including laryngitis, hoarseness, infections, allergies, postnasal drip and asthma (GERD occurs in ≈ 50% of these children).
- Apnoea especially in infants.

Prevention/control

- Recurrence of healed oesophagitis can be prevented by diet/lifestyle modification e.g. avoidance of food triggers, eating small frequent meals, elevation of the head of the bed.

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SECTION 4:

CARDIOLOGY

MANYIKE, C.

4.1 Foetal and Neonatal circulation

Foetal circulation

- The right and left ventricles exist in a parallel circuit.
- The placenta provides for gas and metabolites exchange.
- The lungs are vasoconstricted.
- The ductus venosus, foramen ovale and the ductus arteriosus maintain the parallel circuit.
- Oxygenated blood from the placenta (PO_2; 30-35 mmHg) gets to the foetus via the umbilical vein.
- About 50% of the umbilical venous blood enters the liver while the rest flows through the ductus venosus and joins the poorly oxygenated inferior vena cava blood from the lower part of the foetal body.
- This mixture with a PO_2 of about 26-28 mmHg enters the right atrium and is preferentially directed across the foramen ovale to the left atrium.
- The blood then flows into the left ventricle and is ejected into the ascending aorta, supplying the brain and upper extremities.
- Then the foetal superior vena cava blood (PO_2; 12-14 mmHg) enters the right atrium and preferentially traverses the tricuspid valve to the right ventricle.
- The blood is ejected into the pulmonary artery from the right ventricle.
- About 90% of this blood (PO_2; 18-22 mmHg) flows through the patent ductus arteriosus to the descending aorta to perfuse the lower extremities.

- About 65% of the descending aortic blood flow returns to the placenta.
- The remaining 35% perfuses the foetal organs and tissues.

Neonatal circulation

The transition from foetal to neonatal circulation entails:

- Rapid decrease in pulmonary vascular resistance due to mechanical expansion of the lungs and increase in the arterial PO_2 at birth.
- Increase in systemic vascular resistance because of the removal of the low resistance placental circulation.
- Establishment of the adult series circuit with the output from the right ventricle flowing into the pulmonary circulation.
- The shunt through the ductus arteriosus becomes left to right because of the increase in systemic vascular resistance.
- The high arterial PO_2 of the blood flowing through the ductus constricts the ductus arteriosus leading to its closure forming ligamentum arteriosus.
- The increased volume of pulmonary venous blood returning to the left atrium increases the left atrial volume and pressure sufficiently to close the foramen ovale.
- Removal of the placenta from the circulation also results in the closure of the ductus venosus.
- The left ventricle is now coupled to the high resistance systemic circulation and its wall thickness and mass begin to increase.
- The right ventricle on the other hand is also coupled to the low resistance pulmonary circulation, and its wall thickness and mass decrease slightly.

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4.2 Pulmonary Hypertension

Epidemiology

- Pulmonary hypertension occurs at any age, but in the older age group females outnumber males in a ratio of 1.7:1. In younger patients there is equal representation of both genders.

Pathophysiology

- Hypercoagulable states or immunologic disorder plays a role in some patients.
- It could be genetic with autosomal dominant familial primary pulmonary hypertension being preponderant in females.
- This involves mutation of the gene on chromosome 2q33.
- Other potentially disease-causing genes including chromosomes 2q31 and 12q13 have been identified.
- Other predisposing factors are viral infection (HHV8), human herpes virus 8; diet pills (fenfluramine) have been implicated.
- Pulmonary hypertension is associated with precapillary obstruction of the pulmonary vascular bed as a result of hyperplasia of the muscular and elastic tissues and a thickened intima of the small pulmonary arteries and arterioles.
- Atherosclerotic changes may be found in the larger pulmonary arteries.
- In children, veno-occlusive disease may account for some cases of primary pulmonary hypertension.
- Chronic pulmonary parenchymal disease, persistent obstruction of the upper airway, congenital cardiac malformations, recurrent pulmonary emboli, alveolar capillary dysplasia, liver disease, autoimmune disease and moya-moya disease are some other causes.
- Pulmonary hypertension places an afterload burden on the right ventricle which results in right ventricular hypertrophy.
- Dilatation of the pulmonary artery is present and pulmonary valve insufficiency may occur.
- The later stages of the disease are characterized by dilatation of the right ventricle, tricuspid insufficiency and decrease in cardiac output.
- Arrhythmias, syncope and sudden death are common. The World Health Organization has classified pulmonary hypertension into groups I-V.

Clinical features

History

- The characteristic complaints are exercise intolerance, fatiguability, occasional precordial chest pain, dizziness, syncope or headaches.

Physical findings

- There may be peripheral cyanosis.
- The patient may have cold extremities and a grey appearance associated with low cardiac output.
- The jugular venous pressure is elevated if right heart failure has occurred. There will be hepatomegaly and oedema.
- The heart is moderately enlarged and a right ventricular heave may be noted.
- The first heart sound is often followed by an ejection click as a result of the dilated pulmonary artery. The 2^{nd} heart sound is narrowly split, loud and sometimes booming in quality. It is frequently palpable at the upper left sternal border.
- A presystolic gallop rhythm may be audible at the lower left sternal border. The systolic murmur is soft and short and is sometimes followed by a blowing decrescendo diastolic murmur caused by pulmonary insufficiency.
- In later stages, a holosystolic murmur of tricuspid insufficiency is appreciated at the lower left sternal border.

Diagnosis

- Chest X-ray shows a prominent pulmonary artery and right ventricle. The pulmonary vascularity in the hilar area is prominent while that in the periphery is decreased.
- The electrocardiogram shows right ventricular hypertrophy and a spiked P-wave.
- Cardiac catheterization shows a normal pulmonary capillary wedge pressure.

Differential diagnosis

- Pulmonary venous stenosis and mitral stenosis are important in differential diagnosis.

Treatment

- Oral nifedipine is useful as well as a continuous infusion of prostacyclin (prostaglandin I_2).
- Other medications are nitric oxide, bosentan and sildenafil.
- Anticoagulation may be useful in those who have had pulmonary thromboembolism.
- Definitive therapy is heart-lung or lung transplantation.

Complication/prognosis

- Lethal arrhythmias are a serious complication. Patients with primary pulmonary hypertension diagnosed in infancy often have rapid progression and high mortality.

Prevention/control

- Early detection and treatment.

Counselling

- Let the patient know about primary pulmonary hypertension and the fact that it can progress rapidly with high mortality.

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4.3 Congenital Heart Diseases–Cyanotic

- These are congenital heart lesions characterized by cyanosis (bluish discoloration) due to desaturation at various levels.

Epidemiology

- Cyanotic heart diseases include Tetralogy of Fallot (TOF), Transposition of the Great Arteries (TGA), Total Anomalous Pulmonary Venous Return, Ebstein Anomaly of the Tricuspid Valve, Tricuspid Atresia, Truncus Arteriosus, Single Ventricle, Hypoplastic Left Heart Syndrome and Pulmonary Atresia.
- These lesions can exist in combination with other lesions e.g. TGA with Ventricular septal defect or PDA and some of them are Duct dependent e.g. TGA, without which it will be incompatible with life.
- They affect both males and females but some more often occur in males e.g. TOF and TGA.

Pathophysiology

- The cause of congenital cyanotic heart diseases is multifactorial.

Transposition of the Great Arteries is more common in children of diabetic mothers.

- In simple (isolated) TGA, the aorta originates from the right ventricle and the pulmonary artery from the left ventricle; whereas, in corrected TGA, the ventricles are inverted with the right atrium connected to the left ventricle and the left atrium to the right ventricle.
- The great arteries are transposed with the aorta arising from the right ventricle and the pulmonary artery from the left ventricle.
- Hence, there is double inversion–atrioventricular and ventriculoarterial.
- Desaturated blood from the right atrium reaches the transposed left ventricle, flows into the transposed pulmonary artery and then into the lungs, while oxygenated blood from the left atrium reaches the transposed right ventricle and gets into systemic circulation through the transposed aorta.
- There are always other defects e.g. VSD associated with corrected TGA.

Tetralogy of Fallot

- Comprises pulmonary stenosis, VSD, overriding aorta and right ventricular hypertrophy.
- It is associated with polycythaemia and hypercyanotic spells.

Tricuspid atresia

- A situation in which no outlet from the right atrium into the right ventricle exists and right and left communication is through an ASD or PFO.
- There may be a PDA and VSD to aid mixing.

Others:

- ***Ebstein anomaly*** of the tricuspid valve involves downward displacement of an abnormal tricuspid valve into the right ventricle.
- ***Double outlet right ventricle*** is a situation in which both the aorta and the pulmonary artery arise from the right ventricle. The only outlet to the left ventricle is a VSD.
- ***Total anomalous pulmonary venous*** return involves the emptying of the pulmonary veins into the right side of the heart–right atrium, coronary sinus or superior vena cava.
- ***Truncus arteriosus*** has a single arterial trunk arising from the heart and supplying the systemic, pulmonary and coronary circulations.
- The truncus overrides a VSD and receives blood from both ventricles. The truncus may have 2 to 6 valve cusps.
- ***Single ventricle*** is characterized by both atria emptying through a common atrioventricular valve or through two separate valves into a single ventricular chamber.
- ***Hypoplastic left heart*** syndrome is characterized by underdevelopment of the left side of the heart involving atresia of the aortic and mitral valves and hypoplasia of the ascending aorta.
- The right ventricle maintains both the pulmonary and systemic circulations.
- The rudimentary left ventricle communicates with the right side of the heart through an ASD or a PFO.

Clinical features–***history***

- There is cyanosis, dyspnoea, and some present with failure to thrive.

Clinical feature-*physical findings*

- Cyanosis is the hallmark of these lesions. Conjunctival hyperaemia is common with TOF.
- There is also finger clubbing and FTT.
- There may be systolic and diastolic murmurs and tachycardia and tachypnoea.
- Some are prone to heart failure e.g. TAPVR and Truncus Arteriosus.

Diagnosis

- Chest X-ray: some have a characteristic X-ray appearance e.g. TOF shows a boot-shaped heart while TGA shows an egg-on-side cardiac silhouette.
- The Ebstein anomaly of the tricuspid valve shows box-shaped cardiomegaly, TAPVR has a "snowman" appearance.
- The lung field could be oligaemic or plethoric depending on whether or not there is pulmonary stenosis.
- ECG shows which side of the heart is dominant; which chamber is enlarged and whether there are arrhythmias.
- Echocardiography is used to make a definitive diagnosis. It shows the structural anomalies and the type of lesions.
- Cardiac catheterization determines the saturation and pressures in each chamber.

Differential diagnosis

- Any cardiac lesion could be a differential diagnosis of the other until a 2 D-echo is done.

Treatment

- This could be medical or surgical.

Medical treatment involves giving prostaglandin in duct dependent lesions like TGA;

- Propranolol, phenylephrine, morphine, oxygen, $NaHCO_3$, Dextrose containing fluid, as well as adopting the knee-chest position in hypercyanotic spells in TOF;
- Also, erythropheresis for severe polycythaemia in TOF.

- Heart failure (e.g. in TAPVR) if present will be managed.

Surgery is the definitive treatment of cyanotic heart lesions, e.g.

- Blalock-Taussig shunt–anastomosis between subclavian and pulmonary arteries.
- Rashkind's balloon atrial septostomy and Jantene (arterial switch) operations for simple TGA and the double-switch procedure for corrected TGA, etc.
- Surgeries, however, are not without their complications.

Complications/prognosis

- Failure to thrive, recurrent chest infection, infective endocarditis and cardiac failure are some of the complications.
- Heart block and other arrhythmias can follow cardiac surgery.
- Prognosis in untreated cases is poor.

Prevention/control

- Prevention is through prenatal diagnosis with consequent termination of pregnancy in severe cases.
- Control lies in the careful medical and surgical management of cases of congenital cyanotic heart lesions and their sequalae.

Counselling

- This involves both prenatal and postnatal counselling.
- A mother who is pregnant with a foetus that has serious congenital heart lesion should, along with the husband, be counselled on the option of having the pregnancy terminated.
- Those with babies who have cyanotic heart disease will be counselled on the nature of the disease, the natural history and the likely outcome.

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4.4 Congenital Heart Disease–Acyanotic

- These are congenital heart diseases that are not associated with cyanosis, but they are potentially cyanotic, especially from the 2nd decade of life in untreated patients when Eisenmenger syndrome develops.

Epidemiology

- Congenital acyanotic heart diseases include atrial septal defect (ASD), ventricular septal defect (VSD) and atrioventricular septal defect (AV canal or endocardial cushion defect).
- Others are patent ductus arteriosus (PDA), coarctation of the aorta, partial anomalous pulmonary venous return, and aorticopulmonary window defect.
- These are the major acyanotic heart diseases. They do not have equal sex predilection.
- Atrial septal defect occurs more in girls than boys in a ratio of 3:1, while coarctation occurs more in boys than girls in a ratio of 2:1.

Pathophysiology

- These are left to right shunts with multifactorial causes. PDA is a component of the rubella syndrome while endocardial cushion defect is found mainly in Downs patients.
- ***PDA*** is characterised by the shunting of blood from the proximal part of the descending aorta into the patent ductus. There may be paradoxical emboli.
- ***AV* septal defect** involves atrial septal defect and ventricular septal defect in close proximity resulting in an abnormal AV valve with consequent mitral or occasionally tricuspid insufficiency.
- ***ASD*** involves a defect in the atrial septum with a shunt from the left atrium to the right atrium. It is found in Holt-Oram syndrome (hypoplastic or absent radii, 1st degree heart block, ASD) as autosomal dominant inheritance while the majority are sporadic.
- ***VSD*** is a defect in the ventricular septum, allowing blood to shunt from the left to the right ventricle. It is the most common cardiac malformation accounting for 25% of congenital heart disease.
- ***Partial Anomalous Pulmonary Venous Return*** involves some pulmonary veins returning anomalously to the superior or inferior

vena cava, right atrium or the coronary sinus to produce a left to right shunt.

- ***Coarctation of the aorta*** involves constriction of the aorta of varying degrees.
- It can occur at any point from the transverse arch to the iliac bifurcation, but 95% occur just below the origin of the left subclavian artery at the origin of the ductus arteriosus.
- In mild cases, there is a net left to right ductal shunting while in severe cases right ventricular blood is ejected through the ductus to supply the descending aorta.
- This results in differential cyanosis with the upper part of the body being pink and the lower part blue.
- ***Mitral valve prolapse*** occurs when one or both mitral leaflet/s especially the posterior leaflet bulges into the left atrium towards the end of systole.
- It is sporadic, more common in girls and may be inherited as an autosomal dominant trait with variable expression.
- ***Aorticopulmonary window defect*** involves a communication between the ascending aorta and the main pulmonary artery.
- ***Others*** are congenital mitral stenosis, mitral insufficiency and tricuspid regurgitation, pulmonary valve and aortic valve stenosis.
- They can occur in isolation or in combination with other cardiac diseases.

Clinical feature–*history*

- Mild cases are asymptomatic. Severe cases present with recurrent chest infections, easy fatiguability, exercise intolerance, failure to thrive and cardiac failure e.g. severe VSD.
- Patients with coarctation may complain of headache from hypertension, weakness and pain in the legs especially with exercise.
- Aortic stenosis presents with exercise intolerance, dizziness, syncope and sudden death.
- In pulmonary stenosis, there is exercise intolerance.
- Mitral prolapse presents with chest pain and palpitation.

Clinical feature–*physical findings*

- Some are asymptomatic. Some show features of heart failure and respiratory infections.

- ASD presents with an ejection systolic murmur and mid diastolic murmur due to increased flow across the pulmonary and tricuspid valves respectively. In ASD, the 2nd heart sound is split and fixed.
- VSD is characterised by a pansystolic murmur.
- PDA is characterised by a machinery murmur and a bounding pulse.
- In coarctation of the aorta, there is hypertension of the upper extremities and radial femoral delay. There are weak lower extremity pulses.
- Aorticopulmonary window defect presents with features of heart failure in infancy. There may be mild cyanosis.

Diagnosis

- Diagnosis of individual acyanotic heart disease is made using their distinguishing features.
- ECG, chest X-ray and 2D-echocardiography are all helpful in making a diagnosis.
- ECG may show evidence of chamber hypertrophy or arrhythmias.
- Chest X-ray may show normal lung fields, plethoric lung field in pulmonary oedema in cases like moderate to large VSDs or PDAs and cardiomegaly if there is heart failure.
- 2D-ECHO is used for a definitive diagnosis.

Differential diagnosis

- Any of the acyanotic heart diseases could be a differential of the other until a definitive diagnosis is made with 2D-echo.

Treatment

- This could be medical or surgery.
- ***Medical treatment*** involves treating chest infection in VSD, ASD and PDA and also cardiac failure.
- Hypertension in coarctation of the aorta is treated.
- Infective endocarditis prophylaxis especially in VSD is given.
- In severe coarctation of the aorta, a prostaglandin infusion is given to maintain the patency of the ductus.
- ***Surgery*** is the ultimate treatment for these conditions.

- It ranges from the closure of the shunt/defect, ligation to valve repair or replacement.

Complications/prognosis

- These are failure to thrive, recurrent chest infection, recurrent heart failure, and even sudden death in aortic stenosis.
- Coarctation may be complicated by a cerebrovascular accident.
- Prognosis is good in treated cases.

Prevention/control

- This is achieved by early diagnosis and treatment.

Counselling

- Parents and patients are educated about their disease, the natural history and outcome, if untreated.

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4.5 Infective Endocarditis

- Infective endocarditis is defined as an endovascular microbial infection of cardiovascular structures. Endocarditis in other words means valvulitis.

Epidemiology

- Endocarditis cuts across various age groups. It is rare in infants; however, in infants, it is as a result of congenital cardiac lesion and the use of indwelling catheters.
- In older children, it is as a result of congenital cardiac lesion and rheumatic heart disease, while in adolescents, it is as a result of congenital cardiac lesion, rheumatic heart disease and intravenous drug use.
- Prosthetic valves are also affected.
- Microorganisms implicated in infective endocarditis are bacteria, fungi and viruses.
- The leading bacterium in infective endocarditis is streptococcus viridans, followed by staphylococcus aureus.
- S. aureus attacks healthy cardiac tissues. Coagulase negative staphylococci are also important.
- Gram-negative organisms like enterococcus, pseudomonas, haemophilus, Neisseria species and fungi species (candida, histoplasma and Cryptococcus) are important and predispose to endocarditis in neonates, the immunocompromised and drug addicts.

Pathophysiology

- Endocarditis occurs where there is turbulent blood flow especially a shunt lesion.
- This causes endocardial damage with consequent aggregation of platelets and fibrin at the site to form vegetation.
- Bacteria and other microorganisms are deposited on the vegetation to set up another inflammatory reaction that attracts a further deposition of platelets and fibrin.
- The source of the bacteraemia could be skin sepsis or oral sepsis. Other sources are pyelonephritis, osteomyelitis, pneumonia; oral, gastrointestinal and urogenital manipulations.

Clinical feature–*history*

- The patient will complain of fever, headache, arthralgia, myalgia, malaise, anorexia, vomiting.

Clinical features–*physical findings*

- There may be weight loss, anaemia, splenomegaly, and signs of vasculitis, namely, Osler node, Janeway lesions and splinter haemorrhages.
- There may be a new murmur or a changing murmur.
- A cerebrovascular accident, brain abscess, meningismus, increase in intracranial pressure, altered sensorium, and heart failure may be seen in infective endocarditis.

Diagnosis

- Blood cultures, both aerobic and anaerobic are very important. A total of 3 to 6 blood culture samples are collected from different venepuncture sites within 24 hours. Blood culture is positive in 90% of the cases.
- Acute phase reactants–the erythrocyte sedimentation rate and leucocyte counts are elevated. There could be microscopic haematuria.
- 2D-Echocardiography including transoesophageal and transthoracic echocardiography is important in evaluating the heart for vegetation.
- Duke's criterion that is based on microbiologic, echocardiographic and pathologic criteria is used to make a diagnosis.

Differential diagnosis

- Sickle cell disorder and juvenile rheumatoid arthritis are the differentials.

Treatment

- Treatment is done using penicillin or cephalosporin or vancomycin in the case of penicillin allergy and aminoglycoside. A total of 4 to 6 weeks of treatment is required. Amphotericin B is used in fungal endocarditis.

Complications/prognosis

- Chronic debility, conduction disturbances, embolic strokes, aneurismal rupture and cardiac failure are the complications. Prognosis depends on early presentation and proper treatment in which it is good.

Prevention/control

- Good dental hygiene is the key to the prevention of infective endocarditis.
- Proper treatment of rheumatic fever and adequate prophylaxis of rheumatic heart disease, including those with either native or prosthetic valves are important.
- Proper prophylaxis of the rheumatic heart disease patient for dental, gastrointestinal and urogenital manipulation is absolutely necessary.
- A high index of suspicion is required in the diagnosis of infective endocarditis.

Counselling

- Patients and their parents should be educated about the morbidity and mortality of infective endocarditis and about the need for good dental hygiene.

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4.6 Myocarditis

- Myocarditis is the inflammation, necrosis or mycocytolysis of the myocardium. It could present alone or as part of a disease condition e.g. rheumatic fever.

Epidemiology

- The incidence of myocarditis in children is unknown, though there appears to be a male preponderance. It can present as an acute or fulminant or chronic condition.
- Major causes are adenovirus, coxsackieviruses B, and enteroviruses; others are influenza, cytomegalovirus, hepatitis, rubella, herpes simplex virus, varicella, mumps, HIV and respiratory syncytial virus.
- Other rare causes are bacterial, fungal, spirochaetal and protozoal infections.
- There are non-infectious causes like toxins (diphtheria), drugs (amphotericin B), autoimmune and hypersensitivity reactions and collagen vascular diseases like systemic lupus erythematosus.

Pathophysiology

- This depends on the host's immune system.
- However, there may be a fulminant inflammatory process characterized by cellular infiltrates, cell degeneration and necrosis, and subsequent fibrosis.
- In many patients, the disease may go unrecognised with spontaneous resolution or may progress to a chronic state resulting in dilated cardiomyopathy.

Clinical feature–*history*

- A high index of suspicion is required to make a diagnosis of acute myocarditis because the clinical features vary greatly.
- Initially there is a low-grade fever, lethargy, pallor, decreased appetite and abdominal pain.
- There may also be excessive sweating, palpitation, chest pain, rashes and exercise intolerance.
- Later in the course of the illness, respiratory distress, syncope and sudden cardiac arrest may occur.

Clinical feature–*physical findings*

- A neonate may initially have fever, severe heart failure, respiratory distress, cyanosis and distant heart sounds.
- Others are weak pulses, and tachycardia out of proportion to the fever, mitral insufficiency as a result of the dilatation of the valve annulus, a gallop rhythm, acidosis and shock.
- An older patient with acute myocarditis may initially present with acute congestive heart failure.

Diagnosis

- Chest X-ray, depending on the stage, may reveal cardiomegaly and evidence of pulmonary oedema.
- Electrocardiogram will show sinus tachycardia, reduced QRS complex voltage, and ST-segment and T-wave abnormalities and evidence of arrhythmias.
- Echocardiography demonstrates poor ventricular function, and often a pericardial effusion and mitral regurgitation.
- Myocarditis can be confirmed by endomyocardial biopsy.
- If positive, serum viral titres are helpful, negative titres do not vitiate the diagnosis.
- The sedimentation rate, leucocyte count, heart enzymes (creatine phosphokinase and lactate dehydrogenase) and brain natriuretic peptide may be elevated in acute or chronic myocarditis.
- Polymerase chain reaction (PCR) can identify specific viral RNA or DNA.

Differential diagnosis

- Diseases mimicking myocarditis are pericarditis, fibroelastosis of the endocardium, anomalous origin of the left coronary artery, hereditary mitochondrial defects, idiopathic dilated cardiomyopathy and carnitine deficiency.

Treatment

- The general principles of management include:
- ***Exercise restriction:*** Bed rest prevents an increase in viral replication and should be advocated. Exercise increases myocardial inflammation and necrosis with myocarditis and so it is

recommended that patients with myocarditis abstain from vigorous exercises for several months.

- ***Decongestive measures:*** Inotropic drugs–digoxin and diuretics, etc., are the prime drugs to bring about a dramatic improvement in decongestion.
- When oral therapy is possible, an after load reducing drug such as captopril–1-3 mg/kg/day every 8 hours or Enalapril–0.2 mg/kg/day divided every 12 hours should be given.
- Sodium nitroprusside has been used to regulate systemic resistance.
- More recently a phosphodiesterase inhibitor such as intravenous milrinone has been used in inotropy.
- Dopamine and epinephrine are also useful especially in those with poor cardiac output and systemic hypoperfusion. These drugs should be used with caution because of their arrhythmogenic properties in patients with myocarditis. Digoxin when used will be started with half the dose.
- ***Anticoagulation:*** Systemic anticoagulation may be required because inflamed endocardium may be predisposed to thrombosis.
- ***Arrhythmias:*** These should be treated vigorously and may require the use of intravenous amiodarone. In the presence of life-threatening ventricular arrhythmia an implantable cardioverter defibrillator or an implantable pace-maker is considered.
- ***Mechanical assistance:*** When myocarditis is refractory to standard medical therapy, intensive medical support and mechanical assistance like implantation of a left Ventricular Assist Device (LVAD).
- Aortic balloon pump and extracorporeal membrane oxygenation can be performed as a bridge to heart transplantation.
- ***Immunosuppressive therapy:*** Intravenous immunoglobulin in a dose of 2 mg/kg is recommended.
- Corticosteroid in a dose of 2 mg/kg and tapered to 0.3 mg/kg daily for a period of 3 months is recommended.
- The benefit of interferon has also been reported.
- ***Heart transplantation:*** This is done in myocarditis when other measures have failed.

Complication/prognosis

- The prognosis of symptomatic acute viral myocarditis in neonates is poor. Patients with lesser symptoms have a better prognosis, and complete resolution has been reported. The prognosis in older

patients who have progressed to chronic dilated cardiomyopathy is also poor without therapy.

Prevention/control

- This is achieved by using the appropriate vaccines e.g. mumps vaccine for endocardial fibroelastosis (EFE).

Counselling

- The need for vaccination and vigorous treatment of cases should be emphasised. The likely outcome of acute viral myocarditis should also be discussed.

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4.7 Pericarditis

- Pericarditis is inflammation of the pericardium with effusion into the pericardial sac.

Epidemiology

- Everybody is involved. The cause could be bacterial, including tuberculosis, viral and connective tissue conditions. It could be acute, subacute or chronic.

Pathophysiology

- It is as a result of inflammation of any cause and transudation into the pericardial sac.

Clinical features–*history*

- There is chest pain. Other complaints are fever, cough, dyspnoea, abdominal pain and vomiting.

Clinical features–*physical findings*

- Physical findings in pericarditis include neck vein distention, pericardial friction rub, narrow pulses, tachycardia, pulsus paradoxus and muffled heart sounds.

Diagnosis

- Chest x-ray shows an enlarged heart which may show the characteristic water-bottle appearance.
- 2D-Echo shows and measures fluid in the pericardial sac and evaluates other cardiac functions.
- There are ST elevation and T wave inversion with low QRS complexes.
- Full blood count, blood culture, serology/viral studies can reveal the cause.
- Analysis of pericardial aspirate is also important in diagnosis.

Differential diagnosis

- These include viral and acute benign pericarditis, purulent pericarditis, tuberculous pericarditis, acute rheumatic fever, juvenile rheumatoid arthritis and neoplastic disease.
- Others are uraemia, postpericardiotomy syndrome and constrictive pericarditis.

Treatment

- This depends on the cause and severity.
- Antibiotic, anti-tuberculous, anti-viral measures, steroids and non-steroidal anti-inflammatory agents can be used depending on the cause.
- Bed rest and pericardiocentesis depending on the degree of the effusion are important.
- Heart failure if present should be vigorously addressed.

Complications/prognosis

- This depends on the cause, early diagnosis and treatment.
- It could lead to constrictive pericarditis or death.
- Prognosis is good with early diagnosis and treatment.

Prevention and control

- This borders on early diagnosis and the treatment of predisposing conditions like pneumonia and tuberculosis.

Counselling

- This entails education of the masses on the causes and natural history of pericarditis and the necessary preventive measures like early diagnosis and treatment.

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4.8 Rheumatic Heart Disease

- Rheumatic heart disease is a sequalae of rheumatic fever.
- It involves various degrees of valvular injuries with the left sided valves–mitral and aortic—more involved than the right sided valves– tricuspid and pulmonary.

Epidemiology

- Rheumatic heart disease presents as regurgitation (incompetence) and/or stenosis of the above valves. The age incidence of rheumatic fever is 5 to 15 years.
- Regurgitation of the valves is more common and can present a few months after an attack of acute rheumatic fever while stenosis takes years to develop but can be seen in young children in developing countries because of the early onset of rheumatic fever.
- Rheumatic fever, hence rheumatic heart disease is associated with overcrowding and poor socioeconomic conditions.

Pathophysiology

- Rheumatic heart disease follows acute rheumatic fever which is caused by group A beta haemolytic streptococcus.
- This results from a cross reaction between the antibodies to the organism and cardiac tissues, with the valves more vulnerable resulting in valvulitis.
- The consequences are scarring and fibrosis leading to various degrees of shortening, thickening, rigidity, deformity, retraction and fusion of the valve cusps.
- The most common valve lesions are mitral regurgitation, mitral stenosis and aortic regurgitation. It is always mitral regurgitation and aortic regurgitation or stenosis.
- Aortic stenosis is not common in childhood and tricuspid valve involvement is very rare.
- Heart failure is the hallmark of rheumatic heart disease.

Clinical feature–*history*

- There may be a past history of pharyngitis.
- ***Mitral regurgitation***–easy fatiguability and shortness of breath.

- ***Mitral stenosis***–mild stenosis is asymptomatic, moderate stenosis causes shortness of breath on exertion and severe stenosis causes easy fatigue, shortness of breath at rest, palpitation, orthopnoea, paroxysmal nocturnal dyspnoea, cough and haemoptysis.
- ***Aortic regurgitation***–a child may remain asymptomatic for many years.
- Severe regurgitation presents with exercise intolerance, shortness of breath on exertion and chest pain.

Clinical feature–*physical findings*

- ***Mitral regurgitation***–there is hyperdynamic precordium; the apical impulse is displaced laterally and inferiorly.
- There are a blowing apical pansystolic murmur that radiates to the left axilla, a 3rd heart sound, atrial fibrillation and a mid-diastolic murmur.
- ***Mitral stenosis***–there is a low frequency mid-diastolic murmur at the apex, accentuated by exercise which is often accompanied by a loud 1st heart sound, atrial fibrillation and a diastolic opening snap.
- Severe cases present with signs of pulmonary hypertension.
- ***Aortic regurgitation***–there is a blowing decrescendo early diastolic murmur maximal at the mid to lower left border, which is loudest sitting forward with the breath held in expiration.
- The following are also present: hyperdynamic apex, the apical impulse is displaced laterally and inferiorly and wide pulse pressure.
- Collapsing pulses, visible pulsations in the suprasternal notch and neck vessels and a systolic murmur at the upper right sternal border.

Diagnosis

- Asymptomatic patients may have normal results.
- In severe and symptomatic patients, chest x-ray will show cardiomegaly and evidence of pulmonary oedema.
- ***In mitral regurgitation***, ECG shows left atrial enlargement and left ventricular hypertrophy; and signs of pulmonary hypertension.
- ***Mitral stenosis*** shows radiological and electrocardiographic evidence of left atrial enlargement. There is evidence of pulmonary oedema. ECG changes of right ventricular hypertrophy and right axis deviation are present when there is pulmonary hypertension.

- ***In aortic regurgitation***, there is ECG and chest X-ray evidence of left ventricular hypertrophy and cardiomegaly respectively. There may be evidence of ventricular ectopics on ECG.
- Echocardiography is very important in the diagnosis of rheumatic heart disease.

Differential diagnosis

- Cardiomyopathy and infective endocarditis.

Treatment

- Medical and surgical.

Medical treatment:
- To take care of cardiac failure and prophylaxis against the recurrence of rheumatic fever; and infective endocarditis.
- Those with a mechanical prosthesis will be on anticoagulation therapy.

Surgical treatment:
- ***Mitral regurgitation***–
- Mitral valve repair or mitral valve replacement with a mechanical valve or bioprosthesis.
- ***Mitral stenosis***–
- The options for treatment are an open or closed mitral commissurotomy.
- Mitral valve replacement
- A percutaneous catheter balloon mitral commissurotomy.
- ***Aortic regurgitation***–
- Treatment includes aortic valve reconstruction.
- Aortic valve replacement with an aortic homograft or mechanical valve and transferring the patient's own pulmonary valve to the aortic position–the Ross procedure.
- Annual echocardiography is important.

Complications/prognosis

- Cardiac failure, arrhythmias and death.

- Prognosis depends on the proper treatment of pharyngitis, rheumatic fever and prophylaxis; and heart failure.

Prevention/control

- This involves the proper treatment of pharyngitis, rheumatic fever and prophylaxis of rheumatic fever.
- Improvement in socioeconomic standards and avoiding overcrowding.

Counselling

- Educate patients about pharyngitis, rheumatic fever and rheumatic heart disease, their consequences, and how to prevent them.

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4.9 Cardiac Failure

- Cardiac failure occurs when the heart is unable to produce an adequate cardiac output to maintain tissue perfusion (metabolism).

Classification

New York Heart Association (NYHA)

- Class I Asymptomatic
  - No limitation to ordinary physical activity–no fatigue, dyspnoea or palpitation.
- Class II Mild limitation of physical activity
  - Unable to climb stairs.
- Class III Moderate to marked limitation
  - Shortness of breath on walking on a flat surface.
- Class IV Severe, orthopnoea, breathless even at rest
  - No physical activity possible.

Ross Classification: Heart failure in infants

Mild–Intake of <3.5 ounces/feed (≈102 ml)

- Respiratory rate >50/min;
- Abnormal respiratory pattern;
- Diastolic filling sounds;
- Hepatomegaly.

Moderate–Intake <3 ounces/feed (87.3 ml) or time taken per feed >40 mins

- Diastolic filling sounds;
- Respiratory rate >60/min;
- Moderate hepatomegaly.

Severe–Heart rate >170/min

- Decreased perfusion–mottling of hands and feet;
- Severe hepatomegaly.

Epidemiology

- All the paediatric age groups are affected; and of course, the foetus.
- Causes include cardiac, renal, endocrine, haematologic, infections, pulmonary and iatrogenic.
- The most common cause in our environment is haematologic-anaemic heart failure.

Pathophysiology

- Cardiac function obeys the Frank-Starling principle. Cardiac failure could be as a result of an intrinsic cardiac problem, volume overload or pressure effect.
- All these impose strain and stress on the heart so that at a certain point the heart can no longer cope, and when the compensatory mechanisms also fail, the heart will be said to have failed.

Clinical features–*history*

- ***Infants*–**There will be inadequate intake, sweating at the breast, weakness (sleepiness), restlessness, irritability, weight loss (FTT), weak cry and noisy laboured breathing.
- ***Older children***–Fatigue, exercise intolerance, anorexia, abdominal pain, dyspnoea, orthopnoea and maybe paroxysmal nocturnal dyspnoea are the features.

Clinical features–*physical findings*

- ***Infants***–It mimics respiratory tract infection with intercostal and subcostal retractions, tachycardia, tachypnoea and the flaring of ala nasi. There may be facial swelling; displaced apex beat and hepatomegaly. Gallop rhythm and basal crepitation are present.
- ***Older children***–They will present with oedema and hyperdynamic precordium. Others are elevated JVP, displaced apex beat, tachypnoea, tachycardia, gallop rhythm, basal crepitation and hepatomegaly.

Diagnosis

- Chest X-ray shows cardiomegaly and evidence of pulmonary infection and oedema.
- ECG shows chamber hypertrophy, the presence of arrhythmias and cardiac axis.
- Echocardiography is used to assess cardiac defects and evaluate cardiac functions.
- FBC and S/E/U/Cr are also done.

Differential diagnosis

- This is age dependent affecting the foetus e.g. tachyarrhythmia, severe anaemia;
- Premature neonate e.g. fluid overload, PDA;
- Full term neonate e.g. asphyxial cardiomyopathy, coarctation of the aorta;
- Infants and toddlers e.g. VSD, tachyarrhythmias, metabolic cardiomyopathy;
- Children/adolescents: rheumatic fever, acute hypertension (AGN) and viral myocarditis.

Treatment

- This includes supportive, medical and surgical treatments.
- ***Supportive***–Bed rest, salt restriction, fluid restriction (a strict input/output chart) and proper attention to diet and feeding. Oxygen should be given if needed.
- ***Medical***–Digoxin (0.04-0.06 mg/kg), Frusemide (1.0-2.0 mg/kg), Spironolactone (2-3 mg/kg), Chlorothiazide (20-40 mg/kg), Dopamine (2-10 ug/kg/min), Dobutamine (2-20 ug/kg/min), Isoproterenol (0.05-0.5 mcg/kg/min), Amrinone (0.75 mg/kg bolus, then, 5-10 mcg/kg/min), Milrinone (0.25-1.0 ug/kg/min) and Captopril (0.5-6.0 mg/kg) are all useful in the medical management of cardiac failure.
- Digoxin, diuretics and any of the above are used in combination.
- ***Surgery***–This is for congenital and acquired causes of heart failure like VSD and rheumatic heart disease (mitral valve disease).

Complications/prognosis

- Chronic debility (FTT) and death. Prognosis is good if diagnosis and treatment are instituted early.

Prevention/control

- This depends on the cause. Preventable causes like anaemia and rheumatic fever can be treated, while hypertension can be controlled.

Counselling

- Parents and older children should be counselled about heart failure, the causes and the need to avoid preventable causes, and the likely outcome of poorly managed cardiac failure.

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4.10 Shock

- Shock is the state where available oxygen delivery is insufficient to meet tissue oxygen requirements.

Epidemiology

- Shock affects all age groups. Shock is classified as hypovolaemic, cardiogenic, distributive, septic, obstructive and dissociative.
- ***Hypovolaemic*:** haemorrhage and dehydration from any cause (gastroenteritis, volvulus, burns and peritonitis).
- ***Cardiogenic*:** arrhythmias, cardiomyopathies, heart failure, valve disease, congenital heart disease, myocardial contusion and infarction.
- ***Distributive*:** abnormalities of vasomotor tone e.g. septicaemia, anaphylaxis, neurogenic (loss of sympathetic vascular tone secondary to spinal cord or brainstem injury), anaesthesia and vasodilating drugs.
- ***Obstructive*:** tension pneumothorax, haemopneumothorax, cardiac tamponade, pulmonary embolism, hypertension, coarctation of the aorta and flail chest.
- ***Dissociative*:** profound anaemia, carbon monoxide poisoning and methaemoglobinaemia.
- The common feature in all these is insufficient oxygen delivery with consequent anaerobic metabolism.

Pathophysiology

- Any of the above conditions can result in shock where the common final pathway is loss of vascular tone, vasodilation with decreased cardiac output resulting in decreased vital organ perfusion.
- In the early stage of shock compensatory mechanisms–increase in heart rate, stroke volume, and vascular smooth muscle tone, are initiated to maintain blood pressure to preserve perfusion to vital organs such as the brain, heart and kidney, leading to compensated shock.
- All of this will cause initial vasoconstriction. The respiratory rate is increased to promote the excretion of CO_2 to compensate for increased CO_2 production and metabolic acidosis occurring due to poor tissue perfusion.

- Increased renal excretion of hydrogen ions and the retention of bicarbonate occur in an effort to maintain normal pH.
- The vascular volume is maintained by rennin-angiotensin-aldosterone and atrial natriuretic factor axes, cortisol and catecholamine synthesis and release, and secretion of antidiuretic hormone.
- If the above process fails, and in the absence of treatment, decompensated shock develops which is characterised by vasodilation and vascular collapse, decreased cardiac output and poor tissue perfusion.
- In this phase, vascular injury leads to capillary leakage that results in a decrease in intravascular volume which exacerbates shock.
- Increase in capillary permeability is worsened by bacterial endotoxin and inflammatory mediators like tumour necrosis factor and interleukin resulting in increased transcapillary depletion of intravascular volume.
- This causes tissue damage that leads to multisystem organ dysfunction and death.

Clinical features–*history*

- History is that of the precipitating factor. It could be gastroenteritis leading to severe dehydration.
- It could be fever in septicaemia; chest pain in pulmonary embolism, myocardial infarction, etc.

Clinical features–*physical findings*

- The physical findings in shock depend on the stage–early and late; and the cause.
- *Early phase of shock in hypovolaemia* is characterised by a change in mental status, tachycardia, tachypnoea, poor peripheral pulses, cool extremities, oliguria and hypotension as a late manifestation.
- There may also be dry mucous membrane, dry axillae and poor skin turgor.
- Supine hypotension and tachycardia are hallmarks of hypovolaemia.
- In the early phase of septic shock there are warm extremities, bounding pulses, tachycardia, tachypnoea, adequate urination and mild metabolic acidosis.

- *Cardiogenic shock* presents with cool extremities, delayed capillary filling time (>2secs), hypotension, poor peripheral or central pulses, tachypnoea, increasing obtundation and decreased urination.
- Uncompensated shock presents with obtundation and oliguria.
- *Haemorrhagic Shock Encephalopathy Syndrome*: This is common in children younger than 3 years.
- It is characterised by encephalopathy, fever, shock, watery diarrhoea, severe disseminated intravascular coagulation, and renal and hepatic dysfunction.
- There is also hypotension, seizures and other severe neurologic findings as a result of cerebral oedema.

Diagnosis

- Diagnosis is based on history and physical examination.

Differential diagnosis

- This is equally based on history and physical examination. It could be hypovolaemic, cardiogenic or neurogenic, etc.
- Others are acute kidney injury, acute respiratory distress syndrome, acute adrenal insufficiency and adrenal crisis.
- Diabetic ketoacidosis, disseminated intravascular coagulation, neuroleptic malignant syndrome, toxic epidermal necrolysis, toxic shock syndrome and transfusion reaction.

Treatment

- Pay attention to ABCD: A–airway; B–breathing; C–circulation; and D–dextrose. Ensure a patent airway; ensure the patient is breathing well.
- Once the airway is patent, give oxygen through a face mask, if the patient is hypoventilating (oxygen saturation using a pulse oximeter <94%), give oxygen through a bag-valve-mask device.
- Ensure circulation through intravenous or intraosseous access.
- Correct hypoglycaemia using dextrose containing fluid.
- Having ensured the above, normal saline or lactated ringer solution is given at 20 ml/kg over 5-10 mins.

- In cardiogenic shock care is taken not to give too much fluid to avoid exacerbating heart failure.
- In severe hypovolaemic, septic or anaphylactic shock up to 60-80 ml/kg of fluid may be required over 1-2 hours.
- Fluid therapy should be given until there is improvement in heart rate, blood pressure, urine output, level of consciousness and capillary refill time.
- In shock, a choice is usually made between crystalloids (normal saline) and colloids (albumin). In haemorrhagic shock, either fresh whole blood or packed cells are used.
- In shock, deficit, on-going losses and maintenance must be addressed.
- Maintain central venous pressure at 4-8 cmH_2O if possible.
- Care should always be exercised to find and address the cause of the shock e.g. pulmonary embolism, pericardial effusion, coarctation of the aorta, sepsis, etc.
- Failure of the above measures calls for the use of vasoactive agents.
- Cardiogenic shock benefits from dopamine.
- Warm shock should receive norepinephrine while patients with cold shock should receive epinephrine.
- Intravenous vasopressin is used for catecholamine-resistant shock.
- Hydrocortisone in stress doses is used especially in some patients with septic shock.
- Dobutamine and milrinone are useful in cardiogenic shock.
- In distributive shock phenylephrine and vasopressin are useful while anaphylactic shock benefits from epinephrine.
- In neonates, calcium that acts as a direct myocardial stimulant can be used.
- If tachyarrhythmia is the cause of the shock, up to three synchronous electrical shocks at 0.5, 0.5 and 1 joule should be given.
- Coagulation disorders, liver function abnormalities, acidosis and hypercarbia should be vigorously addressed.
- In shock that is not responding to the above measures, extracorporeal membrane oxygenation or ventricular assist devices are used.

Complication/prognosis

- Untreated, and shock that did not respond to treatment will result in end organ damage and death. Prognosis is good if diagnosis and treatment are instituted early.

Prevention/control

- Early diagnosis and treatment of conditions that will lead to shock are a good preventive measure; and control entails good management of shock.

Counselling

- This is the education of parents and patients about shock and the likely outcome.

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4.11 Cardiomyopathy

- Cardiomyopathy is disease of the heart of unknown origin. This is a misnomer because with advances in medicine a clear-cut diagnosis can be made.

Epidemiology

- Three types of cardiomyopathies are recognised–Dilated, Hypertrophic and Restrictive. Any age group can be affected.
- ***Dilated cardiomyopathy*** could be familial with an autosomal dominant/recessive, X-linked or mitochondrial inheritance pattern.
- Other causes are virus, metabolic, systemic and familial muscle and neuromuscular disorders, doxorubicin, tachyarrhythmias, congenital and acquired abnormalities of the coronary arteries and familial hypercholesterolaemia.
- ***Hypertrophic cardiomyopathy*** has an autosomal inheritance pattern.
- Other causes are coarctation of the aorta, critical aortic stenosis, glycogen storage disease, or mucopolysaccharidoses.
- ***Restrictive cardiomyopathy*** has many theoretical causes–
- Malnutrition, serotonin, vitamin E deficiency, obstruction of cardiac lymphatics, rheumatic heart disease, malaria, DCM and thorium excess.
- Others are magnesium deficiency, cerium excess, viruses, schistosomiasis, filariasis, toxoplasmosis, intestinal parasites and eosinophilia and degranulated eosinophils.
- It affects mainly those aged 5 to 15 years; males more than females.
- The poor are more affected and it is mainly a tropical disease.

Pathophysiology

- The above causes lead to intrinsic myocardial disease, with fibrosis and hypertrophy, affecting cardiac contractility.
- All of these lead to the various pathological manifestations like dilatation, hypertrophy and restriction (restrictive, EMF) to cardiac functions.
- The cardiomyopathies ultimately lead to cardiac failure.

Clinical feature–*history*

- ***Dilated cardiomyopathy*** presents with anorexia, cough, abdominal pain, dyspnoea on exertion and irritability.
- ***Hypertrophic cardiomyopathy*** presents with weakness, fatigue, dyspnoea on exertion, palpitation, angina pectoris, dizziness, syncope and risk of sudden death.
- ***Restrictive cardiomyopathy*** presents with either right or left heart failure. Complaints are weakness, exercise intolerance and dyspnoea.

Clinical history–*physical findings*

- ***Dilated cardiomyopathy***: tachycardia, narrow pulse pressure, raised JVP, oedema, hepatomegaly, gallop rhythm, and holosystolic murmur of mitral and tricuspid insufficiency. Later, there will be cool and pale skin and decreased arterial pulse.
- ***Hypertrophic cardiomyopathy*** presents with a brisk pulse, prominent left ventricular lift and double apical impulse, normal 1st and 2nd heart sounds and an ejection systolic murmur.
- ***Restrictive cardiomyopathy*:**
  - *RV EMF* presents with proptosis, parotid swelling, cyanosis, digital clubbing, pedal oedema, raised JVP, small volume pulse, arterial fibrillation, a normal but distant heart sound, gallop rhythm, tricuspid incompetence murmur, gross ascites and enlarged pulsatile liver.
  - *LV EMF* presents with signs of left heart failure, accentuated P2 and murmur of mitral incompetence. A patient with EMF is described as having an Egg-on-Stick appearance.

Diagnosis

- ***Dilated cardiomyopathy*:** ECG shows combined atrial enlargement, ventricular hypertrophy and T-wave abnormality.
- Chest X-ray shows cardiomegaly and pulmonary congestion. Pleural effusion may be present.
- Echocardiography shows dilatation of the left atrium and ventricle with poor contractility. There is decreased flow velocity through the aortic valve; and mitral regurgitation.
- ***Hypertrophic cardiomyopathy*:** ECG shows left ventricular hypertrophy and signs of Wolff-Parkinson-White syndrome.

- Chest X-ray shows cardiomegaly with a prominent left ventricle.
- Echocardiography shows left ventricular hypertrophy with the involvement of the ventricular septum.
- ***Restrictive cardiomyopathy*:** Chest X-ray may show a normal heart. In RV EMF there is pulmonary oligaemia while in LV EMF there is pulmonary congestion. ECG shows rhythm abnormalities.
- Echocardiography shows a thickened endocardium with a small ventricular cavity, and a dilated atrium with/without thrombi. There may be pericardial effusion, dilated RV outflow tract, paradoxical septal motion, M-shaped septal motion and ballooning of the mitral valve leaflets.
- Cardiac catheterization shows a dip and plateau pressure pattern in the ventricles and elevated atrial pressure.
- Endomyocardial biopsy, FBC (eosinophilia), stool and urine microscopy and skin snip are done.

Differential diagnosis

- Other causes of heart failure.

Treatment

Medical

- ***Dilated cardiomyopathy***: Digoxin for heart failure; antiarrhythmic drugs or AICDs, anticoagulation is needed. Cardiac transplant is done in recalcitrant cases.
- ***Hypertrophic cardiomyopathy*:** Avoid competitive sports because of sudden death. Digitalis or vigorous diuresis is contraindicated in most patients.
- Avoid isoproterenol infusion and other inotropic agents. B-adrenergic blocking agents (propranolol) and calcium channel blockers (verapamil, nifedipine) are useful but not used in infancy. Ventricular septal myotomy and mitral valve replacement could be done.
- ***Restrictive cardiomyopathy*:**

Medical:

- Digoxin, diuretics, antiarrhythmic drugs, prednisolone, hydroxycarbide, vincristine, leukapheresis, anticoagulation and abdominal paracentesis are done.

***Surgery*:**

- Decortication, valve repair/replacement, pericardiotomy, modified Fontan's operation (R-atrium to pulmonary artery or inferior vena cava to PA) are all surgical options.

Complications/prognosis

- Chronic debility and sudden death. Prognosis is unpredictable.

Prevention/ control

- This is difficult considering the aetiologies of the cardiomyopathies. However, avoidance of cardiotoxic agents, improvement of socioeconomic conditions, and early treatment of known predisposing factors can help.

Counselling

- Parents and patients should be educated about cardiomyopathy and the likely outcome of the disease.

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SECTION 5:

NEUROLOGY

IGWE, W.

5.1 Coma (The Unconscious Child)

- Coma is a state of deep, unarousable, sustained pathologic unconsciousness in which the person shows no meaningful response to environmental stimuli.

Pathophysiology

- Consciousness requires two components: arousal (wakefulness) and awareness. **Arousal or wakefulness** is dependent on the function of the Reticular Activating System (RAS). **Awareness** is mediated through cerebral cortical neurons and their reciprocal projections to and from the major subcortical nuclei.
- Awareness requires arousal, but not vice versa.
- Coma therefore results if there is dysfunction in either the RAS or the cerebral cortex.
- RAS dysfunction, mostly caused by structural lesions in the brain stem, tends to present with focal neurologic findings while cerebral cortical dysfunction is often caused by toxic/metabolic processes and presents with non-focal neurologic findings.

Causes:

- Coma can result from metabolic/toxic or structural/intrinsic pathologies.
- ***Cerebral hypoxia/ischaemia***–severe anaemia, apnoea, asphyxia, carbon monoxide poisoning, respiratory failure, shock, and cerebrovascular events.
- ***Seizure disorders***–postictal, status epilepticus.

- ***Infectious***–encephalitis, meningitis, septic shock.
- ***Raised intracranial pressure***–SOL, cerebral oedema, hydrocephalus.
- ***Metabolic/endocrine***–DKA, hypoglycaemia, hypernatraemia, hyponatraemia, liver failure, renal failure.
- ***Toxic***–substance abuse, drug overdose.
- ***Trauma***–traumatic brain injury.

Immediate management

- Attend to airway, breathing and circulation.
- If a traumatic cause is possible, immobilize the cervical spine and arrange an urgent neurosurgery consult.
- Insert an intravenous line for the collection of samples and for drugs.
- Do a random blood glucose; if low, administer IV dextrose.
- Assess and monitor pulse, respiratory rate, BP, temperature, pulse oximetry ± ECG monitoring and conscious state.
- Look carefully for subtle signs of a continuing convulsion and abort seizures.
- Look for signs of raised ICP and treat using mannitol and/or dexamethasone.

Diagnosis:

History and examination

- Time-course of changes in mental state.
- Past and recent history including medications: seizures, diabetes, infection, cardiac, previous similar episodes (metabolic conditions), trauma.
- Family history e.g. seizure disorders.
- Full systemic examination with particular attention to a neurologic examination.
- ***Where is the lesion?***
- *Supratentorial*: focal hemispheric signs, progression from head to feet, Cheyne-stokes respiration, flexor posturing (previously called decorticate), pupillary abnormalities.
- *Infratentorial*: dilated pupils with poor light response, abnormal respiratory pattern, cranial nerve palsies, absent caloric/doll's eye text, extensor posturing (previously called decerebrate).

- *Metabolic*: motor signs are symmetric, pupillary reactions are preserved, abnormalities of acid-base balance.
- Determine the depth of coma using the Glasgow Coma Scale.

Paediatric Glasgow Coma scale

	>5 years	<5 years
Eye opening		
E4	Spontaneous	
E3	To voice	
E2	To pain	
E1	None	
C	Eyes closed (by swelling or bandage)	
Verbal		
V5	Orientated (in person or place or address)	Alert, babbles, coos, words or sentences to usual ability (normal)
V4	Confused	Less than usual ability, irritable cry
V3	Inappropriate words	Cries to pain
V2	Incomprehensible sounds	Moans to pain
V1	No response to pain	
T	Intubated	
Motor		
M6	Obeys commands	Normal spontaneous movements
M5	Localises to supraorbital pain (>9 months of age) or withdraws to touch	
M4	Withdraws from nailbed pain	
M3	Flexion to supraorbital pain (decorticate)	
M2	Extension to supraorbital pain (decerebrate)	
M1	No response to supraorbital pain (flaccid)	

- A score of 15 indicates normal neurologic function;
- Scores of 13-14 indicate mild neurologic dysfunction;
- Scores of 9-12 indicate moderate dysfunction;
- Scores of 3-8 indicate severe dysfunction.

***Investigations*:**

- In the light of the possible diagnosis, consider these investigations:
- Full blood count;
- Serum electrolytes, urea and creatinine, arterial blood gas;
- Random blood glucose, liver function tests;
- Urine drug ± metabolic screen;
- Culture of blood and urine;
- EEG/CT scan/MRI;
- Lumbar puncture–CSF analysis, culture, antigen tests, PCR, etc.

Specific treatment

- Depends on the cause of the coma.

Differential diagnosis

- ***Vegetative state*–**extensive damage to the cortex such that it cannot be aroused and sustain normal cognitive functions. The eyes open in response to verbal stimuli and sleep/wake cycles exist, but there are no motor localizing responses and verbal commands cannot be obeyed.
- ***Akinetic mutism***–a state of apparent alertness with normal eye movements but no speech or other voluntary movements. It is due to lesions of the upper brain stem.
- ***Locked-in syndrome***–results from pontine lesions. Consciousness is preserved but there is impaired motor output.
- ***Psychogenic unresponsiveness***–usually a female who exhibits odd behaviour and psychosocial problems. The caloric test/doll's eye test is normal.
- **Prognosis**: about 50% of children with non-traumatic coma have a good prognosis. Abnormalities of pupillary reactions and delay in the return of motor responses are unfavourable prognostic signs.

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5.2 Seizure Disorders (Epilepsies)

Definitions

- Seizures are paroxysmal involuntary alterations of brain function that can manifest as either convulsions, impairment of consciousness, behavioural abnormalities, sensory disturbances, or autonomic dysfunction.
- Convulsions are the abnormal and involuntary motor manifestations of seizures. The word convulsion is often used as a synonym for seizure, but not all seizures are convulsive in nature.
- They can occur after a metabolic, traumatic, anoxic, or infectious insult to the brain.
- ***Seizure disorder or epilepsy*** is a chronic condition of recurrent seizures. It is a sign of underlying brain dysfunction.
- Seizures provoked by a reversible insult (e.g. fever, hypoglycaemia) do not fall under the definition of epilepsy because they are a short-lived, secondary condition rather than a chronic state.
- **Epilepsy syndrome** refers to a group of clinical characteristics that consistently occur together, with a similar seizure type, age of onset, electroencephalographic (EEG) pattern, precipitating factors, inheritance pattern, natural history, and response to antiepileptic drugs (AED).
- **Status epilepticus** is a clinical or electrical seizure lasting at least 30 minutes, or a series of multiple seizures lasting 30 minutes without complete recovery of consciousness in between seizures.

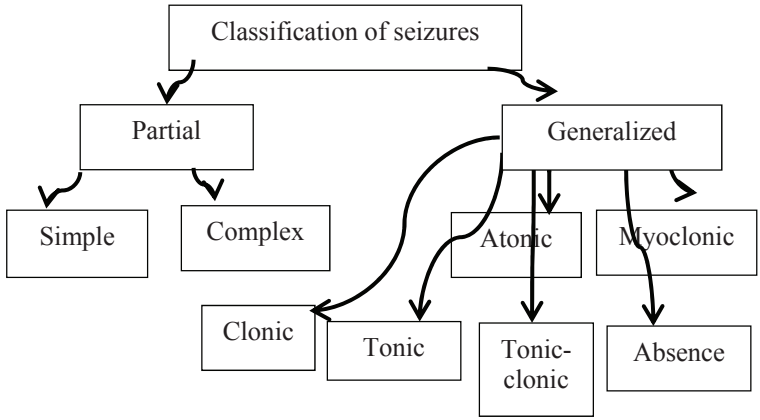
Epidemiology

- Epilepsies occur most commonly at the extremes of life. The incidence is highest in the new-born and higher in childhood than in later life.
- Prevalence flattens out after 10-15 years. Childhood epilepsy often remits (50% chance of remission).

Classification

- Classification is based on (a) seizure type, (b) aetiology, and (c) EEG pattern.

- Classification according to seizure type subdivides epilepsy into partial or generalized epilepsies.
- In partial forms, seizures begin focally in a restricted area of the cortex.
- Partial seizures are subdivided into simple and complex partial seizures.
- Consciousness is preserved in simple partial seizures while it is impaired in complex partial seizures.
- In the generalized type, seizures arise diffusely from both hemispheres usually with impairment of consciousness from the onset.
- Types of generalized seizures: clonic, tonic, tonic-clonic, absence, myoclonic and atonic seizures.



- It is said to be symptomatic if the underlying cause is identified and idiopathic if the cause is unknown.
- In the cryptogenic type, a cause is presumed.
- Common epilepsy syndromes include West, Lennox-Gastaut, febrile seizures, and Rolandic seizures.

Aetiology

- In 60-70% of cases, the cause is unknown (idiopathic).
- Known causes include congenital malformations/developmental CNS disorders, perinatal events (including hypoxia, trauma,

metabolic disorders), infections and infestations, metabolic defects and injury to the brain.

Pathophysiology:

- The onset of seizures appears to occur when a small group of abnormal neurons undergoes prolonged depolarization associated with the rapid firing of repeated action potentials.
- These abnormally discharging epileptic neurons recruit adjacent neurons or neurons with which they are connected into the process.
- A clinical seizure occurs when the electrical discharges of a large number of cells become abnormally linked together, creating a storm of electrical activity in the brain.
- Seizures may then spread to involve adjacent areas of the brain or through established anatomic pathways to other distant areas.
- Seizures can be viewed as resulting from an imbalance between excitatory and inhibitory processes in the brain i.e. decreased inhibitory neurotransmission, which is primarily by gamma-amino butyric acid (GABA), or enhanced excitatory neurotransmission, which is primarily mediated by the acidic amino acid, glutamate.

Clinical Features

Partial seizures

- These depend on the seizure type.
- *Simple partial (SPS):* SPS can start at any age. Seizures may be motor, sensory, autonomic or psychic.
- Motor seizures may involve any part of the body and may spread in a fixed pattern.
- Consciousness is preserved. EEG shows focal spikes.
- *Complex partial seizures (CPS)*: Can start at any age.
- CPS may begin as SPS with or without an aura, followed by impaired consciousness. It may start with an alteration of consciousness from the onset.
- An aura is a vague, unpleasant feeling, epigastric discomfort or fear.
- Automatisms are a common feature of CPS and occur following the loss of consciousness and may persist into the postictal phase.
- Automatisms seen in infants include lip smacking, chewing, swallowing and excessive swallowing.

- In older children, automatisms occur as semi purposeful, uncoordinated, and unplanned gestures such as picking and pulling at clothing, rubbing or caressing objects and running or walking aimlessly.
- EEG shows focal spikes in the temporal lobe and its connections.

Generalized seizures:

- *Absence seizure*: Onset is 4-14 years and it often resolves by 18 years.
- It consists of a brief episode of staring with impairment of awareness and responsiveness that begins without warning and ends suddenly, leaving the patient alert and attentive.
- It can be simple or complex. In simple absence seizures, the patient only stares.
- In complex absence seizures, staring is accompanied by simple automatic movements such as the blinking of eyes, drooping of the head, or chewing.
- *Simple (typical) absence*: Duration is short (10-45 seconds), patients are usually unaware of an occurrence.
- Recovery is abrupt without after effects.
- An EEG pattern of a 3 per second spike and waves is characteristic and may be precipitated in a large percentage of patients by hyperventilation.
- About 25-50% of patients go on to develop generalized tonic-clonic seizures (GTC).
- Development and intelligence are usually normal and the long-term prognosis is good, particularly in patients who do not develop GTC.
- It is important to differentiate from complex partial seizures, since treatment and prognosis vary.
- In contrast to absence, complex partial seizures usually have a longer duration (minutes vs. seconds), are often preceded by an aura, and typically have a brief period of postictal confusion.
- In addition, the EEG pattern is markedly different between the two seizure types.
- *Complex (Atypical) absence*: Onset is 1-7 years. Presentation is similar to typical absence except that loss of responsiveness during seizure is often less complete and more gradual in onset and cessation.

- Also clonic, tonic and atonic components (i.e., increase or decreases in muscle tone) are more pronounced than in typical absence.
- It is commonly seen in patients with Lennox-Gaustaut syndrome in conjunction with myoclonic, atonic and tonic seizures.
- EEG shows a slow spike and wave (<2.5 Hz) discharge. It is not precipitated by hyperventilation and is often associated with mental retardation or structural CNS damage.
- Response to therapy and long-term prognosis are dependent on the presence of underlying neurologic damage and/or mental retardation. A good response is seen in only 20-30% of patients.
- *Myoclonic seizures*: Myoclonic seizures occur at any time in childhood but mainly at 2-7 years.
- It consists of shock-like violent contractions of muscle groups, singly or repetitively usually associated with no, or a brief loss of, consciousness.
- EEG shows atypical slow (1-2 Hz) spike-wave complexes and bursts of high voltage generalized spikes with a diffuse slow background.
- *Tonic seizures*: Characterized by sudden bilateral stiffening of the body, arms, or legs. Tonic seizures usually last less than 20 seconds and are more common during sleep.
- It is primarily seen in younger children; and frequently occurs with other seizure types and in various epilepsy syndromes.
- Duration is 10-60 seconds, with brief, if any, postictal symptoms.
- *Atonic seizures*: Onset is usually between 2 and 5 years.
- Presents as a sudden and total loss of muscle tone and posture that causes eyelids to drop, the head to nod and the patient to fall to the ground–a "drop attack"; not necessarily associated with loss of consciousness.
- May or may not have postictal symptoms.
- Average duration is 10-60 seconds; brief, if any, postictal symptoms.
- Other seizure types are common in patients with atonic seizures. Atonic seizures may be observed in conjunction with myoclonic seizures and atypical absence (Lennox-Gaustaut Syndrome).
- *Generalized Tonic-Clonic*: Loss of consciousness is quickly followed by a sudden fall to the ground.

- In the tonic phase, muscles become rigid and the simultaneous contractions of the diaphragm and chest muscles may produce the characteristic "epileptic cry".
- The patient's eyes roll up or turn to the side and the tongue may be bitten.
- The rigidity is replaced shortly by a series of synchronous clonic movements of the head, face, legs and arms.
- Autonomic changes also observed include: increased blood pressure, heart rate, and bladder pressure; pupillary mydriasis; hypersecretion of skin and salivary glands; cyanosis of skin.
- Although onset may occur at any age, it most commonly occurs during the second decade of life.
- Average duration is 2-5 minutes.
- Postictally, the patient is lethargic and may sleep for several minutes to hours.
- Incontinence occurs in the early postictal phase in about 35% of patients. Prognosis is good with seizure control in 70-85%.
- *Neonatal epilepsy:* The neonatal period is the most vulnerable period of life for developing seizures.
- Neonatal epileptic seizures often constitute a neurological emergency demanding urgent diagnosis and management.
- Neonatal seizures are paroxysmal, repetitive, and stereotyped events.
- They are usually clinically subtle.
- There is no recognizable post-ictal state. Generalized tonic-clonic seizures probably do not occur.
- There are 5 main types of neonatal seizures: Subtle seizures (50%), Tonic seizures (5%), Clonic seizures (25%), Myoclonic seizures (20%), and Non-paroxysmal repetitive behaviours.
- The prevalence of neonatal seizures is approximately 1.5%.
- The overall incidence is 3 per 1,000 live births (57 to 132 per 1,000 live births in pre-term infants).
- Eighty per cent occur in the first 1 to 2 days to the first week of life. The aetiology of neonatal seizures is extensive and diverse.
- Hypoxic-ischaemic encephalopathy is the most common cause (80% of all seizures in the first 2 days of life).
- Prognosis is cause-dependent because the main factor that determines outcome is the underlying cause and not the seizures.

- Despite high mortality (approximately 15%) and morbidity (approximately 30%), 50% of neonates with seizures achieve a normal or near-normal state.
- One-third of the survivors develop epilepsy.
- Neonatal seizures often impose significant difficulties in their differentiation from normal or abnormal behaviours of neonates.
- As a rule, any suspicious repetitive and stereotyped events should be considered as possible seizures requiring video-electroencephalogram (video-EEG) confirmation.

Epilepsy syndromes:

- Common epilepsy syndromes include–
- ***Infantile Spasms***: Consist of the sudden flexion of the head with abduction and extension of the arms, accompanied by flexion of the knees and often a little grunt or cry.
- Spasms may be extensor, flexor or most commonly mixed flexor and extensor. Each spasm is brief (<5 seconds) and they commonly occur in clusters.
- Onset is most commonly between 4 and 7 months of age.
- Mental retardation is seen in about 80-90% of patients. Interictal EEG usually shows a hypsarrhythmia pattern.
- ***West syndrome***: Characterized by spasms, developmental retardation, and a hypsarrhythmia pattern on the EEG.
- Spasms may be flexor (jackknife), extensor or mixed flexor-extensor.
- Unique among seizure types in the responsiveness to ACTH/corticosteroids. Prognosis is poor.
- Spasms may disappear by the age of 4 years, but the child may be profoundly handicapped and retarded.
- Patients who are normal prior to onset and who respond to therapy have a slightly better prognosis.
- ***Febrile seizures:*** are seizures secondary to fever without evidence of central nervous system pathology occurring in children between 6 months and 6 years of age.
- Seen in about 2-5% of children before 6 years; peak incidence is 2 years of age. Febrile seizures have a strong genetic predisposition.
- Primarily occur as generalized tonic-clonic seizures, but partial seizures occur in 10-15% of patients.
- Two main types: simple and complex.

- Simple febrile seizures are brief (<15 mins), generalized and do not recur within 24 hours of the first one.
- Complicated febrile seizures are prolonged (>15 mins) and focal and multiple seizures occur within 24 hours of onset. Prognosis is better for simple febrile seizures compared to complicated febrile seizures.
- ***Lennox-Gastaut Syndrome***: It is characterized by the triad of intractable mixed seizures, mental and developmental retardation, and a slow spike and wave pattern on the EEG.
- Seizures (tonic, atonic, atypical absence, myoclonic, and tonic-clonic) usually begin between 1 and 6 years and respond poorly to antiepileptic drugs. Behavioural problems are common.
- ***Benign epilepsy with centro-temporal spikes (Rolandic epilepsy):*** presents as nocturnal or diurnal seizures or both.
- The most characteristic sign is a partial motor or somatosensory seizure involving the face.
- Tonic-clonic seizures may also occur, especially during sleep.
- The seizures are infrequent (some patients require no medications), easily controlled with antiepileptic drug therapy, and stop spontaneously by the age of 15.
- Mental development is unaffected.
- ***Juvenile myoclonic epilepsy***: These myoclonic seizures, with or without tonic-clonic or absence seizures, usually begin shortly before or after puberty.
- Myoclonic and tonic-clonic seizures most often occur in the early morning, shortly after the patient awakens.
- Mental development is normal. In most patients, seizures are well controlled by valproic acid alone, but the disorder requires life-long therapy.
- ***Landau-Kleffner Syndrome (acquired epileptic aphasia)***: this is rare epilepsy in which a child loses previously acquired language abilities and has seizures or epileptiform abnormalities in the EEG.
- Seizures, behavioural and psychomotor disturbances occur in 75% of patients.

Diagnostic Evaluation:

- ***History***–the medical history of the patient and the family history: a description of the seizure–it is important to obtain exact details of the episode from the patient and an eyewitness.

- Note the details of events preceding the seizure and after the seizure.
- ***Physical and Neurological Examination:*** Any abnormal physical/neurologic features should be documented.
- ***Laboratory data***: Electroencephalography (EEG)–Role: confirm the presence of epilepsy, the classification of seizure type, the long-term prognosis.
- EEG findings alone do not confirm or rule out epilepsy. It is important to correlate EEG findings to clinical events.
- Approximately 5% of patients without epilepsy have epileptiform discharges on the EEG. Of patients with epilepsy, only about 50% have epileptiform activity on the first EEG.
- Detection of an abnormal EEG is enhanced by the use of multiple recordings and specific activating techniques.
- EEG patterns with clinical correlations include:
- 3 Hz spike and wave complex: absence seizures.
- Slow spike and wave complex: minor motor seizures (i.e., atypical absence, tonic, atonic).
- Hypsarrhythmia: infantile spasms spike and wave complex: myoclonic seizures.
- Neuroimaging Studies: Magnetic resonance imaging (MRI) or computed tomography (CT) are useful in identifying structural lesions in the brain.
- MRI appears more sensitive in detecting lesions in patients with epilepsy.
- Consider in patients > age 18, in children with partial seizures, and in the presence of abnormal neurologic findings, or focal slow-wave abnormalities on the EEG.

Differential diagnosis:

- Including breath-holding attacks, syncope, nightmares and tics.

Treatment:

Drug treatment principles

- Drug selection–use a drug appropriate to the seizure type.
- Start with one drug in the conventional dosage and increase the dosage until the seizures are controlled. If the seizures are not controlled, gradually switch to another before using two drugs.

- Counselling on the use of medication.
- Follow-up.
- Long-term management: continue AED until the patient is seizure-free for at least 2 years.
- Withdrawal of AED: discontinue AED gradually.
- Drug use according to the seizure type:
  - Phenobarbitone/Phenytoin–generalized seizures, SE;
  - Ethosuximide–absence;
  - Carbamazepine–partial, GTC;
  - Benzodiazepines–atonic;
  - Valproate–broad spectrum;
  - Levitiracetam–partial, generalized, myoclonic.
- Other treatment modalities for intractable seizures include a ketogenic diet, surgery and vagus nerve stimulation.

Prognosis

- It is difficult to give a precise prognosis. About 10-15% will relapse after an adequate course of AED.
- Risk is low if seizures are easily controlled, in certain genetic types, there is normal neurodevelopment before seizures.
- Relapse risk is also low in primary generalized tonic-clonic seizures, absence seizures and Rolandic seizures.
- Prognosis is poor for infantile spasms and juvenile myoclonic seizures.

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5.3 Neural Tube Defects

- Neural tube defects (NTDs) are the second most common severe disabling human congenital defect.
- They are classified based on the site of involvement such as cranial and spinal, or into open (neural tissue exposed) or closed (neural tissue not exposed).
- Open NTDs are readily visible at birth, with the majority being discovered at antenatal ultrasonography.
- Closed NTDs may remain undetected for years, especially in the absence of cutaneous markers.

Cranial NTDs

- Anencephaly.
- Encephalocoele (meningocele or meningomyelocele).

Spinal NTDs

- Spina bifida cystica (myelomeningocele, meningocele)
- Spina bifida occulta.
- Congenital dermal sinus.
- Caudal agenesis.

Epidemiology/Etiology

- NTDs are among the most common birth defects with an incidence of about 5/1000 total births.
- Anencephaly and spina bifida account for up to 95% of all NTDs. At birth, an NTD is more common in girls than boys with a female to male ratio of 1.2:1.0. Incidence is also noted to be higher among the low socioeconomic class.
- Risk factors include pregestational insulin-dependent diabetes, maternal obesity and maternal folic acid deficiency before conception and in early pregnancy.
- In utero exposure to anticonvulsants such as valproic acid and carbamazepine has been associated with an increased risk of spina bifida (both are folate antagonists).

- The largest single risk factor for giving birth to a child with an NTD is a family history of a previous pregnancy resulting in an NTD.
- The risk of spina bifida and/or anencephaly in the siblings of affected individuals is 3-8%.

Pathogenesis

- The brain and spinal cord are formed from the embryonic neural tube.
- The process of neural tube formation is complex, in which a flat sheet of thickened ectodermal cells (neural plate) is converted into a tube.
- The fusion of the neural tube occurs early in pregnancy from day 21 to day 28 after conception.
- Abnormal closure of the neural plate results in NTDs.

Clinical presentation

- Open NTDs are apparent at birth. Closed NTDs have a variable presentation.

Anencephaly*:*

- The cranial vault is absent exposing brain tissues, which are often malformed. Up to 75% of the anencephalic foetuses are stillborn with the remainder dying shortly after birth.

Cephaloceles:

- Brain matter herniates through a skull defect. A **cranial meningocele** contains only meninges; an **encephalocele** contains brain tissue; a **ventriculocele** contains part of the ventricle within the herniated part of the brain.
- Other associated brain abnormalities include; agenesis of the corpus callosum or abnormal gyration.
- Posterior cephaloceles occur most often as occipital encephaloceles. They may be associated with a severe cerebellar defect e.g., Chiari III malformation.
- Anterior cephaloceles may protrude into the nose, ethmoid or orbit.
- They often include olfactory tissue and frontal lobe tissue.
- Cephalocele usually occurs as an isolated lesion but may be part of syndromes such as Meckel-Gruber or Walker-Warburg syndrome.

Spinal dysraphism:

- Spina bifida includes ***spina bifida occulta*** and ***spina bifida cystica.***
- Spina bifida occulta:
  - Spina bifida occulta is the most common form of spina bifida.
  - It is a defect of the posterior arch of one or more lumbar or sacral vertebrae (often L5 and S1).
  - It is an incidental radiologic finding and may be considered as a normal variant.
  - It may present as a nevus, a hairy patch, dimple, sinus or a subcutaneous mass. Spina bifida occulta can cause asymmetrical lower motor neuron weakness associated with wasting, deformity and diminished reflexes.
  - There may also be progressive gait disturbance with spasticity and impaired bladder control.
- *Spina bifida cystica*
  - May be either a meningocele without neural tissue or a myelomeningocele where the spinal cord forms part of the cyst wall.
- *Meningocele:*
  - Protrusion of the meninges outside the spinal canal accounts for 5% of cases of spina bifida cystica.
  - There is no associated hydrocephalus, and a neurologic examination is often normal.
- *Myelomeningocele*:
  - Accounts for about 80-90% of spina bifida cystica. About 80% occurs in the lumbosacral area consisting of a sac covered with a thin membrane that may leak CSF.
  - Paralysis of the lower limbs, bladder and bowel incontinence, and hydrocephalus are the most common clinical complications.
  - Severe mental retardation is present in 10-15% of these patients.
  - The level of lesion is best assessed by determining the upper limit of sensory loss; however, at all levels there is a disturbance of bladder and bowel control.
  - Hydrocephalus is seen in about 90% of cases at birth. Chiari malformation may also be seen in 70%.
- *Dorsal dermal sinuses*
  - Often found in the occipital and lumbosacral areas and can connect the skin surface to the dura or to an intradural dermoid cyst. Open dermal sinuses can cause recurrent meningitis.
- *Lipomyelomeningocele*

  - This presents as a bulge in the lumbosacral region normally lateral to the midline.
  - It is a lipoma or lipofibroma attached to the spinal cord. They are often associated with a meningocele.
- *Diastematomyelia*
  - The sagittal cleft divides the spinal cord into two halves, each surrounded by its pia mater. The cord may be transfixed by a bony or cartilaginous spur.
  - This usually occurs in the low thoracic or lumbar regions. Overlying skin abnormality is present in 75% of cases and X-rays show abnormalities in most cases, including abnormal segmentation of vertebrae, spina bifida and scoliosis.

Diagnosis

- MRI is the imaging of choice.
- CT scan is used in direct visualization of the bony defect.
- Ultrasound is used for antenatal screening.

Prenatal screening*:*

- Prenatal screening is possible by the measurement of the maternal serum alpha fetoprotein or ultrasound.
- Alpha fetoprotein in maternal serum: it is best detected at 16-18 weeks of pregnancy but may miss closed defects.
- Ultrasound: is an effective technique for detecting NTDs in utero. Amniocentesis: this is only used when it has not been possible to obtain adequate ultrasound images; it is used to measure alpha fetoprotein and neuronal acetylcholinesterase.

Management

- Requires a multidisciplinary team to address the associated physical, developmental, hearing, visual and learning difficulties that may occur in NTD.
- An open NTD should be covered with a sterile saline dressing.
- The baby should be positioned in the prone position to prevent pressure on the defect.
- Open NTDs should be closed promptly if there are no contraindications.
- Hydrocephalus requires a ventriculoperitoneal shunt placed at the time of myelomeningocele closure.

- Symptomatic Chiari malformations: suboccipital craniotomy and decompression of the posterior fossa and tonsils.

Complications include

- Infections, especially recurrent meningitis and urinary tract infections.
- Motor and sensory problems, particularly lower-limb paralysis.
- General learning disability and developmental delay.
- Bladder and bowel dysfunction.
- Seizure disorders.

Prognosis

- This depends on the nature of the defect and associated malformations.

Prevention

- Periconceptional folate supplementation, which must begin before conception for it to be effective.
- A daily dose of 400 micrograms before conception and during the first 12 weeks of pregnancy is recommended.

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5.4 Hydrocephalus

- Hydrocephalus is the excessive accumulation of CSF with ventricular dilatation. It may be congenital or acquired. Variants of hydrocephalus include:
- ***Communicating*:** this occurs when full communication occurs between the ventricles and the subarachnoid space (SAS) allowing CSF to flow from the ventricles to SAS. It may be due to overproduction of CSF (rarely), defective absorption of CSF (most often), or venous drainage insufficiency (occasionally).
- ***Non-communicating hydrocephalus*** occurs when the CSF flow is obstructed within the ventricular system or in its outlets to the arachnoid space, resulting in impairment of the CSF flow from the ventricular to the subarachnoid space (SAS).
- ***External pressure hydrocephalus*** is enlarged SAS without ventricular dilatation (this may be a normal finding in early infancy).

Pathophysiology

- CSF is produced mainly by the choroid plexus of the lateral and fourth ventricles.
- It flows from the lateral ventricles through the foramina of Monroe into the third ventricle.
- It then traverses the narrow aqueduct of Sylvius to enter the fourth ventricle.
- CSF exits the fourth ventricle through the paired lateral foramina of Luschka and the medial foramen of Magendie into the basal cisterns.
- The CSF is primarily absorbed by the arachnoid villi in SAS.
- Intracranial pressure rises with the resultant dilatation of the ventricles if the production of CSF exceeds absorption, if resistance to CSF flow is increased, or if venous sinus pressure is increased.

Epidemiology

- The incidence of congenital hydrocephalus is 3 per 1,000 live births; generally, incidence is equal in males and females (the exception is Bickers-Adams syndrome, an X-linked hydrocephalus transmitted by females and manifested in males).
- The incidence of acquired hydrocephalus is not known exactly due to the variety of disorders that may cause it.

Aetiology

- Obstructive or non-communicating hydrocephalus results from an abnormality of the aqueduct or lesion in the 4th ventricle.
- Stenosis of the aqueduct could be inherited as X-linked recessive, or be associated with neurofibromatosis.
- Other causes of aqueductal blockage include intrauterine infections, subarachnoid haemorrhage and meningitis.
- Obstructive hydrocephalus could also result from a vein of Galen malformation, lesions or malformations of the posterior fossa including tumours, Chiari malformations and Dandy-Walker syndrome.
- Non-obstructive or communicating hydrocephalus results from subarachnoid haemorrhage, CNS infections, leukaemic infiltrations, iatrogenic (e.g., Hypervitaminosis A, by increasing the secretion of CSF or by increasing the permeability of the blood-brain barrier, can lead to hydrocephalus) and brain trauma.

Clinical manifestations

- Clinical features of hydrocephalus are variable and depend on age of onset, the type of lesion causing obstruction and the duration and rate of rise of intracranial pressure.
- ***Infants***–an unusually big head or a rapid increase in head size, a wide and bulging anterior fontanel, widely separated cranial sutures, prominent scalp veins, sun-setting eyes, and long tract signs (spasticity, hypertonia, hyper-reflexia and clonus).
- ***Older children***–headache, vomiting, nausea, papilloedema, blurred or double vision, sun-setting eyes, problems with balance, poor coordination, gait disturbance, urinary incontinence, slowing or loss of developmental milestones, lethargy, drowsiness, irritability, or other changes in personality or cognition including memory loss.
- Percussion of the skull may produce a “cracked pot” or Macewen sign indicating separation of the sutures.

Investigations

- Computed tomography (CT) scanning: to assess the size of ventricles and other structures.
- Magnetic resonance imaging (MRI): to assess for Chiari malformation or cerebellar or periaqueductal tumours.

- Trans-fontanel ultrasonography in infants: to assess for intraventricular haemorrhage and follow-up for possible progressive hydrocephalus.
- Skull radiography: detects erosion of sella turcica ("beaten copper cranium") (can also be seen in craniosynostosis), and to confirm correct positioning after the VP shunt procedure.

Differential diagnosis

- Chronic subdural effusions (empyema, haematoma).
- Storage diseases (e.g. mucopolysaccharidoses).
- Neurofibromatosis.
- Familial megalencephaly.
- Hydranencephaly.
- Brain tumours (gliomas, craniopharyngioma, pituitary tumours, CNS lymphomas).

Treatment

- Depends on the cause.
- Medical treatment is a temporary measure to reduce the rate of CSF production using Acetazolamide and Furosemide.
- Surgical treatment is the preferred treatment option using Ventriculoperitoneal shunt insertions. Shunt revisions are scheduled according to the child's growth rate.

Complications

- Visual problems, cognitive dysfunction, incontinence, gait abnormalities.
- Related to medical treatment (electrolyte imbalance and metabolic acidosis).
- Related to surgical treatment (features of increased intracranial pressure (ICP) can be as a result of shunt obstruction or disconnection), subdural haematoma is secondary to over shunting. Seizure disorders.
- Related to Shunts (infections, a conduit for extraneural metastases of certain tumours e.g. medulloblastoma, and shunt erosion through the skin).

- VP shunt complications include peritonitis, inguinal hernia, and perforation of abdominal organs, intestinal obstruction, volvulus, and CSF ascites.

Prognosis

- Long-term outcome is related directly to the cause of hydrocephalus. Developmental disabilities, reduced intelligence quotient, abnormalities of memory and visual problems are more common in hydrocephalic children.

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5.5 Cerebral Palsy

- Cerebral palsy (CP) is the most common developmental disorder associated with lifelong motor impairment and disability in children.
- It is a group of permanent disorders of the development of movement and posture, causing activity limitation, that are attributed to non-progressive disturbances that occur in the developing foetal or infant brain.
- These motor disorders may be accompanied by disturbances of sensation, perception, cognition, communication, behaviour and epilepsy.

Epidemiology

- Cerebral palsy is the leading cause of childhood disability affecting function and development. In developed countries, the overall estimated prevalence is 2-2.5 cases per 1000 live births.
- The prevalence among preterm and very preterm infants is substantially higher.
- In the developing world, the prevalence is not well-established because of a paucity of data, the lack of healthcare access and inconsistent diagnostic criteria.
- All races are affected and it is more prevalent among the low socioeconomic class because of lack of access to good healthcare.

Etiology

- The causes can be identified in 50-75% of cases and these can be due to:
- Prematurity/multiple gestations;
- Cerebral malformations;
- Infections including the central nervous system (intrauterine and extra uterine);
- Trauma e.g. intracranial haemorrhage, head injuries;
- Hypoxic ischaemic encephalopathy;
- Metabolic e.g. NNJ, hypoglycaemia;
- Chromosomal and genetic disorders;
- Neonatal seizures.

Pathophysiology

- CP results from an insult or injury to the brain before birth or in early childhood that leads to the formation of abnormal neural connections.
- This presents as difficulties in controlling and coordinating muscle activities manifesting as muscle stiffness (spasticity), poor muscle tone, uncontrolled movements, and problems with posture, balance, coordination, walking, speech, swallowing, and many other functions.
- While the underlying abnormality of the brain is presumed to be permanent and non-progressive, the clinical manifestations and severity of functional impairment often change over time.

Classification

- Classic patterns are based on the dominant movement disorder and limb involvement:
- Pyramidal (spastic) cerebral palsy (80%), due to cortex/pyramidal tract lesions, is the most common type.
- This type of cerebral palsy presents with spasticity, hyperreflexia, clonus, and an extensor plantar response.
- This may present as:
  - Spastic hemiplegia (20-30%)–Cerebral palsy predominantly affects one side of the body, including an arm and a leg, with the involvement of the upper extremity more than the lower extremity.
  - Spastic diplegia (30-40%)–Both lower extremities are more involved than the upper extremities.
  - Spastic quadriplegia (10-15%)–Involves all 4 extremities and the trunk.
  - Extrapyramidal or dyskinetic CP (10-15%) presents with extrapyramidal signs and abnormal involuntary movements. These may present as athetoid, chorea or dystonic CP.
  - Ataxic: (5-10%) This type affects balance and coordination. The gait is unsteady with difficulty in quick movements that require a great deal of control, such as writing.
  - Hypotonic–Presents as truncal and extremity hypotonia with hyperreflexia and persistent primitive reflexes.

- Mixed cerebral palsy–Is a mixture of different types of cerebral palsy; typically characterized by a mixture of spastic and dyskinetic components.
- Functional classification systems generally divide patients into mild, moderate, and severe types (depending on functional limitations).

Clinical presentation

- Signs of cerebral palsy may not be noticeable in early infancy but become obvious as the child's nervous system matures.
- Early signs include delayed motor milestones, persistence of primitive reflexes, and handedness before the age of 18 months.
- Pyramidal lesions are most clearly associated with spasticity, hypertonia, and increased deep-tendon reflexes, and frequently with overflow reflexes (e.g. crossed adductor spread) and an extensor plantar response.
- Extrapyramidal lesions are often associated with choreoathetosis and dyskinesias, abnormal postural control, and coordination deficits.
- Other possible impairments related to brain damage include epilepsy, speech impairment, intellectual deficits, urinary incontinence, variable sensory/proprioceptive loss and psychosocial abnormalities.
- Difficulty with swallowing and poor oromotor skills are among the first clinically identifiable symptoms in the neonatal period.
- Ambulatory children with CP typically have a spastic gait.
- Seizure disorders are seen in up to a third of individuals with CP.
- Those with spastic quadriparesis or hemiparesis seem more likely to have seizures than children with spastic diplegia or ataxic CP.
- Cognitive deficits are seen in around 50% of people with CP.
- Learning disabilities and sensory disorders are especially common in conjunction with a seizure disorder.

Diagnosis

- The diagnosis is generally based on the clinical picture.
- There are no definitive laboratory studies for diagnosis of CP.
- Cranial imaging studies (CT Scan & MRI) are necessary for evaluation of the extent of brain damage.

Differential diagnosis

- Down syndrome.
- Congenital Hypothyroidism.
- Inherited Metabolic Disorders.
- Metabolic Myopathies.
- Metabolic Neuropathy.
- Movement Disorders.
- Traumatic Peripheral Nerve Lesions.

Complications

- Complications due to CP may affect many systems.
- Skin: decubitus ulcers and sores.
- Orthopaedic: contractures, hip dislocation, and/or scoliosis.
- Gastrointestinal and nutritional: failure to thrive (due to feeding and swallowing difficulties), gastroesophageal reflux, constipation and obesity (occurs less frequently than failure to thrive).
- Respiratory: increased risk of aspiration pneumonia (due to oromotor dysfunction), chronic lung disease/bronchopulmonary dysplasia.
- Neurologic: epilepsy, hearing/visual impairment.
- Cognitive/psychological/behavioural: mental retardation (30-50%), most commonly associated with spastic quadriplegia, attention-deficit/hyperactivity disorder, learning disabilities, poor academic performance, low self-esteem and increased prevalence of depression.

Management

- Adequate management is possible with a multi/interdisciplinary team approach, keeping the child and family at the centre of every decision.
- Paediatricians depend on the expertise of numerous colleagues, including neuro, general and orthopedic surgeons, physio-, occupational, speech and language and psychotherapists, nursing specialists, teachers and social workers, all working together to reduce the functional effect of the physical impairment on the child.

- Medical management: for abnormal movements anticholinergics/ antiparkinsonian drugs are used.
- Baclofen/benzodiazepines are useful for the treatment of spasticity.
- Surgical interventions include intrathecal pump infusions of baclofen for dystonia/spasticity, selective dorsal rhizotomy and surgical procedures for the correction of scoliosis and joint contractures.

Prevention

- Good antenatal care.
- Prevention/effective management of preterm deliveries.
- Prevention/early diagnosis and treatment of infections. Appropriate management of neonatal hyperbilirubinemia.

Prognosis

- Prognosis is related to the severity and associated medical complications.
- With appropriate interventions, children with CP can be fully integrated academically and socially.
- Patients with quadriplegia are more likely to have epilepsy and severe cognitive impairment than those with diplegia or hemiplegia.
- Approximately 25% of children will have mild involvement with minimal or no functional limitation in ambulation, self-care, and other activities.
- About 50% are moderately impaired to the extent that complete independence is unlikely but function is satisfactory.
- Only 25% are so severely disabled that they require extensive care and are not ambulatory.
- The disappearance of primitive reflexes and sitting by 2 years of age are signs predictive of eventual ambulation.
- Children who do not sit by the age of 4 years are not likely to ambulate. Patients with severe forms of cerebral palsy may have a significantly reduced life span, although this continues to improve with appropriate health care.

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5.6 Acute Bacterial Meningitis

- This is an acute severe inflammation of the meninges affecting the pia, arachnoid, and subarachnoid space that occurs in response to the presence of bacteria and bacterial products.
- Suspected bacterial meningitis is a medical emergency and hence immediate efforts must be taken to establish the diagnosis and commence empirical antimicrobial treatment urgently.

Etiology

- A wide range of bacteria causes purulent meningitis.
- From the neonatal period, up to 3 months of life, common causative agents include: group B streptococci (GBS), Coliform bacilli (especially Escherichia coli and other gram-negative enteric bacilli such as Klebsiella, Enterobacter, and Salmonella) and Listeria monocytogenes.
- In infants and younger children, Streptococcus pneumoniae, Neisseria meningitidis, and H. influenzae type b (rare in areas with routine Haemophilus vaccination) are the most common pathogens.
- Children older than 5 years are almost exclusively affected by S. pneumoniae and N. meningitidis.
- Neisseria meningitides groups B, C, Y, and W-135 are the predominant serogroups associated with invasive disease whereas the group A strain accounts for epidemic disease in many countries, especially sub-Saharan Africa.
- In immunocompromised hosts and in patients undergoing neurosurgical procedures, meningitis can be caused by various different bacteria such as Staphylococcus species, gram-negative enteric bacilli, or Pseudomonas aeruginosa.

Epidemiology

- Bacterial meningitis in children is most common in those younger than 4 years, with a peak incidence in those aged 3-8 months.
- In developing countries, gram-negative enteric bacilli are the predominant organisms causing bacterial meningitis in newborns; however, group B streptococci and L monocytogenes have been isolated increasingly.

- Infections are mostly acquired by vertical transmission, but nosocomial transmission is also important, especially in preterm infants with low birth weight who require long-term intensive care.
- Viridans streptococci, enterococci, staphylococci, and non-typeable H. influenzae strains can also cause meningitis.
- About 25% of infants with septicaemia develop meningitis. H. influenzae type b meningitis is mainly a disease of infancy. Most cases are seen in children aged 3 months to 3 years.
- Meningococcal and pneumococcal meningitis are at their highest rates in the first year of life and are rarely seen in infants younger than 3 months of age.
- Although poor living conditions increase the risk of meningitis, other factors, such as crowded day-care facilities, contribute to the frequency of disease.
- Most cases of meningitis arise sporadically; only meningococcal infections can occur in epidemic form.

Pathogenesis

- Meningitis usually follows invasion of the bloodstream by organisms that have colonized mucosal surfaces.
- In neonates, pathogens are acquired during birth through contact with the birth canal, aspiration of maternal intestinal/genital secretions, and from nosocomial pathogens.
- In infants and older children, organisms which normally colonize the nasopharynx are disseminated into the blood stream following a viral infection that damages the mucosal surfaces.
- Subsequently, organisms penetrate weak sites in the blood-brain barrier (choroid plexus and cerebral capillaries) and reach the subarachnoid space (SAS).
- Organisms can also reach the SAS via direct extension of infections from paranasal sinuses, the middle ear, CSF rhinorrhoea, congenital dural defects, neurosurgical procedures, penetrating head injury and skull fractures, or from extension from suppurative parameningeal focus.
- Inflammation noted in the SAS and resulting neurologic damage are due to the activation of the host's inflammatory response by the microorganisms and their products (the cell wall and membrane components).

Clinical manifestations

- The clinical picture depends on the patient's age; the younger the patient, the more subtle and atypical are the manifestations. The classic manifestations noted in older children and adults are not seen in infants.
- Children younger than 3 months: nonspecific symptoms such as hyperthermia or hypothermia, changes in sleeping or eating habits, irritability or lethargy, vomiting, high-pitched cry, or seizures.
- High index of suspicion required for diagnosis in this age group.
- Children beyond 3 months: fever, chills, vomiting, photophobia, and severe headache. Occasionally, the first sign of illness may be convulsions. Irritability, delirium, drowsiness, lethargy, and coma can also develop.
- The most consistent physical findings in older children are the signs of meningeal irritation (nuchal rigidity associated with Brudzinski and Kernig's signs).
- Other manifestations may be associated with specific infections e.g. petechial and purpuric rash are seen in meningococcaemia.
- The rapid development of multiple haemorrhagic eruptions in association with a shock-like state is almost pathognomonic of meningococcaemia (Waterhouse-Friderichsen syndrome).
- The presence of a chronically draining ear or a history of head trauma with or without skull fracture is most likely to be associated with pneumococcal meningitis.

Diagnosis

- Definitive diagnosis of meningitis is dependent on the examination and culture of CSF: cloudy fluid, increased white blood cell count with a predominance of polymorphonuclear leucocytes, a low glucose concentration in relation to serum value, a raised concentration of protein, and a positive stained smear and culture for the causative microorganism.
- The probability of seeing bacteria on a gram-stain of CSF is dependent on the number of organisms present.
- Very early in the illness, the cell count may be normal despite a positive CSF culture.
- The gram-stained smear and culture may be negative in pretreated patients in spite of abnormal protein, glucose and leucocytes values.

- ***Non-culture methods*:** Non-culture tests should be considered for patients who need earlier identification of pathogens or have previously received antibiotics, or whose initial CSF Gram stain is negative.
- Such tests include the latex agglutination test and PCR.

Treatment

- Empiric antibiotics must be parenteral and broad spectrum enough to cover suspected pathogens in each age group. Treatment may be modified according to the organism isolated and sensitivity if there is no response to empiric therapy.
- ***Neonates***: ampicillin + aminoglycoside or ampicillin + Cefotaxime.
- Treatment should last for 10-14 days for group B streptococcus/ L. monocytogenes or 3 weeks for gram-negative enteric organisms.
- ***Infants of 1-3 months****:* ampicillin + ceftriaxone/or cefotaxime. Vancomycin may be used in areas of S. pneumoniae resistance. However, there are reports of ampicillin resistance.
- ***Children older than 3 months****:* monotherapy with cefotaxime or ceftriaxone. Duration of treatment: Neisseria (1 week), H. influenzae (7-10 days), S. pneumoniae (10-14 days).
- ***Supportive and adjunctive treatment***
- Treat; hypoglycaemia (IV 10% dextrose infusions), seizures with anticonvulsants (diazepam/phenobarbitone).
- Reduce intracranial pressure (mannitol, restrict fluids).
- Control fever by using antipyretics.
- Parenteral dexamethasone (0.15 mg/kg 6 hourly for 4 days) given early (before or with the first parenteral antibiotic) reduces the inflammatory response in SAS (useful in meningitis due to HIB and S. pneumoniae).

Complications

- Circulatory collapse/disseminated intravascular coagulation (usually due to Neisseria Meningitidis).
- Focal neurologic deficits: hemiparesis/hemiplegia, cranial nerve palsies, hearing/visual deficits.
- Hydrocephalus.
- Brain abscess.
- Seizure disorders.

- Subdural effusions (mainly in children <2 yrs.).
- Cerebral palsies.
- Cognitive defects.

Prognosis

- The prognosis depends on the infectious agent, the age of the child, the child's general health, and the promptness of diagnosis and treatment.
- Patients at risk for high mortality and morbidity include newborns, those living in low-income countries, and those infected with Gram-negative bacilli and Streptococcus pneumoniae.
- Despite improvements in antibiotic and supportive therapy, death and complication rates remain significant.
- In neonates, mortality is 15-20%, whereas in older children, it is 3-10%.
- The highest mortality is due to meningitis caused by S. pneumoniae, followed by H. influenzae type b and N. meningitides.

Prevention/Vaccination

- Universal Hib vaccination for children from 2-3 months. Polyvalent meningococcal vaccines containing A, C, Y, W-135 for children at risk of N. meningitidis e.g. asplenic/complement deficiency (given from 2 years).
- Conjugate pneumococcal vaccine from 2 months of age (given at 2, 4, and 6 months of life).
- ***Chemoprophylaxis:*** Rifampicin for all household contacts of Hib/meningococcal meningitis. IM ceftriaxone (125 mg stat for those <12 yrs. and 250 mg stat for those >12 yrs.) eliminates nasopharyngeal carriage of meningococcus.

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5.7 Encephalitis

- Encephalitis is inflammation of the brain parenchyma.
- It is a potentially devastating diffuse or focal neurological syndrome with different aetiologies.
- Although it primarily involves the brain, it often involves the meninges as well (meningoencephalitis).
- Viruses are the most common causes and these often present acutely.
- Sub-acute or chronic presentations are characteristic of particular pathogens, especially in immune-compromised individuals.

Etiology

- Encephalitis can be caused by infection directly or indirectly, or result from non-infectious causes (antibody-mediated).
- Direct infections of CNS can be caused by viruses (the most common cause), bacteria, parasites and fungi.
- Indirect causes may be due to an acute demyelinating process resulting from prior infections outside the CNS.
- Non-infectious causes may follow immunization (known as acute disseminated encephalomyelitis; ADEM).
- ***Viruses***: mumps, measles, rubella, enteroviruses, herpes simplex (HSV), cytomegalovirus (CMV), Epstein-Barr (EBV), Pox group, HIV, rabies, lymphocytic choriomengitis, and dengue. Globally, the most common viral cause of sporadic encephalitis in adults and children is HSV.
- ***Non-viral***: rickettsia, fungi (Cryptococcus), protozoa (T. gondii), bacterial pathogens, such as Mycoplasma species and rickettsia are rare and invariably involve inflammation of the meninges out of proportion to their encephalitic components.
- Parasites and fungi are rare causes of encephalitis, and usually affect immune-compromised patients.
- ***Noninfectious causes*** include the demyelinating process in acute disseminated encephalitis. In many cases, a cause is not identified despite extensive investigations.

Pathophysiology

- Portals of entry are virus specific. Many viruses are spread through person-to-person contact though most cases of HSE (herpes

simplex encephalitis) are thought to be a reactivation of dormant HSV in the trigeminal ganglia.
- Mosquitoes or ticks transmit arbovirus, and rabies virus is transferred via an infected animal bite or secretions.
- Some viruses, e.g. varicella-zoster virus (VZV) and cytomegalovirus (CMV), develop clinically apparent encephalitis only in immune-compromised states.
- Generally, viruses replicate outside the CNS and gain entry into the CNS either by haematogenous spread or by travelling along neural pathways (e.g., rabies virus, HSV, VZV).
- The entrance of the virus into the brain leads to the disruption of cell function, perivascular congestion, haemorrhage, and a diffuse inflammatory response that disproportionately affects grey matter over white matter.
- Immune-mediated mechanisms have a predilection to the white matter where it causes multifocal demyelination (observed in acute disseminated encephalitis and post infectious encephalomyelitis seen most commonly in measles infection, Epstein-Barr virus and CMV infections).

Epidemiology

- The highest incidence is in infants. There is no sex predilection but individuals at the extremes of age are at highest risk.
- HSV is the most common cause of encephalitis with HSV type 1 accounting for about 90% of cases. About 10% of HSV encephalitis is due to HSV type 2 especially in neonates in whom it causes a disseminated infection.
- Older infants and children are much more likely to have localized CNS infection exclusively due to HSV type 1.
- VZV is a common cause of encephalitis while CMV encephalitis occurs almost exclusively in the immune-compromised.

Clinical features

- The symptoms and signs are often non-specific. They may however present with a prodrome consisting typically of several days of fever, nausea and vomiting, lethargy, and myalgia followed by severe headache, altered consciousness, meningism, seizures, focal neurological signs, behavioural changes or speech and language disturbances.

- There is often an overlap with acute bacterial meningitis, as either may have common features including fever, headache and meningism. In this situation, patients are often described as having meningoencephalitis.
- Children who are immune-compromised may have a more sub-acute presentation. History of a rash may be present in those with chickenpox (VZV), slapped cheek syndrome (parvovirus), and hand, foot and mouth disease (enterovirus).
- The history of the presence of a cold sore or stomatitis (caused by HSV type 1) may be relevant. Parotitis, abdominal pain (pancreatitis) or testicular pain (orchitis) may be present in those with mumps.

Investigations

- ***FBC***: The full blood count may show lymphocytosis in viral encephalitis.
- ***Blood cultures*** may identify bacteria or fungi. Specific clinical findings should direct sampling from other sites, such as the nasopharynx, urine, stool and throat.
- ***Throat swab*** for identification of respiratory viruses, measles or enteroviruses, Chlamydophilapneumoniae and M pneumonia (culture, PCR or immunofluorescence).
- ***Nasopharyngeal aspirate:*** respiratory viruses (influenza A, parainfluenza, adenoviruses and respiratory syncytial virus (RSV)) using PCR, antigen detection or culture.
- ***Stool samples*** may reveal infection with enteroviruses, mumps virus or measles viruses through PCR or culture.
- ***Vesicles***: swab should be taken from the vesicle for detection of VZV or HSV by immunofluorescence or PCR.
- ***Serological testing***: Serum and CSF IgM antibodies or a rising IgG concentration may allow the identification of infection with HSV, VZV, CMV, EBV, RSV, adenovirus, influenza A and B virus, parainfluenza and enteroviruses, rotavirus, M pneumoniae and arboviruses.
- ***CSF Analysis***: CSF should be sent for the following investigations in all children with suspected encephalitis: microbiology (microscopy, culture and sensitivity analysis), virology (PCR for HSV types 1 and 2 and VZV), and biochemistry (glucose, lactate). The CSF may show mononuclear pleocytosis and a moderately

elevated protein level, or the CSF red blood cell count may be raised (haemorrhagic encephalitis).

- The presence of eosinophils suggests infection with helminths, but it is also seen with toxoplasma infection, Rickettsiae rickettsii and infection with M pneumoniae. A decreased CSF glucose concentration suggests a bacterial, fungal or protozoan aetiology.
- About 10% of patients with viral encephalitis may have a normal CSF, especially in the early stages of the illness. The gold standard for the diagnosis of encephalitis is identification of the infectious agent in the CSF.
- For virus detection, isolation in cell culture has now been replaced by the amplification of a specific nucleic acid from CSF by PCR.
- **Neuroimaging (CT, MRI):** provides direct evidence of brain involvement from an infectious process.
- **EEG**: a sensitive indicator of cerebral dysfunction showing non-specific diffuse high amplitude slow waves of encephalopathy. The EEG may show the typical pattern of periodic lateralizing epileptiform discharges in the temporal lobe with slow-wave complexes occurring at intervals of 2-3 s. in HSV encephalitis.

Management

- Supportive measures include the treatment of immediate complications such as reduced consciousness, seizures and raised intracranial pressure, circulatory support and the treatment of aspiration pneumonias.
- Empiric Treatment should be guided according to the likely aetiology. Usually broad-spectrum antimicrobials and antiviral treatment should be initiated pending the results of diagnostic studies.
- ***Specific treatment****:* Acyclovir 10 mg/kg 8 hourly (HSV, VZV).

Prognosis

- The prognosis is dependent on the virulence of the virus and the patient's health status. Very young age (<1 yr.), an immune-compromised status, and preexisting neurologic conditions are associated with poorer outcomes.
- HSV encephalitis in neonates and children is associated with poor long-term neurological outcomes despite appropriate therapy.

- Untreated HSE has a mortality of 50-75%, and virtually all untreated or late-treatment survivors have long-term motor and mental disabilities.
- SSPE is uniformly fatal, although the disease course may last from several weeks to many years.
- VZVE has a mortality of 15% in immune-competent patients and virtually 100% in immune-suppressed patients.
- Rabies encephalitis and acute disseminated encephalitis have virtually 100% mortality.

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5.8 Lesions of the upper and lower motor neurons

Upper motor neuron consists of;

- Corticospinal neuron; Corticonuclear neuron (corticobulbar).
- Cerebral cortex (pyramidal tract) –> Precentral gyrus (motor strip) → internal capsule (posterior limb) → brainstem → spinal cord.
- 85% cross to the opposite side.
- ***Upper motor neuron (UMN) lesions*** are lesions arising from the cerebral cortex and corticospinal tracts down to, but not including, the anterior horn cell in the dorsal spinal cord (interruption of the corticospinal and corticonuclear tract along its course).
- **Lower motor neuron consists of:**
- Neurons from the brain stem and spinal cord:
  - efferent motor fibres;
  - terminal axons and motor end plates;
  - muscle fibres.
- Anterior horn cells in spinal cord → nerve roots → nerve plexus → peripheral nerves.
- ***Lower motor neuron (LMN) lesion***–is any lesion originating from the anterior horn cell, peripheral nerve, neuromuscular junction, or muscle (degeneration of the motor neuron and peripheral nerves).

Pathogenesis

- The activities of skeletal muscle are controlled by the central nervous system (CNS) through the Upper motor neuron (UMN) and the Lower motor neuron (LMN).
- The UMN controls the LMN activities through two different pathways–Pyramidal and Extra pyramidal tracts.
- Upper motor neurons (UMN) are the first order neurons and are responsible for conveying impulses for voluntary motor activity through descending motor pathways that make up the upper motor neurons (cortico-spinal and cortico-bulbar tracts).
- The UMN through the LMN exerts supra-nuclear control over the LMN of the cranial and spinal nerves.
- About 85-90% of cortico-spinal fibres decussate at the inferior part of the medulla and continue as the lateral cortico-spinal tract, while the remaining 10-15% continue to descend ipsilaterally as the anterior cortico-spinal tracts.
- Unilateral pyramidal tract lesions above the point of decussation will thus result in weakness opposite to the site of the lesion.

- The extrapyramidal tract is involved in gross automatic motor movements, works with the autonomic nervous system to help with posture and muscle tone and has more influence over midline structures than those in the periphery.
- Lower motor neurons (LMN), or second order neurons are cranial and spinal nerves.
- LMNs arise from motor neurons in the spinal cord and the motor component of cranial nerve nuclei in the brain stem (those in cranial nerves innervate the skeletal muscles associated with the movements of the eyes, tongue, chewing, swallowing, and vocalizing).
- ***Pseudobulbar palsy*** (bulbar relates to the medulla)–results from a bilateral upper motor neuron lesion of the corticobulbar pathways in the pyramidal tract. It produces bilateral UMN weakness of the muscles of the tongue (XII), face (VII), speech and swallowing (IX, X).
- ***Bulbar palsy*** is a similar disorder to pseudobulbar palsy but is caused by lower motor neuron lesions. It presents as LMN weakness of the muscles innervated by the facial (VII), glossopharyngeal (IX), Vagus (X) and hypoglossal (XII) nerves. A speech deficit occurs due to paralysis or weakness of the muscles of articulation, which are supplied by these cranial nerves.

Clinical features–Upper motor neuron lesion

- Initial phase–flaccid limbs and loss of deep tendon reflexes.
- Long term–spasticity and hyperreflexia. Muscle weakness in general involves the whole limb e.g. monoplegia, hemiplegia, paraplegia.
- Weakness shows a predilection for certain muscle groups in a pyramidal distribution i.e. in the upper limbs, weakness occurs more in extensors than flexors while in the lower limbs weakness occurs more in flexors than extensors.
- Dual innervations from each hemisphere result in the sparing of the upper face, muscles of mastication, the palate and tongue with a unilateral UMN lesion.
- Ankle & patella clonus–extensor plantar response.
- Absent abdominal reflexes.
- Pseudo-bulbar palsy.

Causes of UMN lesions

- Cerebrovascular accident (stroke) is most common.
- Intracranial tumours.
- Cervical spine injury.

Clinical features of Lower motor neuron lesions

- Muscle wasting.
- Muscle weakness–may involve muscle groups in the distribution of a spinal segment/root, plexus or peripheral nerve, or, generalized limb involvement affecting proximal or distal muscles or following a specific distribution, e.g. fascioscapulohumeral dystrophy.
- Hypotonia.
- Loss of reflexes.
- Fasciculation/Fibrillations.
- Associated changes in the skin, hair and nails.
- Bulbar palsy.

Causes of LMN lesions

- Motor neuron disease.
- Peripheral nerve neuropathy e.g. Diabetic neuropathy.
- Poliomyelitis–anterior horn cell affected.
- Spinal cord injury/tumours–with nerve root compression.

Localizing the site of lesion

- *UMN lesions*–contra lateral weakness with UMN signs occurs for lesions above the decussation of the pyramids whereas it is on the same side for lesions below the decussation.
- *Spinal cord lesions* often give UMN signs below the level of the lesion and LMN signs at the level of the lesion.
- C1–C5
  - Upper limbs: UMN
  - Lower limbs: UMN
- C6–T2
  - Upper limbs: LMN
  - Lower limbs: UMN
- T3–L3

  - Upper limbs: normal
  - Lower limbs: UMN
- L4–S2
  - Upper limbs: normal
  - Lower limbs: LMN
- The site of lesions can further be localized by the associated symptoms e.g.
- A lesion of the motor cortex may be associated with frontal signs, dysphasia, hemianopia, disturbance of higher sensory function e.g. agnosia.
- A brain stem lesion may also cause dysarthria, dysphagia, Horner's syndrome, cerebellar signs, spinothalamic sensory loss.
- A cord lesion may also cause sphincter symptoms, a sensory level, and bilateral motor signs.
- Root lesions may present with back pains and sciatica.
- Weakness of the biceps with absence of the biceps reflex, with upper motor neuron signs in the legs suggests cord disease (e.g. a disc) at C5/6 (LMN at that level, UMN below).
- Weakness of thumb abduction, wasting of the thenar eminence and numbness in the thumb and lateral 21/2 fingers suggest median nerve pathology.

Investigations

- These will depend on the suspected underlying cause but will involve routine blood tests, imaging of the brain and brain stem (either CT scan or MRI) and electromyography.

Management

- Treatment will be directed to the underlying cause.
- Postural changes can help with drooling of saliva and may prevent aspiration in patients with bulbar palsy.
- Supportive measures may include baclofen and physiotherapy for spasticity, anticholinergics for drooling.
- Management should involve speech and language therapists.

Complications

- Paralysis.

- Incontinence (urinary/faecal).
- Pressure sores.
- Seizure disorders.
- Psychological dysfunction.
- Progression of underlying disease.

Prognosis

- This depends on the underlying cause.

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5.9 Cerebellar disorders

- Disorders of the cerebellum can arise from congenital, acquired or hereditary conditions.
- The cerebellum is prone to most nonspecific diseases affecting other parts of the CNS as well as certain diseases specific to it.

Neuroanatomy

- The cerebellum lies dorsal to the pons and medulla and consists of two lateral cerebellar hemispheres and a medial portion, the vermis.
- It is connected to the cerebrum by three pairs of peduncles. It receives inputs from spinal cord, cortical and subcortical structures.
- Although the cerebellum does not initiate movement, it interacts with areas of the brain that initiate movement thus promoting synchrony and the accuracy of movement required for purposeful motor activity.
- The modulation and coordination of muscular activity by the cerebellum are important in skilled voluntary movement, posture and equilibrium.

Aetiology

- Congenital: developmental anomalies (cerebellar hypoplasia, Dandy-Walker syndrome, Arnold-Chiari malformation), cerebral palsy.
- Infections: viral; acute e.g. varicella, chronic e.g. HIV, post-viral syndrome (e.g. post infection cerebellar syndrome); bacterial (meningoencephalitis/abscess), parasitic (toxoplasmosis).
- Toxins: heavy metals, carbon monoxide poisoning.
- Space occupying lesions: Posterior fossa tumours/intracranial abscess–may cause hydrocephalus and conning of cerebellar tonsils.
- Vascular: stroke, usually with other brain stem features.
- Drugs: barbiturates, phenytoin.
- Metabolic: Wilson’s disease.
- Trauma.
- Genetic.

Features of cerebellar disorders

- As the cerebellum is associated with motor control, lesions produce a range of movement disorders (ataxias).
- Lesions of the midline vermis cause truncal ataxia, while lesions of the cerebellar hemispheres cause limb ataxia on the ipsilateral side. Speech disturbance occurs in bilateral lesions.
- ***Incoordination of movement (ataxia):*** This can involve the limbs, gait, speech and eye movements. This may present as ataxic gait (limbs/trunk), dysmetria i.e. difficulty bringing the limbs smoothly and accurately to a specific target in space, dysdiadochokinesia, intention tremor, decomposition of movement, dysarthria (slurred speech) and nystagmus.
- Midline lesions can produce severe gait and truncal ataxia. As they extend they can cause fourth cranial nerve lesions and severe ipsilateral arm tremor, marked nystagmus, vertigo and vomiting, and blockage of CSF flow (obstructive hydrocephalus).
- Cerebellar hemisphere lesions can produce classic ipsilateral limb ataxia (intention tremor, past pointing and mild hypotonia). Limb rebound can be demonstrated by gently pushing down an outstretched arm and then suddenly releasing, causing the arm on the affected side to suddenly fly upwards. Lateral lesions tend to produce more subtle nystagmus (maximal looking towards the side of the lesion).
- ***Hypotonia***: may present with pendular deep tendon reflexes.
- ***Disequilibrium and vertigo/vomiting.***
- ***Delays in the initiation and termination of movement.***

Examination

- Check eyes: ophthalmoplegia, nystagmus, papilloedema.
- Get the patient to stick out his/her tongue and move it from side to side (movement slowed).
- Ask the patient to repeat "baby hippopotamus"–look for dysarthria and abnormal speech rhythm.
- Examine arms for limb ataxia: rebound of outstretched arms, finger-nose test for past pointing, dysdiadochokinesis.
- Examine leg co-ordination with the heel-shin test.
- Check limb power, tone and reflexes–mild hypotonia and hyporeflexia.

- Ask the patient to sit up with arms crossed–looking for truncal ataxia.
- Ask the patient to walk heel-to-toe (to elicit any gait ataxia).

Diagnosis:

- Diagnosis is clinical and often by imaging.

Investigations:

- Blood tests–FBC, LFT, copper and ceruloplasmin.
- Electroencephalogram (EEG). Neuroimaging, typically MRI.

Treatment:

- Treatment is usually supportive unless the cause is acquired and reversible e.g. surgery for structural lesions (tumour, hydrocephalus).

Prognosis:

- Depends on the cause.

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SECTION 6:

RESPIROLOGY

ABONYI, L. E.

6.1 Upper respiratory tract infection

- Upper respiratory tract infections (URTI) are acute infections of the upper airway namely the nose, sinuses, pharynx and larynx.
- Commonly, tonsillitis, pharyngitis, laryngitis, sinusitis, otitis media and the common cold.

Epidemiology

- Incidence is about 18.8 billion worldwide and about 3000-4000 deaths per year.

Classification

- ***Rhinitis*–**Inflammation of nasal mucosa.
- ***Laryngitis*–**Inflammation of the larynx.
- ***Rhino sinusitis*–**Inflammation of the nose and the nasal sinuses: frontal sinuses, etc.
- ***Rhino pharyngitis or the common cold***–Inflammation of the nares, pharynx, hypopharynx, uvula and tonsils.
- ***Pharyngitis***–Inflammation of the pharynx, hypopharynx, uvula and tonsils.
- ***Epiglottitis***–Inflammation of the superior portion of the larynx and the Supraglottic area.
- ***Laryngotracheitis***–Inflammation of the larynx, trachea and subglottic area.
- ***Tracheitis***–Inflammation of the trachea and subglottic area.

Aetiology

- Viruses, namely Respiratory syncytia virus (RSV), Rhinovirus, Influenza virus, Para-influenza virus, Adenovirus and Enterovirus are common causes.
- Bacterial causes are implicated in about 15% of cases and include group A beta haemolytic streptococcus, S. Pyogenes and Pneumonia, H. influenza, C. diphtheria, and B. pertussis.
- Group A beta haemolytic streptococcus pharyngitis usually presents with the sudden onset of pains on swallowing and fever.
- Otitis media and sinusitis are common complications of streptococcal pharyngitis.

Clinical features

- It is characterized by cough, sore throat, running nose, nasal congestion, headache, low grade fever, facial pressure and sneezing.

Treatment

- Treatment depends on the underlying cause. Judicious use of antibiotics in the case of bacterial URTI may reduce complications otherwise it is not indicated for viral URTI and can lead to drug resistance, increased cost of treatment and usually no change in duration or severity of the disease.
- A single oral dose of nasal decongestant in the common cold is moderately effective in relieving congestion in adults but not recommended for children less than twelve years old.

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6.2 Croup

- A heterogeneous group of mainly acute and infectious illnesses causing bark-like cough, hoarseness and stridor.
- Also called laryngotracheobronchitis.
- Most common cause of stridor in children.
- Viral causes include Para-influenza (most common cause), RSV, Influenza, Adenovirus, Measles and rarely Mycoplasma Pneumonia (Atypical bacteria).

Epidemiology

- Eighty per cent (80%) of cases occur in children under five years.
- The peak age range is 6 months to 3 years.
- It is commoner in males, ratio 3:2.

Pathophysiology

- Infection starts from the nasopharynx and spreads downward to the larynx and trachea.
- Mucosal swelling and secretions encroach on the airway from the subglottic area.
- Inflammation in the small airway in severe cases may cause atelectasis, ventilation/perfusion mismatch and hypoxia.

Clinical history

- Presence of upper respiratory prodrome like rhinorrhoea, pharyngitis and mild cough.
- Progression of symptoms.
- Change in voice or aphonia.
- Preference for the sitting position over lying.
- Associated activity e.g. eating, playing with toys.

Physical examination

- Vital signs–there may be fever, increased respiratory rate.
- General appearance is the child looking toxic, irritable or anxious which may suggest hypoxia.

- Severity–stridor, decreased air entry and the presence of drooling of saliva.
- If the child prefers a tripod/sniffing position, it suggests laryngeal or higher air way obstruction e.g. epiglottitis.

Diagnosis

- Diagnosis is clinical however AP x-ray of the neck may show the "steeple sign" which is subglottic narrowing.
- Lateral x-ray of the neck is important to rule out a foreign body, acute epiglottitis, and retropharyngeal abscess.

Differential diagnosis

- Infections e.g. epiglottitis, diphtheria, retropharyngeal abscess.
- Tumours e.g. subglottic haemangioma.
- Trauma e.g. laryngeal fracture, foreign body.
- Metabolic–hypocalcaemia.
- Congenital e.g. Tracheomalacia, vascular ring.
- Immunologic–spasmodic croup has an allergic component.

Treatment

- Humidified inhalation using a steam-filled room or a cool mist tent.
- Racemic epinephrine via nebulizer, 0.5 mls of 2.25% solution diluted with normal saline.
- Steroids though there are conflicting findings but may be beneficial, Dexamethasone 0.6 mg/kg single dose parenterally or orally.
- In case of pending respiratory failure, the patient should be admitted into ICU for intubation and airway management.

Complications

- Respiratory failure, Dehydration, Pulmonary oedema, Hypoxia.

Prognosis

- Begins to recover after 3-5 days, most patients recover completely.
- Some children who had croup have a higher likelihood of increased bronchial reactivity.

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6.3 Foreign body aspiration

Background/Epidemiology

- The defence mechanisms to keep the airway free and clear of extraneous matters include
- Physical actions of the epiglottis and arytenoid cartilage in blocking the airway.
- Intense spasm of the true and false vocal cords when any object comes near it.
- Highly sensitive cough reflex with afferent impulses generated throughout the laryngo-tracheobronchial tree.
- More common in children less than 3 years, the peak age is 1-2 years.
- 73% occur in children less than 3 years.
- There is no racial predilection.
- Slightly more common in males.
- Aspiration is the most common cause of unintentional injury in children younger than 1 year in the USA.

Pathophysiology

- Aspiration of a foreign body is more common in children because they cannot chew well due to the lack of molar teeth, leaving chunks of food to be swallowed.
- The propensity to talk, laugh and play while chewing is high.
- Children often examine even nonfood substances with their mouth.
- Most common entities aspirated are small food items such as nuts, peanuts, improperly chewed pieces of meat, sunflower seeds, fragments of raw carrots, dried beans, popcorn, water melon seeds, small toys or their parts, etc.
- The commonest site of lodging is the right main bronchus because of the anatomy of the trachea bifurcation where the left is more acute.

Clinical presentation

- A child usually presents with a sudden episode of coughing or choking while eating with subsequent wheezing, coughing or stridor.

- Sometimes the choking episode is not witnessed and at other times it is not recalled at the time of history taking.
- The worst-case scenario is when acute aspiration causes total or near total occlusion of the airway resulting in death or hypoxic brain damage.
- Sometimes aspiration is not suspected and the child will present with persistent cough or recurrent cough, recurrent pneumonia, lung abscess or focal bronchiectasis, haemoptysis.

Examination

- Auscultation may reveal new abnormal airway sounds such as wheezing, stridor or decreased breath sounds.
- Examination findings are often but not always unilateral, if it passes the carina the breath sound is usually asymmetric.
- Lack of abnormal findings upon physical examination does not preclude the possibility of an airway foreign body.

Differential diagnosis

- Asthma, bronchitis, pneumonia.

Work up

- X-ray, most foreign bodies are food materials and are radiolucent.
- May show an area of focal over inflation or atelectasis, or opacification of the distal lung.
- CT scan, chest CT may show the material in the airway, focal airway oedema or focal over inflation.
- Bronchoscopy, if history and physical are diagnostic, there is no need for work up. Rigid bronchoscopy should be done.

Treatment

- Heimlich manoeuvre–if the child is in respiratory distress and is unable to talk or cry, complete airway obstruction is probable and the likelihood of morbidity or mortality is high.
- Bronchodilators or steroids should not be used to remove a foreign body.
- Unless there is evidence of bacterial infection of the secretion an antibiotic is not recommended.

- Prompt rigid bronchoscopy for removal within the same day is the gold standard of treatment.

Complications

- Atelectasis, bronchiectasis, lung abscess and rarely pneumomediastinum or pneumothorax as a complication of removal.

Prognosis

- Is excellent if removal is early.

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6.4 Childhood asthma

Introduction/Epidemiology

- Asthma is a chronic inflammatory disorder of the airway characterized by increased airway hyper responsiveness and mucus production leading to variable airway limitation that is at least partially reversible.
- An estimated 150 million people are affected worldwide with an estimated 5 billion dollars as the pharmacotherapeutic cost.
- In Nigeria asthma is second only to pulmonary tuberculosis as a chronic disease of childhood.
- The incidence is increasing worldwide and is more common in urban rather than rural areas.

Pathophysiology

- Chronic inflammation is now accepted as the major disorder in asthma, many cells and cellular elements play a role, in particular mast cells, eosinophils and epithelial cells.
- The inflammation also causes an increase in the existing bronchial hyper responsiveness to a variety of stimuli.
- The pathologic features of asthmatic airways include, denudation of the airway epithelium, mucus overproduction, goblet cell hyperplasia, basement membrane thickening with variable sub epithelial fibrosis, bronchial smooth muscle hyperplasia and cellular infiltration with eosinophils, lymphocytes and neutrophils.
- In an acute exacerbation, bronchoconstriction occurs quickly to narrow the airways in response to exposure to a variety of triggers including allergens, irritants and viral infection.
- Airway limitation results from bronchial spasm, mucosal oedema and excessive tenacious secretions.
- Triggers in asthma include, viral infection, dusts, pollutants, allergens e.g. pollen, animal dander, certain foods, exercise, drugs, and physiologic factors like stress.

Clinical features: history

- Symptoms and signs depend on the severity. Symptoms are usually variable, intermittent, worse in the night and may have triggers e.g. exercise, drugs.

- Common symptoms include, wheeze, shortness of breath, cough, chest tightness.
- There may be a family history of asthma or a personal history of other atopic conditions.

Physical examination

- There may be respiratory distress, evidence of hyperinflation, hyper resonance on percussion and respiratory rhonchi on auscultation.

Investigation

- Reduced lung function using a spirometer, PEFR, FEV1, FVC.
- Provocation tests, six-minute aerobic exercise, a metacholine or histamine test.
- Other ancillary investigations e.g. blood eosinophils, IgE levels, pulse oximetry, chest radiograph (when indicated) and stool microscopy for the ova of parasites.

Differential diagnosis

- Reflux oesophagitis, tracheo-oesophageal fistula,
- Bronchiolitis, pneumonia, pulmonary tuberculosis, laryngeal papillomatosis,
- Congestive cardiac failure, dilated cardiomyopathies,
- Foreign body aspiration and tracheomalacia.

Treatment

- The National Heart, Lung and Blood Institute (NHLBI) developed the current asthma management guidelines that have 4 components for optimal management as follows:
- Regular assessment every 2-4 weeks until good control is achieved.
- Monitoring every 2-4 times per year to maintain good control and good lung function.
- Control of factors leading to asthma severity, eliminate or reduce problematic environmental exposures and treat comorbid conditions like sinusitis and gastro-oesophageal reflux.
- Asthma pharmacotherapy, long-term control versus quick relief medication, classification of asthma severity for anti-inflammatory

pharmacotherapy, the step-up-step-down approach and asthma exacerbation management.
- Patient education, provide a 2-part care plan, a daily management and action plan for asthma exacerbation.
- For a child, the parents, the child as well as the school teacher will be educated.

Severity of asthma

- Every asthmatic patient can only be properly managed if properly classified based on the severity category of the patient and the severity of the episode or attack. There are 4 disease categories (GINA guidelines) namely intermittent, mild persistent, moderate persistent and severe persistent.
- **Intermittent:** day symptoms ≤2 day per week, night symptoms ≤2 nights per week. PEF ≥80%. No daily medication is required.
- **Mild persistent:** day symptoms >2 per week, night symptoms >2 nights per month, PEF ≥80%. The preferred treatment is low-dose inhaled corticosteroid.
- **Moderate persistent:** day symptoms daily, night symptoms 1 night per week, PEF >60% but <80%. The preferred treatment is a low-medium dose of inhaled corticosteroid plus a long-acting inhaled B_2 agonist.
- **Severe persistent:** day symptoms are continuous, night symptoms are frequent, PEF <60%. The preferred treatment is high-dose inhaled corticosteroid plus a long-acting inhaled B_2 agonist.

Severity and management of an asthma episode or attack

- Four levels are identifiable: mild, moderate, severe and life-threatening.
- **Mild**: PEF >60%, FEV1 >60%, SaO_2 ≥94%, talks in sentences, pulse rate is normal.
- Treatment is salbutamol inhalation, 4-6 puffs for <6 years and 8-12 puffs for >6 years.
- **Moderate:** wheeze is loud, talks in phrases, PEF 40-60%, FEV1 40-60%, SaO2 94-90%, pulse rate is elevated 100-200.
- Treatment is salbutamol nebulization every 20 minutes for 2 doses then inhalation every 1-4 hours.
- **Severe/Life threatening**: patient may be cyanosed, confused or altered sensorium, chest may be silent, FEV1 <40%, PEF <40%, SaO_2 <90%, pulse rate >200.

- Treatment is nebulized salbutamol every 20 minutes for 3 doses; if no improvement, do continuous nebulization with IV salbutamol at 15 μg/kg and ipratropium, oral prednisolone 1 mg/kg for 5 days.

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6.5 Rhinitis

- Rhinitis is also called the common cold and because the sinus mucosa is involved it is more correctly termed rhino sinusitis.
- It is a viral illness with symptoms of rhinorrhoea, and nasal obstruction. Systemic symptoms like fever and myalgia are absent or mild.

Aetiology

- Common pathogens include rhinoviruses, coronaviruses, respiratory syncytial viruses (RSV) and human metapneumovirus.

Epidemiology

- It is more common in cold periods (the rainy season and the harmattan season) than other periods.
- Young children have an average of 6-8 colds per year and the frequency decreases with age to about 2-3 episodes per year in adults.
- Children in out-of-home daycare during the first year of life have an increased frequency of colds.

Pathogenesis

- The viruses are spread by small particle aerosols, large particle aerosols and direct contact.
- The respiratory viruses have evolved different mechanisms to avoid host defences.
- Rhinovirus and adenovirus result in the development of serotype-specific protective immunity.
- Influenza has the ability to change antigens presented on the surface of the virus and behave as though there were multiple viral serotypes.
- Viral infection of the nasal epithelium can be associated with the destruction of the epithelial lining e.g. Influenza and adenovirus.
- There is no apparent histologic damage as in rhinovirus, RSV and coronavirus.
- Regardless of the type, infection is associated with an acute inflammatory response characterized by the release of a variety of

inflammatory cytokines and infiltration of the mucosa by inflammatory cells which are responsible for the symptoms.

Clinical features

- Symptoms occur 1-3 days after infection, the first symptom is usually a sore throat or a scratchy throat then nasal obstruction and rhinorrhoea, with cough in about 30% of cases.
- Influenza, RSV and adenovirus are more likely to be associated with fever than rhino and corona viruses.
- The duration of illness is usually 1 week; about 10% of cases may last up to 2 weeks.
- A change in colour of the nasal discharge is not an indication of sinusitis or bacterial super infection.
- Examination of the nasal cavity shows a swollen erythematous nasal turbinate.
- The main task of a physician is to exclude other pathologies that are more serious or treatable.

Differential diagnosis

- A foreign body in the nasal cavity, sinusitis, Pertussis, congenital syphilis.

Investigation

- Lab studies are not usually helpful, viral culture, PCR and viral serology can detect the virus but usually not indicated. Bacterial cultures are only useful if group A streptococcus or Bordetella pertussis is suspected.

Treatment

- Treatment is symptomatic. Antibacterial therapy is of no benefit.
- Neuraminidase inhibitors like oseltamivir reduce the frequency of influenza-associated otitis media but the limitation is that it must be started within 48 hours to have good effect.
- Fever is infrequently associated with the common cold and an antipyretic is not indicated.
- For rhinorrhoea, first generation antihistamine reduces it by 25-30%; the effects appear to be related to anticholinergic effects.

- Sore throat is usually mild; aspirin should not be used because of Reye syndrome in children with influenza.
- Cough is usually not severe and suppression with drugs is usually not necessary.
- Other remedies like vitamin C and inhalation of warm humidified air are not effective.

Prevention

- Chemoprophylaxis or immunoprophylaxis are not available for the common cold; influenza vaccine is available but influenza causes only a small percentage of colds.
- Interrupting the chain of transmission is useful, the use of a protective face mask and good hand washing are important.

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6.6 Lower respiratory tract infection

Introduction

- A lower respiratory tract infection is infection below the level of the larynx.
- It includes bronchiolitis, bronchitis, pneumonias, lung abscess and laryngotracheobronchitis (CROUP).

Epidemiology

- The estimated incidence of LRTI is 30 per 1000 per year. It affects about 150 million worldwide and leads to about 2.7 million deaths per year.
- It is more common in males and amongst preterm infants.

Aetiology

- Viruses namely influenza, RSV, Human metapneumovirus, Varicella zoster virus.
- Bacterial causes include Strep. Pneumoniae, Haemophilus influenza, and Staphylococcus, Influenza can affect both the upper and lower respiratory tract.

Clinical features

- Symptoms of LRTI include shortness of breath, weakness, fever, cough and fatigue.

Pathophysiology

- The pathologic process is acute inflammation of the airways and pulmonary tissues due to viral or bacterial infections below the level of the larynx.
- About 45% of children hospitalized for pneumonia are of viral aetiology.

Treatment

- Antibiotics for bacterial cases.

- Supportive treatment including fluids, oxygen, bronchoscopy and surgery (where indicated).

Prevention

- Vaccination helps in preventing pneumonia, the vaccine is mostly against influenza viruses, adenovirus, measles, rubella, streptococcus pneumonia, Haemophilus influenza and Bordetella pertussis.
- LRTIs place a considerable strain on the health budget and are generally more serious than upper respiratory tract infections.

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6.7 Pneumonia

Introduction

- Pneumonia is inflammation of the lung parenchyma.
- It causes approximately 3 million deaths worldwide particularly in developing countries, and accounts for about 29% of under-five deaths.
- There are about 158 million episodes of pneumonia per year.
- Pneumonitis is used for non-infectious cases e.g. aspiration, hydrocarbons, foreign bodies and radiation injuries, however some scholars use the words interchangeably.

Aetiology

- Bacteria; Streptococcus pneumonia, Haemophilus influenza type B, Staphylococcus aureus, Klebsiella pneumoniae, Mycoplasma pneumoniae, Chlamydia pneumonia, Streptococcus pyogenes.
- Viruses; Respiratory syncytia virus, Influenza and Para influenza viruses, Adeno viruses, Measles virus.
- Fungus; Mucomycosis, Histoplasma capsulatum, Aspergillus species.
- A combination of pathogens is found in 25-40% of cases.
- Risk factors for developing pneumonia include; lung diseases like asthma, cystic fibrosis, anatomic problems like tracheoesophageal fistula and gastroeosephageal reflux disease.
- Others are neurologic disorders e.g. cerebral palsy, immunodeficiency disorders, haemoglobinopathies e.g. sickle cell anaemia.

Epidemiology

- Pneumonia is more common in those under five years of age, the peak age is 2-3 years and it decreases slowly afterwards. It is more common in winter and fall in the United States of America.

Pathogenesis

- The lower respiratory tract is usually kept sterile by defence mechanisms namely the mucocillary escalator, secretory IgA, the cough reflex, macrophages and other immunoglobulins.

- Viral pneumonia usually results from the spread of infections along the airway leading to injury of the respiratory epithelium, obstruction from swelling, and increased secretions which can lead to atelectasis, oedema and ventilation-perfusion mismatch in severe cases.
- Viral pneumonia may be complicated by secondary bacterial infection.
- In bacterial pneumonia, the pathologic process varies according to the organism e.g.:
- Staph aureus manifests by confluent bronchopneumonia which is often unilateral and characterized by the presence of areas of haemorrhagic necrosis, irregular areas of cavitation of lung parenchyma resulting in pneumotocele, emphysema or bronchopulmonary fistulae.
- In cases of recurrent bacterial pneumonia, an underlining disorder should be sought for such as agammglobulinaemia, hypogammaglobulinaemia, chronic granulomatous disease, cystic fibrosis, ciliary dyskinesia and tracheoesophageal fistula.

Clinical features

- **History:** pneumonia is often preceded by symptoms of upper respiratory infection. Tachypnoea is the most consistent clinical manifestation of pneumonia.
- Fever is usually present and higher in bacterial than in viral pneumonia.
- In severe cases, there may be cyanosis and respiratory fatigue.
- In older children bacterial pneumonia may begin suddenly with chills and rigor and high temperature, cough, chest pains, rapid respiration, anxiety and occasional delirium.
- **Examination** reveals crackles, rhonchi and signs of respiratory distress, reduced breath sounds over the affected area.
- There may be abdominal distension from swallowed air or ileus.
- The liver may be palpably enlarged because of downward displacement of the diaphragm secondary to hyperinflation or congestive heart failure.
- Other findings may be due to complications like pleural effusion, empyema and pneumothorax.

Investigation

- Chest radiograph may reveal an infiltrate which may be patchy or homogenous depending on the type of pneumonia; it may also reveal a complication such as pleural effusion, empyema and pneumothorax.
- A complete blood count may be useful in differentiating bacterial from viral pneumonia. In bacterial pneumonia the WBC count is usually in the range of 15000-40000/mm^3 with granulocyte predominance while in viral pneumonia WBC may be normal or elevated but with lymphocyte predominance. ESR and C-reactive protein levels are elevated.
- A definite diagnosis of bacterial infection requires the isolation of the organism by culture: the blood culture yield for pneumococcal pneumonia is about 10%.
- Lung aspiration has a higher yield but is invasive and rarely recommended.

Treatment

- Treatment of suspected bacterial pneumonia is based on the presumptive cause, the age of the child and the severity of the illness.
- Mild cases–the first line drug is amoxicillin, and the second line: cefuroxime, amoxicillin clavulanate.
- Atypical bacteria e.g. Mycoplasma pneumonia, chlamydia pneumonia; macrolides like azithromycin are preferred.
- Severe or hospitalized children: parenteral cefotaxime or ceftriaxone is indicated.
- If staph pneumonia is suspected, vancomycin or clindamycin should be included.

Prognosis

- For uncomplicated community-acquired pneumonia, the prognosis is good.
- There is clinical improvement within 48-96 hours. Complications should be suspected if the patient is not improving on appropriate antibiotic therapy.

Complications

- Direct spread from bacterial infection in the thoracic cavity like pleural effusion, empyema and pericarditis.
- Haematologic spread like meningitis, suppurative arthritis and osteomyelitis.

Prevention

- Hib vaccine, 13 valent pneumococcal conjugate vaccine and measles have reduced the incidence of pneumonia hospitalization in countries where it is universally given.

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6.8 Pleurisy, Pleural effusion and Empyema

Pleurisy

- Pleurisy is inflammation of the pleurae which impairs their lubricating function and causes pain when breathing.
- The most common cause in children is bacterial pneumonia, heart failure, rheumatologic cases and metastatic intra-thoracic malignancy.
- Other causes include–tuberculosis, lupus erythematosis, aspiration pneumonitis, uraemia, pancreatitis and rheumatoid arthritis.
- Inflammatory processes in the pleura are divided into three types namely, dry or plastic, serofibrinous and serosanguinous or empyema.

Dry or plastic pleurisy

- This may be associated with bacterial pulmonary infections or in the course of upper respiratory tract infections, tuberculosis and connective tissue diseases e.g. Rheumatic fever.

Pathology

- It is usually limited to the visceral pleura with a small amount of serous fluid and adhesions between the pleural spaces.

Clinical features

- Major signs and symptoms are those of the primary disease. The principal symptoms are pains exaggerated by chest movements e.g. coughing or straining. The pain is usually a dull ache, localized on the chest wall and referred to the shoulder.
- Friction rub may be heard early in the disease and there may be a dull percussion note.
- Chest X-ray shows a diffuse haziness of the pleural space or a sharply demarcated dense shadow indistinguishable from a small amount of pleural exudate.

Differential diagnosis

- Pleurodynia, trauma to the rib cage (fracture), herpes zoster, gall bladder disease.

Treatment

- The mainstay is the treatment of the underlying disease e.g. antibiotics for bacterial pneumonia.
- Immobilization or the use of cough syrup is not indicated.

Serofibrinous pleurisy

- Serofibrinous pleurisy is most commonly associated with lung infections or inflammatory conditions of the mediastinum or abdomen, connective tissue diseases like systemic lupus erythematosus (SLE), periarthritis and rheumatic fever.

Clinical features

- It is usually preceded by dry or plastic pleurisy. Initial features are those of the dry type but as fluids accumulate pleuritic pains may subside.
- When fluid becomes large there may be cough, dyspnoea, retractions, orthopnoea or cyanosis.
- Physical findings depend on the amount of effusion. There may be a dull percussion note, reduced tactile fremitus, and a shift of mediastinum away from the affected side and reduced or absent breath sounds.
- In addition, there may be signs of the underlying illness e.g. crackles, rhonchi in pneumonia.
- Chest X ray shows a homogenous density obliterating the normal lung markings. A small effusion may reveal the obliteration of the costophrenic and cardiophrenic angles or the widening of the interlobar septa.

Differential diagnosis

- Empyema, hydrothorax, haemothorax, chylothorax.

Investigations

- Thoracocentesis–fluid is used for specific gravity, usually >1.015 for serosanguinous exudate, cell count and culture and sensitivity. Cytology for malignant cells. Protein levels >3 g/dl suggest exudates. Pleural fluid lactate dehydrogenase >200 iu/l, PH less than 7.20 in exudates.

Treatment

- Treat the underlying disease. In large effusions draining the fluid gives symptomatic relief. If a large amount of fluid greater than one litre is drained, rapid re-expansion pulmonary oedema may occur. If the fluid becomes purulent, tube drainage with an underwater seal is preferred.
- Analgesics may be required.
- Specific antibiotic therapy and oxygen supplementation may be given in acute pneumonia.

PURULENT PLEURISY (EMPYEMA)

- This is defined as the accumulation of pus in the pleural space. The most common cause is pneumonia due to streptococcus pneumonia. Staphylococcus aureus is more common in developing countries.
- The incidence due to Haemophilus influenza has reduced since the introduction of Haemophilus influenza type B vaccine (HIB vaccine).

Epidemiology

- It is more common in infants and pre-school age children and complicates pneumonia in 5-10% of cases.

Pathology

- Empyema has 3 stages namely; exudative, fibrinopurulent and organizational.
- During the exudative stage; fibrinous exudate forms on the pleural surface while in the fibrinopurulent stage; a fibrinous septa forms causing loculation of the fluid and the thickening of the parietal pleura while during the organizational stage there is fibroblast

proliferation and pockets of loculated pus with thick abscess cavities.
- If the pus is not drained, a bronchopulmonary fistula and pyothorax may form.
- The dissection of pus through the chest wall is called empyema necessitans.

Clinical features

- Initial signs and symptoms are those of bacterial pneumonia. Most patients are febrile with respiratory distress and may appear very ill.
- Physical examination findings depend on the severity and may reveal tracheal deviation to the contralateral side, a dull percussion note, and a decreased breath sound on the affected side.
- Thoracocentesis differentiates it from serofibrinous pleurisy as it yields pus.

Investigations

- Chest X-ray shows homogenous opacity but the absence of a shift of fluid with a change of position which suggests loculated empyema. The effusion is empyema if the gram stain is positive for bacteria. PH is less than 7.2 (acidic) and neutrophil is greater than 100,000/litres.
- In pneumococcal empyema, the culture yield is about 38% of cases. Pneumococcal PCR analysis is helpful in culture of negative cases.

Complications

- Bronchopulmonary fistula or pyopneumothorax.
- Purulent pericarditis.
- Pulmonary abscess.
- Peritonitis, Osteomyelitis.

Treatment

- A systemic antibiotic is indicated and the selection is based on the in vitro sensitivity or on the likely organisms suspected.
- Thoracocentesis and possibly chest tube drainage with or without a fibrinolytic agent.

- If empyema is diagnosed early, antibiotic therapy and thoracocentesis achieve a cure. Antibiotic treatment is required for 3-4 weeks because resolution is slow.
- Video-assisted thoracoscopic surgery (VATS) or open decortication may be required in some cases.
- Fibrinolytic agents used include; streptokinase and urokinase mixed with normal saline.

Prognosis

- Long-term clinical prognosis for adequately treated empyema is excellent.

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6.9 Bronchiolitis

Introduction

- Acute bronchiolitis is an inflammatory airway disease leading to the narrowing and obstruction of the airway.
- It is more common in infants and predominantly caused by virus. Respiratory syncytia virus is responsible for more than 50% of the causes.
- Other causes include Para influenza virus, adenovirus, mycoplasma and occasionally human metapneumo virus.

Epidemiology

- It is seasonal with a peak during winter and early spring. Bronchiolitis is more common in infants and younger children. It has a male preponderance.
- Other risk factors include infants delivered prematurely, day-care attendance, non-breastfed infants and children living in crowded conditions.

Pathophysiology

- A host of anatomic and immunologic factors seem to play a significant role in the severity of the clinical syndrome, RSV infection incites a complex immune response.
- Eosinophils degranulate and release eosinophil cationic protein which is cytotoxic to airway epithelium.
- Other mediators include the IgE antibody, chemokines like interleukin 8, macrophage inflammatory protein (MIP) 1a and the altered regulation of surfactant proteins A and B.
- All these suggest a complex cellular dysregulation producing the clinical syndrome of bronchiolitis which is characterized by bronchial obstruction with oedema, mucus and cellular debris.
- This syndrome is more severe in young infants because resistance to air flow is inversely proportional to the fourth power of the radius of the bronchial passage.

Clinical features

- History of onset, duration and associated factors, birth history including the gestational age of birth, the history of intubation or the oxygen requirement are important.
- Acute bronchitis is usually preceded by exposure to older children with minor respiratory syndrome within the previous week.
- The infant usually develops a mild upper respiratory tract infection with sneezing and rhinorrhoea, fever and reduced appetite.
- This is followed gradually with respiratory distress, paroxysmal wheezy cough, dyspnoea and irritability. Very young infants less than 2 months may present with apnoea.
- Physical examination may reveal respiratory distress, tachypnoea, rhonchi and in severe cases hypoxaemia and hypercarbia.

Investigation

- Chest radiograph may show evidence of hyperinflation of the chest and patchy atelectasis.
- Pulse oximetry may show decreased saturation depending on severity.
- A trial of a bronchodilator in a wheezing infant may help in diagnosing asthma and differentiating it from bronchiolitis.
- A full blood count may show leukocytosis.

Treatment

- Treatment of a wheezing patient depends on the underlying cause, the use of bronchodilators like albuterol is unpredictable.
- The use of inhaled corticosteroid may be helpful in children that have atopy, food allergy or eczema otherwise there are conflicting reports about the benefits in bronchiolitis.
- The use of ipratropium bromide is contraindicated.
- The mainstay of treatment is supportive, if the patient is hypoxaemic, the use of humidified cool oxygen is indicated. The use of a sedative is contraindicated because of respiratory depression.
- Nasogastric feeding is required in very tachypneoic children to prevent aspiration.
- Nebulized epinephrine may be helpful.

- Antibiotics have no benefit except in cases complicated with bacterial pneumonia.

Prognosis

- The case fatality rate is less than 1%, mortality and morbidity are worse in infants that have comorbidities like congenital heart disease, bronchopulmonary dysplasia and immunodeficiency.
- Death is attributable to apnoea, uncompensated respiratory acidosis or severe dehydration.

Prevention

- Preventing child-to-child or adult-to-child transmission by scrupulous hand washing especially in the nursery, at day care or in the hospital.
- Periodic immunization with Pulivisumab which works as a passive immunoprophylaxis for children at high risk of mortality.

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6.10 Pneumothorax

- A pneumothorax is the accumulation of extra pulmonary air within the chest.
- It most often results from the leakage of air from the lung. It can be primary or secondary, spontaneous, traumatic, iatrogenic or catamenial.
- A primary spontaneous pneumothorax occurs in someone without trauma or an underlying disease.
- A secondary spontaneous pneumothorax is a complication of a lung disorder but without trauma.
- A catamenial pneumothorax is when it is associated with menses and results from the passage of abdominal air through diaphragmatic defects into the chest cavity.
- A pneumothorax can occur in pneumonia usually with emphysema, secondary to a pulmonary abscess, infarct, the rupture of cysts or an emphysematous bleb in asthma and staphylococcus pneumonia.
- A patient that has cystic fibrosis, Ehlers-Danlos disease or Marfan syndrome has increased risk.

Pathophysiology

- Air enters the pleural space leading to lung collapse, hypoxaemia occurs due to alveolar hypoventilation and there may be a ventilation-perfusion mismatch.
- In a tension pneumothorax, there is an increase of positive pressure in the pleural space leading to lung compression, mediastinal structures shift to the contralateral side and there is decreased venous return and cardiac output.

Clinical features

- The onset of symptoms in a pneumothorax is usually abrupt and the severity is dependent on the extent of lung collapse and the extent of the underlying lung disease.
- There may be history of pain, dyspnoea and cyanosis.
- There may be a displacement of intrathoracic organs to the contralateral side.
- There is respiratory distress, retractions and a resonant percussion note and decreased breath sounds on the affected side.

- Chest X-ray shows a clear area of the pneumothorax (no lung markings). Ultra sound can also be used to make the diagnosis.
- In a tension pneumothorax, there may be evidence of circulatory collapse and the hearing of a hiss when a needle or tube is inserted.

Differential diagnosis

- Diaphragmatic hernia, Emphysema, Large pulmonary cavity, Overexpansion of the lung with contralateral atelectasis.

Treatment

- Treatment depends on the extent of lung collapse and the nature and severity of the underlying disease. Pleural pain may require an analgesic.
- In an emergency tension pneumothorax needle aspiration may be required and is as effective as a tube thoracotomy.
- In cases of recurrent, secondary or under tension, or if there is a greater than 5% lung collapse, chest tube drainage is necessary.
- In recurrent cases chemical pleurodesis using talc, doxycycline or iodopovidone can be done to form strong adhesion between the lung and the chest wall by sclerosis.
- An open thoracotomy through a limited incision with the plication of blebs, the closure of the fistula, the stripping of the pleura and basilar pleural abrasion is also effective in a recurrent pneumothorax.

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6.11 Tuberculosis in children

Introduction

- Tuberculosis is a chronic inflammatory disease characterized by vague constitutional symptoms and a protracted course of illness.
- Evidence of the disease dates back to 5000 BC but it was not until 1812 that Robert Koch discovered the tubercle bacilli as the cause of tuberculosis.

Epidemiology

- Tuberculosis is an infectious disease globally; about 30% of the world's population is infected by the organism that causes TB and about 8-9 million people develop the disease annually.
- Ten per cent occur in children under 15 years and there are about 3 million deaths per year of which 250,000 are children. The lifetime risk of the progression to the disease is 5-10%.
- There has been a resurgence of the incidence in the last 20 years globally because of the worsening economic situation, multi-drug resistance, the HIV pandemic and the increase in the number of displaced persons due to wars, conflicts and insurgence.

Microbiology

- Aetiologic agents for tuberculosis include Mycobacterium Tuberculosis, M. Bovis, M. Africanus and M. Microti. Mycobacterium Avian Complex is an opportunistic infection.
- They are G-resistant, non-motile, non-sporulating, aerobic pleomorphic rods.
- Their cell wall contains peptidoglycan and complex lipids which resist discoloration by acid and alcohol, hence they are classified as acid-fast bacilli.
- They multiply slowly and remain viable in macrophages.
- The most important transmission source is the sputum of persons with open TB.

Pathophysiology

- TB is a chronic inflammatory disease in which inflammation of prolonged duration takes place with tissue destruction and attempts at repair proceeding simultaneously.
- The tubercle bacilli being of low toxicity evoke an immune response called delayed hypersensitivity reaction.
- The specific type of chronic inflammation in Tb is called granulomatous inflammation and when it involves a focal area it is called granuloma which is referred to as a tubercle which is classically characterized by the presence of a central area of caseous necrosis.
- The primary infection is usually situated in the sub-pleural region and measures about 2 mm to 2 cm in diameter, it is called the primary focus and with regional lymph node involvement it becomes the primary complex or Ghon's complex.
- It may be symptomless or associated with minor symptoms like malaise, anorexia or muco-cutaneous manifestations like erythema nodosum or phlyctenular conjunctivitis.
- The primary complex may be contained by the host immune system or may progress to active disease (the risk of progression is about 15% in the first 10 years).
- The potential outcome is that the disease may be contained, progress to primary parenchymal disease or a reactivation disease later in life.
- The primary infection can progress to an active disease in the following ways;
- The primary focus and regional nodes may merge and give rise to an area of consolidation.
- Extensive caseation and liquefaction can develop and give rise to cavity formation.
- Atelectasis or emphysema may result from inflamed nodes compressing the bronchi.
- Nodes may erode into blood vessels giving rise to a haematogenous spread to other organs (disseminated TB).
- Affected nodes may develop fibrosis and encapsulations and harbour viable TB bacilli, persisting for years and becoming a source of reactivation later.
- It takes different time periods for the development of clinical evidence of various forms of TB from the time of the primary infection e.g. Pulmonary TB occurs within a few months of the

primary infection, miliary and meningeal TB 2-3 months, TB adenitis 3-9 months, bones and joints several years, and renal and gonadal TB over a decade (Wallgren timetable).

Pulmonary tuberculosis

- It is the most common form of TB, occurring alone or in combination with other forms in 70% of cases.

Clinical features

- Early symptoms are usually vague and include chronic cough (>21 days), fever, anorexia, weight loss or failure to thrive and haemoptysis.
- Clinical signs include dyspnoea, tachypnoea, and localized wheezing.
- There may be decreased breath sounds, crepitation or bronchial breath sounds. A chest examination may be normal.
- In older children, there may be productive cough and chest pain.

Investigation

- A tuberculin skin test e.g. the Mantoux test, the antigen used is a purified protein derivative (PPD) which contains 5 tuberculin units given intra dermally and read after 24-72 hrs.
- It proves infection but not necessarily indicates the disease state. Interpretation: 0-4 mm negative, 5-9 mm borderline, >10 mm positive, irrespective of the BCG vaccination.
- In HIV infected children and severely malnourished children, greater or equal to 5 mm is positive.
- Chest Radiograph, there is no specific pathognomonic sign of TB in the X-ray but suggestive signs include hilar adenopathy, parenchymal lesions like patchy infiltrates, consolidations, atelectasis, pleural effusions and cavities.
- Bacterial investigations, sputum or gastric washing for AFB stain. Microbiologic isolation is difficult in children. ESR is usually markedly elevated. New methods of diagnosing TB include, Lipoarabinomanan (LAM), Antigen capture ELISA assay (Gene xpert), BACTEC, MODS, PCR.

Differential diagnosis

- Pneumonia from other organisms, lung abscess, bronchiectasis, pulmonary neoplasms, congenital heart disease.

Miliary tuberculosis

- It is the most severe form of disseminated TB. The clinical manifestation is variable depending on the organism load, organ affectations and the immune status of the child.
- In addition to signs observed in pulmonary TB, there may be generalized lymphadenopathy, hepatosplenomegaly, and respiratory distress.
- Signs of meningeal irritation are observed in about 20-40% of cases.
- Differential diagnosis of the miliary picture on x-ray: sarcoidosis, eosinophilic pneumonia, pulmonary fungal infection, chicken pox pneumonia, childhood histiocytosis syndrome and lymphocytic interstitial pneumonia (LIP).

CNS tuberculosis

- It comprises TB meningitis and tuberculoma. TB meningitis occurs 2-6 months after the primary infection and is more common in children aged 6 months to 4 years.

Clinical features

- There are 3 stages:
- Stage 1: presents with non-specific features e.g. fever, headache, weight loss and irritability.
- Stage 2: there may be lethargy, nuchal rigidity, seizures, vomiting and cranial nerve palsy.
- Stage 3: hemiplegia or paraplegia, coma, decerebrate rigidity, opisthotonus, and papilloedema on a fundoscopy.
- Additional investigation: cerebrospinal fluid examination (CSF) may be straw-coloured or clear and colourless, CSF WBC is in the range of 10-500 cells/mm with lymphocyte predominance, Zeil-Nelsen (ZN) stain may yield AFB, glucose is low while protein is high.
- Prognosis is good in stage 1 but poor in stage 3.

TB of superficial lymph nodes

- It occurs 3-9 months after the primary infection, may be unilateral or bilateral, glands are usually discrete, mobile, firm and non-tender but may become matted together later.
- There may or may not be constitutional symptoms.

- Additional investigation: fine needle aspiration or an excision biopsy of the node for histology

TB of the spine

- The vertebrae are commonly the most important bones affected by TB.
- Organisms spread via a lymphatic or haematologic source to the spine.

Clinical features

- These include back pains, spinal rigidity and the limitation of spinal movement, kyphosis and scoliosis with or without gibbus.
- It may progress to paralysis which may be quadriplegia or paraplegia depending on the level of involvement.
- Additional investigation: a radiograph of the affected vertebral column which may show the destruction of the vertebral body.
- Complications include para-spinal abscess, psoas abscess, and retropharyngeal abscess.

Differential diagnosis

- Idiopathic scoliosis, acute non-tuberculous osteomyelitis, rickets, Burkitt lymphoma and histoplasmosis dubosii of the spine.

TB treatment

- Combination therapy is the rule, directly observed treatment, short-course (DOTS) is desirable at least during the intensive phase.
- First line anti-TB drugs (essential drugs, WHO) include rifampicin, pyrazinamide, isoniazid, ethambutol and streptomycin.
- The first four drugs are used during the intensive phase while isoniazid and rifampicin are used for the continuation phase.

Revised treatment guidelines for childhood TB (2013):

- TB meningitis, Miliary TB and osteoarticular TB: the intensive phase is 2 months while the continuation phase is 10 months.
- For TB pulmonary, TB lymphadenitis and other forms, the intensive phase is 2 months while the continuation phase is 4 months.
- For drug resistant TB, second line drugs (WHO, reserve drugs) are used.

Prevention

- Case finding and effective treatment, contact tracing and INH prophylaxis, BCG immunization and the general improvement of the standard of living are paramount in the prevention of TB.

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SECTION 7:

NEPHROLOGY

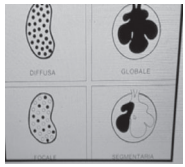
EZEONWU, B. U.

7.1 Acute glomerulonephritis (AGN)

Definition

- A group of glomerular diseases characterized anatomically by the inflammation of the glomerulus and clinically by acute nephritis.
- Acute nephritis is a syndrome of acute glomerular injury with:
  - Acute kidney injury (AKI); oliguria, azotaemia, elevated creatinine;
  - Circulatory overload from salt and water retention manifesting as hypertension, peripheral ± pulmonary oedema;
  - Haematuria with red cell casts;
  - Proteinuria which can be in the nephrotic range (nephritic-nephrotic syndrome) of >200 mg/mmol.

Basic definitions that describe the histologic findings that may be seen:



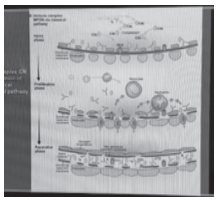
- ***Focal*:** involving <50% of the glomeruli on light microscopy (**LM**).
- ***Diffuse*:** involving >50% of the glomeruli on LM.
- ***Segmental*:** involving part of the glomerular tuft, usually focal.
- ***Global*:** involving the entire tuft and can be focal or diffuse.
- ***Proliferative*:** an increased number of cells in the glomerulus from the proliferating glomerular cells or infiltrating circulatory inflammatory cells. Exudative is when the increase in the number of cells is due to infiltration with circulatory neutrophils.
- ***Crescents*:** accumulation of the cells within the bowman's space, compressing the capillary tuft.

- **Glomerulosclerosis:** segmental or global capillary collapse with little or no filtration.

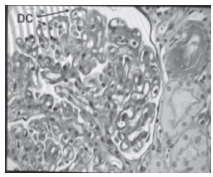
Major causes of AGN in children:

- ***Post streptococcal*** (~80% of AGN), other infectious agents are Staph, E. coli, salmonella, Syphilis, TB, CMV, HBV, HCV, EBV, malaria, Schistosomiasis, candida, PCP, and Cryptococcus.
- Other causes of AGN with their most frequent renal manifestation (RM), pathogenesis (P), glomerular pathology on LM, on fluorescence microscopy (FM) and electron (EM) include:
- ***Henoch-Schonlein purpura (HSP):*** **RM;** gross/microscopic haematuria, proteinuria, nephrotic syndrome (NS), **P;** unknown, may be an immune complex formation following the production of polymeric galactose deficient IgA in response to infection or immunization, **LM;** focal segmental mesangial proliferation ± diffuse and crescents, **FM;** IgA ± IgG and C3, **EM;** mesangial deposits.
- ***IgA nephropathy IgAN:*** **(Berger disease)**
- Causes recurrent gross or microscopic haematuria ± mild to nephrotic range of proteinuria without any systemic disease (unlike in HSP) such as SLE, Henoch-Schonlein purpura, rheumatoid arthritis, Reiter's syndrome, hepatic cirrhosis and ankylosing spondylitis with mesangial IgA deposits.
- IgA is the main Ig in mucosa secretions. Low levels in normal serum and in monomeric forms. The polymeric forms are usually catabolized in the liver.
- In humans, there are 2 subclasses: IgA_1 and IgA_2, but it is only IgA_1 that forms the nephritogenic deposits.
- In IgAN, there is defective β1-3 galactosyl-transferase activity in B cells with excessive synthesis of galactose deficient IgA_1. There are increased serum polymeric forms.
- Increased production of IgA can only cause disease in genetically predisposed individuals. An abnormal response to respiratory or GIT exposure to environmental agents (virus, food proteins such as gluten, bacteria) occurs in these individuals.
- IgA and IgA immune complexes are trapped in the mesangium where they activate an alternative pathway and initiate glomerular injury. Normal serum C3 level.
- Defective hepatobiliary clearance of the complexes leads to secondary IgAN.

- Males > females, older children and young adults, gross haematuria 1-2 days following respiratory infection, less commonly GIT or UTI.
- **RM;** gross/microscopic haematuria (1-2 days following URTI) ± proteinuria, typically ANS, others are NS, nephritic-nephrotic, rarely RPGN. Haematuria lasts a few days, subsides and then returns every few months. Proteinuria is the strongest prognostic factor. **LM** as in HSP.
- In **FM**, there is deposition of IgA > trace staining, often with C3 and properdin ± IgM, IgG and this is diagnostic, no C4 and no C1q. The presence of C1q staining > trace: consider lupus nephritis.
- EM confirms the presence of an electron dense deposit in the mesangium ± subepithelial/subendothelial.
- ***Membranoproliferative (mesangiocapillary: if there is mesangial predominance) GN*:** divided on **FM** into 3:
  - Ig deposit via the classical pathway (monoclonal from lymphoproliferative diseases and polyclonal from infections and autoimmune diseases),
  - C3 deposits from the dysregulation of the alternate pathway (C3 glomerulopathy C3GN and dense deposit disease DDD),
  - No deposits (in chronic thrombotic microangiopathy): endothelial damage is followed by repair which results in the formation of double contours and mesangial proliferation.



- It can be primary (idiopathic) or secondary. Primary was formerly divided into type 1 and type 2 (dense deposit disease DDD).
- Secondary MPGN follows chronic antigenaemia with chronic immune complex deposition as seen in SLE, HCV, HBV, endocarditis, and HIV.
- Persistent or episodic antigenaemia leads to persistent deposition of the immune complex in the subendothelial space (since the circulating complex is large and cannot traverse the GBM).
- Inflammatory cells are recruited hence the "proliferative and inflammatory" components.
- **RM;** whatever the source and composition of the deposit, an inflammatory reaction ensues and if severe, irreversible injury occurs with glomerulosclerosis.
- The most common cause of chronic GN in older children and young adults. Hypertension and haematuria are common and persistent low serum C3 is the hallmark.



- **LM;** mesangial and endocapillary proliferation, lymphocytes within glo capillaries, enlarged and hypercellular glo, lobular accentuation and double contours.
- The endothelium facing the mesangial area attaches directly to the mesangial matrix without the intervening GBM therefore circulating immune complexes have direct access to the mesangium and to the subendothelial space without having to cross the size selective GBM barrier.
- **FM;** IgG deposit type: a full house with C3 in a granular pattern + IgG, C1q and C4.
- In the C3 type: no IgG, no C1q, no C4, only C3 (in DDD there is only an intramembranous deposit whereas in C3GN there is subendothelial and mesangial deposits ± subepithelial).
- In chronic TMA, there are no deposits.
- **EM;** The displaced epithelium forms a second GBM on which they will attach: double contouring or a tram-track appearance or duplicated GBM.
- Subendothelial deposits type I and deposits in the lamina densa in type II (dense deposit disease).
- ***Anti-neutrophilic cytoplasmic antibody (ANCA)*** associated vasculitides: Wegener's disease (granulomatosis polyarteritis GPA), Churg-Strauss syndrome (eosinophilic GPA)
- ***Ventriculo-atrial shunt nephritis***, HUS, TTP, and SLE.

Acute proliferative GN

- Characterized histologically by the diffuse proliferation of glomerular cells with an influx of leucocytes caused by immune complexes incited by exogenous (post-infectious) or endogenous (in SLE) antigens. The prototype is post-streptococcal GN.

Acute post-streptococcal GN (APSGN)

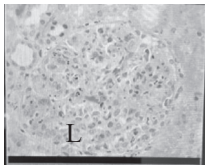
- Caused by nephritogenic strains of group A β haemolytic strep, 7-15 days after pharyngitis and/or tonsillitis (M types 12, 4, 1, 3) and 4 to 6 weeks after impetigo, eczema, and pyoderma (M types 49, 55, 57, 60 associated with overcrowding, poor hygiene).

Pathogenesis

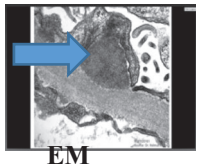
- Immune complex mediated GN. Probably, antigens are deposited within the glomeruli and complement fixation is activated.
- Antigens so far isolated are the zymogen precursor of exotoxin and glyceraldehyde phosphate dehydrogenase, which initiate the classical immune response.

Pathophysiology:

- Deposition of antigens within the glomerulus induces an antibody response leading to the activation of several proinflammatory mediator pathways.
- There is a decreased glomerular filtration surface, reduced GFR, and a proportionate reduction in renal blood flow. Tubular function is preserved but distal tubular flow is decreased due to the reduced GFR with a resultant increase in distal tubular reabsorption via the renin-angiotensin-aldosterone pathway.
- The reduced filtration and increased absorption lead to oliguria, volume overload.
- With a severe reduction in GFR solutes are retained; urea, phosphate, potassium, acids.
- **LM;** there is diffuse infiltration of glomeruli by neutrophils and monocytes, diffuse proliferation of endothelial and mesangial cells, the swelling of endothelial cells, and crescent formation in severe cases, thus the capillary lumen is obliterated (bloodless glomeruli).



- **FM** shows granular IgG and C3 in the glomerular basement membrane (GBM) and mesangium,
- **EM** shows subepithelial humps.



EM

Clinical features

- It occurs in children of 4-12 years, M > F, smoky cola-coloured urine, oedema in 85%, oliguria, malaise, anorexia and lethargy are non-specific.
- Gross haematuria in 25-33%, microscopic haematuria in 100%.

- Hypertension in 25-33% ± encephalopathy (seizure, headache, vomiting, coma), circulatory congestion with dyspnoea, orthopnoea and cough, dilutional anaemia.

Laboratory findings

- Active urine sediments with RBCs, and cellular, granular casts. A non-nephrotic range urine-protein-creatinine ratio (UPCr), 4% may show massive proteinuria.
- An anti-streptolysin O titre of >333 Todd unit or >200 IU/L or a rising titre in post pharyngeal APSGN (not very helpful because it is found in up to 20% of healthy children and bound by skin lipid).
- ***Streptozyme*** assay detects antibodies to other strep antigens such as DNAse B, hyaluronidase.
- ***C3*** is low, also in SLE, MPGN, shunt nephritis, HBV, and HCV.
- ***C4*** is normal unlike in SLE, MPGN, shunt nephritis, HBV, and HCV where it is low.
- ***ANCA*****,** ANA, ds-DNA, CR protein, LFT, electrolytes, creatinine, calcium, phosphate, FBC, ESR.
- ***Renal*** scan, cx-ray.
- ***Other*** specific tests: blood film, stool culture if HUS, blood culture if sepsis, Igs if IgA.
- ***Indications*** for a renal biopsy:
  - low C3 longer than 3 months,
  - age less than 4 and >15 years
  - UPCr >200 mg/mmol,
  - recurrent nephritis,
  - moderate proteinuria for >6 months,
  - extra-renal features such as purpuric rash, arthralgia, malar rash, etc.
  - microscopic haematuria >12 months,
  - Rapidly progressive GN (RPGN) which is glomerular disease (proteinuria, haematuria, RBC casts), rapid loss of renal function with rising creatinine over days or weeks,
  - Family history.

Management

- It is supportive:

- Initial fluid restriction; insensible loss 200-400 mls/m^2 (20-40 mls/kg) plus the previous day's output and additional losses and salt restriction till the oedema subsides and urine output increases.
- Bed rest, no protein restriction except in renal failure and give protein of high biologic value (fully utilized with little or no nitrogenous waste).
- Diuretics in circulatory congestion, antihypertensives (avoid ACEIs), adequate calories.
- Antibiotics if an active infection exists so as to prevent the spread of the nephritogenic strain to close contacts, this does not reverse the GN, management of ARF if present.

Course/prognosis

- Excellent prognosis: >95% have a full recovery within 2-3 weeks, <1% progress to Chronic GN, <1% develop RPGN (crescentic GN) requiring immunosuppression.
- The C3 level returns to normal by 8-10 weeks.

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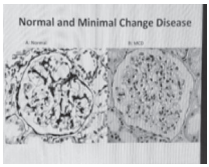
7.2 Nephrotic syndrome

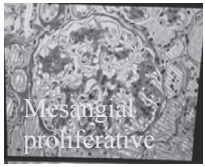
Definition

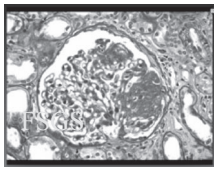
- Syndrome of heavy proteinuria, hypoalbuminaemia, massive generalized body swelling and hypercholesterolnaemia.

Epidemiology

- The peak age is between 2 and 6 years. The male to female ratio is 2:1. The Finnish type occurs more in Scandinavia.
- ***Nephrotic syndrome (NS) can be congenital***: The first 3 months of life either from TORCHES infection or the most common cause of congenital NS; the Finnish type which is an autosomal recessive disorder due to a mutation in the gene that encodes nephrin (*Infantile NS*: 3-12 months) **OR**
- ***Primary/Idiopathic*** with no systemic disease and the majority will be clinically steroid sensitive (SSNS) and histologically minimal change disease (MCD) in 85%, mesangial proliferative histology in 5%, and Focal Segmental Glomerulosclerosis in 10% **OR**



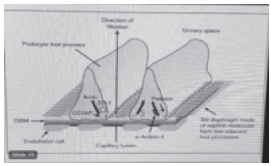




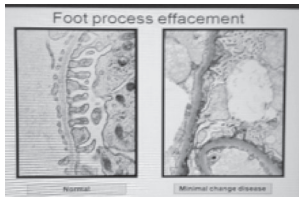
- ***Secondary NS*** in which NS is a secondary feature of glomerular diseases such as post-infectious GN, membranous nephropathy (isolated or in association with hepatitis B, syphilis, neuroblastoma, SLE, gold), membranoproliferative GN, lupus nephritis, HIVAN, Henoch-Schonlein purpura nephritis.

Pathophysiology

- The size and the charge dependent barrier function of the glomerulus are due to: fenestrated (70-100 nm diameter) endothelial cells, the collagenous porous and anionic glomerular basement membrane (GBM) and the visceral epithelial cells i.e. the podocyte whose interdigitating foot processes are separated by a 20-30 nm wide filtration slit diaphragm.



- The slit diaphragm maintains the size-selective distal diffusion barrier to the filtration of proteins. Three proteins identified (nephrin, podocin and CD2 associated protein) form a molecular connection with the actin cytoskeleton to ensure an effective barrier function.
- Normally the size-selective glomerular cells allow low molecular weight (LMW) proteins (Ig light chains, α1/β2 microglobulin, retinol-binding protein and amino acids) to filter in the urine but restrict macromolecules (albumin, IgG).
- In terms of size and charge, the albumin molecular radius is 36Å/70 kilodaltons and highly anionic and therefore not filtered via the anionic 42Å glomerular pore.



- In NS, there is both size-selective (neutral IgG is filtered) and charge-selective (anionic albumin, plasma proteins are filtered) defects because of injury to podocytes that produce polyanionic acid proteoglycans of GBM; heparan sulphate.
- In MCD, some immune T dysfunction results in the elaboration of cytokine that causes visceral cell injury/effacement of foot processes with loss of glomerular polyanions leading to proteinuria.
- Albumin leaks heavily leading to hypoalbuminaemia. The 99% usually reabsorbed by the proximal tubule is also catabolized in tubular lysozymes. Oncotic pressure reduces, extravasated (extravascular) fluids at the arteriolar end of the capillaries are not reabsorbed at the venular end and fluid accumulates, vascular spaces are under filled, renal blood flow reduces (GFR), sodium and water retention occur in response which is still extravasated **(the underfill theory)**.
- More likely, is the fact that there is overfilling of the vascular spaces from primary sodium retention unless the plasma albumin concentration falls below 1.5-2 g/dL.
- This is so because the distribution of fluid between the vascular spaces and the interstitium is dependent on the transcapillary oncotic pressure gradient (capillary oncotic pressure minus interstitial oncotic pressure).
- And hypoalbuminaemia is associated with a parallel decline in interstitial albumin concentration due to the lower entry of albumin

into the interstitium, so the transcapillary oncotic pressure gradient is near normal till the plasma albumin concentration falls to <1.5-2 g/dL.

- Therefore, unless the plasma albumin concentration falls below 1.5-2.0 g/dL, oedema in NS is due to the overfilling of the vascular spaces because of abnormal sodium retention that occurs in glomerular diseases due primarily to the increased tubular reabsorption of sodium in the collecting tubules **(overfill theory)**.
- In a damaged glomerulus Na delivery is low and reabsorption is high so that the net urine Na is small. Proteinuric nephrons retain salts (the presence of protein in the tubules induces the salt retention in overfill theory) so in diffuse podocyte disease, there is marked oedema while in focal disease there may not be oedema because the normal nephrons compensate.
- This overfill theory has been hypothesized to follow unresponsiveness to atrial natriuretic peptide and increased Na-K-ATPase activity.
- Evidence for this is that as the steroid corrects the defect in NS, there is significant urinary sodium excretion with the partial resolution of oedema before any substantial increase in plasma albumin concentration is noted.
- These two theoretical mechanisms explain the massive oedema.
- As the liver replaces the lost proteins, other lipids are synthesized (LDL, VLDL which convey lipids into the arterial wall) but the HDL which retrieves cholesterol from the arterial wall is low (synthesis requires protein) also there is the loss of lipoprotein lipase in urine. These lead to hypercholesterolnaemia.
- The contraction of intravascular volume will lead to haemoconcentration and acute renal failure.
- The oedema, ascites, the loss of β properdin and Immunoglobulins in urine predispose to infection.
- The accumulation of lipids, the loss of antithrombin III in urine and haemoconcentration lead to thrombosis.

Clinical features

- ***History*** of recurrent body swelling, initially at the area of low tissue pressure (periorbital) and waning as the patient ambulates (gravitates), foamy urine ± reduced urine volume and frequency, haematuria, skin rash, arthralgia, exposure to heavy metals, insect bite (secondary causes).

- ***Findings*** of varying degrees of fluid retention; facial puffiness, pitting leg oedema, ascites, scrotal/labial oedema, pleural effusion. Normal blood pressure (may be high in secondary NS).

Diagnosis

- ***Definitive diagnosis*** is the demonstration of nephrotic range proteinuria (≥3+ with a urinary dipstick, an on-the-spot urine protein creatinine ratio of >2 mg/mg OR >300 mg/g OR >30 mg/mmol, urine protein excretion of >40 mg/m^2/hour OR >300 mg/dL), hypoalbuminaemia of <25 g/L OR 2.5 g/dL and hypercholesterolnaemia of >220 mg/dL OR >6 mmol/L.
- ***Other ancillary*** investigation results may show elevated PCV, normal electrolyte, urea and creatinine.
- eGFR = Ht x K/creatinine value in mg/dL (Schwartz) **K**: 0.45 for children up to 2 years; 0.55 for children above 2 years and adolescent females; 0.70 for adolescent males.
- Recently modified Schwartz for eGFR for all genders and ages = 0.413 x (height in cm/serum creatinine in mg/dL).
- ***Normal eGFR values*** 2-8 weeks (65.8 ± 24.8), >8 weeks (95.7 ± 21.7), 2-12 years (133.0 ± 27.0), 13-21 years males (140.0 ± 30.0), 13-21 years females (126.0 ± 22.0)**,** ± abnormal in secondary NS.
- Calcium and phosphate, full blood count, HBsAg, HBC, ASO titre, C_3 complement level, antinuclear antibody, autoantibody to double-stranded DNA, genotype, malaria parasite, ESR, RVS, urine M/C/S (risk of infection and also a trigger of relapse) for casts and UTI, Chest x-ray, 2D-ECHO, renal biopsy.
- Abdominopelvic ultrasound scan for the kidney including the renal size is normal but it may be abnormal in secondary NS.
- **Renal length:** for ≤1 yr. = 4.98 + 0.155 x age in months. For >1 yr. = 6.79 + 0.22 x age in years.

Differential diagnosis

- ***AGN*****;** Not recurrent, oedema is usually not massive, proteinuria is not heavy, has a red blood cell cast, circulatory overload (hypertension, dilutional anaemia), a normal lipid profile.
- ***Kwashiorkor*****;** Suggestive nutritional history, no proteinuria, oedema is non-pitting.
- ***Protein-losing enteropathy;*** suggestive history, no proteinuria, increased faecal α_1- antitrypsin.

- ***Congestive cardiac failure;*** Tachycardia, tachypnoea, tender hepatomegaly, no proteinuria.
- ***Hepatic failure;*** Jaundice, hypoalbuminaemia, hyperammonaemia with cerebral dysfunction, oedema, fetor hepaticus, hyperestrogenaemia with palmer erythema and spider angiomas.

Treatment

- Admit in the first presentation, relapse with complications, haemoconcentration (>48%),
- ***Supportive*:**
  - Monitor BP, weight, pulse volume, capillary refill time, JVP.
  - Input/output (normal urine flow rate is 1-4 mls/kg/hour), abdominal girth, sodium restriction to 1.5-2 g (60-80 mmol)/24 hours, high biologic value (animal) protein 0.8-1.0 g/day.
  - Plasma transfusion if serum albumin is <20 mg/dl: 1 g/kg (5 mls/kg) of 20% albumin over 2-4 hours, frusemide 1-2 mg/kg.
  - Oral (IV in severe NS because of intestinal wall oedema) frusemide 1-2 mg/kg/day in 2 ÷ doses ± thiazides, metolazone.

Definitive for SSNS:

- The KDIGO (Kidney Disease: Improving Global Outcomes) Clinical Practice Guideline for the treatment of steroid sensitive nephrotic syndrome (SSNS) is as follows;
- **Prednisolone** 60 mg/m^2/day (2 mg/kg/day) single morning dose for 4-6 weeks (max 60 mg), then 40 mg/m^2 (1.5 mg/kg) alternate mornings for 2-5 months (max 40 mg), with tapering e.g. reduce monthly by 25%. If febrile illness develops while on an alternate day steroid, change to a daily steroid at the same dose as the alternate day dose until the illness is resolved to reduce the frequency of relapse. 4-12 weekly follow-up with daily home urinalysis to detect proteinuria before oedema ensues.
  - ***With steroid therapy***, the patient can go into remission i.e. *3 consecutive days of trace or zero proteinuria* (>90% of cases), relapse (>70%), can become a frequent relapser, steroid dependent or steroid resistant.
  - ***It is advised*** that following a relapse, urine M/C/S, FBC, MP, should be done and the suspected or confirmed trigger treated; UTI, URTI, observe while on treatment (if there is no peripheral

oedema). After treatment if the patient still has ≥2+ proteinuria or oedema abinitio, then start the steroid.

- ***Infrequent relapsing SSNS*** *3 consecutive days of ≥2+ proteinuria following a home dipstick;* recommence prednisolone 60 mg/m^2/day single morning dose till remission, then an alternate dose for 4 weeks and follow up.
- ***Frequently relapsing SSNS*** *≥2 relapses in 6 months after the initial steroid response* and ***Steroid dependent SSNS*** *relapse on steroid therapy or within 14 days of discontinuation*; reinduce remission, an alternate dose for 3 months. If not effective, give the alternate dose daily.
- If steroid toxicity develops, add steroid sparing agents in the form of alkylating agents, Levamisole, calcineurin inhibitors (CNIs), MMF, rituximab:
- Cyclophosphamide 2 mg/kg/day for 12 weeks after remission is achieved with steroid OR 500 mg/m^2 per dose in 200-250 mls of 5% D/S over 2-4 hours, monthly for 3 months.
- Chlorambucil 0.1-0.2 mg/kg/day for 8 weeks, a 2^{nd} course of alkylating agent is not advised.
- Levamisole at 2.5 mg/kg/alternate days for 12 months, thereafter, taper prednisolone as above.
- Cyclosporin at 4-5 mg/kg/day in 2 doses for 12 months ± alternate day steroid.
- Tacrolimus 0.1 mg/kg/day in 2 doses for 12 months.
- MMF 1200 mg/m^2/day in 2 doses for 12 months.
- Use Rituximab only if others fail or a serious adverse effect with another therapy develops.
- Steroid resistance, *no resolution of proteinuria on steroid 60 mg/m^2*: 8 weeks of therapy are needed to define this.
- CNIs for 6 months and stop if partial (at least a 50% decrease of proteinuria from the initial value) or complete remission is not achieved, otherwise continue till 12 months. Combine with low dose steroid 0.1-0.5 mg/kg/48 hourly and ACEIs/ARBs OR MMF ± high dose steroid.
- Secondary NS Cyclophosphamide, Cyclosporin, MMF, etc.
- Indications for renal biopsy in NS: age <1 year or >12 years on presentation. Atypical features: rash, macroscopic haematuria, low plasma C3, etc. Moderate to severe hypertension, Persistent ARF, Frequent relapser, Before cytotoxic therapy, Steroid resistance, Steroid dependent NS.

Complications of NS

- Due to the disease; acute renal failure, infection (peritonitis, sepsis, cellulitis by strep pneumoniae and gram negative), thrombosis, hypothyroidism, hypocalcaemia, abdominal pain from peritonitis or ischaemia of mesenteric vessels.
- Due to drugs like steroids, cyclophosphamide, cyclosporin, frusemide, etc.

Prognosis of NS

- Over 70% of SSNS patients will relapse and 50% of them will develop frequently relapsing or steroid dependent disease.

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7.3 Acute kidney injury

Definition

- Acute kidney injury: AKI (formerly acute renal failure) is a clinical syndrome characterized by a rapid reduction in renal excretory function due to varied causes. An abrupt or rapid decline in renal function as evidenced by a rapid rise in serum creatinine or a decrease in urine output.
- An increase in serum creatinine (SCr) by ≥0.3 mg/dl (≥26.5 μmol/l) within 48 hours or an increase in SCr to ≥1.5 times the baseline which is known or presumed to have occurred within the prior 7 days or a urine volume <0.5 ml/kg/h for 6 hours and divided into pre-renal (volume responsive AKI), renal or post-renal.
- ***Pre-renal AKI*** is functional and not associated with any additional histopathological change, due to decreased renal perfusion, which leads to a reduction in the glomerular filtration rate (GFR).
- It can result from hypovolaemia (vomiting, diarrhoea and haemorrhage), decreased effective circulating volume (CCF, vasodilatation of septic shock, fluid redistribution of nephrotic syndrome) and drugs (ACEIs, NSAIDS, diuretics, cyclosporin A, Tacrolimus, quinine).
- ***Renal*** or Intrinsic AKI occurs when there is damage (potentially reversible) to the structures of the nephron, such as the glomeruli (glomerulonephritis), tubules (interstitial nephritis, rhabdomyolysis, ATN which can be ischaemic or toxic), or vessels (HUS, vasculitis, malignant hypertension). Acute tubular necrosis (ATN) is a major cause and it follows ischaemic or nephrotoxic injury to the kidney.
- ***Post-renal*** AKI is due to urinary outlet obstruction; renal stone, urethral stricture, etc.
- AKI is more common in hospitalized patients due to the complication of other systemic illnesses such as sepsis, with a poorer prognosis especially if renal replacement therapy is indicated.
- Pre-renal AKI and ischaemic ATN may occur as a continuum of the same pathophysiological process and together account for 75% of the causes of AKI.

Pathophysiology

- SCr clearance depends on the GFR whose driving force is the gradient from the glomerulus to the Bowman space. GFR = Glomerular hydrostatic pressure minus the Bowman capsule hydrostatic pressure minus the glomerular oncotic pressure. Glomerular pressure depends primarily on renal blood flow (RBF) and is controlled by the combined resistances of renal afferent and efferent arterioles. GFR is auto-regulated with changes in the mean arterial pressure (MAP) via the myogenic mechanism, and tubuloglomerular and neuro-hormonal feedback.
- In the myogenic mechanism, the afferent arteriole constricts with an increase in MAP and dilates with a decrease in MAP.
- In tubuloglomerular feedback, when there is increased distal salt delivery (high GFR), the macula densa responds by releasing adenosine which constricts the afferent arteriole and GFR reduces. When there is low salt delivery, the macula densa activates the juxtaglomerular apparatus to release renin which activates angiotensinogen to angiotensin.
- In neuro-hormonal feedback, when there is low renal perfusion, angiotensin II is released leading to the constriction of the efferent arteriole > the afferent arteriole, renal vasodilators: prostaglandin E2 and prostacyclin antagonize the vasoconstriction.
- Regardless of the cause of acute kidney injury (AKI), reductions in RBF represent a common pathologic pathway for decreasing GFR.
- AKI may develop in 3 clinical patterns: as an adaptive response to severe volume depletion and hypotension, with structurally intact nephrons; in response to cytotoxic, ischaemic or inflammatory insults to the kidney, with structural and functional damage; and with obstruction to the passage of urine.
- Pre-renal injury is reversible once the volume is restored otherwise intrinsic AKI due to ischaemic acute tubular necrosis (ATN) results. When renal perfusion is compromised, the afferent arterioles relax their vascular tone to decrease renal vascular resistance and maintain renal blood flow. Intra-renal prostaglandins mediate vasodilatation of the renal microvasculature to maintain renal perfusion and tubules respond to decreased renal perfusion by appropriately conserving salt and water, increasing urine osmolality and decreasing urine sodium.
- In intrinsic AKI, prolonged ischaemia of the nephrons leads to vascular and tubular defects: the loss of the brush border and cell

polarity (resulting in decreased GFR) and neutrophils' adherence to damaged endothelium with the release of inflammatory cytokines will lead to patchy tubular necrosis and apoptosis (resulting in an increase in SCr) then desquamation of the cells (cast formation) with tubular lumen obstruction (resulting in renal failure) and glomerular filtrate back leak.

- Endothelial injury with ATP depletion, alteration in endothelin or nitric oxide, prostaglandin regulation of vascular tone, resultant vasoconstriction, impaired autoregulation and oxygen radical production occur.
- Thus, the primary event is tubular damage with the failure to reabsorb filtered solute, then compensatory renal vasoconstriction with a reduction in GFR.
- Dedifferentiation of viable cells may follow, with proliferation and differentiation to normal epithelium

Clinical features of the trigger illness

- Diarrhoea, bloody in HUS, birth asphyxia, previous UTI, poor urine stream, recent throat/skin infection, vomiting, convulsion, poor capillary refill time, etc.
- AKI can be classified using the **RIFLE** staging criteria developed by the Acute Dialysis Quality Initiative (ADQI). It uses SCr and urine output and includes 3 levels of renal dysfunction (**R**isk, **I**njury, **F**ailure) and 2 clinical outcomes (**l**oss and **e**nd stage renal disease).
- The use of SCr is limited because as GFR falls creatinine secretion increases and the rise in serum creatinine is less, and the creatinine excretion is much greater, than the filtered load, resulting in overestimation of the GFR.
- The AKI criteria in use in the paediatric population include paediatric RIFLE (pRIFLE), the Acute kidney injury network (AKIN), neonatal KDIGO (nKDIGO), and neonatal RIFLE (nRIFLE).
- Biomakers for structural injury (neutrophil gelatinase–associated lipocalin NGAL, IL-8) appear early in the stage and reflect tubular injury while those of functional injury (serum cystatin C, SCr) appear during the failure stage and reflect changes in GFR.
- To accommodate the small changes in SCr not captured by RIFLE, acute kidney injury network (AKIN) criteria were formulated. They identify all stage 1 diseases missed by RIFLE but miss most of I and F stages of RIFLE, thus both sets of criteria are used to identify AKI.

- **Stage 1** AKIN SCr increases to ≥0.3 mg/dl (≥26.5 mmol/l) or ≥150% to 200% (1.5- to 2-fold) from the baseline. Note that the definition of urine output is common to both AKIN and RIFLE.
- **Stage 2** AKIN is >200% to 300% (2- to 3-fold) from the baseline.
- **Stage 3** AKIN is >300% (3-fold) from the baseline or ≥4.0 mg/dl (≥354 mmol/l) with an acute increase of at least 0.5 mg/dl (44 mmol/l) or on RRT.
- Other criteria for AKI are shown in the table below.

Stage	Creatinine criteria		Urine output criteria		
	pRIFLE	**nKDIGO**	**pRIFLE**	**nKDIGO**	**nRIFLE**
Risk (1^k)	eCrCl decrease by 25%	SCr rise ≥0.3 mg/dL within 48 hrs or rise ≥1.5-1.9 x reference SCr within 7 days	Urine Output <0.5 mls/kg/h or 8 hours	>0.5 ml/kg/hr and ≤1 ml/kg/hr	Urine Output <1.5 mls/kg/hr for 24 hours
Injury (2^k)	eCrCl decrease by 50%	SCr rise ≥2.0-2.9 x reference SCr	UO <0.5 mls/kg/hfor 16 hours	UO >0.3 ml/kg/hr & ≤0.5 ml/kg/hr	UO <1 ml/kg/hr for 24 hrs
Failure (3^k)	eCrCl decrease by 75% or <35 mls/min/1.73m^2	SCr rise ≥3 x reference SCr or SCr ≥2.5 mg/dL* or receipt of dialysis	UO <0.3 mls/kg/hr for 24 hours or anuric for 12 hours	≤0.3 ml/kg/hr	UO <0.7 mls/kg/hr for 24 hrs or anuric for 12 hrs
Loss	Persistent failure >4 weeks				
ESRD	Persistent >3 mths				

^{k} = Stages of nKDIGO. Reference SCr = previous lowest SCr level. UO = urine output * = SCr of 2.5 mg/dL represents GFR of <10 mls/min/1.732m^2

- **M**anagement of AKI involves an evaluation for cause and for possible reversal, monitoring urine output and Scr for severity then treating according to the stage and cause, with evaluation after 3 months for resolution or worsening.
- Determination of SCr, electrolytes, urea, FBC, ultrasound, urinalysis and microscopy are important.
- Management of AKI depends on the stage. However, the initial conservative management includes fluid, electrolyte and blood pressure control.
- Fluid management is aimed at correcting a deficit, insensible loss (400 mls/m^2 or 30 mls/kg/day), other ongoing losses and urine output. Replace 100% of urine if euvolaemic, 50-75% if overloaded.
- Fluid replacement is in the form of 0.9% saline ± dextrose or given as feed if tolerated. 0.45% saline is used in hypernatraemia and if <118 mmols/L 3% is used, bolus of albumin in nephrotic syndrome.
- Hyperkalaemia is managed by correcting acidosis with bicarbonate, nebulized salbutamol, a glucose/insulin combination, calcium reparations, polystyrene sulfonate.
- Hourly input/output recording, BP, twice daily weighing, daily urinalysis, SCr, urea, electrolytes.
- Adequate nutrition to prevent catabolism but fluid restriction limits this. NGT feeding can be utilized; 20-30 kcal/kg/day with 0.8-1 g/kg of protein. Protein free diet if urea is >40 mmol/L.
- Hypertension (HTN) is due to overload or intense vasoconstriction from hypovolaemia, the first treatment is furosemide. Then dialysis with no response. Calcium channel blockers can be administered while preparing for dialysis especially if there is encephalopathy. If HTN persists despite dialysis, give nifedipine.
- Monitor random blood sugar and target 110-149 mg/dl, insulin may be used.
- Dialysis in life-threatening changes in electrolytes, acid-base balance and fluid: K >6.5 mmol/L, urea >40 mmol/L (30 in neonates), furosemide resistant severe fluid overload with pulmonary oedema, severe hypo/hypernatraemia wih oliguria, severe acidosis, multisystem failure.
- Polyuria may occur on recovery, so input/output monitoring, replace volume by volume with normal saline at two-thirds of the previous day's intake.
- Prognosis depends on cause; it is better with pre renal AKI.

- Long-term follow up of the patient except for pre renal AKI: monitor the BP, proteinuria and SCr (if initially high or if proteinuria and hypertension develop).

Outcome of acute kidney injury (AKI)

- **Rapid reversal of the AKI** as shown by a fall in the initial high SCr to a normal value, the return of eGFR to a normal value and a urine flow rate of ≥1.5 mls/kg/hour within 48 hours of the AKI. This reversal will be described as sustained when AKI reversal has continued for a minimum of 48 hours.
- **For** a **persistent AKI**, the SCr value and urine flow rate remain within AKI limits between days 3 and 7 of the AKI.
- **A repeat episode of AKI** can occur and this is evident by the neonate fulfilling the SCr and urine criteria for AKI after a period of sustained reversal from the documentation of a previous AKI.
- **Incomplete recovery** with improvement of acute kidney injury from a more severe to a lesser stage within 7 days but without complete recovery (a return to baseline SCr).
- **Mortality** can occur within 7 days of initiating the renal insult heralded by a sustained increase in SCr levels, worsening oligoanuria and the deterioration of the clinical state.
- **Acute kidney disease (AKD)** is a post AKI condition defined by **the** KDIGO AKI workgroup as
  - any acute condition that impacts kidney function including AKI, eGFR <60 ml/min/1.73 m^2, a decrease in GFR by >35%, an increase in serum creatinine of >50% or any kidney damage lasting <3 months,
  - It includes all cases of complete recovery from AKI with no structural or functional damage but still at risk for long-term events,
  - Cases with a return of SCr values to the baseline but with evidence of ongoing renal injury (new onset or worsening proteinuria and/or hypertension) or the loss of renal reserve (nephrectomy) and
  - Cases of SCr values above the baseline.
  - Acute kidney disease has 3 stages of severity and the AKI can progress to any of the stages depending on the severity of the AKI.
- **Subacute AKD** may occur when there is a slow worsening of renal function within the first 7 days of the initial insult but which did

not meet the criteria for AKI and has persisted for 3 months. This can be seen in patients who received nephrotoxic medications such as aminoglycosides, for a prolonged period of time.

- **Chronic Kidney Disease (CKD)** is defined as abnormalities of kidney structure or function, present for 3 months (>90 days), with implications for health. Whereas AKI is an abrupt decrease in kidney function within 7 days, CKD is defined as a continuum of the same damage for greater than 90 days and has stages of severity.

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7.4 Chronic kidney disease (CKD)

Definition

- **Chronic kidney disease** is defined as abnormalities of kidney structure or function, present for 3 months (>90 days), with implications for health, including abnormalities in the composition of the blood or urine or abnormalities in imaging tests.
- GFR <60 mL/min/1.73m^2 for 3 months or more, with or without kidney damage.

Aetiology

- For children under five years, congenital abnormalities are common: dysplasia, hypoplasia, obstructive uropathy. Those above five years commonly have glomerulonephritis (HUS, nephritic syndrome, FSGS, SLE, etc.) and inherited disorders such as Alport syndrome. Metabolic renal diseases and some inherited disorders (polycystic disease) can occur at any age.

- **Table 10.4.1. Classification of chronic kidney disease**

Stage	Description	GFR in mL/ min/1.73/m^2	Action
1.	Kidney damage with normal or ↑ GFR	≥90	Diagnosis and treatment, Treatment of comorbid conditions, slowing progression, CVD risk reduction
2.	Kidney damage with mild ↓ GFR	60-89	Estimating progression
3.	Moderate ↓ GFR	30-59	Evaluating and treating complications
4.	Severe ↓ GFR	15-29	Preparation for kidney replacement therapy
5.	Kidney Failure	<15 (or dialysis)	Replacement (if uraemia is present)

Pathogenesis:

- Once a renal disease destroys functioning nephrons and reduces the GFR to about 30-50% of normal, systemic hypertension (from loss

of renal mass) and an increase in the single nephron GFR (SNGFR) occur and progression to ESRD becomes inevitable and at a relatively constant rate irrespective of the primary and/or underlying renal disease.

- Secondary/putative factors that propel the progression include persistent proteinuria, hyperfiltration injury, hyperlipidaemia, systemic or intrarenal hypertension and renal calcium-phosphate deposition.
- Two histologic features of progression are FSGS and tubulointerstitial fibrosis.
- With the loss of nephrons, there is both functional and structural adaptation of the surviving nephrons.
- The functional adaptation is an increase in SNGFR with a reduction in glomerular arteriolar resistance which is uneven (afferent > efferent). Dilatation of afferent arterioles results in the elevation of intraglomerular pressure (hence an increase in the transcapillary hydraulic pressure gradient) due to more transmission of systemic pressure and an increase in renal plasma flow. These two effects are exacerbated by the systemic hypertension.
- The structural adaptation is the compensatory hypertrophy of the surviving nephrons with an increase in volume of the glomerular tuft, an increase in the number of visceral epithelial cells, a reduction in the cell density of the epithelium within the enlarged tuft.
- Conditions with too few functioning nephrons such as morbid obesity and intrauterine growth restriction (IUGR), are at risk of SNGFR.
- Both adaptations also result in endothelial and epithelial cell injury and present clinically as proteinuria (hyperfiltration leads to proteinuria too).
- Accumulation of protein within the mesangium leads to mesangial hyperplasia, infiltration of monocytes/macrophages with the elaboration of mediators of chronic inflammation and fibrosis (notably transforming growth factor β, IL-6, fibroblast growth factor), further sclerosis occurs, more nephrons are lost and a vicious cycle of increasing glomerular blood flow and hyperfiltration. These changes initially manifest histologically by FSGS.
- Ischaemia of tubules distal to the sclerosis, inflammation in the adjacent interstitium and the loss of peritubular blood supply result in tubulointerstitial injury. Protein on the other hand has a direct toxic effect on the tubules, and also activates the tubules to

elaborate cytokines that mediate fibrosis. Immunoglobulin, iron in transferrin and lipids are components of filtered protein that can cause tubular injury too.
- Uncontrolled systemic hypertension can cause arteriolar nephrosclerosis and hyperfiltration.
- Hyperphosphataemia leads to calcium-phosphate deposition in the interstitium and blood vessels.

Clinical features

- Clinical manifestations of CKD: there may be headache, anorexia, oedema, fatigue, vomiting, proteinuria, haematuria, polydipsia, growth failure, hypertension, pallor, sallow colour, etc.

Pathophysiology of CKD

- Acidosis: a decrease in GFR, acid excretion, ammonia production and bicarbonate reabsorption.
- Sodium retention from excess renin and oliguria, while sodium wasting may occur if there is tubular damage.
- Hyperkalaemia results from reduced GFR (at <10 mls/min/m^2) and metabolic acidosis.
- Anaemia: occurs at GFR <35 mls/min/m^2, normocytic normochromic, low reticulocyte. Primarily due to inadequate production of erythropoietin by the kidney. Other factors are iron/folate deficiencies, a decrease in RBC lifespan due to uraemic toxins (guanidinopropionic acid), gastrointestinal blood loss (~6 mls/m^2/day), marrow depression from uraemia, ACE inhibitors (ACEIs), aluminum toxicity and blood sampling.
- Hypertension from circulatory overload and excessive renin production.
- Bleeding: defective platelet function from uraemic toxin notably guanidinosuccinic acid.
- Infection results from impaired immunity and granulocyte function.
- Neurologic symptoms from uraemia, hypertension and aluminum toxicity.
- Hyperlipidaemia from decreased plasma lipoprotein lipase activity.
- Pericarditis: uraemia, hypertension, fluid overload.
- Glucose intolerance is from tissue insulin resistance.

- Renal osteodystrophy (ROD): inadequate production of 1, 25-dihydroxycholecalciferol, hypocalcaemia, hyperphosphataemia and secondary hyperparathyroidism.
- Growth failure: poor caloric intake, anaemia, renal osteodystrophy, acidosis, growth hormone resistance resulting from a lack of insulin-like growth factor.

Investigations

- Help to confirm the aetiology, the complications and for the follow-up of treatment and will include FBC, blood film, reticulocyte count, electrolytes, creatinine and GFR, calcium and phosphate, skeletal survey, hormonal assay, urinalysis and m/c/s, ultrasonography, echocardiography, etc.

Treatment

- Is aimed at slowing progression, maintaining normal growth/development and replacing lost renal function.

Slowing progression

- Reduce proteinuria using ACEi and angiotensin I receptor blocker which reduces intraglomerular pressure via the dilatation of afferent arterioles. Can cause hypotension, a rise in creatinine and the depression of erythropoiesis.
- Control hypertension with sodium restriction, ACEi, loop diuretics. Calcium channel and β blockers can be used if they fail.
- Dietary lipid restriction. Statin helps to lower the lipid level in adults but there is no information on children yet. No protein restriction in children as the benefit has not been established.
- Treat anaemia with erythropoietin and iron.

Normal growth and replacement of lost renal functions

- Nutrition and growth: Provide adequate calories for age, correct acidosis, treat anaemia and ROD.
- Human growth hormone can be used if the above fail. Vomiting may be due to gastro-oesophageal reflux requiring anti-reflux medications; ranitidine, domperidone.
- Gastrostomy works better than nasogastric tube if vomiting is problematic.
- Correct water and electrolyte imbalance. Reduce phosphate by dietary restriction, use phosphate binders and vitamin D analogs.

- Urinary tract and respiratory infections are common and should be treated appropriately, modifying the doses of medications and the dosing intervals.
- Education and counselling, then psychological and emotional support to parents and older patients.
- When ESRD ensues, optimal medical management no longer corrects the abnormalities which therefore calls for renal replacement therapy (RRT) i.e. dialysis and transplantation.

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7.5 Urinary tract infection/Pyelonephritis

Definition

- The urinary tract produces, collects and eliminates urine and includes the kidneys, ureters, urinary bladder, and urethra.
- It is divided into two: the upper urinary tract (kidneys and ureters), and the lower urinary tract (bladder and urethra).
- Urinary tract infection (UTI) is defined as the presence of a pathogen anywhere along the urinary tract, which should otherwise be sterile.

Epidemiology

- Incidence in Nigeria is 5-11%, in USA 2.4-2.8%, 8-35% in the malnourished. It is highest in infancy and lowest in those above 7 years. It occurs more in males below 3 months, thereafter there is a female preponderance.
- Other risk factors are uncircumcised males, sickle cell anaemia, low birth weight, diabetes mellitus, immune deficiency, sexually active adolescent females, urolithiasis, a foreign body in the urinary tract, uropathogenic E. coli, residual urine (obstruction, reflux, constipation, dysfunctional voiding, etc.)
- 75-90% E. coli, then Klebsiella, Enterococci faecalis, Proteus, Staph saprophyticus in sexually active female adolescents, strep group B in neonates, fungi after instrumentation, adenovirus especially in males.

Pathogenesis

- Retrograde ascent of infected urine (bacteria from faecal flora colonize the perineum, then via the urethra to the bladder), Fimbriae adhere to mucosal receptors on the uroepithelium, the production of inflammatory cytokines: transforming growth factor β-1 (TGFβ-1), vascular endothelial growth factor (VEGF), etc., destruction of pathogen ± tissue damage (renal scarring).
- Factors predisposing to scarring: young age with acute pyelonephritis, delayed antibiotic therapy and its recurrence, then severe vesicoureteric reflux, congenital obstructive uropathy and the presence of activating variants in TGFβ-1 and VEGF.

Classification

- ***By Site***: Upper UTI/Pyelonephritis (34-70%) or lower UTI/Cystitis Urethritis
- ***By severity*:** Complicated or Uncomplicated UTI.

Clinical features

- First UTI; or
- Recurrent UTI which is
  - 2 or more episodes of Pyelonephritis; or
  - 1 episode plus 2 episodes of cystitis; or
  - >3 episodes of cystitis.
- It can either be Unresolved UTI,
- Persistent UTI; or
- Re-infection.
- Asymptomatic or Symptomatic UTI.
- ***Atypical UTI*:** Very ill, abdominal/bladder mass, poor urine flow, raised creatinine, septicaemia, no response to appropriate antibiotic within 48 hours, UTI with non-E. Coli organism.
- Features depend on age: for those younger than 3 months– irritability, fever, vomiting, lethargy, poor feeding and failure to thrive.
- For those 3 months and older–fever, frequency, dysuria, abdominal pain, loin tenderness, vomiting, poor feeding and dysfunctional voiding.
- Other less frequent features are haematuria, offensive urine, cloudy urine and malaise.
- Generally, a lower UTI presents with low grade or no fever, frequency, dysuria while an upper UTI will have fever, loin tenderness and evidence of systemic illness.

Diagnosis:

- High index of suspicion. The gold standard is isolating the organism via culture. The urine collected is sent to the lab within 1 hour or refrigerated at $<4^0$C for 24 hours as bacteria doubles every 20 minutes.
- NICE guidelines for urine collection techniques include: clean catch in a sterile container, absorbent urine collection pads, a catheter specimen or suprapubic tap.

- For a clean catch specimen, growth of a $>10^5$ colony forming unit (CFU), the catheter is 10^4, then any growth from the suprapubic specimen is diagnostic.
- The bag method is not NICE recommended but can be used for screening and if positive, another sample collected via the other routes will be sent for culture. Genitalia are cleaned with sterile water
- ***A Urinary strip*** can be used in the clinic. Leucocyte esterase (LE) is 83% sensitive, a low specificity of 78% especially in girls (also in fever, vulvovaginitis, balanitis, dehydration, acute glomerulonephritis, etc.).
- Nitrite for nitrate splitting microbes is 98% specific but 53% sensitive. When both are positive or only nitrite, treat for UTI but if only LE is positive, treat if the clinical features are supportive. When both are negative, UTI is excluded.
- ***Microscopy*** in the side lab can be helpful. The presence of 2-3 moving organisms/high power field (HPF) of uncentrifuged urine or 15-20/HPF of centrifuged urine is equivalent to 100,000 organisms.
- The presence of both bacteria (bacteriuria) and WBC (pyuria) has 99% specificity whereas bacteriuria without pyuria is almost always a contamination
- **For imaging studies:** children <6 months with a response to treatment with 48 hours, do an ultrasound by 6 weeks of infection but if atypical or recurrent, U/S is done during acute infection and voiding cystourethrography (VCUG) and dimercaptosuccinic acid (DMSA) are required, 4-6 months following acute UTI.
- For children 6 months to <3 years: if there is a response, no imaging studies; if atypical U/S is done during acute UTI and then DMSA; if recurrent, ultrasonography (U/S) is done 6 weeks after the acute UTI then DMSA.
- For children ≥3 years: no imaging studies except U/S during an acute UTI in atypical cases and if a recurrent UTI, U/S 6 weeks after the UTI and DMSA too.

Treatment

- Early treatment can prevent or reduce renal damage.
- Local antibiotic sensitivity is recommended, the oral route except if toxic or in urosepsis.

- Duration is 7-10 days for an upper UTI and shorter for a lower UTI.
- Some parenteral medications are Ceftriaxone, Ceftazidime, Cefotaxime, and Gentamycin.
- Oral preparations are Cefixime, Cefpodoxime, Cefuroxime, Amoxicillin-clavulanate, etc.
- Repeat m/c/s by the 3rd day if there is no improvement or the 7th day if there is improvement.

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7.6 Renal tubular acidosis (RTA)

Definition

- A diverse group of renal tubular transport disorders that involves defects in proximal bicarbonate reabsorption, distal excretion of hydrogen ions or both, in the face of normal GFR and with resultant hyperchloraemic normal anion gap metabolic acidosis.
- In chronological order of description, there are 4 types: type 1 or classical (hypokalaemic) distal RTA (dRTA), type 2 or proximal RTA, type 3 or mixed RTA and type 4 or hyperkalaemic RTA.

Distal RTA (TYPE 1)

- An impaired ability to secrete hydrogen ions (H^+) in the collecting duct where sodium (Na^+) is reabsorbed in exchange for potassium ions (K^+) or H^+. Thus K^+ needs to be secreted for optimal Na^+ reabsorption leading to hypokalaemia and a urine pH that is always >5.5. Loss of sodium bicarbonate leads to hyperchloraemia.
- dRTA results from a genetic secretory defect in the H^+-ATPase pump on the luminal side of alpha intercalated cells of the collecting tubule;
- OR an epithelial Na channel (ENaC) voltage defect with decreased Na reabsorption in the adjacent principal cells of the cortical collecting tubule. This Na reabsorption normally creates a lumen-negative electrical potential that promotes the retention of secreted H^+ in the lumen and secretion of K^+. Thus, there is metabolic acidosis and ***hyperkalaemia*** due to reduced excretion of K in urine. This is seen in obstructive uropathy, sickle cell disease, and severe volume depletion.
- OR increased permeability of the apical membrane or the tight junction so that secreted H^+ in the tubular lumen re-enters the cells. This is seen with amphotericin B which interacts with membrane sterols and creates holes for this back diffusion. Others are SLE, amiloride use.
- There is failure to thrive, features of hypokalaemia: polydipsia, polyuria, constipation, muscle weakness. Nephrolithiasis and nephrocalcinosis (hypercalciuria from calcium carbonate released from bones in response to chronic acidaemia; hypocitraturia because filtered citrate in the urine which is naturally chelate urinary calcium is reabsorbed in the proximal tubule to be

converted to bicarbonate in response to intracellular acidosis; a high urine pH with Calcium/Phosphate precipitation).

Proximal RTA (TYPE 2)

- Impairment in proximal bicarbonate reabsorption, rarely isolated, mostly associated with generalized proximal tubular dysfunction (Fanconi syndrome) or it can follow exposure to Ifosfamide.
- Normally, about 80% of the filtered bicarbonate, 90% of phosphate and all of the glucose are reabsorbed in the proximal tubule.
- In the proximal RTA, there is bicarbonate loss in urine, urine pH can be <5.6 (normal distal acidification), failure to thrive, hypokalaemia (aldosterone effect in response to sodium loss because 60% of sodium is reabsorbed at the proximal tubule), rickets (bone mineral loss due to acidaemia).
- Nephrocalcinosis does not occur: bone buffering is less because the acidosis is mild to moderate; high urinary citrate (which chelates calcium) due to incomplete reabsorption from the proximal tubular defect; low urine pH will prevent the precipitation of calcium.

Mixed RTA (TYPE 3)

- Mixed lesions of types 1 and 2 and it is due to inherited carbonic anhydrase deficiency.

Hyperkalaemic RTA (TYPE 4)

- There is aldosterone deficiency (in congenital adrenal hyperplasia, Addison's disease, exposure to cyclosporin, ACEI) or resistance (in acute pyelonephritis, obstructive uropathy as the cortical collecting tubule is injured, SLE, Diabetes mellitus, tubule-interstitial diseases) with sodium wasting, and retention of H^+ and K^+.
- The hyperkalaemia impairs ammonium production in the proximal tubule, hence low urine ammonium and reduced acid secretion. Urine acidification is normal.

Diagnosis

- Diagnosis of RTA requires the determination of electrolytes, the anion gap, renal function, calcium, phosphate, urinalysis with urine pH.

Treatment

- The replacement of bicarbonate is the mainstay of treatment.
- Distal RTA (type 1) requires 2-4 mEq/kg/24 hours of sodium bicarbonate, to prevent renal failure from nephrocalcinosis.
- For proximal RTA (type 2), treatment is difficult, a high dose of sodium bicarbonate up to 20 mEq/kg/24 hours is used, which is still lost in urine.
- In type 4 RTA, in addition to bicarbonate, K^+ intake is restricted, treatment for hyperkalaemia and mineralocorticoids replacement in the deficiency state.

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7.7 Posterior urethral valve

Introduction

- The posterior urethral valve (PUV) is the most common cause of obstructive uropathy in children, affecting males.
- Three variations exist:
- **Classical/type I** is a membrane which balloons during voiding to obstruct urine flow,
- **Type II** consists of folds in the proximal urethra but it is not obstructive and less common,
- **Type III** is a circular diaphragm which tears off with retrograde catheterization.

Pathogenesis

- When foetal urine commences, the valve produces back pressure leading to vesico-reflux, hydroureter, hydronephrosis, calyceal rupture (the calyx is a weak point), urinoma and varying degrees of renal dysplasia (which could also be primary).
- There is bladder neck hypertrophy, bladder wall thickening, trabeculation and sacculation.
- Renal function before and after relief of the obstruction depends on the degree of renal dysplasia.
- Antenatally, a third trimester scan can diagnose PUV: bilateral hydronephrosis, hydroureter, bladder wall thickening and dilatation of posterior urethra.
- Oligohydramnios occurs in severe obstruction with attendant pulmonary hypoplasia, because the branching of bronchioles requires amniotic fluid.

Clinical features

- There may be poor stream, straining at micturition, dribbling of urine, urine retention, palpable bladder, recurrent UTI, failure to thrive.
- Tubular damage predominates resulting in sodium and bicarbonate loss and secondary hyperkalaemia.

Investigations

- Micturating cystourethrography (MCU) confirms the diagnosis as it shows all the structural abnormalities.
- The renal function test, electrolytes, urine culture and other ancillary investigations can be done.
- The degree of renal dysplasia is determined by a dimercaptosuccinic acid (DMSA) scan done three months after relief of the obstruction and treatment of the infection.

Treatment

- The mainstay is valve ablation as early as possible so that spontaneous filling and emptying of the bladder needed for normal development in infants can be achieved.
- If ablation is not feasible as planned, urinary diversion with vesicostomy or bilateral ureterostomies can suffice as temporary measures.
- For post-obstruction diuresis, volume is replaced for volume, the sodium and bicarbonate imbalance is corrected.
- ***Follow up*** is to monitor renal function, sodium, acidosis, BP, antibiotics to prevent UTI because residual hydronephrosis can persist for years and VUR may be present in about 50%.
- Somatic growth assessment, check MCU is done three months post ablation.
- A long-term complication of PUV is CKD in about 30%, requiring renal replacement therapy later.
- ***Favourable prognostic features*** are a normal scan at 18-24 weeks gestation, post-bladder decompression creatinine of 0.8-1.0 mg/dL, and visualization of the corticomedullary junction.
- Others are absence or a lesser degree of pulmonary hypoplasia, development of the “popoff ” valve in utero (which prevents high bladder pressure/reflux into one or both kidneys thereby preserving renal function), no Oligohydramnios, no cortical cysts in both kidneys and no diurnal wetting after 5 years.

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7.8 Haemolytic uraemic syndrome (HUS)

Definition

- A syndrome comprising: acute kidney injury (AKI), thrombocytopaenia and microangiopathic haemolytic anaemia. A renal limited thrombotic microangiopathy.
- Thrombotic microangiopathy TMA is a histologic description of a syndrome of haemolysis, consumptive thrombocytopaenia and tissue ischaemia (platelet aggregation and thrombotic occlusion of small vessels). Two classical clinical forms are thrombotic thrombocytopaenic purpura TTP and HUS. In TTP, there are neurological manifestations ± minimal or no AKI, while in HUS, it is AKI ± minimal or no neurologic features.
- HUS is classified into typical, atypical and secondary HUS. Classification based on the presence of diarrhoea can be misleading because some typical (formerly diarrhoea positive) HUS may not have diarrhoea and atypical HUS may be triggered by diarrhoea.

Typical HUS

- More than 80% are preceded by acute enteritis caused by Shiga (verotoxin)-producing E. coli 0157:H7, less common are Serotypes 0111 and 1103.
- It is more common in children under 4 years. Cows are the main reservoirs so contaminated undercooked beef, fruits, water, fruit juice, vegetables, and unpasteurized milk are sources, even person to person.
- Beta lactams, cotrimoxazole and gut transit slowing agents increase the risk.
- This verotoxin is absorbed from the intestine and causes capillary and arteriolar endothelial injury and localized clotting in the kidney.
- **NB for TTP:** vWF is released from endothelial cells as a large polymer but cleaved to a mature polypeptide matrix for haemostasis by zinc metalloproteinase ADAMTS13. Cleavage can be impaired by the IgG autoantibody against the enzyme or its mutation, thus large multimers enter the circulation, bind and activate platelets leading to spontaneous platelet aggregation, platelet-rich fibrin-poor thrombus (deposited in the brain/

kidney/mesenteric vessels) and systemic microangiopathy. An inflammatory or prothrombotic stimulus initiates this process.

- Mechanical damage to red blood cells occurs as they pass through the altered vasculature, giving rise to microangiopathic haemolytic anaemia.
- Intrarenal platelet adhesion and damage result in thrombocytopaenia.
- There is thickening of the glomerular capillary wall, narrowing of the lumen and widening of the mesangium.
- Fibrin thrombin within these vessels may cause cortical necrosis and in severe cases, sclerosis and occlusion may occur.

Clinical features

- Usually, bloody diarrhoea, with vomiting, fever, abdominal pain. 5-10 days later, pallor, irritability, oligoanuria, lethargy.
- Dehydration, shock, jaundice, hypertension, rectal prolapse, petechiae, and hepatosplenomegaly may occur.
- CNS features are the most common extrarenal manifestations: seizures, cerebral oedema, cranial nerve palsies, coma, herniations, etc.
- Cardiomyopathy, necrotizing pancreatitis with diabetes, renal cortical necrosis with the risk of chronic kidney disease (CKD).
- Intestinal strictures are uncommon.

Diagnosis

- Anaemia, fragmented, burr and helmet cells on blood film, thrombocytopaenia, mild reticulocytosis, elevated plasma haemoglobin, diminished plasma haptoglobin, a direct Coombs test is negative, leukocytosis, normal PTT.
- Mild microscopic haematuria/proteinuria, AKI, which may be mild or severe requiring dialysis.
- Other investigations are: verotoxin serology and Polymerase chain reaction (PCR), urine and stool M/C/S, EEG, ECG, MRI, Computerized Tomographic scan of the brain/abdomen.

Treatment

- Early diagnosis and supportive care, electrolytes, nutrition, transfusion, dialysis and control of hypertension. Avoid

plasmapharesis (except in CNS involvement: no replaceable factor indicated) and antibiotics (paradoxic increase in shiga toxin release).
- Avoid platelet transfusion except if there is life-threatening bleeding, because this will supply the platelets and worsen the pathology.

Prevention

- Hand washing, avoid improperly cooked beef, unpasteurized milk and notify cases.

Prognosis

- Acute mortality of 5-10%, ESRD/CKD stage 5 in 5-10%. Proteinuria, CKD, hypertension may occur after 20 years of apparent recovery in 20-60%. Poor renal prognostic factors include neutrophilia, shock, anuria for >2 weeks, cortical necrosis, and Central Nervous System (CNS) involvement.

Atypical HUS

- Diarrhoea negative HUS, caused by Shigella dysenteriae type 1 (shiga toxin), strep pneumoniae (neuraminidase/Thomsen Freidenreich antigen/T antigen), Salmonella, Campylobacter, HIV, influenza, Varicella, Echovirus, Coxsackievirus, Epstein-Barr.
- It can occur at any age, usually there is no diarrhoea, but hypertension and renal dysfunction with CKD are more common although not worse. CNS manifestation is common.
- The neuraminidase cleaves N-acetylnuraminic acid on the cell membrane of the RBC/platelet and glomeruli exposing the T antigen which reacts with the anti-T antibody (T activation) leading to thrombotic microangiopathy (TMA). However, not all strep causes T cell activation because of variation in the quantity and activity of the enzyme and the amount of anti-T antibody from the patient.
- Activation is likely to follow severe pneumococcal infection and it is cleared once the infection is treated with antibiotic.
- The direct Coombs test is positive. The arterioles show intimal cell proliferation, vessel wall thickening and lumen narrowing.

- Often familial: autosomal recessive or dominant with varied complement abnormalities and deficiency of ADAMTS13 (von Willebrand factor cleaving proteases).
- In the scenario of normal ADAMTS13, increased plasminogen activator inhibitor and endothelial injury (causing the loss of or decreased VEGF and then TMA) are likely.

Treatment

- Antibiotic, plasmapharesis for the idiopathic/familial atypical HUS, a high success rate with Eculizumab (humanized monoclonal antibody against C5).

Prognosis

- 25% mortality in the initial episode, long-term dialysis in 50% of survivors.

Secondary HUS

- Drugs associated with HUS include cyclosporin, Tacrolimus, oral contraceptive, quinine, cytotoxic drugs, mitomycin, ticlopidine, etc.
- Other secondary causes are malignancy, post-renal transplantation, methylmalonic acidaemia, pregnancy, SLE, systemic sclerosis and irradiation.

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7.9 Hypertension

Definition

- Hypertension is defined as average systolic blood pressure (SBP) and/or diastolic BP (DBP) that is ≥95th percentile for gender, age, and height on 3 occasions.
- Prehypertension in children is defined as average SBP or DBP levels that are ≥90th percentile but <95th percentile or BP levels >120/80 mm Hg in adolescents.
- If BP is ≥95th percentile, it is staged: **Stage 1** is BP levels from the 95th to 99th percentile plus 5 mmHg while **Stage 2** is levels ≥ the 99th percentile plus 5 mmHg.
- Auscultation is the recommended method of measurement using a standard clinical sphygmomanometer and a stethoscope placed over the brachial artery pulse.
- The child must have been sitting quietly for about 5 minutes, with feet on the floor and not crossed (SBP increases by 2-8 mmHg), the back supported (otherwise DBP increases by 5 mmHg). The right arm is used for consistency and because of the likelihood of coarctation of the aorta, which gives a false low BP on the left.
- A mercury manometer or aneroid, a cuff with an inflatable bladder width of 40% of the arm's circumference and of a length to cover 80-100% of the arm circumference are required.
- The first Korotkoff sound is the SBP while the 5th/disappearance is the DBP. If the 5th occurs at zero, the muffling/4th Korotkoff is used as the DBP.
- ***Primary/essential*** hypertension in children occurs in children and adolescents who are overweight, may have sleep-disordered breathing, a positive family history of hypertension and cardiovascular disease, but it is usually mild or stage 1 and less common than in adults.
- ***Secondary hypertension*** is more common in children than in adults and over 80% have underlying renal pathology.

Epidemiology

- Prevalence in Nigeria is between 1-5.8%, with urban areas more affected than rural.

- ***Transient hypertension*** can follow acute glomerulonephritis, haemolytic uraemic syndrome (HUS), steroid therapy, acute kidney injury (AKI), nephrotic syndrome, etc.
- ***Chronic hypertension*** could be from renal causes (renal dysplasia, obstructive uropathy, HUS, reflux nephropathy, renal tumours, Chronic kidney disease, etc.), coarctation of the aorta, endocrine causes (Cushing, phaechromocytoma, Conn's, hyperthyroidism).

Clinical features

- Presentation is variable depending on the aetiology. However, there could be headache, vomiting, blurred vision, polyuria, epistaxis, polydipsia, irritability, heart failure, etc.
- There may be tachycardia, pallor, obesity, moon facie, diaphoresis, growth retardation, murmur, apical heave, ambiguous genitalia, thyromegaly, etc.
- For stage 1 hypertension, repeat on 2 occasions and if confirmed, commence evaluation but stage 2 is an immediate evaluation and the ***screening tests*** include urinalysis, urine m/c/s, full blood count (FBC), platelet, electrolytes, creatinine, uric acid, glucose, fundoscopy, lipid profile, and calcium.
- Specific tests would include Echocardiography, ultrasound, urine/serum catecholamines, urine protein and creatinine excretion, hormonal assay (thyroid, adrenals). Others are ambulatory BP monitoring for those with "white coat" hypertension, renin profiling, renal biopsy, magnetic resonance angiography, etc.

Treatment

- This includes the pharmacologic and non-pharmacologic approach.
- ***The non-pharmacologic*** lifestyle modification includes regular exercise 30-60 minutes daily, a reduction in the sedentary lifestyle, reduction in salt, potassium, cigarette, alcohol, and caffeine intake, weight control, and modification of risk factors such as diabetes and hyperlipidaemia.
- ***Pharmacologic management*** is indicated when lifestyle modification fails, in symptomatic hypertension, target organ damage or in secondary hypertension and the aim is to reduce blood pressure to the 95^{th} percentile or the 90^{th} if there are comorbidities.

- A single drug is advised which could be from the following classes: Angiotensin Converting Enzyme inhibitors (Lisinopril, Ramipril), angiotensin receptor blockers (losartan), calcium channel blockers (amlodipine, Nifedipine), diuretics (frusemide, hydrochlorothiazide).
- The single drug is increased gradually until the maximum recommended dose is reached and if BP is not controlled, a second drug from a different class is introduced.
- During pharmacologic treatment, lifestyle modification continues and in some children with uncomplicated primary hypertension (overweight), ***"step down"*** treatment may apply after a long period of controlled BP. However, lifestyle modification must be continued.
- Acute hypertension/hypertensive crisis can be a hypertensive emergency or hypertensive urgency.

Hypertensive emergency

- This is a severe symptomatic elevation in BP with evidence of acute target organ damage: the brain (encephalopathy manifesting with lethargy, coma and seizure), heart (Congestive Cardiac Failure, pulmonary oedema), kidney (acute renal failure) and eyes (papilloedema).
- There is the need to reduce BP within minutes to hours using an intravenous antihypertensive such as Labetalol or hydralazine.

Hypertensive urgency

- This is a severe elevation of BP without severe symptoms or evidence of acute target organ damage. BP is lowered over days to weeks with an oral antihypertensive such as clonidine, hydralazine or minoxidil.

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7.10 Water and electrolytes

Hypernatraemia

- Plasma osmolality is determined by plasma sodium concentration, which is regulated by changes in water balance.
- Abnormal sodium concentrations are largely due to changes in water and rarely changes in sodium (Na).
- Plasma Na >145 mmol/L and due to too little water or rarely too much salt. Fractional excretion of Na: (FENa) [urine Na/urine creatinine]/[plasma Na/plasma creatinine] is a better guide to differentiate. Usually <1% but in dehydration <0.3%.
- The normal defence against hypernatraemia is the stimulation of antidiuretic hormone (ADH) and thirst but the latter is the major protective response. Thus, those with hypernatraemia usually lack thirst expression.
- When it is due to ***too little water***, there is clinical dehydration, weight loss, high plasma Na. However, the clinical dehydration is masked by the movement of water from cells to extracellular fluid (ECF).
- Causes include extra renal water losses in diarrhoea, excessive sweating and fasting, osmotic diuresis as with diuretics, post-obstructive diuresis, and glycosuria. Urine osmolality is >500 mOsm/kg. Also in diabetes insipidus, but urine osmolality is <300 mOsm/kg with hyposthenuria.
- When it is due to ***salt excess***, there is increased body weight and signs of volume overload. It is caused by salt poisoning, central hypodipsia, and reset osmostat.
- ***Investigations*** will include plasma and urine electrolytes, urea, creatinine, and glucose.
- ***Treatment:*** An acute case is corrected rapidly within 24-48 hours whereas the chronic state is corrected slowly because of the intracellular osmotically active low molecular weight organic molecules generated to prevent the movement of water out of the cells/intracellular dehydration.
- The tonicity of the fluid used (regardless of the dextrose component) should not exceed that of urine. Ideally, 0.9% saline is used but in the concentrating defect and diabetes insipidus with low urine osmolality, dextrose water or dextrose in 0.18% is used.
- Correct shock with 0.9% saline at 20 mls/kg over 30 minutes repeating as necessary. Fluid volume includes deficit, maintenance

(for 48 hours) and ongoing loss and is given over 48 hours. Oral rehydration solution (ORS) can be used if not in shock.
- If due to salt excess, it will correct spontaneously with normal renal function.
- If oliguria persists after correction, consider AKI due to acute tubular necrosis and dialysis may be indicated. Renal vein thrombosis may also complicate hypernatraemia.

Hyponatraemia

- Plasma Na <135 mmol/L due to the retention of water in excess of sodium or the loss of Na in excess of water.
- When it is due to ***too much water***, there is oedema and weight increase and causes include nephrosis, congestive heart failure, protein losing enteropathy, cirrhosis, SIADH secretion, polydipsia and chronic kidney disease with low GFR.
- When it is due to ***too little salt***, there is dehydration with weight loss and this can occur in losses via the gastrointestinal tract, cystic fibrosis, sweat losses, congenital adrenal hyperplasia, adrenal insufficiency, hypothyroidism and obstructive uropathy.
- In acute conditions, water moves into the cells leading to cell swelling and signs of raised intracranial pressure.
- ***Investigations*** include plasma and urine electrolytes, urea then glucose, albumin, liver function, lipid profile, thyroid and adrenal function tests.
- ***Treatment*** is either by water restriction or the administration of sodium.
- Water restriction in an oedematous state, polydipsia and some cases of SIADH secretion whereas oral salt can be used in GIT losses. The target is a plasma Na level of 125 mmol/L.
- In symptomatic acute hyponatraemia, hypertonic saline 3% saline (containing 513 mEq/L) is used at 2-3 mls/kg until symptoms resolve. Daily Na increase should not exceed 10 mmol.
- Hormonal replacement if indicated.

Hyperkalaemia

- Plasma potassium (K) >5.3 mmol/L due to impaired cell entry (metabolic acidosis, insulin deficiency and hyperglycaemia), increased cell release (rhabdomyolysis, tumour lysis syndrome, trauma, crush injury) or decreased urinary excretion (markedly

reduced GFR, potassium sparing diuretics, NSAIDs, ACE Inhibitors, adrenal insufficiency).

- In metabolic acidosis, the excess hydrogen ions are buffered in the cells and chloride, which is the major ECF anion, moves into the cells in a limited amount and so to maintain electroneutrality, K moves into the ECF.
- In uncontrolled diabetes mellitus, hyperglycaemia and hyperosmolality cause water to move out of the cell in the osmotic gradient thereby increasing the intracellular concentration of K, which passively leaves the cell through the selective K channels.
- With a marked reduction in GFR, there are few nephrons to excrete the K load and also the decreased distal delivery of sodium and water in the ensuing oliguria leads to hyperkalaemia.
- Aldosterone release is stimulated by angiotensin II via renin from the kidney and also an increase in plasma K concentration. Hypoaldosteronism occurs in renal failure with impaired renin secretion, use of potassium sparing diuretics, adrenal dysfunction and tubular resistance to aldosterone. These conditions will impair renal K excretion.
- Haemolysed blood samples can cause pseudohyperkalaemia so also excessive shaking of blood samples, leukocytosis, thrombocytosis.
- ***Clinically,*** cardiac arrhythmia and muscle weakness can occur. The presence of ECG changes represents an emergency and includes peaked T waves, the loss of P wave, widening of the QRS interval, ST depression and bradycardia, heart block, and cardiac arrest in levels >10 mmol/L.
- ***Treatment*** involves antagonizing the K effect on the heart (calcium gluconate: onset several minutes, wanes rapidly), driving K into the cell (β2 adrenergic agonist, insulin/glucose, sodium bicarbonate: onset 30-60 minutes, lower at a rate of 0.5-.5 mEq/L, lasting several hours) and the removal of K from the body (diuretics, cation exchange resins: onset 2-3 hours, dialysis).
- In asymptomatic cases with levels <6 mmols/L, loop diuretics and K restriction can suffice. At 6-6.5 mmol/L without symptoms, sodium polystyrene sulfonate (kayexalate) is used at 1 g/kg in 4 divided doses orally or rectally.
- In symptomatic cases where the onset of resin cannot be awaited, nebulized salbutamol is easily and safely administered at 2 hourly intervals up to 3 times at 2.5 mg for the under 5s, 5 mg for 5-10 years, 7.5 mg for 10-15 years, and 10 mg per dose for >15 years.

- Or an insulin/glucose combination: 10 units of regular insulin in 100 mls of 50% D/W (because of the risk of hypoglycaemia), mix properly, then give 1 ml/kg over 10 minutes. There is a risk of hypoglycaemia with the insulin and volume overload with the glucose.
- Or sodium bicarbonate at 2.5 mmol/kg. This can be repeated depending on the volume, sodium and potassium status of the patient.
- For life-threatening cases, the initial treatment is with 10% calcium gluconate at 0.5 mls/kg or 0.1 ml/kg of 10% calcium chloride over 5 mins. Dialysis is indicated in recalcitrant cases.

Hypokalaemia

- K <3.5 mmol/L. Rarely an emergency except in acute cases. It follows the loss of body K via GIT (gastroenteritis, NGT drainage) or kidney (loop/thiazide diuretics, aldosterone excess, renal tubular acidosis) or entry into Intracellular fluid in metabolic alkalosis.
- ***Clinically***, most are asymptomatic but with levels <3 mmol/L, muscle weakness occurs, paralysis, ileus, rhabdomyolysis, myoglobinuria, tetany, postural hypotension due to autonomic insufficiency then polyuria, polydipsia (resistance to ADH due to decreased levels of ADH-sensitive water channels: aquaporin-2), cardiac arrhythmia.
- ECG changes including ST depression, a flat T wave, the appearance of a U-wave, prolonged QT and QRS, and an increased QRS interval.
- ***Diagnosis*** is by careful history, drug history, plasma Na, K, Ca, Mg, creatinine, glucose, renin activity, aldosterone, cortisol, renal scan and skeletal survey for evidence of RTA.
- Urine Na, Ca, K, creatinine, Mg, pH, glucose and cortisol.
- **Treatment** is administration of K except in the shift of K into the cell. An oral supplement is recommended but in severe cases with arrhythmia, IV KCl is used with ECG monitoring.

Hypercalcaemia

- Total Calcium (Ca) corrected >2.6 mmol/L, ionized >1.3 mmol/L.
- It is the most abundant mineral in the body, >98% is in bone. About 40% is bound to protein (mostly albumin), 10% is

complexed to bicarbonate/phosphate, and 50% is the free active ionized form.

- The normal plasma value is 2.1-2.6 mmol/L. 1mmol/L = 2.5 mg/dL. Corrected calcium in mmol/L = the measured total Ca in mmol/L + 0.02 (40-albumin in g/L).
- ***Causes*** are numerous: hyperparathyroidism, CKD, vitamin D intoxication, vitamin A toxicity, milk-alkali syndrome, leprosy, subcutaneous fat necrosis, hypo/hyperthyroidism, 1-α hydroxylase activity in granulomatous diseases (tuberculosis, sarcoidosis, and lymphoma), certain malignancies, etc.
- ***Clinically*** there may be failure to thrive, nephrolithiasis, constipation, reduced GFR, polyuria, hyporeflexia, short corrected QT-interval, metastatic calcification, venous thrombosis.
- Investigations include blood gases, thyroid function test, bone marrow biopsy, Mantoux, skeletal survey, ECG, parathyroid scan, and others depending on the suspected aetiology.
- ***Treat*** asymptomatic cases by removing the cause. However, in acute symptomatic cases, hyperhydration is done with 3 $L/m^2/24$ hours of 0.9% saline. This volume expansion will reduce sodium reabsorption in the proximal tubules, which is passively followed by Ca absorption.
- Others include the use of diuretics to reduce Ca absorption in Henle's loop, corticosteroid, calcitonin, dialysis and the use of bisphosphonate.

Hypocalcaemia

- Total Ca (corrected) <2.1 mmol/L and ionized Ca <1.2 mmol/L.
- ***Causes*** in neonates include asphyxia, prematurity, RDS, infant of diabetic mother, etc., and in older children, there could be hypothyroidism, vitamin D deficiency, hypomagnesaemia (cofactor for PTH release), hypercalciuria, hyperphosphataemia, tumour lysis, rhabdomyolysis, acute pancreatitis, hungry bones syndrome, alkalosis, acute leukaemia, drugs: frusemide, laxatives.
- ***Clinically***, there could be paraesthesia, tetany, seizures, myopathy, psychosis, dementia, depression, Chvostek/Trousseau signs, laryngospasm, dry skin, eczema, hair loss, brittle nails, lenticular cataracts, tooth enamel hypoplasia, hypotension, prolonged QT, arrhythmia, CCF.
- ***Treatment*** of acute symptoms is with the use of 10% Ca gluconate 0.3 ml/kg over 10-30 minutes, until the Ca level normalizes.

Bradycardia may occur. Give magnesium if low: 0.2 ml/kg of 50% Mg sulphate. Maintenance can be with an oral supplement at 50-75 mg/kg of elemental Ca in 4 doses.

Hypermagnesaemia

- Plasma magnesium (Mg) >1.0 mmol/L (2.5 mg/dL). It is the second most abundant cation in the body within the bone, <1% in the ECF of which 30% is albumin bound, 10% is complexed to bicarbonate and phosphate, and the rest is the active ionized form.
- It is a very rare condition in the state of the normal renal function. However, it can occur in CKD, antacids/laxative use, cell necrosis with the release of Mg, hypothyroidism and Addison's disease.
- ***Clinically***, at levels >2.0 mmol/L, there could be lethargy, drowsiness, ileus, nausea, hyporeflexia, urinary retention, prolonged PR and QT, wide QRS. Coma, apnoea if severe.
- ***Diagnosis*** is via history, renal function test, thyroid function test and others.

Hypomagnesaemia

- Mg <0.7 mmol/L. And it could be from renal tubular damage, malabsorption, malnutrition, hypoparathyroidism, infant of diabetic mother, hyperthyroidism, hypercalcaemia, phosphate depletion, IUGR, thiazides, Tacrolimus, aminoglycosides, etc.
- ***Clinically*** asymptomatic until level <0.5 mmol/L: tremor, tetany, weakness, Torsade De Pointes.
- ***History*** is essential: renal disease, drugs, hypokalaemia, hypocalcaemia, etc.
- ***Treat*** acute symptom with 10% Mg Sulphate at 0.1-0.2 mmol/kg.

Hyperphosphataemia

- Below 2.1 mmol/L in infants, 1.4 mmol/L in adults. It is the most abundant anion and 99.9% is in bone and teeth, <0.1% in plasma.
- It follows renal disease with impaired excretion, tumour lysis, thyrotoxicosis, acidosis, etc.
- Symptoms are those of the accompanying hypocalcaemia.
- Treat acute cases with saline infusion if renal function is intact otherwise dialyze.

- In chronic kidney disease, dietary restriction, phosphate binders such as calcium and Mg carbonate are used.

Hypophosphataemia

- <1.2 mmol/L in infants, <0.8 mmol/L in adults.
- It could follow increased renal excretion as seen in hyperparathyroidism, vitamin D deficiency, renal tubular defect, alkalosis, hypophosphataemic rickets, phosphate binders, etc.
- Chronic condition will lead to rickets.
- Skeletal survey, urea, creatinine, electrolytes, albumin, Ca, alkaline phosphatase, urine phosphate creatinine ratio, etc.
- Depending on the underlying cause, phosphate and vitamin D supplementation is done.

Acid-base balance

- Plasma pH is 7.4 (7.35-7.45) and it is maintained via the regulation of CO_2 (35-45 mmHg) by the lungs (respiratory) and bicarbonate (20-28 mEq/L) by the kidney directly by reabsorption or indirectly via the excretion of hydrogen ions (metabolic).
- The kidney excretes acid in urine based on the acid load: sulphuric acid from sulphur-containing amino acids, methionine mostly, from animal protein.
- Children produce 2-3 mEq/kg of H^+ in 24 hours from dietary protein, the incomplete metabolism of carbohydrates and fats and bicarbonate loss (for a bicarbonate lost in stool, one H^+ is gained). Secretion of H^+ in the proximal tubule (with Na reabsorption) is coupled to the production of intracellular bicarbonate, which replaces the filtered bicarbonate (HCO_3).

Metabolic acidosis

- It is due to the loss of bicarbonate, impaired H^+ excretion or the addition of acids endogenously or exogenously.
- It can be normal or increased anion gap metabolic acidosis. The anion gap (AG) is the difference between the measured cation (Na) and the measured anions (Cl, HCO_3), also the difference between the unmeasured cations (K, Mg, Ca) and the unmeasured anions (protein, phosphate, urate, sulphate).

- It actually represents the number of unmeasured anions in the plasma and is calculated by subtracting the two main plasma anions from the main plasma cation: Na - (Cl-HCO_3) = 8-16 mmol/L.
- Normal AG is due to bicarbonate loss from the GIT or renal with concomitant loss of Na. Chloride increases to maintain neutrality. Thus, it is referred to as hyperchloraemic metabolic acidosis: diarrhoea, renal tubular acidosis, aldosterone deficiency, etc., are possible causes.
- In increased AG, there is an accumulation of acids composed of H^+ and anions (e.g. lactate anions), the H^+ not buffered by bicarbonate raises the pH and the accumulated anions increase the AG: **m**etformin, **u**raemia, **l**actic acidosis, **e**thanol, **p**araldehyde, **a**cetyl salicylate, and **k**etoacidosis (Diabetes Mellitus, starvation) are conditions in which increased AG metabolic acidosis occurs.
- Treat the cause: rehydration, oxygen, sepsis, renal tubular acidosis, renal failure, etc.

Metabolic alkalosis

- Plasma bicarbonate >28 mmol/L, pH >7.40. The kidney responds by increasing base excretion, so for metabolic alkalosis to occur, there is failure of the kidney to excrete the added base. Based on the urinary chloride level, metabolic alkalosis can be chloride responsive or chloride resistant.
- During gastric loss, HCl is lost and bicarbonate accumulates (production of H^+ by gastric mucosa generates bicarbonate).
- The ensuing alkalosis is maintained by the accompanying volume depletion (caused majorly by Cl loss, minimally by Na and K losses) which impairs the renal response: reduced GFR leads to reduced filtered bicarbonate, proximal tubular Na and bicarbonate reabsorption increases and also aldosterone causes bicarbonate reabsorption, loss of K and excretion of H^+ in exchange for Na.
- Therefore, chloride is required to correct the volume depletion (chloride responsive with urine Cl <15 mEq/L). Another cause is diuretic use.
- In increased aldosterone activity: adrenal adenomas, renin secreting tumours, and Cushing's (cortisol has some mineralocorticoid activity), there is sodium retention with volume expansion, hypokalaemia and metabolic alkalosis as H^+ is excreted in exchange for Na. Urinary Cl is not low because there is no volume depletion (>20 mEq/L).

- Features are those of the underlying condition, hypokalaemia, hypocalcaemia (ionized Ca binds to albumin in alkalosis).
- Treat the underlying cause, if Cl is responsive replace volume and K with NaCl and KCl so that the kidney can excrete the excess bicarbonate.

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7.11 HIV-Associated Nephropathy (HIVAN)

Introduction

- Human immunodeficiency virus (HIV) affects the kidney and may result from the direct effect of the virus on renal epithelial cells, immune-complex mediated vasculitis, the hyperviscosity of blood secondary to hyperglobulinaemia, various opportunistic infections and also drugs.
- The most common chronic renal parenchymal disease in HIV-positive patients is HIV-associated nephropathy (HIVAN).
- HIVAN is defined as the presence of proteinuria with microcystic tubules, mesangial hyperplasia and/or collapsing focal segmental glomerulosclerosis.
- It is a feature of advanced HIV infection although it can also occur early in an asymptomatic patient and even at the time of seroconversion.

Risk factors

- They include low a CD4 cell count, old age, a longer duration of HIV infection, advanced HIV disease, a high viral load, the absence of HAART treatment and the black race.
- For the apparent racial disposition, a genetic basis was hypothesised involving the Duffy antigen receptor for the chemokine (DARC) that binds chemokines.
- There is the upregulation of DARC in renal endothelial and epithelial cells of patients with HIVAN.
- Individuals with the Duffy antigen, carry on their RBC and blood circulatory system, a larger number of chemokines, conferring protection against HIV-1.
- About 68% of the population of African descent, have a mutation in DARC, which confers in them, a DARC-negative phenotype with increased susceptibility to HIV-1 infection.
- DARC acts as a sink (binder) for excess circulating chemokines, therefore, in pathologic states (such as HIV infection) in which excess chemokines play a role, the number of circulating chemokines available for binding in renal tissues is higher in DARC-negative individuals.

- The accumulation of chemokines in renal tissues increases the risk of developing renal injury and about 11% of the HIV burden in Africans is attributed to the DARC-negative phenotype.
- DARC is also the RBC receptor for Plasmodium vivax. Thus, Africans have a high prevalence of DARC promoter polymorphism, which results in the preferential suppression of DARC expression in the red blood cell membranes over the other cells.
- There is also a high prevalence of renal disease in HIV non-infected family members of African Americans with HIVAN suggesting a genetic predisposition of these patients to develop renal disease independent of HIV status.
- Therefore, the podocytes of African Americans have an increased susceptibility to detach, dedifferentiate and/or proliferate when exposed to cytokines, viral proteins and/or whenever they become infected with HIV.

Pathophysiology

- Glomerular injury in HIVAN is caused by the direct HIV infection of renal epithelial cells, but CD4 (required for HIV entry into cells) and chemokine coreceptors (that determine the cell permissiveness to productive HIV infection; CXC for the HIV R4 strain and CC for the HIV R5 strain) have not been demonstrated in all renal cell membranes.
- Thus, the mechanism by which HIV-1 gains access to human renal epithelial cells is still being studied.
- The C-type lectin DEC-205 acts as an HIV-1 receptor in renal tubular cells. Following DEC-205 mediated internalization of HIV into renal tubular cells, the virus does not proceed through reverse transcription, and the infection is therefore non-productive.
- The renal tubular cells with this replication competent virus can infect encountering T lymphocytes and macrophages.
- The virus that is internalized by DEC-205 is targeted for lysosomal degradation, but how they persist in the renal tubular cells is not yet known.
- There is expression of CD4 receptors and chemokine coreceptors in renal mesangial cell membranes only and when infected, there is infiltration of the interstitium by inflammatory cells, notably the T lymphocytes, neutrophils and macrophages.

- These inflammatory cells elaborate many cytokines that mediate glomerular injury through the production of proteases that damage epithelial and vascular basement membranes.
- Platelet-derived growth factor (PDGF) stimulates mesangial cell proliferation while transforming growth factor (TGF-ß), which is strongly fibrogenic, stimulates the synthesis and inhibits the degradation of mesangial matrix proteins, leading to mesangial hypercellularity and an increase in mesangial matrix.
- This mesangial hyperplasia is a histologic feature in the early stage of HIVAN.
- The mechanisms by which HIV infects the mesangial and tubular cells have been demonstrated but that for podocyte, which is predominantly affected in HIVAN, is not yet well understood.
- The podocytes are terminally differentiated and usually do not proliferate following glomerular injury.
- However, in glomerulopathy associated with HIV, the viral proteins cause dysregulation of the podocyte cell cycle with increased podocyte proliferation, apoptosis, cellular dedifferentiation and altered cellular polarity.
- These changes in podocytes are due to the direct result of HIV protein expression, specifically the negative effector (Nef) gene or P_{24} which induces podocyte proliferation and dedifferentiation.
- The proliferating podocytes induce pressure on the glomerular basement membrane and cause the collapse of the renal capillaries.
- There is extensive effacement of podocyte foot processes and the podocytes undergo apoptosis.
- The glomerular changes lead to an alteration in size and the loss of anionic charges, leading to proteinuria which is the hallmark of HIVAN.
- The protein accumulates in the mesangial matrix and this protein infiltration stimulates the mesangial cells to proliferate and secrete cytokines that mediate glomerular sclerosis.
- Following the collapse of the renal capillaries, there is a loss of nephrons and compensatory hypertrophy of the remaining glomeruli leading to glomerular sclerosis.
- There is a further reduction in nephron mass and a vicious cycle of glomerulosclerosis.
- This collapsing focal segmental glomerulosclerosis (FSGS) is the major histologic (biopsy) feature of HIVAN.

- Many of the glomeruli are globally sclerotic and interspersed among those that have segmental or collapsing sclerosis.
- Thus, the focal variant of the glomerulosclerosis may be an early morphologic feature.
- The collapsing glomerulopathy of HIVAN is distinguished from idiopathic focal segmental glomerulosclerosis and heroin associated nephropathy by the greater number of collapsed glomeruli, prominent microtubular cystic dilatation, severe tubular degeneration and interstitial inflammation of the former.
- HIVAN presents with heavy proteinuria, azotemia, hypoalbuminaemia and hyperlipidaemia. Proteinuria and azotemia are the common clinical findings.
- Oedema and hypertension are not common, because of the marked tubular-interstitial lesions that lead to a decreased ability to conserve sodium.
- In children, it is less fulminant with death occurring within two years after detection unlike in adult patients, where the nephropathy progresses rapidly within a few weeks, to end-stage renal disease (ESRD) and death, if untreated.
- HIVAN is difficult to diagnose clinically, because it has no single specific morphologic feature however, a clinical finding of proteinuria can be an early indicator of the condition, better still, microalbuminuria.

Treatment

- Highly active antiretroviral therapy (HAART) prevents the onset of HIVAN, and if already developed, it induces remission and slows progression to ESRD. However, patients who develop HIVAN despite a high CD4 cell count may not respond optimally to HAART.
- The angiotensin converting enzyme inhibitors and the receptor blockers can be used to control proteinuria.

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7.12 Nephroprevention

Introduction

- The prevalence of kidney disease is rising in Nigeria; 4 per million children in 2004, 20 per million in 2010 and 14.9 per million in 2012. Management is also largely unavailable, unaffordable and inaccessible; for acute peritoneal dialysis (APD), the access rate ranges from 10.9% to 47.8%.
- In most centres, there are no paediatric haemodialysis units, chronic dialysis programmes or paediatric renal transplantation programmes and most patients cannot afford or sustain the available management option due to poverty.
- Prevention becomes the only beneficial and sensible option.
- The knowledge of the pattern of kidney disease in our environment is important for an effective prevention strategy and the pattern is highly influenced by geographical location and socioeconomic and cultural factors.
- Acute kidney injury commonly follows; diarrhoeal diseases, complicated malaria, toxic nephropathy, sepsis and tumour lysis syndrome.
- While chronic kidney diseases are the sequel to; nephrotic syndrome, posterior urethral valve, chronic pyelonephritis, glomerulonephritis and HIV-associated nephropathy (HIVAN).
- Contributory factors therefore would include; poverty, overcrowding, ignorance, scabies, retroviral disease (RVD) and diarrhoeal diseases.
- The prevention of kidney diseases could be primary, secondary or tertiary.

Primary prevention

- This involves measures aimed at the promotion and sustenance of good renal health.
- Detecting obstructive uropathy as early as possible via the history of the urinary stream in neonatals/infancy.
- Avoidance of possible aetiological agents such as the indiscriminate use of herbal medications, prompt treatment and control of infections like urinary tract infection (UTI), scabies, impetigo, the proper use of oral rehydration solution (ORS).

- Others are a pollution-free environment and the rational use of Nephrotoxic drugs (Ciprofloxacin, NSAIDs) and compounds that contain heavy metals.
- Reduction in low-birth-weight deliveries.
- Kidney disease may sometimes be prevented by controlling the other diseases that can predispose to it; hypertension, obesity, RVD, diabetes mellitus, diarrhoeal diseases.
- A healthy lifestyle with regular exercise and a reduction in cholesterol.

Secondary prevention

- It includes the early detection of the asymptomatic phase of the disease especially in at-risk patients.
- Early detection of the asymptomatic phase of kidney disorder plays a significant role in preventing mortality from the disease.
- The difficulty of identifying the onset of renal disease can be resolved by the early screening of the patient which can identify individuals with subclinical chronic kidney disease (CKD) who may potentially benefit from early interventions or identification e.g. a CKD such as HIVAN can be reversed if detected at the early stage of microalbuminuria, so also some other CKDs.
- Urinalysis is the frequently used screening tool (and as such, needs confirmation).
- Proteinuria, microalbuminuria, nitrite, and leucocyte esterase are commonly screened for in urine.

Tertiary prevention

- The cascade of events following nephron damage includes compensatory hypertrophy of the surviving nephrons, glomerular capillary hypertension and glomerular endothelial damage.
- This leads to a vicious cycle of nephron loss with podocyte injury, mesangial cell proliferation and infiltration of inflammatory cells.
- Tertiary prevention comprises of measures aimed at ameliorating or arresting or slowing down the progression of kidney disease.
- Certain factors mediate the progression of renal disease;
    - Susceptibility factors which increase the risk of CKD such as low birth weight and morbid obesity;

  - Initiation factors which directly cause renal damage: an untreated UTI, chronic tubulointerstitial diseases, untreated diabetic nephropathy and chronic glomerulonephritis;
  - Progression factors which accelerate the deterioration of renal function: hyperglycaemia, hypertension, proteinuria, hyperlipidaemia, nephrotoxins, possibly anaemia.
- These events and factors are targets of tertiary nephroprevention.

Proven strategies

- The use of antihypertensive, antiproteinuric agents: ACE Inhibitors and Angiotensin receptor blockers, the intake of high biologic value protein, blood sugar control in diabetic nephropathy, treatment of infections, the institution of HAART in RVD.
- Other experimental strategies; the use of antioxidants, endothelin receptor antagonists.

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SECTION 8:

DERMATOLOGY

OJINMAH, R. U. AND ONYEKONWU, C.

8.1 Eczema/Atopic Dermatitis (Onyekonwu and Ojinmah)

Introduction

- Atopic eczema (atopic dermatitis) is a chronic and intensely pruritic cutaneous inflammatory condition that may also have a strong association with other atopic disease processes like bronchial asthma, allergic conjunctivitis, allergic rhinitis and food allergies.

Epidemiology

It usually starts in early infancy, within the first six months of life. However, all age groups and both sexes are affected.

- It is currently estimated that 10-20% of children and 1-3% of adults in developed countries are affected. In Nigeria, independent studies in two tertiary health care centres by Olumide and Nnoruka estimate that prevalence is between 3.1% in 1986 and 8.5% in 2004 respectively.
- In the unpublished data of skin clinic attendees in the University of Nigeria Teaching Hospital, atopic eczema accounted for about 12% of cases. About half of these occurred in children aged 12 years and below.

Pathophysiology

- A tendency towards the development of atopic dermatitis is a complex relationship between genetic predisposition (a personal or family history of type 1 allergies), immunological mechanisms and exposure to environmental allergens.

- It is often associated with raised levels of serum immunoglobulin E (IgE).
- Filaggrin is a protein which has a pivotal role in the maintenance of an effective skin barrier through producing a natural moisturizing factor, the contribution to the architecture of the stratum corneum and influencing the pH balance of the skin.
- Mutations in the filaggrin gene are thought to contribute to the disease process. It has also been observed that this mutation deprives the skin of an essential reservoir of acidic metabolites leading to an increase in protease function as well as impaired anti-staphylococcal activity.

Clinical Features

- Atopic eczema is classified into infantile (0-2 years), childhood-onset (2 years to puberty) and adolescence/adult onset variants.
- Infants may present with a history of facial rash, especially around the cheeks.
- The neck, scalp and trunk may also be involved but the napkin area is usually spared.
- Extensor involvement is common at this age but itching may not be a predominant feature.
- In the childhood-onset variant, patients present with flexural, itchy eruptions which eventually become lichenified with constant rubbing of the skin.
- Lesions are commonly seen in the antecubital and popliteal fossae. The neck, wrists and ankles may also be involved. The skin is usually dry. There may be periorbital hyperpigmentation, increased palmar creases and increased susceptibility to allergens.
- Regardless of age, the itching associated with atopic eczema generally continues throughout the day and may worsen at night, leading to sleep loss and considerable impairment in quality of life.

Diagnosis

- This is based on specific criteria that take into account the patient's history and clinical manifestations. Various diagnostic criteria have been proposed and validated but these are beyond the scope of this book. Using simplified criteria proposed by Williams et al., diagnosis is made based on the presence of one major and three or more minor criteria.

- The **major** criterion is the presence of itchy skin eruptions while the **minor** criteria include a history of itching in skin creases, a personal or family history of asthma or allergic rhinitis and a personal history of general dry skin in the last year, among others.

Differential diagnosis

- Scabies, especially in infants, may present with pustules on the palms, soles, genitalia and between the fingers. A family history of atopy and the distribution of lesions are helpful.
- Others include infantile seborrhoeic dermatitis (a history of cradle cap, hypopigmented macules or patches, diaper rash), psoriasis and allergic contact dermatitis.

Treatment

- Topical agents are the mainstay; even in severe cases that require systemic therapy, they still play a role. Different combinations of these agents that address different aspects of the disease pathogenesis may be used.
- **Moisturisers**: An integral part of treatment is to lubricate the skin and reduce the evaporation of water. The application of moisturiser should be soon after a bath.
- **Non-soap cleansers**: Hypoallergenic and fragrance-free synthetic detergents.
- **Diluted bleach baths and intranasal mupirocin**: These are recommended for patients with moderate to severe atopic eczema to help reduce the frequency of *S. aureus* skin infections, and the need for systemic antibiotics in patients with heavily colonized skin.
- **Wet wrap treatment** (WWT): This is recommended in patients with significant flares and or recalcitrant disease. A topical agent applied to the skin, usually topical steroids, is covered by a wetted layer of bandages, gauze or cotton suit followed by a dry second layer.
- **Topical steroids**: These are the mainstay of anti-inflammatory therapy recommended in patients who have not made a good response to proper skin care and the regular use of emollients. The choice of steroids used will depend on the patient's age, body surface area, degree of xerosis and cost. Monitor for cutaneous side effects with the long-term use of potent steroids.

- **Topical calcineurin inhibitors**: The second class of topical anti-inflammatory agents. Tacrolimus is for moderate to severe atopic eczema while pimecrolimus is for mild to moderate disease. Common side effects include a stinging sensation at the site of application.
- **Topical antibiotics and antihistamines**: Evidence for the utility of these agents in the management of atopic eczema is low. Topical antihistamines are not advised due to the possibility of contact sensitization.
- **Systemic therapies**: These include short-term oral steroids, steroid sparing drugs such as cyclosporine and methotrexate, and the use of phototherapy. However, these therapies should be reserved for severe disease and are recommended only by a specialist.

Complications/Prognosis

- A chronic condition which may lead to growth retardation in children, both as a result of the disease condition itself and as a side effect of chronic steroid therapy.
- Children with a strong family history of atopy may develop bronchial asthma.
- However, prognosis is generally favourable with most children outgrowing the condition by adolescence.

Counselling

- The patient outcome is better when patients and/or their caregivers receive proper education about the disease, the need for continued adherence to proper skin care practices, and the appropriate use and application of topical therapies.

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8.2 Impetigo (Ojinmah and Onyekonwu)

Definition

- This is a contagious superficial bacterial infection of the skin with the manifestation usually restricted clinically to the stratum corneum (cornual layer) of the epidermis.

Clinical forms

- Non-bullous impetigo (or impetigo contagiousa of Tilbury Fox).
- Bullous impetigo.

Sites of predilection

- The face (especially around the nose and mouth), scalp, ears, hands and other exposed parts.

Epidemiology

Non-bullous impetigo:

- There is worldwide occurrence with frequent large outbreaks.
- The causative organism could be Staphylococcus or Streptococcus.
- In warm and humid climates (tropics), the Streptococcal form predominates while in temperate regions, the Staphylococcal variety is more common.
- Peak seasonal incidence is in late summer.
- Incidence, in a survey in Holland, was between 0.017 and 0.021, in Norway 0.017, and in the United Kingdom 0.01 events per person-year.
- Pre-school and young school-age children are most often affected.
- In adults, males predominate.

Bullous impetigo

- There is worldwide occurrence but it is usually sporadic.
- Staphylococcus is implicated.
- Clusters of cases may occur in families, communes, barracks and sports camps, and larger outbreaks are occasionally seen in institutions.
- It is most frequent in the summer months and occurs in all ages

though it is more common in childhood.

- It may be especially widespread in the newborn (impetigo neonatorum) leading to the outdated terminology of pemphigus neonatorum.

Note that for both non-bullous and bullous impetigo Staphylococcus aureus (phage group II) is responsible while Strep. Pyogenes is the most common cause among Streptococcal organisms with occasional isolation of Strep. Group G and Group C.

Risk factors

- Younger age, crowded conditions (schools and crèches), warm humid weather, contact sports, and pre-existing dermatitis.
- Transmission is via direct contact with the organism and penetration through skin weakened by inflammation or abrasion.

Sources

- Fomites, room dust, toys, biting insects and some non-biting flies of the genus Hippelates.

Pathophysiology

- In the **bullous form**, there is a release of exfoliative (epidermolytic) toxin which is thought to act as a trypsin-like serine protease and cleave desmoglein 1 (cell adhesion protein) to form the blister. In addition, the exfoliative toxin acts as a superantigen, and stimulates B and T lymphocytes to proliferate in the same milieu thus worsening the inflammation.
- Histologically, the action of the toxin produces large blisters by triggering an epidermal split which occurs just below the granular layer of the epidermis. Neutrophils are seen in the blister cavity which may also contain cocci. Neutrophil and lymphocyte infiltration of the upper dermis (around the blister/bulla) is the rule.
- The **non-bullous variety** produces tiny and transient blisters which easily break down to yield crusts. This is suspected to be as a result of direct cytotoxic action of the bacteria though the histology is similar to that of bullous impetigo.

Clinical features

Non-bullous

- Typical lesions start on normal or excoriated skin as rapidly developing vesiculopustular rashes on erythematous bases. They quickly rupture with creamy/honey-coloured exudates.
- The exudate rapidly spreads to adjacent skin by contact to set up new lesions. The exuding serum subsequently dries to form honey-coloured "stuck on" crusts which are the hallmark of impetigo. There may be fever and other constitutional symptoms.
- There is a tendency to spontaneous resolution in 2-3 weeks but a prolonged course is common particularly in the presence of a parasitic infestation of the skin (e.g. scabies), eczema, in hot or humid climates.
- Post inflammatory hyper or hypopigmentation may occur in heavily pigmented skin.

Bullous

- Thin-walled flaccid bullae ranging from 0.5 to 3 cm or more develop rapidly on involved sites. They rupture easily and persist for 2-3 days.
- The contents are at first clear, later cloudy. After rupture; thin, flat, brownish crusts occur.
- The lesions often favour the sites of existing skin disease, especially heat rashes (miliaria) or minor injuries such as insect bites.
- The buccal mucous membrane may be involved. Regional adenitis occurs rarely.

Diagnosis

- This is based on clinical suspicion.
- A wound swab M/C/S is also beneficial.

Differential diagnosis

- Staphylococcal scalded skin syndrome, Ecthyma, Pemphigus, Pustular psoriasis.
- Erythema multiforme major (Steven Johnson's syndrome).

Treatment

Mild

- Remove crusts with saline solution, olive oil or dilute antiseptic.
- A twice daily application of appropriate antibiotics: Mupirocin, Fusidic acid, Bacitracin or Neomycin.

Severe (widespread rashes, affectation of mucous membrane or with lymphadenopathy)

- Removal of crusts as above.
- Appropriate systemic antibiotics should be deployed e.g. Erythromycin, Ampicillin and Cloxacillin combination, Flucloxacillin and Dicloxacillin.

Complications

- Cellulitis, Acute glomerulonephritis.
- Scarlet fever, Urticaria, Erythema multiforme.

Prevention

- Discourage close contact and exchange of fomites between the index case(s) and other children.
- Neonatology health workers especially should be screened to make sure that their skin and upper airway are free of the pathogenic strain of bacteria.

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8.3 Ecthyma (Ojinmah and Onyekonwu)

Definition

- Ecthyma is a purulent bacterial skin infection which involves the entire epidermis and is characterized by the formation of adherent crusts, beneath which ulceration occurs.

Epidemiology

- In Europe, most cases occur in children while in the tropics where the disease condition is much more common due to high environmental temperature and humidity, it may occur at any age.
- No racial or sexual dominance.
- Predisposition is dependent on poor hygiene, malnutrition, debilitating illnesses, immunocompromisation and minor injuries or skin conditions, particularly scabies and the sites of insect bites.

Aetiology

- Staphylococcus aureus and Group A beta-haemolytic streptococci are the major culprits while Pseudomonas aeruginosa is implicated especially against the background of immunocompromisation.

Clinical features

- Lesions start as small bullae (vesicles) or pustules on erythematous bases which subsequently enlarge and develop hard crusts made up of dried exudate.
- Beneath the exudate lies a purulent irregular ulcer with an indurated base ± painful.

Note that in the presence of pseudomonas, the pus will have a greenish tinge.

- The lesions are usually few but new lesions may develop by autoinoculation over time.
- Ulcers heal to leave punched-out scars.
- The lesions can develop on any part of the body but the buttocks, thighs and legs are most commonly affected.
- Painful regional lymphadenopathy could occur.

Diagnosis

- This is based on clinical suspicion but a wound swab Microscopy, Culture and Sensitivity is most helpful for the isolation of the responsible organism and targeted antibiotics therapy.

Differential diagnosis

- Non-bullous impetigo, Ecthyma contagiosum, Veldt or Desert sore.
- Ecthyma Gangrenosum.

Treatment

- Improved hygiene and nutrition, and the treatment of scabies and any other underlying disease is important.
- ***Removal of crusts:*** Soak a clean towel in a warm dilute antiseptic. Apply the compress gently to moisten crusts for about ten minutes several times per day. Then gently wipe off the soaked crusts.
- ***Topical therapy:*** This is expedient in localized ecthyma after the removal of crusts. Topical antibiotics (fusidic acid or mupirocin) or antiseptics (povidone iodine or hydrogen peroxide cream) could be used. Apply three times a day to the affected areas and the surrounding skin for about a week.
- ***Systemic therapy:*** This is recommended if the infection is extensive or slow to respond to topical therapy. The preferred antibiotic is a penicillin which is active against S. pyogenes and S. aureus such as flucloxacillin or dicloxacillin. The duration of treatment varies as several weeks may be needed to completely resolve ecthyma.

Complications

- Septicaemia, cellulitis.
- Scarring.
- Secondary lymphangitis.
- Post Streptococcal acute glomerulonephritis.

Prevention

- Improve personal hygiene.
- Keep minor skin injuries such as scratches or bites clean.

- Do not scratch or pick at scabs or sores.

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8.4 Hair follicle infections (Ojinmah and Onyekonwu)

Introduction

- We shall in this chapter dwell on some relevant aspects of hair follicle infections.
- Bacterial infection of the skin through the hair follicles is common because the number of resident bacteria on the skin is higher in and around hair follicle orifices than elsewhere on the skin making them the Achilles' heel of the skin.
- The clinical picture of the infection depends on how far down the hair follicle the infection gets established and the number of hair follicles involved within a contiguous group.

Definitions

- Infection when restricted to the follicular orifice/ostium leads to **folliculitis**. If deep-seated/around the hair root, it yields **furunculosis** (furuncle) while a collection of contiguous furuncles with the involvement of the intervening skin produces a **carbuncle**.

Folliculitis

- This superficial hair follicle infection is not always primarily or exclusively infective in origin.
- Physical or chemical injury to the skin may be associated with a folliculitis though the pustules here are usually sterile.

Aetiology

- Staphylococcus aureus, Pseudomonas aeruginosa, Pityrosporum yeast.
- Gram negative bacteria.

Clinical features

- Discreet small yellowish follicular pustules without the involvement of the surrounding skin. The pustules break down to yield pus, blood or both.
- There may be itching or pain.
- Common sites of involvement are the scalp, face and extremities.

Risk factors

- The presence of untreated excoriations, lacerations, surgical wounds or pre-existing dermatitis.
- Immunosuppressive conditions such as HIV, diabetes, malnutrition or malignancies.
- Exposure to topical corticosteroid.
- Long-term antibiotic skin treatment, obesity, wearing tight clothing.
- Using or working with substances that can irritate or block the follicles such as cosmetics, cocoa butter, mineral or motor oil, tar and adhesive dressings or tapes.
- The use of a hot tub, whirl pool, or swimming pool that is not properly treated with chlorine.

Diagnosis

- This is based on the clinical picture. Microscopy, culture and sensitivity of swabs are very helpful in wrapping up the diagnosis and directing antibiotic options.

Differential diagnosis

- Pustular miliaria, subcorneal pustular dermatosis, Impetigo of Bockhart.
- Eosinophilic folliculitis, Tinea infections.

Treatment

- Superficial folliculitis of external chemical or physical origin will settle if the irritant is removed.
- Those that are of mild staphylococcal aetiology could be self-limiting while the more serious variety responds to the application of appropriate topical antibiotics (mupirocin, fusidic acid and Gentamycin) or an antifungal (Ketoconazole, Terbinafine) for 1-2 weeks.

Furuncle (Boil)

Epidemiology

- It is relatively uncommon in early childhood except in subjects with atopic dermatitis, but increases rapidly in frequency with the approach of puberty to become a common disability in adolescence and early adult life. In adolescence, boys are more affected than girls. The peak age of incidence in girls is 14-17 years and 16-19 years for boys.

Aetiology

- Staphylococcus aureus. In sufferers, the infecting strain is haboured in the nares or perineum.

Pathology

- A furuncle is an abscess of the hair follicle, usually of the vellus type.
- The perifollicular abscess is followed by necrosis with the destruction of the follicle.
- S. aureus produced cytotoxin is suspected of playing a role.

Clinical features

- Starts as a hard, tender, red or dusky nodule which enlarges, becomes painful and subsequently suppurates due to central necrosis. It becomes fluctuant, and may rupture spontaneously or on pressure or incision, discharging pus and necrotic material leaving a violaceous macule. The pain subsides thereafter, and the oedema and induration diminish.
- The lesions may be single or multiple and tend to appear in crops.
- Occasionally, there may be fever and mild constitutional symptoms.

Sites of predilection

- They usually develop in hairy areas subject to friction and sweating e.g. neck, face, arms, axillae, breasts, buttocks, and perineum.

Predisposing factors

- Obesity, blood dyscrasias, malnutrition, diabetes mellitus, HIV AIDS, prolonged treatment with systemic corticosteroids or with cytotoxic drugs.

Diagnosis

- Clinical.
- Microscopy, Culture and Sensitivity are necessary in isolating the responsible bacteria and guiding antibiotic therapy.

Differential diagnosis

- Disseminated herpes simplex infection, Acne, Halogen eruptions and Hidradenitis suppurativa.

Treatment

- Each episode may need to be treated with a systemic antibiotic such as Flucloxacillin or another penicillinase-resistant antibiotic.
- A topical antibacterial agent reduces contamination of the surrounding skin.
- Occlusive dressings should be avoided.

Complications

- Scar, Pyaemia and septicaemia are favoured by malnutrition.
- Cavernous sinus thrombosis could follow lesions on the upper lip or cheek.

Carbuncle

Epidemiology

- As in the furuncle above.

Aetiology

- Staphylococcus aureus. Spread is via autoinoculation (from the nares, throat or perineum) or exogenous.

Pathology

- There is a deep-seated infection of a group of contiguous follicles accompanied by intense acute inflammatory changes in the surrounding and underlying connective tissues, including the subcutaneous fat.

Clinical features

- The term carbuncle is derived from the Latin word for a small, fiery coal, and describes the painful, hard, red lump that is the initial stage of the infection.
- It starts as a dome-shaped acutely tender mass that increases in size for a few days, to reach a diameter of 3-10 cm or more.
- Suppuration begins after 5-7 days, and pus is discharged from the multiple follicular orifices. Necrosis of the intervening skin leaves a yellow slough surmounting a crater-like nodule. In some cases, the necrosis develops more acutely without a preliminary follicular discharge, and the entire central core of the lesion is shed, to leave a deep ulcer with a purulent floor.
- Lymphangitis and lymphadenopathy may occur.
- Constitutional symptoms may accompany, or even precede the development of the carbuncle. Fever may be high, and malaise and prostration may be extreme if the carbuncle is large or the patient's general condition is poor.
- In favourable cases, healing slowly takes place over weeks to leave a scar while in the frail and ill, death may occur from toxaemia or from metastatic infection.

Sites of predilection

- Nape of neck, shoulders, hips and thighs.

Predisposing factors

- Diabetes mellitus, malnutrition, cardiac failure, drug addiction.
- Severe generalized dermatoses e.g. exfoliative dermatitis or pemphigus.
- Prolonged steroid therapy.

Diagnosis

- This is based on the clinical picture, and microscopy, culture and antibiotic sensitivity tests on a specimen from the lesion(s).

Differential diagnosis

- Vesiculopustular manifestations of Herpes simplex and Vaccinia.
- Anthrax, Tularemia, Nodulocystic acne, Hidradenitis suppurativa.

Treatment

- Surgical incision and adequate drainage.
- Flucloxacillin, Dicloxacillin and other penicillinase-resistant antibiotics should be given for about 10 days.
- Non-steroidal anti-inflammatory agents are beneficial.
- Investigating for and treating any underlying systemic disease is important.

Complications

- Scar,
- Lung abscess,
- Septic arthritis.
- Cavernous sinus thrombosis (in severe nasolabial lesions).
- Septicaemia,
- Osteomyelitis,
- Perinephric abscesses.

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8.5 Erysipelas and Cellulitis (Ojinmah and Onyekonwu)

Introduction

- Though we shall in this section deal with erysipelas and cellulitis as distinct disease entities, it is pertinent to point out that they may overlap as some authorities view both as a continuum as erysipelas could progress to become cellulitis. Thus, it should not be surprising to see erysipelas defined as superficial cellulitis in some literatures.

Erysipelas

Definition

- It is a bacterial infection of the dermis which overlaps into upper subcutaneous tissue. Its hallmark is a well-defined, raised erythematous edge reflecting the more superficial (dermal) involvement.

Aetiology

- Commonly due to the beta-haemolytic group, a streptococci infection and rarely due to staphylococcus aureus.
- Streptococcus pneumoniae, pseudomonas aeruginosa and campylobacter jejuni have been implicated mostly in the immunocompromised.

Clinical features

- A well demarcated area of erythema, heat, swelling and pain, with a raised edge.
- The face rash follows a butterfly outline, extending over the cheeks as well as the nose.
- Blistering is common and there may be a superficial haemorrhage from dermal vessels into the blisters or intact skin to yield purpura ± peau d'orange over the affected skin.
- Lymphangitis and lymphadenopathy may occur.
- Except in mild cases, there is constitutional upset with fever, chills, rigours, vomiting, headache and malaise.

- Note that classically, this condition starts suddenly and systemic symptoms may be acute and severe.

Sites of predilection

- Legs in up to 80% of cases, face, arms.

Risk factors

- Extremes of age, diabetes, previous episode(s) of erysipelas, obesity.
- Venous disease (e.g. Stasis dermatitis, leg ulceration) and/or lymphoedema.
- Current or prior injury (e.g. trauma, surgical wounds, radiotherapy, athlete's foot).

Diagnosis

- This is based on the clinical picture but if there are blisters, swabs of the fluid should be taken for microscopy, culture and sensitivity to ensure guided antibiotics therapy.
- Commencement of treatment should not await the result of the investigation to avoid the setting in of complications.

Differential diagnosis

- Cellulitis, Fixed drug eruptions, Urticaria vasculitis, Trauma.

Treatment

- Antibiotics therapy should be given in the appropriate dose for 10-14 days.
- Systemic symptoms usually resolve fast, and are then followed by the gradual resolution of the skin component.
- Any of the following antibiotics could be used: penicillin, flucloxacillin, clarithromycin, clindamycin and erythromycin.
- Anticoagulant therapy should be considered if there is associated thrombophlebitis.

Complications

These are rare, but can include:

- Infections distant to the site of erysipelas via haematogenous spread, including infective endocarditis and septic arthritis.
- Post-streptococcal glomerulonephritis.
- Cavernous sinus thrombosis, Streptococcal toxic syndrome (rarer).
- Lymphatic obstruction (especially if recurrent).

Cellulitis

Definition

- This is a common but potentially serious inflammation of subcutaneous tissue in which an infective (generally bacterial) cause is proven or assumed.
- The route of infection is usually through a break in the skin. The affected area has ill-defined borders.
- Special types of cellulitis are sometimes designated by the location of the infection.
- Examples include periorbital cellulitis, buccal cellulitis (over the cheeks), facial cellulitis, and perianal cellulitis.

Aetiology

- Commonly due to streptococcus group A and staphylococcus aureus but other streptococcus groups especially B and G have been implicated in settings of venous or lymphatic compromise.
- Anaerobic cellulitis is relatively rare and usually due to synergistic infection with both aerobic (coliforms, pseudomonas aeruginosa, staph. Aureus) and anaerobic (bacteroides, anaerobic cocci) bacteria.
- Other causes include streptococcus pneumoniae, haemophilus influenza (especially in orbital cellulitis), aeromonas hydrophilia (contamination of injuries by water especially fresh water), vibrio alginolyticus, and pasteurella multocida.

Clinical features

- It usually begins as an area of pain, swelling and erythema that spreads to adjacent skin.

- The involved skin may feel warm to the touch.
- As this erythematous area begins to enlarge, the affected person may develop a fever, sometimes with chills and sweats, tender regional lymphadenopathy may also occur.

Sites of predilection

- Cellulitis can develop on any part of the body but the leg is the most common site (particularly over the shin and the foot), then the arm, and the head and neck areas.
- Following surgery or trauma wounds, cellulitis can develop in the abdomen or chest areas.
- In cases of morbid obesity, cellulitis can also develop in the abdominal skin folds.

Risk factors

- Injury which could be abrasion, insect bite, erosion, ulceration, laceration, fracture or burn.
- Immunocompromised states e.g. Diabetes, malignancies, HIV/AIDS and medications such as corticosteroids, and chemotherapy.
- Skin disorders such as dermatitis of any cause, athlete's foot, chickenpox, measles, papular urticaria, psoriasis, impetigo, and radiation therapy.
- Lymphoedema and venous stasis.
- Past history of cellulitis especially of the feet,
- Intravenous drug use,
- Obesity.

Diagnosis

- Based on the clinical picture but if there is discharge, a swab should be taken for microscopy, culture and sensitivity to ensure guided antibiotics therapy.
- Commencement of treatment should not await the result of the investigation to avoid the setting in of complications.

Differential diagnosis

- Erysipelas, Stasis dermatitis, Deep vein thrombosis, Snake bite.

Treatment

- The same as in erysipelas above. In severe cases, there may be a need for admission, intravenous antibiotics and intravenous fluid administration.

Complications

- Septicaemia, Post-streptococcal glomerulonephritis, Cavernous sinus thrombosis.
- Lymphatic obstruction (especially if recurrent), Necrotizing fasciitis.

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8.6 Erythema Multiforme I (Ojinmah and Onyekonwu)

Introduction

- Erythema multiforme is a spectrum of an acute inflammatory disorder arising from a hypersensitivity response to a wide aetiology with varying modes of manifestation and degrees of involvement of the skin alone or the skin and mucous membrane.
- Its spectrum spans erythema multiforme minor, erythema multiforme major and epidermal necrolysis which is made up of the Stevens-Johnson syndrome and toxic epidermal necrolysis (TEN/Lyell's syndrome) in ascending order of severity.
- In this chapter, we shall deal with the milder end of this spectrum of illnesses: **Erythema multiforme minor and major**

Definition

- Clinically, erythema multiforme minor involves macular, papular or urticarial lesions, as well as the classical **iris**, **bull's eye** or **"target"** lesions, distributed preferentially over the skin of distal extremities with sparing or minimal involvement of mucous membrane e.g. lips or conjunctiva.
- Lesions may involve the palms or trunk.
- It is an acute, self-limited, and sometimes recurring skin condition.
- Erythema multiforme minor with the involvement of two mucosal sites (e.g. lips and conjunctiva or nares) with or without mild constitutional symptoms yields erythema multiforme major.

Aetiology

- Erythema multiforme minor is majorly triggered by infections and minimally by drugs.
- The herpes simplex virus is a major cause (herpes labialis and herpes genitalis).
- Mycoplasma pneumoniae especially in children.
- Other viral infections such as acquired immune deficiency syndrome, adenovirus, cytomegalovirus, hepatitis B and C, mumps, ORF, infectious mononucleosis, lymphogranuloma inguinale, poliomyelitis, variola, vaccinia and varicella.
- A wide range of bacterial infections including rickettsiae.
- Fungal infections such as histoplasmosis.

- Drugs: anti-convulsants, sulfonamides, penicillins, NSAIDS and vaccinations.
- Miscellaneous: carcinoma, lymphoma, leukaemia, lupus erythematosus (Rowell's syndrome), polyarteritis nodosa, sarcoidosis and phototherapy.

Pathogenesis

- There is a fas/fas-ligand induced apoptosis of keratinocytes.

Clinical features

- In general, the course is that of an eruption developing over a few days and resolving in 2-3 weeks. Events of the preceding 3 weeks should be reviewed as this could help in tracing the precipitating agent(s).
- Prodromal symptoms are absent in most cases. If present, they are usually mild, suggesting an upper respiratory tract infection (cough, rhinitis, low-grade fever).
- In erythema multiforme major, fever higher than 38.5^{o}C is seen in a third of cases.
- Skin manifestation is typically with **"target", iris or bull's eye** lesions (a central purpuric ring surrounded by a pale zone which in turn is surrounded by a red zone) symmetrically over acral areas. A few vesicular or bullous eruptions could also occur.
- There may be 1-2 areas of mucosal involvement with small erosions in erythema multiforme major.

Histology

- The most important changes occur in the lower epidermis and upper dermis and involve vacuolar alteration of the basal layer; apoptosis of keratinocytes,
- Limited dermo-epidermal junction involvement and a lymphohistiocytic infiltrate rich in T-lymphocytes around blood vessels with tissue oedema, and vasodilatation.

Diagnosis

- This is based on clinical features and confirmed by lesion biopsy for histology.

- Other possible but non-specific findings include an elevated ESR, moderate leukocytosis, increased levels of acute-phase proteins, and mildly elevated liver aminotransferase levels.

Differential diagnosis

- Vancomycin-induced linear IgA disease, Systemic lupus erythematosus.
- Stem cell transplantation erythematous eruption, Urticaria vasculitis.

Treatment

- Good nursing care.
- Tabs prednisolone 30-60 mg/day, decreasing over a period of 1-4 weeks may be given especially in erythema multiforme major or if bullous skin lesions are present; otherwise, topical corticosteroids are preferred.
- Treat the underlying cause: acyclovir or valacyclovir for herpetic trigger, erythromycin for Mycoplasma pneumonia, etc.
- Withdraw any offending drug.
- Other beneficial agents include thalidomide, dapsone, azathioprine, mycophenolate mofetil and cyclosporine.

Prognosis

- Excellent in EM minor.
- <1% mortality in EM major.

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8.7 Erythema Multiforme II (Epidermal Necrolysis) (Ojinmah and Onyekonwu)

Introduction

- In this section, we examine the severe end of the spectrum of illnesses called erythema multiforme.
- Due to the close causal, pathogenetic and clinical relationship, SJS and TEN will be discussed together. SJS and TEN are represented by a single terminology "Epidermal Necrolysis" (EN).

Stevens-Johnson syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) or Lyell's syndrome

Definition

- SJS was first reported in 1922. It is a severe illness of acute onset, comprising severe inflammatory eruptions involving <10% of the skin (Body Surface Area) especially the trunk and mucous membranes,
- Marked constitutional symptoms of high fever, malaise, myalgia and arthralgia.
- There may be a prodromal systemic illness lasting about 2 weeks before the skin eruptions.
- When 10-30% of BSA is involved, it is called Transitional SJS.
- TEN is an acute and more severe inflammatory skin and mucous membrane disease.
- It manifests typically with sheet-like erosions (epidermal necrosis and detachment) involving >30% of BSA and severe involvement of conjunctival, corneal, irideal, buccal, labial and genital mucous membranes.
- Its prodrome manifests like flu with malaise, fever, rhinitis and conjunctivitis, sometimes accompanied by difficulty in urination.
- This prodromal phase could be as short as 2-3 days or 1 day to 3 weeks before the skin eruptions.
- Note that SJS may evolve into TEN.

Epidemiology

- Epidermal necrolysis (EN) is rare. The overall incidence of SJS and TEN was estimated at 1 to 6 (SJS) and 0.4 to 1.2 (TEN) cases per million person-years.

- EN can occur at any age, with risk increasing with age after the fourth decade, and it more frequently affects females with a sex ratio of 1:0.6.
- Patients infected with HIV and to a lesser degree, patients with collagen vascular disease and cancer are at increased risk.

Aetiology of EN

- This majorly involves drugs:

High risk
- Allopurinol, Phenylbutazone, Nevirapine, Oxicam NSAIDs (e.g. Piroxicam) and Thiacetazone,
- Sulfonamides (especially Sulfamethoxazole, Sulfadiazine, Sulfapyridine, Sulfadoxine and Sulfasalazine),
- Anticonvulsants (especially Carbamazepine, Lamotrigine, Phenobarbital and Phenytoin).

Lower risk
- Acetic acid NSAIDs (e.g. Diclofenac), Aminopenicillins, Cephalosporins, Quinolones, Cyclins and Macrolides.

Doubtful risk
- Paracetamol (Acetaminophen), Pyrazolone analgesics, Corticosteroids, Other NSAIDs (except Aspirin) and Sertraline.
- The role of infectious agents is much less prominent. However, cases of EN associated with Mycoplasma pneumoniae infection, viral disease, and Immunization have been reported.
- Radiotherapy.

Pathogenesis

- The immunologic pattern of early lesions of EN suggests a cell-mediated cytotoxic reaction against keratinocytes leading to massive apoptosis.
- Immunopathologic studies have demonstrated its presence within early lesions of cytotoxic cells including natural killer T cells and drug-specific CD8+ T-Lymphocytes; monocytes/macrophages and granulocytes are also recruited.
- Amplification of the above processes by cytokines has been suspected especially for factors activating “death receptors” on cell membranes, particularly TNF alpha and the soluble Fas ligand as

being responsible for the death of cells on the full thickness scale over large areas of the epidermis and mucous membranes.

Clinical features

- Clinically, EN usually begins 4-30 days after the onset of drug exposure for the first time but with a prior reaction and an inadvertent re-challenge with the same drug, it can appear within a few hours.
- Onset may be preceded by the prodrome as described above.
- There may be typical "target" lesions or atypical erythematous/ purpuric lesions and/or generalized erythema of the skin.
- There may be flaccid blisters and/or sheet-like epidermal detachment. Mucous membrane is involved at 2 or more sites especially oral and respiratory.
- The Nikolsky sign is usually positive.
- The total area in which the epidermis is detached or "detachable" (a positive Nikolsky sign) determines the classification of EN into SJS (<10%), transitional SJS (10-30%) and TEN (>30%).

Histology

- Early lesions are characterized by moderate perivascular mononuclear cell infiltration in the papillary dermis, with epidermal spongiosis and exocytosis.
- Satellite cell necrosis, with the close apposition of mononuclear cells to necrotic keratinocytes, may be seen.
- Macrophages and dendrocytes with a strong immunoreactivity for TNF-alpha predominate in a cell-poor infiltrate.
- The necrotic process involves the epithelial lining of sweat ducts, while hair follicles are much less affected. The dermis is largely unaffected.
- In established TEN, there is full thickness necrosis of the whole epidermis with blister formation.

Diagnosis

- This is based on clinical presentation and confirmed by a histology report from a skin biopsy.

- Other investigations useful in treatment include Blood arterial gas levels (poor O_2 saturation could point to a level of respiratory mucous membrane involvement),
- Serum E/U/Cr (could point to renal involvement and a bicarbonate level <20 mMols indicates poor prognosis), FBC and FBG (>14 mMols indicates poor prognosis).

Differential diagnosis

- Staphylococcal scalded skin syndrome,
- Purpura fulminans.
- Paraneoplastic pemphigus,
- Pemphigus vulgaris, Linear IgA bullous disease.
- Chemical toxicity (e.g. Colchicine poisoning, Methotrexate overdose).

Treatment

- Prompt identification and withdrawal of the offending drug(s).
- SJS and TEN require intensive care hospitalization and nursing like a burns case.
- Supportive care is vital: Maintenance of the fluid/electrolyte balance, keep the environmental temperature at 28-30^{o}C, Early nutritional support could be provided via a nasogastric tube if necessary to promote healing and to prevent bacterial translocation from G.I.T.
- Skin, blood and urine specimens should be cultured for bacteria and fungi at frequent intervals, Lower or no risk antibiotics are suggested where necessary, Antifungals are necessary especially with oral/airway mucous membrane involvement.
- Prophylactic anticoagulation is recommended, Rinse the mouth several times a day with antiseptic or antifungal solution.
- A daily ophthalmologist review and the use of preservative-free emollients, antibiotics or antiseptic eye drops and vitamin A two hourly in the acute phase, and the mechanical disruption of early synechiae is indicated.
- H_2 Receptor blockers or Proton pump inhibitors are beneficial for gut protection, Aggressive debridement is discouraged.
- Definitive therapy could involve the use of any of the following: Corticosteroids, Intravenous immunoglobulin, Cyclosporine,

Plasmapheresis or Haemodialysis, Antitumour necrosis factor agents.

Complications/sequalae

- Sepsis, Hypothermia, Genital adhesion, Bronchiolitis obliterans.
- Ophthalmic complications include chronic conjunctivitis, fibrosis, entropion, trichiasis and symblepharon. There could also be painful corneal ulcerations, scarring and altered vision.
- Post inflammatory hypopigmentation and/or hyperpigmentation of the skin.
- Hypertrophic or atrophic scars.
- Vaginal itching, dryness, pain and bleeding.
- Nail colour changes, dystrophy, ridging or anychia.
- Mouth dryness, altered taste, and late alterations of teeth.
- Oesophageal, intestinal, urethral, and anal stricture.

Prognosis

- The lower the SCORTEN, the better the outcome.
- Mortality is between 5-30%.

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8.8 Superficial Mycosis I (Ojinmah and Onyekonwu)

Introduction

- This involves fungi that can only colonize the stratum corneum of skin, hair and nails.
- In this chapter, we shall discuss dermatophytosis.

Dermatophytosis

Definition

- This is a collection of skin diseases caused by a group of fungi called dermatophytes which simply translates to “skin plants”. It is also known as ringworm or tinea.

Dermatophytes

- This is a label for a group of three types of fungus that commonly cause skin disease in animals and humans.
- These anamorphic (asexual or imperfect fungi) genera are: Microsporum, Epidermophyton and Trichophyton. There are about 40 species in these three genera.
- Their spores can live for more than a year in human skin scales in the environment.
- Anthropophilic dermatophytes are so well adapted to living on human skin that they provoke a minimal inflammatory reaction.
- Zoophilic or geophilic dermatophytes will often provoke a more vigorous inflammatory reaction when they attempt to invade human skin.
- The basic attraction to skin, hair and nails is in the fact that dermatophytes obtain their nutrition from keratin which is abundant in these structures.
- Colonies of dematophytes are usually restricted to the nonliving cornified layer of the epidermis because of their inability to penetrate the viable tissue of an immunocompetent host.
- Invasion does elicit a host response ranging from mild to severe. Acid proteinases, elastase, keratinases, and other proteinases act as virulence factors for the organisms.
- The development of cell-mediated immunity correlated with delayed hypersensitivity.

- An inflammatory response is associated with spontaneous clinical cure, whereas the lack of or a defective cell-mediated immunity predisposes the host to chronic or recurrent dermatophyte infection.
- Note: Trichophyton affects skin, hair and nails. Epidermophyton has a preference for skin and nails while Microsporum affects skin and hairs. This being the result of a targeted preference for specific types of keratin.

Transmission

- This is via direct contact with the infected host (human or animal) or by direct or indirect contact with infected exfoliated skin or hair.
- Susceptibility to infection is increased in the presence of immunocompromisation, a pre-existing injury to the skin such as scars, burns, or high environmental temperature and humidity.

Types of dermatophytosis

Anatomical site	Name
Scalp	Tinea capitis
Face	Tinea Faciei
Trunk/upper & lower limbs	Tinea corporis
Hands	Tinea manuum
Groin/axilla	Tinea cruris (Jock itch)/Tinea axillaris
Feet	Tinea pedis
Nails	Tinea unguium/Onychomycosis

Tinea Capitis

Introduction

- This is predominantly an infection of children.
- Transmission here could be via the hairs trapping airborne spores from another infected child without direct contact.

Aetiology

- Most species of dermatophytes are capable of invading hair but some species (e.g. M. audouinii, T. schonleinii and T. violaceum) have a distinct predilection for the hair shaft. E. floccosum, T.

concentricum and T. mentagrophytes var. interdigitale are exceptional in apparently never causing tinea capitis.

Pathogenesis

- Hair infection starts with invasion of the stratum corneum of the scalp skin.
- Trauma assists inoculation, which is followed after approximately three weeks by clinical evidence of hair shaft infection. Spread to other follicles subsequently occurs.

Types of hair invasion

Microsporum type

- A small-spored ectothrix invasion is caused by M. audouinii, M. audouinii var. rivalieri, M. canis var. distortum, M. equinum or M. ferrugineum.
- The hair shaft is invaded in the mid-follicle, intrapilary hyphae continue to grow inwards towards the hair bulb. Secondary, extrapilary hyphae burst out of the hair and grow in a tortuous manner over the surface of the hair shaft.
- These extrapilary hyphae segment to produce a mass of small arthroconidia (2-3 μm diameter), each one of which becomes rounded off and spherical.
- Fluorescence under Wood's lamp examination is characteristically present.

Trichophyton types

- A large-spored ectothrix (in chains) is caused by T. verrucosum, T. mentagrophytes var. mentagrophytes, T. mentagrophytes var. crinacei, T. menginii or T. rubrum (rarely).
- The arthroconidia (up to 10 μm in diameter) are spherical, arranged in straight chains and also confined to the external surface of the hair shaft.
- They apparently arise from straight primary extrapilary hyphae, rather than hyphae inside the hair. No fluorescence under Wood's lamp examination.
- The endothrix type may be caused by T. tonsurans, T. soudanense, T. violaceum, T. yaoundei, T. gourvilii or T. rubrum (rare).
- Intrapilary hyphae fragment into arthroconidia up to 8 μm in diameter, which are entirely contained within and completely fill the hair shaft.

- Affected hair becomes fragile, breaks off close to the scalp surface, and is non-fluorescent.
- The favic type (favus) is caused by T. schonleinii. Broad regularly septate hyphae and air spaces are seen in the hair shaft, but disarticulated arthroconidia are absent.
- The affected hair is less damaged than in other types of infection and may continue to grow to considerable lengths. Greenish-grey fluorescence is present.

Clinical features

- This is highly variable, depending on the type of hair invasion, the level of host resistance and the degree of inflammatory host response.
- The appearance therefore may vary from a few dull grey, broken-off hairs with a little scaling, detectable only on close inspection, to a severe, painful, inflammatory mass covering most of the scalp. Itching is variable.
- In all types, the cardinal features are partial hair loss with inflammation of some degree.

Small-spored ectothrix types

- The basic lesions are patches of partial alopecia, often in circular shape, but showing numerous broken-off hairs, dull grey from their coating of arthrospores.
- Inflammation is minimal, fine scaling is characteristic, usually with a fairly sharp margin.
- There may be single or multiple of such patches arranged more or less randomly. Note that the severity of inflammation here may vary depending on the specific causative organism.

Kerion

- This manifests as a painful, inflammatory mass in which such hairs that remain are loose.
- Follicles may be seen discharging pus, there may be sinus formation, and on rare occasions, mycetoma-like grains may be found.
- Thick crusting with the matting of adjacent hairs is common. The area affected may be limited, but multiple plaques are not rare, and occasionally a large confluent lesion may involve much of the scalp. Lymphadenopathy is frequent.

- Although this violent reaction is usually caused by one of the zoophilic species, typically T. verrucosum, T. mentagrophytes var. Mentagrophytes.
- Occasionally, a geophilic organism will be isolated, and anthropophilic infections that have been smouldering quietly for weeks may suddenly become inflammatory and develop into kerions if a high degree of hypersensitivity develops. One should also rule out bacterial super infection of a tinea capitis before settling finally for kerion.
- Note that zoophilic organisms can also trigger Agminate folliculitis which is a somewhat less severe inflammatory ringworm of the scalp consisting of sharply defined, dull red plaques studded with follicular pustules.

Endothrix infections

- In T. tonsurans and T. violaceum infections, a relatively non-inflammatory type of patchy baldness occurs. The formation of black dots (swollen hair shafts) as the affected hair breaks at the surface of the scalp is classical in this condition, but this may be inconspicuous.
- There may be minimal scaling over the lesions which are commonly angular in outline rather than round. The common clinical types are grey patch (scaling with patchy hair loss), black dot and diffuse alopecia.
- This might just provoke a low-grade folliculitis which could later turn into kerion. There could be the extension of lesions to the face.
- T. soudanense, T. yaoundei and T. gourvilii which are the three African species can induce very similar lesions.

Favus

- This is provoked by infection with T. Schonleinii, now rare.
- This is characterized by the presence of yellowish cup-shaped crusts known as scutula.
- Each scutulum develops around a hair which pierces it centrally.
- Adjacent crusts enlarge to become confluent and form a mass of yellow crusting.
- In long-standing cases, patches of scarring alopecia could occur.
- This is usually a childhood infection but it could persist into adolescence especially in females.
- Families with several generations affected are well recognized.

Diagnosis

- Clinical suspicion.
- Scalp scraping for KOH microscopy and culture for confirmation.

Differential diagnosis

- Alopecia areata, Tinea amiantacea, Scalp psoriasis, Lichen planopilaris.
- Impetigo secondary to pediculosis of the scalp, Discoid lupus erythematosus.

Treatment

- Topical therapy is only useful in tinea capitis as an adjunct to oral therapy.
- Oral therapy with any of the following: **Griseofulvin** (10 mg/kg/day); **Terbinafine** (<25 kg = 125 mg once daily: 25-35 kg = 187.5 mg once daily: >35 kg = 250 mg once daily); **Itraconazole** (5 mg/kg/day) or **Ketoconazole** (5 mg/kg/day) is recommended.
- All for a duration of 4-6 weeks.
- For kerion and favus, the removal of crusts with a wet compress is beneficial.
- Rule out secondary bacterial super infection where necessary.

Tinea Faciei

Definition

- Infection of the glaborous skin of the face with a dermatophyte fungus.

Aetiology

- T. mentagrophytes var. mentagrophytes and T. rubrum predominate but T. tonsurans, M. audouinii and M. canis are also common causes though other dermatophytes could also be responsible.

Pathogenesis

- Facial skin may be infected either by the direct inoculation of a dermatophyte fungus from an external source such as an infected pet or secondary spread from a pre-existing tinea of another body site.

Clinical features

- An itching or burning sensation which worsens with sun exposure.
- There will often be a history of exposure to animals.
- Erythema is usual with or without scaling. A substantial number of patients present with annular or circinate lesions. An indurated lesion with a raised margin may also be seen.
- A mixture of papules and vesicles among the classical lesions could occur.

Diagnosis

- Clinical suspicion, Skin scraping for KOH microscopy and culture for confirmation.

Differential diagnosis

- Discoid lupus erythematosus, Psoriasis, Seborrhoeic dermatitis.
- Polymorphic light eruption, Bowenoid solar keratosis.

Treatment

- In localized cases that are promptly diagnosed, topical therapy with any one of tolnaftate, terbinafine, ciclopirox or an imidazole works well.
- Where delay has occurred before diagnosis, especially if steroid application has modified the condition, oral terbinafine or Itraconazole is preferred.
- All treatments are for a duration of 3-6 weeks and longer where necessary.

Tinea Corporis

Definition

- A dermatophyte infection of the trunk and extremities excluding hands and feet.

Aetiology

- All known dermatophyte (Trichophyton, Epidermophyton and Microsporum) species can cause T. corporis.

Pathogenesis

- The infection is acquired by the deposition of viable arthrospores or hyphae on the skin.
- The source of infection could be an active lesion on an animal or another human, fomites, soil or spread from an existing infection localized to another site on the same individual.
- Invasion of the skin at the site of infection is followed by centrifugal spread through the stratum corneum. After this period of incubation which lasts 1-3 weeks, the tissue response to the infection becomes evident.
- The characteristic annular appearance of t. corporis results from the elimination of the fungus from the centre of the lesion by the host immune response, and the subsequent resolution of the inflammatory host response at the site.
- This area so cleared usually becomes resistant to re-infection, although a secondary wave of centrifugal spread from the original site may occur with the formation of concentric erythematous inflammatory rings.
- Note that some lesions may lack central clearance.

Clinical features

- Tinea corporis often begins as a pruritic, circular or oval, erythematous, scaling patch or plaque that spreads centrifugally.
- Central clearing follows, while the active advancing border a few millimetres wide retains its red colour and with close inspection can be seen to be slightly raised.

- Multiple lesions may run together to produce "flower petal" configurations.

Diagnosis

- Clinical suspicion.
- Skin scraping (especifically from the raised border) for KOH microscopy and culture for confirmation.

Differential diagnosis

- Localized granuloma annulare, Erythema annulare centrifugum, Pityriasis rosea.
- Nummular eczema, Psoriasis, Subacute cutaneous lupus erythematosus.

Treatment

- Tinea corporis usually responds well to the daily application of topical antifungals such as tolnaftate, terbinafine, ciclopirox or an imidazole.
- For individuals with extensive cases or patients who are severely immunocompromised, a systemic agent may be preferable.
- Systemic therapy is also appropriate in patients who have failed topical therapy.
- Appropriate systemic agents include oral terbinafine, fluconazole, and Itraconazole.

Tinea Manuum

Definition

- This is a dermatophyte infection of the skin of the hand. The infection on the dorsal skin is similar to t. corporis.
- Therefore, in this section, we shall discuss the manifestation over the palmar surface.

Aetiology

- E. floccosum, T. rubrum, T. mentagrophytes var. interdigitale, T. violaceum and T. mentagrophytes var. erinacei which is the only zoophilic species, while all the others are anthropophilic.

Pathogenesis

- It usually follows a foot infection.
- It could also start under rings, wrist watches, sites of deformities or where frictions of any kind have created macerated tissues.
- Poor peripheral circulation and palmar keratoderma could also predispose to infection.

Clinical features

- Hyperkeratosis of the palms and fingers with accentuation of the flexural creases which could be unilateral.
- It could also present as crescentic exfoliating scales, circumscribed vesicular patches, discreet red papular and follicular rashes or erythematous scaly sheets on the dorsum of the hand.

Diagnosis

- Clinical suspicion.
- Skin scraping for KOH microscopy and culture for confirmation.

Differential diagnosis

- Primary irritant contact dermatitis, palmar psoriasis, Syphilis.
- Pityriasis rubra pilaris, Keratoderma, Candida or bacterial intertrigo.

Treatment

- Appropriate oral antifungal agent.

Tinea Cruris

Definition

- This is a special form of tinea corporis involving the crural fold/groin.
- It is far more common in men than women.

Aetiology

- The most common cause is T. rubrum, followed by E. floccosum and occasionally T. mentagrophytes. The source of the infecting fungus is usually the patient's own t. pedis.

Predisposing factors

- Physical activities that result in copious sweating, Obesity.
- Diabetes mellitus and other immunodeficiency states, and the Sharing of towels and sportswear.

Clinical features

- It begins with an erythematous patch high on the inner aspect of one or both thighs (opposite the scrotum in boys). It spreads centrifugally, with partial central clearing and a slightly elevated, erythematous, sharply demarcated border that may show tiny vesicles.
- When caused by T. rubrum, the disease may extend well down on the thighs and up into the pubic region.
- In some cases, it is extremely chronic and progressive, extending onto the perineum and perianal areas, into the gluteal cleft, and onto the buttocks.
- In males, the scrotum is typically spared. This is an important clinical distinction between tinea cruris and candidal intertrigo, as candidiasis in males often involves scrotal skin.

Diagnosis

- The same as in other dermatophyte infections.

Differential diagnosis

- Inverse psoriasis, Erythrasma, Seborrhoeic dermatitis, Candidal intertrigo.
- Allergic contact dermatitis.

Treatment

- Topical antifungal treatment will suffice in some cases but in resistance to topical treatment, oral antifungals are indicated.

Tinea Pedis

Definition

- This is a dermatophyte infection of the feet and/or the toe web spaces.
- Tinea pedis (athlete's foot) is the most common dermatophyte infection encountered in practice. It is often accompanied by tinea manuum, onychomycosis, or tinea cruris.
- Tinea pedis presents in two readily distinguishable clinical forms: acute and chronic.
- Both are contagious, contracted by contact with arthrospores shed by infected individuals onto the floors.

Aetiology

- The acute form is usually caused by Trichophyton mentagrophytes, var. interdigitale, and the chronic form by Trichophyton rubrum.

Clinical features

Acute tinea pedis

- Attacks of acute tinea pedis are self-limited, intermittent, and recurrent.
- They often follow activities that cause the feet to sweat.
- It begins with the appearance of intensely pruritic, sometimes painful, erythematous vesicles or bullae between the toes or on the soles, frequently extending up the instep.

- The disease may be unilateral or bilateral. Secondary staphylococcal infections with lymphangitis often complicate the picture.
- Secondary eruptions at distant sites may occur simultaneously due to a presumed immunologic reaction to the fungus.
- This is a sterile vesicular eruption that often occurs on the palms and fingers, referred to as a dermatophytid (id) reaction.
- This improves as the primary infection is treated.

Chronic tinea pedis

- If untreated, it usually persists indefinitely.
- The disease begins with slowly progressive, pruritic, erythematous erosions and/or scales between the toes, especially in the third and fourth interdigital spaces.
- Interdigital fissures are often present. Extension onto the sole, sides of the foot, and in some cases the top of the foot follows, presenting as chronic scaling ("moccasin ringworm") with variable degrees of underlying erythema.
- The border between involved and uninvolved skin is usually quite sharp, and the normal creases and markings of the skin tend to accumulate scale.

Diagnosis

- The same as in other dermatophyte infections.
- Note that for a vesicular eruption, a specimen should be collected from the inner aspect of the roof.

Treatment

- Topical antifungal therapy for 2-4 weeks could be curative for acute tinea pedis.
- Resistant cases to topical therapy, extensive involvement and chronic cases benefit from oral antifungal therapy for 4-6 weeks.

Onychomycosis

- Trichophyton rubrum and T. interdigitale are the dominant dermatophyte species involved.
- Dermatophyte onychomycosis may be classified into two main types;

- (1) ***superficial white*** onychomycosis in which invasion is restricted to patches or pits on the surface of the nail; and
- (2) ***Invasive, subungual*** dermatophytosis in which the lateral, distal or proximal edges of the nail are first involved, followed by establishment of the infection beneath the nail plate.
- Distal subungual onychomycosis is the most common form of dermatophyte onychomycosis. The fungus invades the distal nail bed causing hyperkeratosis of the nail bed with eventual onycholysis and thickening of the nail plate.
- Diagnosis is confirmed by taking nail clippings or subungual debris for KOH microscopy and fungal culture.
- Oral therapy with Itraconazole 5 mg/kg/day in pulse therapy for 4-6 months for a fingernail infection and 6-8 months for a toenail infection is beneficial. Ciclopirox lacquer has also been found to be useful.

Tinea Axillaris

- This is a dermatophyte infection of the axilla.
- The hot and damp nature of the axilla makes a dermatophyte infection in that area to have a tendency to inflammation and bacterial superinfection.
- The lesions are usually not scaly and are irregular in outline. Pruritus is common.

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8.9 Superficial Mycosis II (Ojinmah and Onyekonwu)

- This section presents a concise summary on pityriasis versicolor and cutaneous candidiasis.

Pityriasis Versicolor

Definition

- It is a common but mild chronic or recurrent yeast infection of the skin, in which flaky discoloured patches can appear on the face, neck, arms and trunk.
- P. versicolor in most cases represents a shift in the relationship between a human and his or her resident yeast flora.
- The term **pityriasis** describes skin conditions in which the scale appears similar to bran.
- The multiple colours of this infection give rise to the second part of the name, **versicolor**.
- Pityriasis versicolor is also known as tinea versicolor.

Aetiology

- It is caused by infection of the epidermis by the Malassezia species (dimorphic lipophilic yeast).
- The most common form found in human infections is Malassezia furfur.

Epidemiology

- There is equal gender affectation.
- In the tropics, the condition is more common with a prevalence of up to 40% in some populations and onset is more often in warmer months.
- Infection could be seen in childhood but is more common from adolescence.
- It has been found to be more common in Cushing's syndrome and malnutrition.
- It does not appear to be more common in AIDS patients.
- Malassezia species do not attack the hair shaft, nails or mucous membranes.

Risk factors

- Possession of oily skin or the application of oils.
- A hot and humid climate, heavy sweating.
- Prolonged close contact with a P. versicolor patient.

Clinical features

- It presents in a variety of forms, but usually as hypopigmented, hyperpigmented, yellowish brown, brown or dark brown macules (with or without background erythema) in irregular or confluent patches of fine dry scales. There could be a perifollicular concentration of scales giving a picture of mottled hyperpigmentation and follicular papules.
- There may be mild itching especially during sweating.
- It usually affects the face, neck, upper trunk, shoulders and upper arms.
- Lesions are rare on other parts of the body.

Diagnosis

- Wood's lamp (black light) examination–yellowish white or copper orange fluorescence may be observed in affected areas.
- Microscopy of skin scrapings using 10% potassium hydroxide to remove skin cells (KOH)–hyphae and yeast cells that resemble spaghetti and meatballs are observed.
- Fungal culture–this is usually reported to be negative, as it is quite difficult to persuade the yeasts to grow in a laboratory. Special culture medium is required.
- Skin biopsy–fungal elements may be seen within the outer cells of the skin (stratum corneum) on histopathology. Special stains may be required.

Differential diagnosis

- Pityriasis rosea, Seborrhoeic dermatitis, Pityriasis alba.
- Early stages of vitiligo, Erythrasma, Secondary syphilis, Hypovitaminosis B.

Treatment

Mild pityriasis versicolor

- Topical antifungal agents have been shown to be beneficial.
- 50:50 Propylene glycol in water.
- 20% Sodium hyposulphate solution.
- 2.5% Selenium sulfide (applied overnight).
- Topical azole cream/shampoo (Econazole, Ketoconazole).
- Terbinafine gel.
- Ciclopirox cream/solution.
- The preferred medicine should be applied widely to all the affected areas for 2-4 weeks.

Extensive p. Versicolor, resistance to topical treatment or the convenience of the patient

- Oral azoles and allylamine are suggested:
- Ketoconazole, Fluconazole, Itraconazole, Terbinafine.
- Treat for 1-2 weeks. Note that recurrence is common.
- Hypopigmentation if present may persist for some months before normalizing.

Superficial Candidiasis (Candidosis)

Introduction

- This is an infection caused by yeast.
- Superficial infections of the mucous membranes and skin are more common though deep invasive disease can also occur.
- It represents a shift in the relationship between a human and his or her resident yeast flora.

Aetiology

- It is caused by yeast of the genus Candida with over 100 members.
- C. albicans is the predominant species isolated from clinical samples in most instances.
- Candida thrives in moisture and on moist surfaces.
- This infection is dependent on the interplay of forces between the host defence mechanism and candidal pathogenicity.
- Infection is usually confined to mucous membranes, skin folds, nail folds and nails.

Clinical patterns

Oral candidiasis (thrush)

- This condition occurs most commonly in the early weeks of life, and the preterm infant may be highly susceptible.
- The characteristic sign is a sharply defined patch of creamy, crumbly, curd-like pseudomembrane, which on removal leaves an underlying erythematous base.
- Unlike milk curds, this pseudomembrane is adherent and hence difficult to remove.
- There may be one or many patches. The tongue and buccal epithelium on the cheeks, the gums or the palate may be affected.
- In cases of immunocompromisation, lesions could extend to the pharynx or the oesophagus with a more severe, prolonged or recurrent manifestation and could be complicated by erosion and ulceration.

Diagnosis

- Clinical suspicion.
- A moist swab or scraping for direct microscopy and culture, for confirmation.

Treatment

- Suspension of Nystatin, amphotericin or miconazole gel applied several times per day. If resistant, fluconazole and itraconazole are beneficial.
- The duration of treatment should vary with severity and the presence of any underlying morbidity but generally 10-14 days is recommended.

Candida intertrigo (flexural candidiasis)

- Any skin fold may be affected, especially in the obese.
- It manifests typically with erythema and a little moist exudation (weepy) starting deep in the skin fold of contact.
- With progression, it spreads beyond the area of contact, presenting with a fringed, irregular edge and subcorneal pustules which rupture to give tiny erosions, and then further peeling of the stratum corneum.
- Satellite lesions which could be papular or pustular are classical. Soreness, and itching, which may occasionally be intense, are usual.
- Bacterial superinfection should be considered.

- Differentials include tinea, erythrasma, flexural psoriasis, seborrhoeic dermatitis, Darier's disease and Hailey-Hailey diseases.

Diagnosis
- Clinical suspicion.
- A moist swab or scraping for direct microscopy and culture, for confirmation.

Treatment
- Topical therapy with azole (e.g. ketoconazole) or polyene (e.g. nystatin) creams for 2 weeks or more.
- Keep the affected area dry: dilute potassium permanganate soaks are beneficial.
- Look out for and treat bacterial superinfection where present.

Napkin candidiasis (diaper candidosis)
- This is a condition that is usually prevalent upon napkin rash.
- In classical instances, subcorneal pustules, a fringed irregular border and satellite lesions are found. The route of infection is usually pathogenic from faeces.
- A moistened swab or a scraping should be obtained for diagnostic purposes especially if there is doubt.

Diagnosis
- Clinical suspicion.
- A moist swab or scraping for direct microscopy and culture, for confirmation.

Treatment
- Topical antifungal regimen for about 2 weeks.
- Change napkins often to keep the affected area dry and hence combat possible underlying napkin dermatitis.

Candida paronychia
- This is chronic inflammation of nail folds.
- This condition is chiefly found among those whose hands are frequently immersed in water e.g. home helps, assistants to food vendors, food vendors, dish washers, etc.
- Toenail folds are not usually affected.
- Typically, several fingers are chronically infected but sometimes, it could be solitary.
- The nail fold is red and swollen, and there is a loss of cuticle, and detachment of the nail fold from the dorsal surface of the nail plate leading to the creation of a potential space (pocketing).

- Occasionally, thick whitish pus may be expressed. There may be marked tenderness.
- Nail dystrophy, dyschromia and onycholysis around the lateral nail fold may occur.

Diagnosis

- Clinical suspicion.
- A moist swab for direct microscopy and culture, for confirmation.

Treatment

- This requires prolonged treatment sometimes lasting 3-6 months.
- Frequent applications of topical polyenes, imidazoles or non-specific remedies such as 4% thymol in chloroform. Lotions are preferable to creams.
- Oral Fluconazole and Itraconazole are also recommended.

Onychomycosis

- In the neonatal period, very rarely, Candida may invade the nail plate, sometimes causing an isolated nail dystrophy with evidence of the penetration of the superior aspect of the nail plate.
- There could also be distal and lateral subungual onychomycosis associated with paronychia.
- Complete destruction of the nail plate could also be seen in some patients with chronic mucocutaneous candidiasis.

Diagnosis

- Clinical suspicion.
- Nail clippings for direct microscopy and culture, for confirmation.

Treatment

- A prolonged course of oral fluconazole or itraconazole is recommended.

Congenital candidiasis

- This is established candidiasis, usually of the skin and birth membranes present at the time of birth, following intrauterine infection.
- Predisposing factors include prematurity and an intrauterine foreign body, usually a retained contraceptive device.
- The skin is the most common site for lesions, which are usually present at birth. The lesions manifest typically as discreet vesicles or pustules on an erythematous base.
- The face and chest are first affected by the rash, which generally spreads over the next few days after delivery. About 10% show evidence of spread to deep sites such as the lungs.

Diagnosis

- Clinical suspicion.
- A moist swab or scraping for direct microscopy and culture, for confirmation.

Treatment

- Topical therapy is beneficial but with extensive disease, oral fluconazole is recommended.

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8.10 Ichthyosis (Ojinmah and Onyekonwu)

Introduction

- Ichthyosis describes dry, rough and thickened skin with scaling over much of the body.
- The ichthyoses are a group of about 28 clinically and genetically heterogeneous skin disorders, characterized by a diffuse, generally uniform and persistent pattern of scaling usually without mucosal or extracutaneous involvement.
- Ichthyosis may be either inherited or acquired. Inherited ichthyosis is usually apparent during the first year of life, often at birth, and continues to affect a person throughout life.
- Acquired ichthyosis may occur as the result of drugs (Statins, Clofazimine, INH, Niacin, and Cimetidine) or medical conditions (Leprosy, HIV, Dermatomyositis, Sarcoidosis) including hormonal disorders, inflammatory, or malignant disorders (Non-Hodgkin's lymphoma, Leukaemia).
- They range in severity from mild ichthyosis vulgaris, to inflammatory and syndromic types and the often lethal harlequin ichthyosis.
- Ichthyoses result from abnormal epidermal differentiation or metabolism. Defective epidermal desquamation (retention) is a feature of some ichthyoses while a prominent inflammatory component occurs in others, usually associated with epidermal hyperproliferation.
- Epidermal fragility is a feature of some keratin mutations, while pruritus may complicate others.
- Complications include the overheating of the body because in rare cases, the skin thickness and scales of ichthyosis can interfere with sweating. This can inhibit cooling.
- In some people, hyperhidrosis can occur. There could also be secondary bacterial infection as a result of skin splitting and cracking.

Types of congenital variety

- There are many types of ichthyoses and an exact diagnosis may be difficult. They are classified by their appearance and their genetic cause.

- Ichthyosis caused by the same gene can vary considerably in severity and symptoms. Some ichthyoses do not appear to fit exactly into any one type.

Ichthyosis Vulgaris

Introduction

- This is the most common type constituting about 95% of the inherited ichthyoses.
- It is an autosomal dominant condition with variable penetrance.
- It is usually noticed after the first year of life commonly around puberty.
- It is more common in temperate climates and among Caucasians with an equal sex distribution. It is worse during cooler months.
- There is a close association with atopic diseases.

Aetiology

- A deficiency of filaggrin (filament aggregating protein) as a result of mutation in the filaggrin (FLG) gene.

Clinical features

- In the neonatal period, the skin may be dry and scaly with more obvious scaling usually from around the 2nd month of life.
- It presents with mild grey or white scales which are small, flaky, semi-adherent with turned-up edges.
- The extensor aspects of the extremities are more affected with a sparing of the flexural creases, nappy areas and palms/soles. There is palmoplantar (creases) hyperlinearity. The trunk, especially the abdominal wall, is often mildly affected. Facial scaling, forehead and perioral scaling, mild dandruff and pinnae scaling. There may be associated keratosis pilaris (follicular hyperkeratosis).

Diagnosis

- Usually based on clinical suspicion but a skin biopsy for histology is confirmatory.

Histopathology

- Skin shows mild hyperkeratosis with a diminished or absent granular layer of the epidermis. The dermis is not affected.

Differential diagnosis

- Atopic xerosis, Eczema craquele, Acquired ichthyosis and Refsum's disease.

Treatment

- The application of creams (creams containing lactic acid and Propylene glycol), emollients (Aqueous cream, Concentrated paraffin), and the use of moisturizing soaps for baths. Creams and emollients should be applied 2-3 times per day.
- Administration of retinoids.
- Avoidance of astringents, low humidity environments and extremes of temperature.

X-linked Recessive Ichthyosis (XLRI)

Introduction

- Affects male offspring only.
- It has a worldwide distribution and may be associated with post mature deliveries and extracutaneous manifestations.

Aetiology

- Deficiency of the enzyme called steroid sulphatase due to mutation on the STS gene.
- There is also an associated underlying lipid metabolic defect.

Clinical features

- Scaling is evident between the first week and the first year of life.
- Scales are coarse and dirty brown.
- Scaling is most prominent on the extensor surfaces of the upper arms, the abdomen, the outer thighs and around the lower legs. The

other parts of the body and flexures are mildly involved with the sparing of the palms and soles.
- Extracutaneous manifestations include corneal opacities; inguinal hernia is more common, unilateral renal agenesis in association with cryptorchidism, testicular maldescent, abnormalities of sperm count and motility, and testicular cancer.

Diagnosis

- Raised serum cholesterol sulphate as detected on serum lipoprotein electrophoresis.
- Steroid sulphatase activity measurement in leukocytes or skin fibroblasts is much reduced or absent.
- Normal levels of serum cholesterol.
- High index of suspicion.
- Skin biopsy for histology.

Histopathology

- Affected skin shows an expanded stratum corneum without parakeratosis or acanthosis. The granular cell layer is usually normal but may be mildly thickened or diminished in some cases.

Treatment

- As in ichthyosis vulgaris.

Lamellar Ichthyosis

Introduction

- Lamellar ichthyosis in the severe form is easily recognized because of the large plate-like scales which are dark unlike the variant called Non-Bullous Ichthyosiform Erythroderma (NBIE) where the scales are fine with background erythroderma.
- It has a worldwide distribution with an incidence of less than 1 in 300,000.

Aetiology

- Autosomal recessive inheritance of transglutaminase (TGase) 1 deficiency with a disorder of cornification or terminal epidermal differentiation.

Clinical features

- At birth, most affected infants present as collodion babies and after shedding the collodion membrane, show a less intense erythroderma than infants with NBIE. Erythroderma is generalized including the flexures, palms and soles.
- There is desquamation, and with increasing age, the dark plates of scales become the dominant feature with the pronounced involvement of the flexures.
- In severe cases, the thick, rigid scale is intermittently shed or splits, causing erythematous patches and deep painful fissures, especially over the highly mobile areas of the skin.
- Limitation of joint movement, flexion contractures and digital sclerodactyly.
- Palmoplantar keratoderma, scarring alopecia, persistent ectropion, eclabium, and congenital hypoplasia of aural and nasal cartilages could occur in severe cases.
- Pruritus is rare.
- There could be growth retardation in severe cases.

Diagnosis

- Clinical suspicion.
- Skin biopsy for histology with electron microscopy.
- TGase 1 immunoassay of cryostat sections of a skin biopsy to confirm TGase 1 deficiency.
- Mutational analysis of the TGM1 gene.

Histology

- Striking compact ortho or hyperkeratosis with variable mild focal parakeratosis.
- There is mild acanthosis though the thickness of the lower epidermis is normal.

- There may be mild papillomatosis, extension and blunting of the rete ridges, and dilatation of the dermal capillaries.

Treatment

- As in Ichthyosis vulgaris plus Topical calcipotriol, 10% urea lotion and topical N-acetylcysteine.

Complication

- Secondary bacterial infections.

Collodion Baby

Introduction

- This term describes the transient, shiny, transparent plastic-like appearance of skin in the neonatal period of a baby who, in general, subsequently develops congenital Ichthyosiform erythroderma.
- There is no reliable figure on the incidence.
- The inheritance pattern is usually autosomal recessive (AR).

Clinical features

- Premature delivery is more common.
- At birth, they present with a generalized glistening, taut, yellowish film stretched over the skin giving the appearance of one dipped in hot wax.
- Normal skin markings are obliterated, the eyelids and sometimes the lips are tethered and everted (ectropion and eclabium), the pinnae may be flattened and the nostrils obstructed.
- Reduced or absent sweating.
- There may be constricting bands around the digits or limbs.
- The collodion membrane cracks and sheds within the first few weeks of life.
- In a greater majority of cases, the features of non-bullous Ichthyosiform erythroderma and lamellar ichthyosis become apparent as the collodion membrane is shed.

Diagnosis:

Clinical suspicion.

Differential diagnosis

- Chrysalis babies, Gaucher type 2 syndrome, Neu-Laxova syndrome.
- Staphylococcal scalded skin syndrome.

Treatment

- Nurse in the neonatal intensive care unit in a humidified incubator.
- Cleansing daily with warm water, sterile aqueous cream or antiseptics and barrier nursing to prevent infection.
- 4 hourly application of an emollient.
- Prompt treatment of any skin infection noticed.
- Lubricating eye drops should be applied to prevent exposure to keratitis in the presence of ectropion.
- Nasal obstruction can be improved by gentle probing with a sterile blunt probe.
- Constricting bands on the limbs should be divided if causing acral pressure effects.
- The parents must be encouraged to nurse and bond with the baby.
- If suckling is poor, pass an N-G tube.

Complications

- Renal failure, Hypothermia, Bacterial sepsis.
- Neurological sequalae of hypernatraemic dehydration.

Others

Bullous Ichthyosiform erythroderma (BIE)

- Also known as Epidermolytic hyperkeratosis (EHK).
- Rare autosomal dominant disorder of keratinization that, in the early phase, is associated with blistering.
- Incidence is 1 in 100,000 live births.
- It results from defective keratin 1 and/or keratin 10 which are found only in the suprabasal compartment in normal epidermis.

Genetic studies revealed a linkage to either of the keratin gene clusters on chromosomes 12q and 17q.

- Onset is at birth with erosions and bullae, followed by thick, waxy scales (sometimes macerated) and erythroderma in childhood.
- Lesions are typically generalized with increasing hyperkeratosis being prominent around the anterior neck, flexures, abdominal wall, infragluteal folds and scalp.
- Yellow-brown, waxy, ridged or corrugated scales build up in skin creases, sometimes forming spiny (hystrix) outgrowths.
- Cobblestone-like keratoses occur over the dorsum of hands and feet, and over the trunk. Keratotic plaques may coat bony prominences, the scalp and the areolae of breasts.
- Chunks of these plaques are easily dislodged, leaving tender erosions where scales accumulate again slowly.
- There could be accompanying body odour and recurrent pyogenic skin infections.
- Spontaneous blistering ceases at adolescence leaving mild erythema and hyperkeratosis.
- **Treatment:** expression of keratolytic preparations (salicylic acid, alpha-hydroxy acid or propylene glycol compounds) with the regular use of antiseptic washes and cleansing lotions.
- Topical calcipotriol and retinoids are beneficial but could be complicated by skin irritation. Emollients are not recommended as they worsen the maceration.

Non-Bullous Ichthyosiform erythroderma (NBIE)

- Sometimes called Congenital Ichthyosiform Erythroderma (CIE) or erythrodermic lamellar ichthyosis.
- Rare and usually severe autosomal recessive inflammatory ichthyosis.
- It occurs in all races but is more seen where consanguineous marriage is common.
- It is characterized by epidermal hyperplasia with increased mitoses and expression of hyperproliferative keratins K6/K16/K17.
- About 90% of cases present as collodion baby at birth while the remaining are erythrodermic from birth, and some are premature. They subsequently shed the collodion membrane and generalized scaly erythroderma subsists.

- There is a wide clinical variation as it pertains to the intensity of the erythroderma and scales. Scales are fine and white.
- Treatment is as in ichthyosis vulgaris but keratolytics and topical retinoids must be used with caution as they can cause skin irritation. Topical steroids are ineffective and readily absorbed, and may cause systemic steroid toxicity, especially in infants.
- Hyperhidrosis with the attendant risk of high body temperature may be aggravated by the occlusive action of ointments. Scarring, ectropion, eclabium and alopecia could be complications.

Harlequin ichthyosis (HI)

- Also known as Harlequin foetus because of the skin patterning and the associated high mortality but HI is more appropriate as survival is possible.
- HI is a very rare autosomal recessive disorder.
- It is invariably associated with stillbirth or early neonatal death but those that survive transmute to a severe erythrodermic ichthyosis.
- Underlying problems are defects in keratin expression and epidermal lipid deposition. Studies show that keratinocytes in HI display excessive cornification and failure of desquamation.
- The affected newborn, usually premature, sometimes stillborn, is encased in massive, thick plates of hyperkeratosis with deep fissures.
- The head may appear small with a boggy feel to the scalp. Facial features are distorted by the presence of thick scales, fissures, severe ectropion and eclabium.
- The nose and external ears are tethered and appear rudimentary. There is a restriction of movement which might on its own or in conjunction with coexisting skeletal deformity lead to respiratory insufficiency.
- There could be an absence of effective sucking with attendant hypoglycaemia, dehydration and renal failure. Temperature instability and infections could lead to death.
- Intensive neonatal care and nursing in a humidified incubator are the rule. The family should from the onset be prepared psychologically to face the consequences of severe, lifelong ichthyosis if they survive.
- The following are beneficial: paraffin-based emollient such as emulsifying ointment applied frequently; skin cleansing with antiseptic washing lotion; insertion of an N-G tube to assist in

feeding; adequate fluid replacement with the aid of an intake/output chart; daily weighing and monitoring of renal function and administration of oral retinoids.

- Complications include, osteopaenia, vit. D deficiency and short stature. There could also be chronic ectropion with possible exposure keratitis and constrictive deformities of ears, hands, and feet.

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8.11 Seborrhoeic Dermatitis (Ojinmah and Onyekonwu)

Introduction

- This is also called dandruff, seborrhoeic eczema and seborrhoeic psoriasis.
- In infants, it is known as cradle cap.
- It is a sub-acute or chronic endogenous dermatitis characterized by a distinctive morphology (red or dark lesions with distinct margins, covered with yellowish, greasy scales) with a predilection for areas rich in sebaceous glands such as the scalp, face and upper trunk.
- Incidence is 1-3%. It may present in infancy, childhood, adolescence or adult life. It is more common in males than females and in people with oily skin.

Aetiology

- Interplay of the following factors: seborrhoea (oily skin), increased colonization of seborrhoeic areas by the commensal yeast Malassezia spp. (Pityrosporum ovale) and genetic susceptibility for an inflammatory response to the overgrowth of Malassezia spp.

Risk factors

- Neurological and psychiatric disorders, such as epilepsy and depression.
- A weakened immune system, such as seen in organ transplant recipients and people with HIV/AIDS, and some cancers.
- Congestive heart failure. Recovery from cardiac arrest or stroke, Neuroleptic drugs.
- Diabetes mellitus, Obesity and Malabsorption states.

Clinical features

- Manifestation is usually within the first 3 months of life and typically the infant is well and not irritable.
- In infancy, it may present as “cradle cap”, a fine greasy, yellowish eruption on the scalp, with matting of the lesions over the anterior fontanelle and vertex.

- The lesions often extend to the hairline, forehead, eyebrows, peri-auricular region, the nasolabial folds, axillae, the sterna and interscapular areas.
- The groin and other intertriginous areas, and even the trunk may be affected. Severe scalp involvement may lead to reversible alopecia.
- Excoriation of the lesions could lead to bacterial superinfection. Candidal superinfection is a likely possibility.
- Blepharitis could be an accompanying feature.
- In children and adolescents, the scalp lesions are drier and manifest as pityriasis capitis (dandruff), the eyebrows, peri-auricular region and nasolabial folds harbour thin, powdery scales, and the skin folds (intertriginous areas) are less affected.
- Itching when present is not troublesome.

Diagnosis

- Based on clinical suspicion.
- Skin scraping for KOH microscopy and Culture–if it yields, Malassezia spp. is helpful.

Differential diagnosis

- Atopic dermatitis, Tinea capitis, Intertrigo, Allergic contact dermatitis.

Treatment

- 1% Hydrocortisone cream with vioform applied morning and night is effective. It should be used for about 2 weeks and then replaced with 2% ketoconazole cream or terbinafine lotion for long-term maintenance.
- If the lesion is exudative, apply compresses of saline or aluminum acetate (Burrow's solution).
- Treat secondary bacterial or candidal superinfection with oral drugs.
- Other topical treatments: 1-2% Sulphur Salicylic Acid ointment compounded with 0.5-1% Hydrocortisone cream and Aqueous cream is beneficial in the treatment of very scaly varieties.
- Selenium sulphide, Ciclopirox and Ketoconazole shampoo.
- Troublesome itching requires systemic antihistamines.

- Moisturizing soaps are beneficial.
- Topical calcineurin inhibitors such as pimecrolimus cream or tacrolimus ointment may be used instead of topical steroids.
- Patients or minders must be informed of the waxing and waning nature of this disorder.

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8.12 Transient skin disorders of the newborn (Ojinmah and Onyekonwu)

Introduction

- These are skin disorders that affect the newborn which could be described as benign or civil with an ephemeral disposition.
- Complete resolution is the rule.

Toxic erythema of the newborn

- Also called **Erythema toxicum neonatorum**.
- This is a misnomer because there is no evidence of toxicity.
- It is the most common pustular eruption in newborns.
- Estimates of incidence vary between 30 and 70%. It is most common in infants born at term and weighing more than 2.5 kg.
- Aetiology is unconfirmed despite many postulations.
- It may be present at birth but in the majority of cases, it appears during the first 48 hours of life, but it may occur at any time until about the 4^{th} day.
- Classic lesions consist of erythematous macules and papules that develop into pustules.
- Each pustule is surrounded by a blotchy area of erythema, leading to what is classically described as a "flea-bitten" appearance.
- These usually occur on the face, trunk, and proximal extremities sparing the palms and soles.
- Presentation with scrotal pustules at birth has been reported.
- The affected infant appears well and stable.
- Spontaneous recovery occurs, usually within 5-7 days but recurrences could be seen, and have been reported as late as the 6^{th} week of life.
- Histologically, the erythematous macules show oedema in the upper dermis, with a sparse and largely perivascular infiltrate principally made up of eosinophils.
- The papular lesions in addition to the above features have eosinophilic infiltration of the structures of the hair follicles. There is an associated blood eosinophilia.
- The diagnosis of erythema toxicum neonatorum is made clinically and can be confirmed by a cytologic examination of a pustular

smear, which will show eosinophilia with Gram, Wright, or Giemsa staining. Peripheral eosinophilia may also be present.
- Differentials include pustular miliaria, transient neonatal pustular melanosis, Incontinenti pigmenti, herpes simplex virus infection, Varicella, impetigo neonatorum, and Malassezia furfur pustulosis.
- No treatment is required.

Miliaria

- This occurs as a result of impedance to the flow of sweat from the eccrine sweat gland by obstruction of the intradermal portion of the sweat duct. It is a very common finding in newborns, particularly in warm climates.
- It affects up to 40% of infants, and usually occurs within the first month of life though some congenital cases have been documented.
- It is suspected to be caused by the interplay of the relative immaturity of the sweat duct in early infancy and the tendency to nurse infants in excessively warm and humid conditions.
- There are two major types: Miliaria crystallina and Miliaria rubra.
- **Miliaria crystallina** appears to reflect an obstruction of a sweat duct within the stratum corneum. It is very common in the neonatal period, probably caused by the delayed patency of the sweat pore. It presents as crops of clear, thin-walled, small superficial vesicles without associated erythema, resembling drops of water.
- They are very delicate and usually rupture within 24 hours to be followed by flaky desquamation. Commonly seen on the forehead, scalp, neck, and upper trunk.
- **Miliaria rubra** ("prickly heat") appears to be caused by a sweat duct obstruction deeper within the epidermis, induced perhaps by increased activity by intraductal microflora.
- This is most frequent during the neonatal period and common throughout infancy. Its pattern of manifestation is due to a deeper obstruction of the duct of the eccrine sweat gland leading to the accumulation of sweat with seepage into surrounding tissues to trigger inflammation.
- It manifests as erythematous papules and papulovesicles on a background of macular erythema. Frequently, some of the lesions are pustular (miliaria pustulosa), but this does not necessarily indicate superinfection. There may be associated itching or pain.
- In severe cases, the child could be restless and distressed. Lesions arise fairly symmetrically in occluded/covered areas of the body,

most often in flexural areas, especially around the neck, groins and axillae. It may also occur locally at sites of occlusion like areas of skin frequently in direct contact with a plastic mattress cover or plastic pants.

- **Miliaria profunda** presents with skin-coloured papules and pustules only.
- No specific treatment is typically needed for miliaria, as lesions usually resolve when the infant is placed in a cooler environment and occlusion is avoided.
- Mild topical corticosteroids can be used for refractory lesions of miliaria rubra.

Milia

- It consists of 1-2 mm pearly white or yellow papules due to the retention of keratin and sebaceous material in the pilacious follicles within the dermis.
- They occur in up to 50% of newborns. Milia occur most often on the forehead, cheeks, nose, and chin, but they may also occur on the upper trunk, limbs, penis, or mucous membranes.
- They disappear spontaneously, usually within the first month of life, although they may persist into the second or third month.
- Milia are a common source of parental concern, and simple reassurance about their benign, self-limited course is appropriate.

Transient neonatal pustular melanosis

- It commonly affects full-term African American children but is not confined to black neonates.
- It has a prevalence that ranges from 4.4-5% among blacks and 0.6-1% for Caucasian infants. Invariably present at birth, it consists of three different phases which coexist.
- The most characteristic component of the eruption is 1-3 mm flaccid, superficial, fragile pustules, with no surrounding erythema. They may occur at any site (including the palms and soles), but prefer the neck, chin, forehead, back and buttocks.
- Sites where the pustules have ruptured are marked by detachable brown crusts which peel off to leave erythematous macules with a surrounding collaret (rim) of scale and finally hyperpigmented macules occur which gradually fade over several weeks to up to 3 months.

- The pigmented macules are a prominent component in blacks and are seen more rarely in other races. Affected infants are otherwise entirely well.
- Diagnosis is usually clinical but microscopic examination of the pustular contents will show polymorphic neutrophils and, occasionally, eosinophils.

Neonatal acne

- Seen in about 20% of infants within the first 1-3 weeks of life and probably not familial.
- Aetiology is unknown though some theories attribute it to the stimulation of sebaceous glands by the maternal and infant androgens or as a result of an inflammatory reaction to skin colonization by the Malassezia species.
- It classically manifests as closed comedones on the cheeks, nose, and forehead although other locations could be involved. Open comedones, inflammatory papules, and pustules can also be seen.
- Typically, it is mild and can be treated with daily cleansing with soap and water, and the avoidance of oils and lotions but 2.5% benzoyl peroxide lotion, 2% ketoconazole cream or 1% hydrocortisone cream can be used if lesions are extensive and persist for several months.

Infantile acne

- A different entity from neonatal acne, this presents typically in the 3rd to 4th month of life.
- It results from hyperplasia of the sebaceous glands secondary to androgenic stimulation and is more common in infant boys.
- Clinically more severe than neonatal acne, it consists of acneiform lesions including inflammatory papules, comedones, and pustules, with occasional nodules in the face.
- The classical clinical course is for lesions to clear spontaneously by late in the 1st year of life, but this can persist into the 3rd year. Treatment is sometimes required, because these lesions can persist and cause permanent scarring, unlike neonatal acne.
- In the presence of mild or moderate inflammation, treatment can be instituted with mild keratolytic agents, such as 2.5% benzoyl peroxide, topical antibiotics (e.g. clindamycin or erythromycin), or weak topical steroids.

- In severe cases, systemic antibiotic therapy or oral isotretinoin can be used.

Infantile acropustulosis

- An uncommon disorder of unknown aetiology which occurs in all races; benign, vesiculopustular, and often a more chronic course than other benign neonatal lesions.
- These can be present at birth or have onset at any time during the first year of life. It clinically manifests as recurrent crops of intensely itchy, 1-4 mm vesiculopustules involving majorly the palms and soles but it could seriously involve the extremities though scattered involvement of other parts of the body may occur. No mucosal involvement.
- There could be excoriation of lesions with erosion and crusting. It heals to leave post-inflammatory hyperpigmented macules.
- There could be intense pruritus, restlessness, loss of appetite and interference with sleep. Recurrences can occur every 2-4 weeks and can last 5-10 days.
- Diagnosis is clinical. These lesion cycles typically resolve within 2 years.
- Moderately potent topical corticosteroid, oral antihistamines and Dapsone are beneficial.

Cutis marmorata

- This is a reticular mottling of the skin that symmetrically involves the extremities and trunk.
- It is a product of the newborn's vascular response to cold and generally resolves with warming of the skin.
- A tendency to cutis marmorata may persist for several weeks or months, or sometimes into early childhood. No treatment is needed, just keep warm.

Harlequin colour change

- It is a benign phenomenon that affects up to 10% of full-term infants, but often goes unnoticed because the infant is usually wrapped up in a bundle.
- It occurs most commonly during the first week of life and may continue for up to 3 weeks. It results from immaturity of the

hypothalamic centre that controls the dilation of peripheral blood vessels. Harlequin colour change occurs when the newborn lies on his or her side.

- It is characterized by intense erythema of the dependent side and blanching of the non-dependent side, with a demarcation line along the midline.
- The colour change develops suddenly and duration ranges from seconds to 20 minutes. It resolves with increased muscle activity or crying.

Sucking Blisters

- This is a diagnosis of exclusion. It presents as oval, thick-walled vesicles or bullae that are filled with sterile fluid. Lesions may have erosion or crusting present.
- Blisters may be unilateral or bilateral and are usually located on the dorsal aspect of the wrists, hands, or fingers of neonates who are noted to suck excessively at the involved regions.
- Treatment is often not needed beyond the protection of affected areas but sometimes topical antibiotic ointments can be used especially with bacterial superinfection or for prophylaxis.

Congenital dermal melanocytosis (Mongolian blue spots)

- These are the most frequently encountered pigmented lesions in newborns, also known as **blue-grey macules**. They are very common in Asian, African, and Hispanic neonates, while they are very uncommon in Caucasian neonates.
- These are characterized by congenital blue-grey pigmented macules with undefined borders. Macules can be 10 cm or more in diameter, and lesions are most commonly found in the sacro-gluteal region, or the region of the shoulders.
- The spots are usually present at birth or appear within the first week of life. They result from the entrapment of melanocytes in the dermis during their migration from their site of origin which is the neural crest into the epidermis.
- These are completely benign lesions which usually fade away within 4 years but can persist for life (especially if aberrantly located distal from the lumbosacral region).

Bronze baby syndrome

- This refers to a diffuse grey-brown discoloration of the skin that can develop in infants 1-7 days after the initiation of phototherapy for hyperbilirubinemia.
- There is no established aetiology yet though suspicions abound. It gradually resolves without sequalae within several weeks after the discontinuation of phototherapy.

Halo scalp ring

- This is a ring-shaped area of alopecia that develops in some infants. This is commonly a temporary, non-scarring alopecia that occurs in newborns especially of primigravidas.
- It has been attributed to unusually prolonged pressure on the vertex of the scalp by the cervix during a difficult delivery, often in primigravidas which leads to caput succedaneum.
- Caput succedaneum consists of soft tissue swelling and bruising that often resolve in several days without sequalae.
- However, hair loss may occur as a consequence of pressure necrosis. The alopecia usually resolves after several years but may be permanent if scarring followed the caput.

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SECTION 9

ONCOLOGY

UDECHUKWU, P. N.

9.1 Benign and malignant tumours

Definition/Epidemiology

- Benign tumours are circumscribed, localized and do not transform into cancer. They arise from disorders of cellular growth and development.
- Malignant tumours are cancerous and progressive, invading and destroying the surrounding tissues and tend to spread to other parts of the body.
- Paediatric malignancies differ from those of adults in the distribution by histology and site as well as prognosis e.g. epithelial tumours of the breast, colon, prostate and lungs are common in adults but rare in children.
- In infancy, embryonic tumours like neuroblastoma, retinoblastoma, nephroblastoma, rhabdomyosarcoma and medulloblastoma which arise from developing tissue are more common and are rare in adults after the cell differentiation process has slowed down.
- Paediatric malignancies like acute myeloid leukaemia, Hodgkin's lymphoma and bone malignancies that are common in adolescents are more similar to those that occur in adults.
- The malignancy rate increases with age in adults while the paediatric age group has 2 peaks: early childhood and adolescence.
- The incidence rates of childhood cancer are slightly more in boys and in whites.
- There has been a decrease in the mortality rate of childhood malignancies in the last 30 years due to the use of aggressive multimodal therapy, the judicious use of blood products like

cytokines and improved supportive care to prevent and treat infections.

- Only a small fraction of paediatric cancers are explained by environmental exposures e.g. ionizing radiations and exposure to chemotherapeutic agents while genetic conditions are involved in less than 5%.
- Epidemiological studies reveal a multifactorial aetiology resulting from an interaction between genetic susceptibility traits and environmental exposures.
- The predominant types of paediatric malignancy in developed and developing countries are shown below:

Table 9.1-1 The predominant cancer types

- The figures represent patients in the 0-15 years age range

Position	Developed		Developing	
	Cancer Type	%	Cancer Type	%
1	Leukaemia	25	Burkitt Lymphoma	43.3
2	CNS Tumour	17	Leukaemia	13.5
3	Neuroblastoma	7	Retinoblastoma	10.8
4	Non-Hodgkin's Lymphoma	6	Nephroblastoma	8.4
5	Nephroblastoma	6	NHL (Non Hodgkin's Lymphoma)	6.0
6	Rhabdomyo Sarcoma	3	Hodgkin's Lymphoma	5.2
7	Retinoblastoma	3	Neuroblastoma	4.0
8	Ewing Sarcoma	2	Rhabdomyo Sarcoma	3

The molecular and cellular biology of cancer

- Cancer occurs principally as a result of alterations that can occur in a wide variety of genes resulting in changes in the normal cellular functions such as signal transduction, cell cycle control, DNA repair, cellular growth and differentiation, translational regulation, senescence and apoptosis.
- Genes involved in oncogenesis include proto-oncogenes and Tumour suppressor genes (TSG). Proto-oncogenes code for various

proteins like transcriptional factors, growth factors, and growth factor receptors that regulate cell growth, division and differentiation.

- Classes of oncogenes based on the mechanism of action include: growth factor, growth factor receptors, signal transducers, transcription factors and factors that interfere with apoptosis.
- Proto-oncogenes are activated to oncogenes via amplification, point mutation and chromosomal translocation.
- Chromosomal translocation can result in fusion genes leading to the production of a chimeric protein with new and potentially oncogenic activity like [t(2;13)] or t(1;13) and [t(11;22)] for alveolar rhabdomyosarcoma and Ewing's sarcoma respectively.
- The Philadelphia chromosomes t(9;22) which result in BCR/ABL protein seen in CML are the best described translocation.

Table 9.1-2 Oncogenic activation with resultant tumours

Mechanism	**Chromosome**	**Genes**	**Protein function**	**Tumour**
Chromosomal translocation	t(9;22)	BCR-ABL	Chimeric tyrosine kinase	CML, ALL
,,	t(14;18)	CMYC	Transcription factor	Burkitt lymphoma
Gene Amplification	Amplicon	MYCN	Transcription factor	Neuroblastoma
Point mutation	1P	NRAS	GTPase	AML

- TSG are involved in regulating cellular growth and apoptosis. Alteration in the regulation of TSG leads to oncogenesis.
- P53 Tumour Suppressor protein prevents damaged cells from dividing and also initiates apoptosis leading to cell death.
- Syndromes predisposing to cancers include the inactivation of TSG as in Li-Fraumeni syndrome, defects in DNA repair seen in Bloom/Fanconi syndrome and defects in immune surveillance as seen in Wisckot-Aldrich syndrome.

Table 9.1-3 Factors associated with oncogenesis
Familial or Genetic susceptibility to Malignancy.

Disorder	Tumour/cancer	Comment
Chromosomal syndromes: Chromosome 11-p deletion with sporadic aniridia	Wilms tumour	Associated genitourinary anomaly, mental retardation. WT 1 gene.
Chromosomal 13q-deletion	Retinoblastoma, sarcoma	Associated with mental retardation, skeletal malformation. Autosomal dominant or sporadic new mutation.
Chromosomal instability. Fanconi Anaemia	Leukaemia, myelodysplastic syndrome, liver neoplasm, GI and GU cancers.	Autosomal recessive, chromosomal fragility, positive diepoxybutane test. Mutation in FANCX gene.
Bloom syndrome	Leukaemia, lymphoma, solid tumour	Autosomal recessive, increased sister chromatid exchange. Mutation in BLM gene.
Ataxia telangiectasia	Lymphoma, leukaemia, CNS & neural solid tumours	Autosomal recessive, sensitive to irradiation, radiomimetic drugs, mutations in ATM TSG
Immunodeficiency syndrome. Wiskott-Aldrich syndrome	Lymphoma, leukaemia	X-linked recessive. WAS gene mutation. Xp 11. 22-23
Severe combined immunodeficiency syndrome	Leukaemia, lymphoma	X-linked mutations in ADA genes
X-linked immunodeficiency syndrome	Lymphoproliferative disorders	X-linked mutation in SH2D1A gene locus

Others Neurofibromatosis 1	Neurofibroma, optic glioma, astrocytoma	Autosomal dominant mutation in TSG NF1.
Neurofibromatosis 2	Bilateral acoustic neuroma, meningioma	Autosomal dominant mutation in TSG NF 2.
Tuberous sclerosis	Fibroangiomatous nevi, myocardial rhabdomyoma	Autosomal dominant.
Li-Fraumeni syndrome	Bone, breast and soft tissue sarcomas	Autosomal dominant mutation in P53 TSG.

- Other factors associated with oncogenesis are: EBV infection, genomic imprinting and increased telomerase activity.

Principles of Cancer Diagnosis

- Diagnosis of cancer in children can be quite challenging as features are variable and it is made after a detailed history, physical examination and investigations have been done.
- A clue to diagnosis can be obtained from the epidemiological point of view. The patient and the family must be informed of the possible diagnosis while evaluation is in progress.
- Common signs and symptoms of cancer in children include: pallor, bruising, persistent fever or infection, pancytopenia, headache with neurologic deficit; headache with vomiting; persistent and unexplained lymphadenopathy; abdominal mass and swelling.
- Uncommon signs and symptoms linked directly to malignancy include superior vena cava syndrome, subcutaneous nodules and leukaemoid reaction.
- Uncommon signs and symptoms not directly linked to malignancy include: chronic diarrhoea, failure to thrive, Cushing's syndrome, polymyoclonus and opsoclonus as well as pseudomuscular dystrophy.
- Investigations include: FBC and blood film, LFT, serum electrolytes, urea and creatinine, alpha fetoprotein and LDH, imaging studies, X-rays, MRI, CT-scan, abdominal ultrasound, PET scans, histology, molecular and histochemistry.

Principles of treatment of cancer in children

- Treatment of cancer in children is complex because of rapid growth and development so multidisciplinary teams and a holistic approach are used. The main principles include:
- ***Early diagnosis*** which minimizes the amount, duration of treatment and recurrent disease.
- ***Staging of cancer*** to determine the extent of the disease as well as enable the oncology team to avoid overtreatment or under treatment.
- ***Multi-modal, multidisciplinary approach to treatment****,* the various paediatric subspecialties are involved in the evaluation and treatment of childhood cancers as they provide modality and multiple supportive care services.
- The mainstay of treatment is chemotherapy alone or in conjunction with surgery, radiation and biologic therapy.
- ***Adverse metabolic emergencies*** like tumour lysis syndrome, bone marrow suppression with anaemia, immunosuppression and thrombocytopenia should be addressed while adequate hydration and agents that lower uric acid levels should be given.
- ***Palliative care****:* includes providing comfort to the patient by relieving pain, anxiety, and suffering, and psychological support.

Complications and Prognosis

- Complications are from the primary disease and the treatment depending on the primary organ of involvement as well as organs of metastasis. They include proptosis, respiratory distress, coma, hemiplegia, blindness, deafness, organ failure, hair loss, sterility, neuro cognitive impairment, altered social function, osteoporosis, new malignancy and growth failure.
- The risk of a 2^{nd} malignancy appearing within 20 years after the initial diagnosis of cancer is about 8%.
- Prognosis is good for most childhood tumours as the cure rate is high. However, early diagnosis is the key factor in this regard.

Prevention and Control

- Routine screening of all infants and children with a view to identifying the disease at the early stages.

- Preventing known risk factors like infection with the Epstein-Barr virus, HIV and other agents that predispose children to malignancy.
- Identify children with immunodeficiency syndromes and monitor them closely.
- Control is achieved mainly by the early detection of cases and prompt treatment.

Counselling

- Frank discussion of all the facts with patients and their parents, the nature of the illness, treatment options and duration.
- The patient should be advised of the need to complete treatment, follow up for evaluation, relapse, complications of the cancer and those of its treatment.

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9.2 Burkitt Lymphoma

Introduction

- Burkitt lymphoma (**BL**) is a cancer of the lymphatic system involving B lymphocytes, named after Dr Dennis Burkitt who first described it in 1958.
- **The endemic variant (**eBL**)** of BL is common in children living in malaria endemic regions of the world like, equatorial Africa, Brazil and Papua New Guinea. Epstein-Barr virus (EBV) infection is associated with this variant, involving facial bone (maxillary, mandible, and orbit), the distal ileum, caecum, kidneys and ovaries.
- **The sporadic type** is common in places where malaria is not holoendemic. Tumour cells are similar to endemic BL but not associated with EBV involving the abdomen especially the ileocaecal junction.
- **Immunodeficiency-associated BL** is associated with HIV infection or occurs in the setting of post-transplant patients taking immunosuppressive drugs. EBV is found in 25-40% of immuno deficiency-associated cases.

Epidemiology

- A high incidence of BL in Africa is noted within a belt extending approximately 10^0 to 15^0 North and South of the Equator.
- Other associated climatic factors include rainfall of above 50 cm, an altitude of 1500 metres above sea level and a temperature of 26^0c.
- It is also found in Brazil, New Guinea and Malaysia.
- Sporadic cases occur in East, Central and South America as well as Europe.
- A male preponderance exists, males are affected 2-3 times more than females. Peak age incidence is 4-7 years.

Pathophysiology

- The exact pathophysiologic mechanism is not known but EBV and malaria infections as well as C-myc oncogene activation are suggested.

- When EBV infects lymphocytes, some escape the T-cell mediated immune response and enter the germinal centre leading to excess B-cell proliferation.
- Malaria inhibits the EBV-specific immune response. The interaction between viral and cellular micro RNA disrupts normal gene expression and translation.
- The translocation of the C-myc oncogene located on chromosome 8 to the genetic loci on chromosomes 14, 2, or 22 that code for immunoglobulins (8;14), (2;8), and (8;22) has been observed. The C-myc gene turns on the immunoglobulin gene resulting in uncontrolled B lymphocytes proliferation.
- Translocation t(8;14)(q24;q32) is the most common, present in 85% of BL.
- Abnormalities in the p53 gene and in death-associated protein kinase contribute to decreased apoptosis leading to cancer cell proliferation.

Pathology

- Classical BL is characterized by a uniform proliferation of medium sized cells with rounded nuclei, stipple chromatin and multiple small nucleoli, and a moderate amount of basophilic cytoplasm with numerous lipid vacuoles.
- The hallmark of BL is the starry sky appearance due to sheets of tumour cells interspersed with large pale macrophages containing fragments of tumour cells because of rapid proliferation and a high rate of apoptosis.
- There is a very high mitotic figure and fraction of proliferation cells (>95%).

Clinical features

- BL has a rapid and aggressive clinical course with frequent bone marrow and CNS involvement so it is considered a medical emergency.

History

- BL commonly presents with painless facial bone swelling (orbit in >50% of cases), looseness of the teeth with gingival swelling.
- Abdominal swelling, vomiting, poor appetite and bone marrow involvement in sBL, while immune deficiency associated BL presents with nodal involvement.

- Acute abdomen, renal failure due to renal involvement or tumour lysis syndrome, cranial nerve involvement (cranial nerves 3 and 7 commonly), headache, visual impairment, and paraplegia may occur.
- Systemic symptoms like fever, weight loss, night sweating and fatigue.

Signs

- Maxillary or mandibular mass, dental anarchy, orbital, abdominal mass, distension, tenderness, ascites, and lymphadenopathy are common.

Diagnosis

(From clinical presentation and evaluation**)**

- Fine needle aspirate (FNA)–cytology, tissue biopsy for histology–node or extra nodal site, lactate dehydrogenase (LDH) level and HIV screening.
- FBC, coagulation studies, uric acid, Serum electrolyte urea and creatinine.
- Head/spinal CT-scan or MRI when meningeal features are present, plain bone x-ray and scan, chest, abdomino-pelvic CT-scan with IV contrast.
- Echocardiography for possible arrhythmias due to cardiac involvement.
- Unilateral bone marrow aspirate and biopsy for every patient with BL.
- LP as part of staging, paracentesis or thoracocentesis for cytogenetic studies.

Differential diagnosis

- For facial swelling: dental cyst, advanced retinoblastoma, and rhabdomyosarcoma should be differentiated.
- Other lymphomas like diffuse large cell, mantle and lymphoma follicular cell.
- Tumours like acute lymphoblastic leukaemia, neuroblastoma and Wilms tumour.

Staging

- Because most people will present with nodal or extra nodal masses, a different staging system has been proposed.

The Ann Arbor system and St Jude/Murphy staging consist of 4 stages:

- *Stage I:* Single tumour (extra nodal), Single anatomic area (nodal).
- *Stage II:* Single tumour (extra nodal) with regional node involvement, Primary gastrointestinal tumour, Lymphoma involving nodal areas on the same side of the diaphragm.
- *Stage IIR:* Consists of completely resected intra-abdominal disease.
- *Stage III:* Lymphoma involving sites on the opposite sides of the diaphragm, all primary intrathoracic tumours, all paraspinal or epidural tumours and extensive intra-abdominal disease.
- *Stage IV:* Consists of any of the above, with CNS or bone marrow involvement (<25%) at presentation.
- The risk adapted approach is used to treat most patients, dividing them into 2 broad groups: low- and high-risk patients.
- **Low-risk** patients have non-bulky disease (<10 cm), early stage (I or II) disease, good performance status, and a normal LDH level.
- **High-risk** patients include all other patients (advanced stages III, IV).

Treatment

- Chemotherapy is the mainstay of treatment but it should be intensive and systemic for this aggressive disease in all stages and rapid administration of successive cycles to prevent tumour regrowth is advocated.
- Three treatment approaches are available:
- ***An Intensive short duration regimen*** like **R-CODOX-M/IVAC** (McGrath regimen) or dose adjusted **EPOCH** and the **CABLGB 9251** protocol.
- ***Long duration chemotherapy*** similar to ALL (acute lymphoblastic leukaemia) treatments like hyper-IVAD and the CALEGB 8811 protocol.
- A combination regimen followed by autologous stem cell transplantation (SCT).
- Most current regimens have added rituximab to previously established chemotherapy regimens. **Rituximab** is a recombinant antibody that targets CD20 on the surface of B lymphocytes.
- Short, intensive regimens are preferred to all types of treatment or SCT.

- The most frequently used regimen is CODOX-M/IVAC with CNS prophylaxis using intrathecal methotrexate with or without cytarabine and hydrocortisone to prevent/reduce CNS relapse.
- Cranial irradiation may be used.
- Other supportive care includes allopurinol, good hydration and transfusions as required with mesna/leucoverin if Ifosfamide/ methotrexate is used.
- **The CODOX-M/IVAC Regimen** (McGrath regimen)– (**c**yclophosphamide, do**x**orubicin, high dose **m**ethotrexate/ **i**fosamide, Etoposide, vincristine, high dose **c**ytarabine).
- The regimen consists of four cycles lasting until blood counts recover (2 cycles of CODOX–M alternating with 2 cycles of IVAC and high-risk patients receive the full 4 but low-risk patients may receive fewer).
- Evaluation of treatment will show complete remission or relapse/refractory.
- BL and DHAP salvage regimen is given to the relapse/refractory group.

Complications and Prognosis

- Complications increase with the extent of the disease and include renal failure resulting from tumour lysis syndrome, or kidney involvement.
- Complications from the treatment are cardiomyopathy, high risk of infection, gonadal dysfunction and secondary leukaemias.
- Up to 90% of patients treated with current intensive regimens have long-term disease-free survival, using EPOCH with rituximab, an 8-year survival rate of 91% for low-risk, 90% for low-intermediate risk, 67% for high-intermediate risk and 31% for high-risk cases has been recorded.
- Patients with relapse disease have a long-term survival rate of 20-50% but with high-dose therapy and an autologous haematopoietic stem cell transplant (HSCT) there is improvement in long-term disease-free survival.

Prevention and Control

- Education, genetic counselling and lifestyle changes to prevent HIV infection.

- Early diagnosis and adequate treatment of cases and also malaria control.
- Expert multidisciplinary clinical care and physical/social rehabilitation.

Counselling/Patient Education

- Provide information about the disease, treatment options and duration, the short-/long-term effects of treatment to patients and the families, like secondary cancers, and potentially fatal infections as well as mortality.
- Emotional support is very vital to the patient and family.

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9.3 Hodgkin's Lymphoma (HL)

Introduction/Epidemiology

- Hodgkin's lymphoma (HL) is a malignant disease of the lymphoid tissue which originates from germinal centre B lymphocyte.
- HL is a potentially curable lymphoma and is called Hodgkin's disease after Thomas Hodgkin who first described it in 1832.
- The incidence shows marked heterogeneity with respect to age, gender, race, geographic area, social class and histological subtype.
- HL is highest among adolescents aged 15 to 19 years and has a bimodal age distribution that differs geographically, peaking in industrialized countries in the middle to late 20s with the second peak after the age of 50 years while in developing countries, the early peak occurs before adolescence.
- A higher incidence occurs in western countries and in westernized populations but HL is less common in Asian countries.
- There is a strong male predominance in the under 5s (M:F = 5.3) and children aged 15-19 years have a slight female dominance (M:F = 0.8).
- The most common subtype among adolescents is nodular-sclerosis (NS). The frequency of mixed cellularity (MC) increases with age, while that of NS reaches a plateau in the group >30 years of age.

Classification

- The new World Health Organization/revised European-American classification of lymphoid neoplasms classifies Hodgkin's lymphoma into 2 distinct entities:
- **Classical Hodgkin's lymphoma** (95% of all cases) which includes: Nodular sclerosis, Mixed cellularity, Lymphocyte-rich and lymphocyte-depleted.
- **Nodular lymphocyte-predominant Hodgkin's lymphoma** (5%).

Risk Factors

- Risk factors for developing HL include variation in the HLA class II region, congenital and acquired immunodeficiency, EBV infection, childhood environment/socioeconomic status, occupational exposure (the wood industry) and cigarette smoking.

- There is an association between early birth order, high maternal education, a low number of siblings, single family dwellings in childhood and occurrence of HL in younger patients in developed countries.

Pathology

- The **Reed-Sternberg** (RS) cell**,** a pathognomonic feature and the hallmark of HL, is a large cell with multilobulated nuclei.
- The RS cell is clonal in origin and arises from the germinal centre B cells.
- HL is characterized by a variable number of RS cells surrounded by an inflammatory infiltrate of lymphocytes, plasma cells, and eosinophils in different proportions, depending on the HL histologic subtype.

Clinical Presentation: History

- Painless lymph node enlargement (neck, most commonly), chest pain, cough, shortness of breath, pruritus and bone pain.
- Drenching night sweats, unexplained fever >38°C, and weight loss of >10% over six months are termed **B** symptoms and are identified in approximately 25% of patients.

Clinical Presentation: Signs

- Lymphadenopathy involving Waldeyer's ring, occipital or epitrochlear, splenomegaly and/or hepatomegaly.
- Alcohol-induced pain at sites of nodal disease is specific but occurs in fewer than 10% of patients.
- Superior vena cava syndrome may develop in patients with massive mediastina! Lymphadenopathy.
- Paraneoplastic syndromes, include cerebellar degeneration, neuropathy, Guillain-Barre syndrome or multifocal leukoencephalopathy.

Diagnosis

- Full blood count; to exclude leukaemia, mononucleosis and other causes of lymphadenopathy, an erythrocyte sedimentation rate greater than 70 carries an unfavourable prognosis.

- Tests for possible differential diagnoses like tests for infectious mononucleosis.
- Liver function and serum protein tests: A rise in lactate dehydrogenase (LDH) and a fall in albumin levels have prognostic significance.
- HIV tests are necessary in patients with suspected Hodgkin's lymphoma.
- Fine needle aspiration of the lymph nodes for cytology.
- An excisional node biopsy for histology allows the diagnosis of lymphoma based on the morphology of the lymph node.
- Chest X-Ray: assess any intrathoracic lymphadenopathy and mediastinal expansion.
- CT-scan of the thorax and abdomen, Lymphangiography and bone marrow for staging and Gallium scans if CT scanning produces equivocal results.

Staging

- The Ann Arbor classification is used most often for Hodgkin's lymphoma but has been modified with the Cotswold classification as shown below:
- Patients with the early-stage disease should be classified into favourable or unfavourable prognosis depending on the presence or absence of mediastinal adenopathy, the presence of symptoms, the level of ESR and the number of lymph node sites involved.
- **Ann Arbor staging system with Cotswold modifications for HL:**
- *Stage I:* involvement of one lymph-node region or lymphoid structure (e.g.: spleen, thymus, Waldeyer's ring).
- *Stage II:* two or more lymph-node regions on the same side of the diaphragm.
- *Stage III:* lymph nodes on both sides of the diaphragm.
- *Stage III (1):* with splenic, hilar, coeliac, or portal nodes.
- *Stage III (2):* with para-aortic, iliac, or mesenteric nodes.
- *Stage IV:* involvement of extranodal site(s) beyond **E** (see below).

Modifying features:

- **A**: no symptoms.
- **B**: fever, drenching night sweats, weight loss greater than 10% in six months,
- **X**: bulky disease: greater than a third widening of mediastinum or greater than 10 cm maximum diameter of nodal mass.

- **E**: involvement of single, contiguous, or proximal extranodal sites.
- **CS**: clinical stage. **PS**: pathologic stage.

Differential Diagnosis

- Malignancies like Non-Hodgkin's lymphoma, Leukaemia and myeloma.
- Infections like mononucleosis, AIDS, cytomegalovirus, and Tuberculosis, tularemia, Toxoplasmosis and others like sarcoidosis.

Treatment

- Before treatment, assess for risk of acute and/or long-term complications: Cardiac and pulmonary function tests are mandatory.
- Current treatment in paediatric patients is risk adapted, involving the use of combination chemotherapy with or without low dose involved-field radiotherapy.
- Risk adapted protocols are based on staging criteria and the rapidity of the response to initial chemotherapy aiming to decrease total drug doses, and treatment duration.
- Male patients should be offered pre-treatment semen cryopreservation.
- General treatment principles include Radiation therapy, Induction chemotherapy, Surgery, Salvage/targeted chemotherapy and Haematopoietic stem cell transplantation.
- The commonly used induction (initial treatment) regimens for HL are:
- MOPP/**C**OPP (mechlorethamine, vincristine, procarbazine, prednisone).
- ABVD (doxorubicin 25 mg/m^2, bleomycin 10 U/m^2, vinblastine 6 mg/m^2, dacarbazine 375 mg/m^2).
- Stanford V and BEACOPP have added mustard/etoposide and cyclophosphamide/etoposide respectively.
- When induction chemotherapy fails, or patients experience relapse, salvage chemotherapy (**ICE/DHAP**) is given. Salvage regimens incorporate drugs that are complementary to those that failed during induction therapy. [ICE (**i**fosfamide, **c**arboplatin, **e**toposide), DHAP (cisplatin, cytarabine, prednisone).]

Complications/Prognosis

- Haematologic toxicity: Anaemia, thrombocytopenia, febrile neutropenia, myelodysplasia or acute leukaemia.
- Pulmonary toxicity, Cardiac toxicity, increased risk of infection/immunodeficiency, thyroid disorders, Oral/dental disorders, salivary gland dysfunction, Gonadal toxicity, secondary cancers like breast cancer. Neurologic: neuropathy, muscular atrophy depression and anxiety.
- Mortality from Hodgkin's lymphoma has been progressively decreasing, with a five-year survival figure now at 81%.
- The International Prognostic Score is based on seven adverse prognostic factors for newly diagnosed advanced HL patients: male sex, aged 45 years or older, stage IV disease, leukocytosis, lymphocytopenia, low haemoglobin and low serum albumin.

Prevention and control

- Early detection and treatment are advocated. Dietary control and lifestyle modification may be necessary.

Counselling

- Points for discussions–the nature of the disease, complications, treatment options and duration, the need to complete treatment and the long-/short-term effects of treatment.
- Patients may need reproductive counselling, as treatment may compromise fertility.

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9.4 Non-Hodgkin's Lymphoma

Aetiology/Epidemiology

- Non-Hodgkin's lymphoma (NHL) is a malignancy that originates in the lymphatic system which is part of the immune system of the body.
- Known risk factors include a weakened immune system from a genetic syndrome e.g. Wiskott-Aldrich syndrome, severe combined immunodeficiency syndrome and children on immunosuppressive therapy.
- Viral infections with HIV, HBV and Epstein-Barr virus and bacterial infections like Helicobacter pylori are also implicated. Most cases have no identifiable risk factors.
- It accounts for more than 6% of all childhood cancers and most lymphomas in children up to 14 years are NHL.
- It can occur at any age but is rare in children under 3 years and only 2% of all Non-Hodgkin's lymphoma occurs in children and teens.
- Overall, the risk of Non-Hodgkin's lymphoma in children increases with age.
- It is about 2 to 3 times more common in boys than in girls, more in Caucasians than in blacks.

Pathology/Pathophysiology

- Non-Hodgkin's lymphomas are high grade and very aggressive.
- They are classified according to their microscopic features like the size and shape and the pattern of growth into 4 pathologic sub-types:
- ***Burkitt Lymphoma (BL)***: In African children, BL constitutes nearly all cases of childhood NHL while in western countries, it constitutes about 40% of childhood NHL and is of B-cell origin. It is the fastest growing tumour.
- ***Lymphoblastic Lymphoma (LL)***: Constitutes 30% of all childhood NHL. Boys are affected twice as much as girls. It develops from T-cells. It often presents as mediastinal masses obstructing respiration and usually spreads to the bone marrow and brain.
- ***Diffuse Large B-cell Lymphoma (DLBCL)***: This accounts for 20% of childhood NH and is mostly of B-cell origin but it can still occur in T-cells. They are not very aggressive and are less likely to

spread to the bone marrow or brain. Present as large mediastinal masses.

- If the bone marrow blast cell population is greater than 25%, it invariably becomes acute lymphoblastic leukaemia.
- ***Anaplastic Large Cell Lymphoma (ALCL)***: Represents about 10% of all childhood NHL. It usually develops from mature T-cells. It may start in the lymph nodes of the neck or other areas and may be found in the lungs, skin, bone and digestive tract.

Clinical Presentation

- History is usually that of jaw swelling. Other symptoms include painless swelling in the neck, underarm, groin, and abdomen, shortness of breath, cough, unexplained weight loss, recurrent fever from repeated infections; night sweats and easy bruising are also common.
- Examinations findings are variable. They may appear wasted with persistent enlarged lymph nodes in the absence of infection, with stridor, and bluish flushing of the face and arm associated with oedema and severe pallor.

Diagnosis (Investigation and Evaluation)

- Blood: Complete Blood Count shows marked lymphocytosis. High Lactate dehydrogenase (LDH) level.
- Liver function test and serum electrolytes, urea and creatinine are deranged in the liver and kidneys metastasis respectively.
- The patient should be screened for HIV, Epstein-Barr virus and HBV.
- CSF, Pleural and peritoneal fluid cytology and biochemistry are also useful.
- Imaging: a Chest X-Ray may detect a tumour or a more enlarged lymph node.
- Abdominal ultrasound, Bone scan, CT scan with Positron Emission Tomography (PET), MRI.
- Biopsy: incisional, excisional or fine needle, on an enlarged lymph node or bone marrow.
- Newer diagnostic techniques include Immunophenotyping, flow cytometry, cytogenetics, fluorescent in situ hybridization (FISH) and polymerase chain reaction (PCR).

Differential diagnosis

- Hodgkin's lymphoma and Tuberculous Adenitis.

Staging

- The staging of NHL is done using St Jude's system. A or B connotes the absence or presence of systemic symptoms respectively. Systemic symptoms include: fever (101 F), night sweats, weight loss >10% body weight and severe itching.
- **Stage 1**: The lymphoma is either as a single tumour not in lymph nodes or in lymph nodes in one part of the body (the neck, groin, and underarm) excluding the chest or abdomen.
- **Stage 2**: A single tumour (extranodal) with regional lymph node involvement. Two or more nodal areas on the same side of the diaphragm. Two single (extranodal) tumours with or without regional node involvement on the same side of the diaphragm. A primary gastrointestinal tract tumour, with or without involvement of the associated mesenteric nodes only, which must be grossly (>90%) resected.
- **Stage 3:** Two single tumours (extranodal) on opposite sides of the diaphragm. Two or more nodal areas above and below the diaphragm. Any primary intrathoracic tumour or intra-abdominal disease.
- **Stage 4:** Any of the above with initial involvement of the central nervous system or bone marrow at the time of diagnosis.

Treatment

- A combination of chemotherapy, surgery and radiation therapy.
- Two treatment protocols exist and they are: French-American-British lymphoma mature B-cell 96 (FAB/LMB 96) and Berlin-Frankfurt-Munich 95 (NHL-BFM) using the COPAD regimen (cyclophosphamide, vincristine, prednisone and doxorubicin).
- Monoclonal antibodies that enhance the immune system have been found useful. Targeted therapy with rituximab is used to treat recurrent childhood NHL.
- High dose chemotherapy with a stem cell transplant is also useful.

Complications/Prognosis

- Complications from NHL include superior vena cava syndrome, respiratory distress, and acute paraplegia in cases involving the CNS. Treatment-related complications include sterility, hair loss, mouth sores, new malignancy, and growth failure.
- The prognosis is excellent for most forms of childhood and adolescent NHL.
- Patients with localized disease have a 90-100% chance of survival and those with advanced disease have a 60-95% chance of survival.
- The variation in survival depends on pathologic subtype, the tumour burden at diagnosis, the presence/absence of CNS disease and the specific sites of metastasis.
- Specific cytogenetic and molecular genetic subtyping can also contribute.

Prevention and Control

- By preventing the known risk factors like Epstein-Barr virus and HIV infection.
- Screening children at greater risk e.g. those with inherited immunodeficiency syndromes, organ transplant, HIV as well as those exposed to radiation.
- Early detection and treatment are the mainstay of control.

Counselling

- Involves the child and parents: on the nature of the illness, treatment options, duration and completion and the need for follow up monitoring. Also, on the possible complications

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9.5 Nephroblastoma

Aetiology/Epidemiology

- Nephroblastoma is an embryonic malignant tumour arising from primitive metanephric blastema, the precursor of the mature kidney.
- It is called Wilms tumour after the German surgeon who first described it in 1899.
- Most nephroblastoma occur sporadically.
- Familial forms are inherited as autosomal dominant with variable penetrance.
- Genetic mutation occurs in about 10% of cases with congenital syndromes like WAGR Syndrome, hemi hypertrophy and Beckwith- Wiedemann syndrome.
- Deletions on bands p13 and p15 of chromosome 11 have been found in WAGR and Beckwith-Wiedemann syndrome patients respectively.
- The presence of embryonal nephrogenic rest increases the chance of developing the tumour and heterozygosity of Chromosome 16q is lost in 15-20% of cases.
- Nephroblastoma is the most common childhood kidney cancer accounting for 6-7% of all cancers in children of 15 years and below.
- Peak age incidence is 2-5 years and has slight female preponderance.
- In association with congenital syndromes, it occurs at an earlier age and is more likely to be bilateral in about 5-7% of cases.

Pathology

- Gross: Large, heterogeneous, with cystic/haemorrhagic and necrotic areas.
- Microscopically: It consists of three types of tissues (triphasic histology): embryonal blastema, epithelial tissues and mesenchymal (stoma).
- Histologically categorized into three groups: **Low Risk** (mesoblastic nephroma, necrotic nephroblastoma), **Intermediate Risk**: (triphasic/focal anaplastic histology) and **High Risk** (blastemal predominance/diffuse anaplasia).

Clinical Presentation

- **History:** Painless abdominal swelling in 60% of cases, painful after trauma causing bleeding or rupture, weight loss, fever, haematuria in 15-25% of cases.
- **Signs:** abdominal mass, Hypertension in 25% of cases +/- distended abdominal veins if there is a tumour thrombus in the inferior vena cava.

Diagnosis

(From clinical presentation/laboratory evaluation)

- Abdominopelvic ultrasonography, CT-scan/MRI to delineate the abdominal mass, its intra renal origin, nature and size and the surroundings for extensions.
- Chest X-Ray for metastasis in the lungs and abdominal X-Ray– calcification.
- Serum electrolyte, urea and creatinine for renal function, urinalysis.
- Full Blood Count, Lactate dehydrogenase (LDH).
- Partial thromboplastin time (PTT) if bleeding diathesis is suspected.
- Attention to the other kidney checking for bilateral involvement.

Differential Diagnosis

- Hydronephrosis, polycystic kidney and chronic pyelonephritis.
- Benign renal tumour like mesoblastic nephroma.
- Other malignant tumours like renal cell carcinoma, non-renal tumours like neuroblastoma, lymphomas and retroperitoneal rhabdomyosarcoma.

Staging

Done after surgery and helps in choosing the best treatment option.

- Stage 1/standard risk: Tumours with intact capsule and completely excised.
- Stage 2/medium risk 1: Tumours extending outside the kidney but completely excised.
- Stage 3/medium risk 2: Tumours with residue either because of rupture or local extension.

- Stage 4/high risk: Tumours with distant metastasis like the lungs, liver or brain.
- Stage 5: Bilateral tumours at diagnosis.

Treatment of Nephroblastoma

- Recommended modalities include surgery, chemotherapy and radiotherapy.
- Preoperative chemotherapy with Actinomycin D and vincristine for 4-8 weeks to reduce tumour bulk and enhance tumour removal at surgery in all patients (SIOP) while NWTSG use it in a horseshoe kidney and IVC extension.
- Doxorubicin is added in pre-surgery treatment for metastatic disease.
- Malnourished patients and those below 12 kg are given two-thirds of the dose of the drugs.

Post-Nephrectomy Treatment

Stage/risk assessment/histology	**Optimal treatment**
Stage 1/standard risk	May not need post-surgical chemotherapy
Stage 2/medium risk 1/favourable)	VA (Vincristine/Actinomycin D) x 27 weeks
Stage 3/medium risk 2/favourable	VAD x 27 weeks (D-Doxorubicin)
Stage 4/high risk/unfavourable	CEDCy x 34 weeks (C-carboplatin, E-etoposide, Cy-cyclophosphamide)
Stage 5/- /favourable	VA x 18 weeks (if disease is in both kidneys <stage 2) or VAD x 24 weeks (if disease is in both kidneys >stage 2)
Stage 5/- /unfavourable	VEDCy x 24 weeks followed by a second look surgery ± more chemotherapy and/or radiotherapy

Prognosis/Complications

- Overall prognosis is up to 90% for 5 years' survival and prognostic factors are the tumour stage and histology.
- Anaplastic histology carries the worst prognosis.
- Young age of onset confers a better prognosis.

- Other prognostic factors include tumour size, chromosomes 1p/16q loss of heterogenicity and the clinical state of the patient like co-morbidity.
- Complications include metastatic lung/liver disease, renal failure, bleeding from acquired von Willebrand disease, tumour rupture and death.
- Treatment-related complications include marrow suppression, growth retardation, cardiac toxicity and secondary malignancy.

Prevention and control

- Early detection and treatment are advocated. Screening of patients with associated syndromes like WAGR and Beckwith-Wiedemann syndrome.

Counselling

- Points for discussions:
- The nature of the tumour;
- Treatment options;
- The need to complete treatment;
- The long-/short-term effects of treatment.

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9.6 Neuroblastoma

Introduction

- Neuroblastoma is an embryonic malignant tumour which develops from primitive neural crest cells of the sympathetic nervous system.
- The most common site is in the adrenal glands but they can also occur in the nerve tissues of the neck, chest, other abdominal sites and pelvis except esthesioneuroblastoma which arises from the maxillary antrum.
- Historically Rudolf Virchow was the first to describe neuroblastoma in 1864 while James Homer Wright described its origin from the primitive neural cell, named it neuroblastoma in 1910 and described the Homer Wright pseudo rosettes (circular clumps of cells in bone marrow samples).
- Neuroblastoma has extreme heterogeneity with a wide pattern of differentiation thus it can spontaneously regress or mature into benign ganglioneuroblastoma or develop into highly malignant neuroblastoma with rapid metastasis and resistance to aggressive multimodal treatment.

Aetiology/Epidemiology

- The majority of cases of neuroblastoma occur sporadically.
- About 1-2% of the cases are familial which have been associated with specific genetic abnormalities e.g. anaplastic lymphoma kinase gene, trisomy 17, DNA ploidy, unbalanced 11q loss of heterozygosity, deletion of the short arm of chromosome 1p, MYCN(N-myc) oncogene amplification within the tumour cells, neurofibromatosis type 1, Beckwith-Wiedemann syndrome and Hirschprung's disease.
- It accounts for 6-10% of all childhood malignancies in Europe and America where it is the most common cancer diagnosed in infancy while in Africa it comes 3rd/4th after lymphomas, nephroblastoma and occasionally rhabdomyosarcoma.
- It has a male preponderance and is more common in Caucasians.
- The median age at diagnosis is 2 years and about 90% are diagnosed by 5 years of age.

Pathophysiology

- The most common symptoms are due to the tumour mass or bone pain from metastasis.
- In 50-70% of cases, metastasis via the lymphatics/blood stream, usually to lymph nodes, long bones, the skull, bone marrow, the liver and skin has occurred at diagnosis.
- Neuroblastoma can secrete catecholamines and/or their precursors leading to Hypertension, diarrhoea and occasionally opsomyoclonus in about 2-3% of affected children.
- The normal adrenal medulla may have neuroblastoma in-situ as part of its normal maturation.

Clinical manifestation

(Depends on the primary site and stage)

- ***History:*** Initial vague symptoms like fatigue, anorexia, limb pain and fever.
- It can present with abdominal swelling, constipation, respiratory distress, limb weakness, pain and limping, diarrhoea, ataxia and weight loss.
- ***Physical findings***: Abdominal mass, irritability, Hypertension, pallor, subcutaneous nodules, peri orbital ecchymoses and oedema.
- ***Staging/Risk stratification***: Staging is done mainly to allow comparisons between studies/experiences and to contribute to risk stratification.
- Risk stratification which considers cytogenetic markers, patients' characteristics and histological appearance is a better predictor of outcome than staging.
- This concept matches aggressive diseases with aggressive drugs and avoids using aggressive treatments in children who have favourable tumours.
- Each child is assigned into very low risk, low risk, intermediate, and high risk groups (New COG risk group assignment) depending on the following; the child's age, the INSS tumour stage, N-myc gene amplification, DNA ploidy and histology.
- The INPC uses ploidy, Amplification of N-myc oncogene within the tumour tissue, unbalanced 11q and loss of heterozygosity for chromosome 1p to classify.
- *Stage L1*; Localized disease without an image-defined risk factor.
- *Stage L2*; Localized disease with image-defined risk factors.

- *Stage M*; Metastatic disease.
- *Stage MS*; Metastatic disease "special" (MS is equivalent to stage 4s of INSS).

Diagnosis

- Made from the clinical presentation, microscopic findings and other laboratory tests.
- Biochemistry–Elevated catecholamines like dopamine, homovanllic acid (HVA) and or vanillyl mandelic acid (VMA) in about 90% of the cases. Serum ferritin, neurone specific enolase and lactate dehydrogenase are useful markers.
- Imaging–123I-mIBG scan, CT-scan, MRI, and immunohistochemistry.
- Histology–Typically, the tumour appears as small, round blue cells with a rosette pattern (Homer-Wright rosettes which are tumour cells around neutrophil). Pseudorosettes are tumour cells around blood vessels.
- Molecular studies–MYCN amplification is +ve in about 25% of cases.

Differential diagnosis

- Neuroblastoma should be differentiated from Wilms tumour in its abdominal presentation, leukaemia due to cytopenia and child abuse due to orbital metastasis.

Treatment

- Each child is assigned to a risk group based on INSS stratifications according to the anatomic stage, age, INPC policy, and amplification of the MYCN oncogene within tumour tissue, that influence treatment selection.
- A risk adapted treatment approach matches clinical/pathologic features with the right treatment modality.

Stage/COG Risk–Group Assignment		Treatment Options
Stages 1, 2–with favourable histology/Low Risk Neuroblastoma		Surgery and chemotherapy ± radiotherapy
Intermediate-risk Neuroblastoma/stage 3 without MYCN amplification, infants with stage 4s & unfavourable histology		Surgery and chemotherapy (CEDCy-Cisplatin, Etoposide, Doxorubicin, Cyclophosphamide), radiotherapy
		Surgery and observation (for infants)
Stages 3 & 4 with MYCN amplification age above 1 year/High-Risk Neuroblastoma/		Chemotherapy (CEDCy, Vincristine), surgery, SCT
		Radiotherapy, isotretinoin (cis-retinoic acid), anti GD2 antibody ch14.18, and interleukin-2/GM-CSF
Stage 4s Neuroblastoma		Observation with supportive care (for asymptomatic patients)
Cord compression		Chemotherapy (for symptomatic patients) ± surgery
Recurrent Neuroblastoma	Recurrence in patients initially classified as low risk	Observation
		Surgery then chemotherapy (with topotecan, cyclophosphamide)
	Recurrence in patients initially classified as intermediate risk	Surgery (complete resection)
		Surgery (incomplete resection) followed by high dose chemotherapy
	Recurrence in patients initially classified as high risk	Second autologous SCT after retrieval chemotherapy (irinotecan and oral temozolomide), 131 I-mIBG alone or in combination with other therapies or followed by stem cell rescue

Complications/Prognosis

- Complications include cord compression, mental retardation or developmental delay, bruising and bleeding. Others are ototoxicity,

nephro/cardiac toxicity, alopecia, thyroid disorder, increased risk of infection, growth failure infertility and secondary malignancy.
- Event-free survival of up to 90% for low-risk and 40-60% long-term survivals in intermediate/low-risk have been achieved.
- The outcome of the advanced disease is poor even with aggressive multimodal treatment except babies with stage 4s. Up to 50% of high-risk cases are refractory.
- Favourable factors include the age below year, no MYCN oncogene amplification, the triploid cytogenetic karyotype and no loss of genetic material from chromosome one.

Prevention and Control

- Early detection and treatment result in a better prognosis and outcome.
- Screening for neuroblastoma with urinary catecholamines has been tried in infants in developed countries like Canada, Germany and Japan.

Counselling

- The counselling should involve details of the nature of the tumour, treatment options available, their cost, the need to comply with treatment and follow up, the short- and long-term effects of neuroblastoma and its treatment.
- For emotional support, patients should be directed to support groups.

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9.7 Other Embryonic Tumours

Introduction

- Embryonic tumours are malignant neoplasms originating from immature tissue or rudiments of an organ during intrauterine or early postnatal life.
- Tumours presenting in later life arise from embryonic rests which are fragments of embryonic tissue still present after embryonic life.
- They are rare after childhood when cell differentiation processes have slowed down with some peaking within the first year of life while others may be present at birth.
- These tumours have similar features as tissues/organs of origin but may form other tissues.
- Having discussed neuro/nephro-blastoma before, embryonic tumours here refer to retinoblastoma, rhabdomyosarcoma, medulloblastoma, teratoma, and hepatoblastoma.

Retinoblastoma (RB)

- RB is a primary intraocular malignancy arising from the immature retina.
- It represents about 3% of childhood tumours and does not have a sex predilection.
- The median age at diagnosis is 2 years for unilateral tumours but less in those with bilateral tumours.
- About 25% of patients have bilateral disease, which is usually hereditary.
- Only 15% of patients have hereditary unilateral disease while the remaining 60% have non-hereditary unilateral disease.
- The **pathogenesis** of inheritance involves mutational or deletional deactivation of both alleles of a retinoblastoma suppressor gene (RBI gene) located on chromosome 13q14.
- In the hereditary form, a germ line mutation alters one allele in both the germ line and the somatic retinal cells and a later somatic mutation alters the other allele in the retinal cells resulting in the cancer. The RBI gene is autosomal dominant.
- Somatic mutation of both alleles in a retinal cell occurs in the non-hereditary form.

- **The histology** of RB is a small, round, blue cell tumour with a rosette formation and various degrees of differentiation.
- It may outgrow its blood supply, resulting in necrosis and calcification.
- Endophytic tumours arise from the inner surface, growing into the vitreous while exophytic tumours grow from the outer retinal layer resulting in retinal detachment.

Clinical presentation

- Strabismus, pain (2^0 to glaucoma), orbital inflammation, and poor vision form the history, while the signs include Leukocoria (white pupillary reflexes/cat's eye) proptosis, hyphaema or pupil irregularity with advancing disease.

Diagnosis

- Diagnosis is established by characteristic ophthalmologic features and confirmed by histological findings.
- Orbital ultrasound scan and CT-scan or MRI are used to evaluate the extent of intraocular disease.
- **Differential diagnosis** includes Hyperplasic vitreous, Coats' disease, Cataract, visceral larva migrans, Choroidal coloboma and retinopathy of prematurity.
- The staging is graded from 1-4 with 1 being solitary or multiple tumours <4-disc diameter in size at or behind the equator, and 4 is advanced, consisting of multiple tumours >10-disc diameter to the ora serrata.

Treatment

- Standard treatment is unilateral enucleation of the eye, if the other eye is normal.
- Bilateral disease: Radiotherapy is used to salvage vision in one eye.
- Enucleation is imperative in the advanced disease or complicating painful glaucoma. Chemotherapy is given as carboplatin + etoposide or cyclophosphamide + vincristine.

Complications/Prognosis

- Includes painful glaucoma, blindness, cataracts, orbital growth deformities, lacrimal dysfunction and retinal vascular disease.
- Prognosis for early disease is good and about 95% of such RB are cured.
- The prognosis for a patient with metastasis is poor.
- Children with germ line RBI are at significant risk of developing secondary malignancies like osteosarcoma.

Rhabdomyosarcoma (RMS)

- RMS is the most common soft tissue sarcoma in children under 15 years of age.
- It arises from rhabdomyoblasts, primitive mesenchymal cells committed to skeletal muscle differentiation and can occur in a variety of organs and tissues, including those that lack striated muscles.
- The sites are: the head and neck (35-40%), bladder (20%), muscles, limbs, chest and abdomen (15-20%) and other sites like the testes.
- Rhabdomyosarcomas are highly heterogenous and malignant.

Epidemiology/Aetiology

- Rhabdomyosarcomas account for 7-8% of all childhood malignant solid cancers with a slight male preponderance.
- They can occur at any age but approximately 87% of patients are below 15 years.
- The incidence at each anatomic site is related to the patient's age and tumour type, with extremity lesions more likely in older children and to have alveolar histology.
- Risk factors for RMS include the following inherited diseases: Li-Fraumeni syndrome, Neurofibromatosis type 1, Beckwith-Wiedemann syndrome, Costello syndrome, Noonan syndrome, Tuberous sclerosis and large for age babies.
- Environmental factors: include parental use of marijuana and cocaine, intrauterine exposure to X-rays and previous exposure to alkylating agents.

Pathology

- The two main histological subtypes of RMS are **embryonal** [60% (with botyroides and spindle cell variants)] and **alveolar** (20-40% of cases). Embryonal RMS has cells similar in appearance to embryo cells aged 6-8 weeks. This is the most common type and has a predilection for the head, neck and the genitourinary tract. It is predominant in males (M:F = 1.5) and peaks in the 0-year age group.
- RMS of embryonal histology arises from mucosa-lined structures of the nasopharynx, middle ear, genitourinary and gastrointestinal tracts.
- The **Botyroides** variant of the embryonal type presents as grape-like lesions.
- **Alveolar** RMS (similar to embryo cells aged 10-12 weeks). This tends to affect older children and has a more aggressive nature with no sex predilection. It is associated with muscles of the trunk and limbs.
- **Pleomorphic** rhabdomyosarcoma (1%) or undifferentiated–this entity is more common in adults and has a tendency to involve muscles of the extremities.

Clinical presentation

- Expanding lump or swelling, which may cause pain. Depending on the site of the tumour:
- Nose–nasal obstruction and discharge,
- Eyes–protrusion of the eyeball,
- Bladder–haematuria and abdomen–pain and change in bowel habit.

Investigations

- FBC may show anaemia; Liver Function Tests: raised Alanine transaminase and raised Lactate dehydrogenase. Urinalysis: shows haematuria. Renal function tests and electrolytes.
- Bone marrow studies may be required (to look for infiltration).
- Radiological imaging like Chest X-Ray, ultrasonography, CT or MRI scanning, positron emission tomography (PET) using radioisotope fluorodeoxyglucose (18^F) (FDG-PET).
- MRI imaging is preferred for the evaluation of the primary tumour site because of its superior ability to characterize soft tissues.

- Bone scan, checking for metastases and biopsy for histology and molecular studies checking for **MyoD1**, an immunohistochemical marker.
- **Staging.** Initially, staging was by the Intergroup RMS Study Group (IRSG) but the Children's Oncology Group (COG) combined the IRSG staging with the tumour, nodes, metastases (TNM) staging system to provide new stages, as follows:
- ***Stage I:*** Disease in favourable sites [the orbit, head/neck (but not parameningeal), genitourinary region (but not bladder or prostate)], or biliary tract.
- ***Stage II:*** Disease of any other primary site (unfavourable sites). Tumours must be ≤5 cm, and no lymph node involvement.
- ***Stage III:*** Disease of any other primary site but >5 cm and/or lymph node involvement.
- ***Stage IV:*** metastatic disease at diagnosis.

Medulloblastoma

- The most common, highly malignant embryonic, posterior fossa tumour in children representing about 20% of all paediatric central nervous system tumours.
- An invasive rapidly groining brain primitive neuroectodermal tumour (**PNET**) which spreads via cerebrospinal fluid (CSF) and metastasizes to different parts of the brain and spinal cord.
- Its embryonal nature is shown by a high incidence in infants and children and by its immature undifferentiated appearance.
- One of the primitive neuroectodermal tumours. Common in children of 5-7 years but it can occur throughout adolescence with a male preponderance.
- Aetiology: Gorlin syndrome, Turcot and Li-Fraumeni syndromes are risk factors.

Pathology

- Gross examination → soft, pink red and well demarcated. They can block the 4th ventricle and aqueduct, causing hydrocephalus.
- Microscopically 4 histologic types: classic, nuclear desmoplastic, large cell anaplastic and medulloblastoma with extensive nodularity. Highly cellular tumours composed of monomorphic

small undifferentiated round cells with neutrophils and a rosette formation.
- Medulloblastoma may show neuronal and glial differentiation.

Clinical features

- Vomiting, stumbling gait, headache, blurred vision, papilloedema, ataxia, strabismus, etc.

Diagnosis

- MRI with gadolinium. Biopsy confirms the diagnosis. Lumbar puncture for CSF sampling.

Treatment

- The treatment approach is stratified into 3:

1. Patients below 3-4 years, high-dose chemotherapy with peripheral stem cell re-infusion.
2. Those above 3 years with surgical total resection (standard-risk receives low-dose radiotherapy and low-dose chemotherapy),
3. High-risk includes–patients >3 years with disseminated disease and bulk residuals after surgery receive high-dose cranial-spinal irradiation.

- Chemotherapy is with lomustine + cisplatin or cyclophosphamide, procarbazine and ifosamide.
- **Complications** include neurocognitive impairment, neuro-endocrine dysfunction, growth failure, hearing loss and secondary malignancy.
- **Prognosis** is poor because of late presentation.
- A recent report shows that the 5-year relative survival rate is 72% for children (1-year) while 20-year survival is 21%.

Teratoma

- A teratoma is a complex tumour that originates from pluripotent germ cells with various cellular components derived from all 3 embryonic layers.
- Embryonal teratoma starts from cells in the sacrum in children, so most frequently occurs around the sacroccocygeal region.

- They may contain well-differentiated cells such as neural, thyroid, liver and lung tissues that are different from the surrounding structures.
- Teratomas are classified into 0-3 types; 0–mature (benign), 1–immature (probably benign), 2–immature (possibly malignant) and 3–frankly malignant.
- Mutational and deletional deactivation of the tumour suppressor gene, located at chromosome 12q is involved in the development of teratomas. Loss of 3p or 11p alleles is associated with about 40-50% of testicular cancers.
- Risk factors include cryptorchidism, pyloric stenosis, Turner's syndrome, and Klinefelter syndrome. P53 abnormality is involved in virtually all teratomas.
- Ovarian teratomas occur due to the failure of extrusion of the 2nd polar body or the re-fusion of it with the ovum. It presents as dermoid cysts (mature) which are benign cystic tumours comprising mainly ectodermal elements but endodermal or mesodermal elements may be involved.
- These cysts contain hair, teeth, skin, bone, neural tissue and sebaceous material.
- In immature teratomas of the ovary, the malignant potential is determined by the amount of neuroblast present.
- Extragonadal teratoma includes pineal teratoma, paraventricular germinoma and presacral teratomas. The syncytiotrophoblast within the germ cell tumour can secrete β-human chorionic gonadotropin.
- Teratomas are found in the midline or gonads; Sacroccocygeal–40% ovary–25%, testes–12%, brain–5% and others–18%.

Investigations

- Alpha fetoprotein in beta-human chorionic gonadotropin (b-HCG) and lactate dehydrogenase (LDH) are usually elevated. Diagnosis is confirmed by Histology.
- Full Blood Count, Electrolyte, urea/creatinine, uric acid, Liver Function tests are done.
- Imaging is for the diagnosis, staging and monitoring of the response (CT-scan, MRI, PET).

Treatment

- Surgery and chemotherapy with cisplatin, etoposide, and bleomycin.

Hepatoblastoma

- Hepatoblastoma is an embryonic tumour involving the liver, occurring mainly within the first 3 years.

Epidemiology

- It is the most common primary liver tumour in children, about 1% of paediatric cancers.
- Male preponderance and congenital abnormalities like hemi-hypertrophy, adenomatosis polyposis, diaphragmatic hernia, and Beckwith-Wiedemann syndrome are associated with it.
- Low birth weight, maternal exposure to paint and metals also increase the risk.

Pathology;

- 4 histological types: foetal, embryonal, macrotrabecular and anaplastic. May be pure foetal/embryonal malignant cells or mixed containing mesenchymal and epithelial elements.
- Epithelial tumours have a homogenous appearance and may contain areas of necrosis, fibrosis, osteoid, calcifications and haemorrhages. They often metastasize.

Clinical presentation

- Weight loss, abdominal swelling, vomiting, abdominal pain and pallor and abdominal mass.

Treatment

- Lobectomy, chemotherapy may be tried with doxorubicin, vincristine, cisplatin, cyclophosphamide and 5-fluorouracil.
- **Complications**; Precautious puberty, osteoporosis and the effects of treatment.

- Long-term survival rates are 75-80%. Pure foetal tumours have the best prognosis.

Prevention and control

- General health promotion through education, as well as early diagnosis and treatment.
- A multidisciplinary approach to give expertise, care and social support.

Counselling

- Some have a hereditary predisposition, so genetic counselling is advocated.
- The nature, cost implications and duration of therapy, likely complications, recurrence and follow up should be explained.

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9.8 Leukaemias

- Leukaemias are a group of haematological malignancy arising from bone marrow in which there is uncontrolled clonal proliferation of white blood cells with a high rate of proliferation and a decreased rate of spontaneous apoptosis leading to abnormal marrow function and subsequent failure.
- It is divided according to the type of cell exhibiting uncontrolled proliferation: Acute lymphoblastic leukaemia (ALL 75-77%), acute myelogenous leukaemia (AML 11-15%), chronic myelogenous leukaemia (CML 2-3%) and Juvenile myelomonocytic leukaemia (JMML 1-2%).
- ALL is most common in children in developed countries accounting for about 26% of cancers diagnosed in children of 0-14 years; in developing countries it comes 2nd to 3rd after lymphomas and embryonic tumours.
- ALL is more common in developed countries, and also more common in boys than in girls and in Caucasians than in blacks.
- There is a striking peak age incidence of 2-4 years in developed countries but no appreciable peak age in developing countries.
- The risk factors are genetic disorders like Down syndrome, Bloom syndrome, Fanconi anaemia, ataxia telangiectasia and neurofibromatosis type 1.
- Environmental factors like ionizing radiation, alkylating agents, Nitrosourea Epipodophyllotoxin and benzene exposure increase the risk of having ALL.
- AML comprises 15% of leukaemia cases in children and 31% in adolescents.
- Risk factors for AML are organic solvents, paroxysmal nocturnal Haemoglobinuria, Li-Fraumeni syndrome and those involved in ALL.

Morphological Classification

- Cellular classification is based on the phenotype/morphology depicted by the cell membrane markers of the malignant cells in the bone marrow.
- Morphology determines the diagnosis but other tests for the classification that would influence prognosis and appropriate therapy are vital.

- The French-American-British (FAB) System classifies ALL into L1- L3. L3/Burkitt's leukaemia is one of the most rapidly growing cancers in humans and requires a different therapeutic approach from other subtypes of ALL.
- Surface markers show that phenotypically ALL are derived from early B cells in about 85-90%, 1-2% are mature B-cells and 10-15% are from T cells.
- In AML, more than 20% of bone marrow cells should be blast cells.
- Flow cytometry, chromosomal and molecular genetic techniques are for diagnostic precisions and a better choice of therapy.
- The FAB System classifies AML into 8 groups (M0-M7). There are in-utero events in the initiation of the malignant process and effectors of the critical signal transduction pathway are involved but additional genetic modification finally leads to disease expression.
- The PCR and fluorescent in-situ hybridization techniques can identify molecular genetic abnormalities and a few malignant cells during follow up.

Clinical manifestations

- **History:** Nonspecific symptoms: anorexia, fatigue and malaise $\pm$ intermittent low-grade fever, then features of bone marrow infiltration ensue:
- Bone/joint pain $\pm$ swelling, epistaxis, high grade fever, exercise intolerance, bruising, and respiratory distress.
- **Signs:** Pallor, Listlessness, purpuric, petechiae lesions, and or mucous membrane, signs of raised intracranial pressure, haemorrhage, hepatosplenomegaly, testicular enlargement, cranial nerve involvement, headache seizures, Lymphadenopathy, bone tenderness, joint effusion and wheezing (obstruction of airway due to anterior mediastinal mass).
- The B cell ALL (common ALL antigen +ve) is the most common immunophenotype with onset at 1-10 years of age. Usually the median leukocyte count is about 33000, thrombocytopenia in 75% of cases, CNS involvement in 5-10% of all types of leukaemia and testicular involvement in 25% of cases.
- For AML, clinical features are mainly those found in ALL and subcutaneous nodules, gingivitis (in M4 and M5), features of DIC

and chloromas [(M2 type of AML with a t(8;21))] translocation seen in the orbit and epidural space.

Diagnosis

- Diagnosis is suspected by features of bone marrow failure, if peripheral blood film suggests leukaemia, bone marrow evaluation should be done to confirm the diagnosis (≥25% of bone marrow cells being lymphoblast).
- Flow cytometry, LDH level, cytogenetic and molecular studies are also useful.
- If CSF contains lymphoblast and leukocyte is elevated, CNS involvement is confirmed and this is advanced stage.
- In AML bone marrow is hypercellular and consists of a monotonous pattern of cells and the presence of myeloperoxidase-containing cells confirms a myelogenous origin and the precise diagnosis.

Differential diagnosis

- Non-malignant conditions like infections with Epstein-Barr virus, cytomegalovirus, and pertussis as well as aplastic anaemia, juvenile rheumatoid arthritis and sickle cell disease.
- Erythroblastopenia of childhood, immune thrombocytopenia and congenital or acquired neutropenia should be considered in single cell line failure.
- Others like neuroblastoma, rhabdomyosarcoma, Ewing's sarcoma and retinoblastomas that invade bone marrow and could have similar clinical and laboratory features should also be considered.

Treatment

- Effective treatment is very important in determining the prognosis.
- Treatment depends on the estimated clinical risk which is determined by 3 predictive factors: age of the patient at diagnosis, initial WBC count and the rate of response to treatment.
- Patients with ALL have 4 prognostic risk groups: low, standard, high and very high-risk based on the predictive factors above.
- **Remission induction** 4-6 weeks with vincristine, asparaginase, dexamethasone (as paragons or a single dose of a long-acting intrathecal (IT) cytarabine and or methotrexate).

- High-risk patients receive daunorubicin additionally. Remission– less than 5% blasts in the marrow and platelets and neutrophil to be near normal levels after 4-5 weeks of treatment.
- **Consolidation/Intensification with CNS prophylaxis**.
- **Delayed Intensification** with induction drugs as well as cyclophosphamide and cytosine arabinoside.
- **Maintenance chemotherapy** for 2 years with oral 6-mecaptopurine and pulse steroid, intermittent intravenous (IV) vincristine and methotrexate (oral and IT).
- A total of 2.5 years duration is required for all the phases.
- **CNS-directed therapy** with IT chemotherapy, cranial irradiation and high dose IV methotrexate.
- Bone marrow transplantation is recommended in leukaemias with high-risk features, relapse and if the leukaemia does not go into remission after successive courses of induction chemotherapy.
- A multidisciplinary treatment approach is recommended to provide supportive care and careful monitoring for infections and adequate nutrition.
- Intensive multiagent drugs can **induce remission** in 85-90% of AML patients (anthracycline and cytosine arabinoside).
- **Intensive post remission consolidation**.
- Patients with a good prognosis will have chemotherapy alone while those with a poor prognostic are considered for matched-sibling stem cell transplantation.
- Chemotherapy alone achieves a cure in about 45-50% of patients while matched-sibling bone marrow or stem cell transplantation after remission can achieve long-term disease-free survival in 60-70% of patients.
- Acute promyelocytic leukaemia (Fab-M3), with a gene rearrangement involving the retinoic acid receptor (PML-RARA), is responsive to all-trans-retinoic acid (tretinion) combined with anthracyclines and cytarabine.

Chronic myelogenous leukaemia (CML)

- CML accounts for 2-3% of cases of leukaemia. About 95-99% of CML will have specific translocation t(9;22)(q34;q11), called Philadelphia chromosome with a BCR-ABL fusion protein.
- CML has 2 major phases: Chronic phase of 3-4 years after onset.
- There is an elevated leukocyte count with mature forms being

predominant and an increased number of immature granulocytes with massive splenomegaly, mild-moderate anaemia and thrombocytosis.

- The 2nd phase is the accelerated/blast crisis phase, when the white blood cell count (WBC) rises rapidly and the clinical picture resembles acute leukaemia with other abnormalities like hyperuricaemia and hyperleukocytosis resulting in increased blood viscosity and decreased CNS perfusion.
- Treatment is with lmatinib, an agent which inhibits the BCR-ABL tyrosine kinase. Hydroxyurea and interferon may be used to control the symptoms. HLA-matched allogeneic stem cell transplantation can achieve a cure in 80% of cases.

Complications/prognosis of leukaemias

- These are mainly due to bone marrow failure from both the disease and the chemotherapy and include anaemia, increased risk of infection and bleeding problems, immunosuppression–viral, bacterial parasitic and fungal infections.
- Long-term effects: neurocognitive impartment, growth failure, obesity, cardiomyopathy, infertility, 2^0 malignancy and psychological problems.
- The 5-year survival is up to 90% by 2003-2009 for ALL, while the 5-year survival rate of children treated for AML by 2003-2009 was 64%.
- The most important prognostic factor is the choice of risk-directed therapy.
- Poor prognostic factors include age less than 1 or greater than 10 years at diagnosis, initial WBC >50,000/L, T-cell immunophenotype, and a slow response to initial therapy, chromosomal abnormalities, hypodiploidy, the Philadelphia chromosome, and MLL gene rearrangement and deletion of the IKZFI gene.
- Favourable characteristics are rapid response to therapy hyperdiploidy, and rearrangement of *TEL/AML I genes.*

Prevention and control

- Minimize radiation exposure during pregnancy including diagnostic CT-scans.

- Potential environmental and genetic risk factors for leukaemia should be minimized by counselling and public education.
- Early diagnosis with prompt and intensive treatment is advocated.

Counselling

- Information concerning the nature, treatment options, duration and side effects of treatment should be given to patients and their families.
- Emotional support should be offered to reduce anxiety, stress and depression.
- Relaxation techniques like guided imagery and participating in volunteering activities or being part of a support group can help people feel better.

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9.9 Sarcoma Botyroides (SB)

Epidemiology

- Sarcomas are malignant tumours composed of connective tissues such as muscle, bone, cartilage, blood and lymphoid vessels.
- RMS is a malignant tumour that arises from rhabdomyoblasts, primitive mesenchymal cells committed to skeletal muscle differentiation but is heterogenous so can occur in a variety of organs and tissues, including those that lack striated muscles.
- SB is a subtype of embryonal RMS that develops from the sub mucosa of hollow organs like the urinary bladder and vagina, cervix, nasopharynx and common bile duct.
- It usually occurs in infants and young children under 8 years and is more common in female infants and young children.
- It is an aggressive tumour arising from embryonic muscle cells.
- It typically appears like a bunch of grapes.

Pathology

- Gross appearance is a grape-like, friable mass, somewhat yellow.
- Microscopically the rhabdomyoblasts are seen as crowded and containing cross striations (small round blue cells) beneath the epithelial lining of the hollow organ.

Clinical Presentation

History:

- Patients may present with vaginal, cervical and bladder growth, urination problems, blood in the urine, polypoid friable and vaginal bleeding.
- Abdominal distension, tenesmus and jaundice.
- **Signs**: Polypoid friable mass in the vagina, cervix, nasopharynx, or buccal cavity.

Diagnosis

- From the clinical presentation of polypoid masses in hollow organs, staging evaluation, radiological imaging and laboratory investigations**.**
- Blood tests: Anaemia seen from FBC.

- Raised Alanine transaminase and Lactate dehydrogenase may show in LFT.
- Urinalysis may reveal haematuria and electrolytes should also be checked.
- Bone marrow studies may be required (to look for infiltration).
- Radiological imaging like Chest X-Ray, ultrasonography, CT or MRI scanning, positron emission tomography (PET).
- MRI imaging is preferred for the evaluation of the primary tumour site.
- Confirmed by the histology of the specimen from a biopsy to be embryonal RMS.
- Bone scan, checking for metastases and a biopsy for histology and molecular studies.

Differential diagnosis

- Malignant conditions like clear cell adenocarcinoma and germ cell tumour.
- Urologic conditions like urethral prolapsed, urethral polyps and genital warts.
- Gynaecological: paraurethral cyst, genital prolapse.

Staging

- Using the International **RMS** clinical **c**lassification into 4 main groups.
- ***Group I:*** Localized disease completely resected, no regional nodes involved.
- 1a: confined to the organ or muscle of origin,
- 1b: Infiltration outside the organ or muscle of origin.
- ***Group II***: Regional disease.
- Microscopic residual disease, no regional nodes involved,
- Regional disease completely resected. Nodes may be involved and/or extension of the tumour into an adjacent organ,
- Regional disease with involved nodes grossly resected but with evidence of microscopic residuals.
- ***Group III:*** Incomplete resection or biopsy with gross residual disease.
- ***Group 1V:*** Distant metastatic disease at diagnosis.

Treatment

- Surgery is recommended for all lesions, provided it is feasible, and as much of the tumour should be removed as possible and to obtain a tissue biopsy.
- Chemotherapy is given after and before surgery.
- Vincristine, actinomycin D and cyclophosphamide (VAC).
- Good results with the use of vincristine, etoposide and ifosfamide (VIE) or replacing etoposide with actinomycin D (VAI).
- Radiotherapy is also recommended.

Complications/Prognosis

- Complications include bladder dysfunction, sex hormone deficiency, second malignancy, metastasis and death.
- The prognosis of children with embryonal rhabdomyosarcoma is determined by age at presentation, site of origin, stage and histopathologic subtype.
- Others are tumour size (widest diameter), resectability, and the presence of metastasis, the number of metastatic sites or tissues involved, and the presence or absence of regional lymph node involvement.
- Vaginal tumours have a better prognosis than those from the cervix.
- A 5-year overall survival rate of 72% can be achieved with VAC.
- In patients with localized disease, overall 5-year survival rates of up to 80% can be achieved with the combined use of surgery, chemotherapy and radiotherapy.

Prevention and Control

- Educate the general public to improve nutrition and the health seeking habit and the primary health care personnel to recognize such cases that need referral early.
- These will eventually lead to early presentation, diagnosis and better outcomes.

Counselling

- The nature of the disease, the cost implication and duration of therapy, likely complications, recurrence and follow up should be explained.

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SECTION 10

HAEMATOLOGY

OPARA, H. I. O.

10.1 Sickle Cell Disease

Epidemiology

- It affects mostly black Africans, and their descendants outside the African continent.
- It also occurs in some Mediterranean, Indian and Arabian populations.
- There are 5 known haplotypes of HbS, which also correspond to the average percentage of HbF and thus, the severity of disease. They are the Benin, CAR/Bantu, Senegal, Saudi/India and Cameroon haplotypes.
- SCA results from the inheritance of HbS from both parents (homozygous HbSS). HbSC and HbSThal also cause sickle cell disease (SCD). The carrier state, HbAS, is not a disease condition.
- Prevalence rate in Nigeria is 5% for SCA while the carrier state is 24%.

Pathophysiology

- In HbS, the amino acid glutamine is replaced by valine in position 6 of the ß chain of the globin molecule.
- At the codon level, thymine replaces adenine–GTG instead of GAG.
- HbS polymerises and becomes insoluble under low oxygen tension, distorting red cell membrane–giving it a “sickle” shape.
- Sickled RBCs cause vaso-occlusion of tiny vessels, leading to painful crisis and, eventually, organ damage.

- Intra-vascular and extra-vascular haemolysis of sickled RBCs results in anaemia and jaundice.
- Damage to the spleen also makes the sufferer more prone to infections.

Clinical features (history)

- Painful swellings of the hand and foot (earliest: 3-6 months).
- Acute painful episodes involving mostly the bones, abdomen or chest.
- Easy fatiguability.
- Jaundice.
- Poor growth.
- Chronic leg ulcers.
- Priapism.
- Stroke.

Clinical features (Physical Findings)

- Anaemia.
- Jaundice.
- Swelling/Tenderness of the limbs.
- Bossing of the skull.
- Gnathopathy.
- Splenomegaly (prior to auto-splenectomy).
- Leg ulcers.
- Priapism.
- Congestive heart failure.

Common forms of presentation

- Vaso-occlusive crisis (including hands and foot syndrome, acute chest syndrome, stroke).
- Hyper-haemolytic crisis.
- Aplastic crisis.
- Sequestration crisis (splenic, hepatic).

Trigger factors

- Infections.

- Extremes of temperature.
- Dehydration.
- Injury.
- Acidosis.
- Stress (physical exertion, psychological).
- Any cause of de-oxygenation.

Diagnosis

- Sickling test.
- Solubility test.
- Haemoglobin electrophoresis (either in alkaline or acidic pH).
- Blood film.
- Iso-Electric Focusing (IEF).
- High Performance Liquid Chromatography (HPLC).

Differential diagnosis

- Other Haemolytic Anaemias.
- Osteomyelitis.
- Rheumatic fever.
- Rheumatoid arthritis.
- Leukaemia.
- Pneumonia (in cases of ACS).

Treatment

- Analgesics–for painful crises.
- Rehydration.
- Oxygen supplementation.
- Treatment of infections–antibiotics, antimalarials.
- Blood transfusions.
- Bone marrow transplantation.
- Other surgical interventions as may be necessary.

Complications/prognosis

- Poor growth.
- Delayed puberty–especially in females.
- Anaemic heart failure.

- Aseptic necrosis of the femoral head.
- Chronic leg ulcers.
- Renal insufficiency.
- Chronic lung disease.
- Retinal damage.
- Stroke.

Prevention/control

- Pre-marriage/pre-natal counselling.
- Prenatal diagnosis.
- Prompt medical attention.
- Vaccinations (against pneumococcus, H. influenza).
- Prophylaxis (antimalarials, antibiotics).
- Supplements (folic acid, anti-oxidant vitamins).
- Stimulation of HbF synthesis (Hydroxyurea, Butyrate).

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10.2 THALASSAEMIA

Definition

- The thalassaemias are hereditary anaemias (mostly autosomal recessive) resulting from a reduction or non-production of one of the normal globins of the adult haemoglobins. The suffix (α or ß) denotes the affected globin.

Epidemiology

- α-Thalassaemias occur among the natives and descendants of South-East Asia, the Middle East, and China.
- ß-Thalassaemias occur among the natives and descendants of the Mediterranean regions. Some Chinese and Asians are also affected.
- Both have a spread related to the geographic distribution of malaria and so may have evolved as a protective trait against malaria.
- Both cause disease in the homozygous state or in combination with other abnormal haemoglobins–Hb S, Hb C, Hb D, Hb E.

Pathophysiology

α-Thalassaemia

- Deletion of 3 or all 4 copies of the α-globin gene causes the disease state.
- 4-gene deletion results in severe intra-uterine anaemia (Hydrops foetalis) and is incompatible with life–α-Thalassaemia major.
- 3-gene deletion results in Hb H Disease.
- Deletion of 2 genes gives the Thalassaemia trait while only one deletion results in a Silent carrier.
- Excess ß-globins, and γ-globins (foetal), form tetramers–Hb H ($ß_4$) and Barth's Hb ($γ_4$).

ß-Thalassaemia

- Non-production of ß chain ($ß^0$) or small amounts ($ß^+$) result in little or no Hb A production, and an excess of α-globins.
- Ineffective erythropoiesis, precipitation of unstable Hb and increased intra-medullary destruction of RBCs result in severe anaemia.
- Increased production of γ-globin leads to increased Hb F.

Clinical features

α-Thalassaemia

- Hb H Disease–moderate microcytic anaemia, splenomegaly, Barth's Hb. A variant, Hb Constant Spring, is more severe.
- Hydrops foetalis.
- Mild microcytic anaemia in those with 2-gene deletion.

ß-Thalassaemia

- Major (Cooley's disease)–normal at birth but develops severe microcytic anaemia within the 1st year of life. There is weakness, poor appetite, poor growth, jaundice, hepatosplenomegaly and congestive heart failure, Thalassaemia facies–as a result of hyperactive membranous bone marrow.
- Intermedia–the same symptoms as above but less severe and it usually develops by the 2nd to 5th year of life.
- Minor (Trait)–Mild microcytosis, increased RBC count.

Diagnosis

- Blood film microscopy.
- Haemoglobin electrophoresis–to detect the type of Hb.
- High performance liquid chromatography (HPLC)–as above.
- DNA analysis–to identify the exact defect and for carrier states.

Differential diagnosis

- Sickle cell disease.
- Other Haemolytic anaemias.

Treatment

- Chronic transfusion–to maintain Haematocrit at 9.5 to 10 g/dL.
- Iron chelation therapy–Desferoxamine–to treat the resultant haemosiderosis. Oral agents, Deferasirox and Deferiprone are also available.
- Splenectomy–can reduce the frequency of transfusions.
- Bone marrow transplant–for curative treatment.

Complications/prognosis

- Iron overload from chronic transfusions.
- Infections–as a result of anaemia, transmission via transfusion or splenectomy.
- Patients can live a normal lifespan except in Thalassaemia major where there is early death.

Prevention/control

- Prenatal counselling among high-risk populations.
- Post-diagnosis counselling.

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10.3 Blood Transfusion and Blood Products

Definition

- Blood transfusion is the safe transfer of whole blood or a fraction of it from a donor to a recipient. Where the donor and the recipient differ, it is called Heterologous. If both are the same individual, it is called Autologous.

Indications for transfusion

- To increase oxygen-carrying capacity–in severe anaemia due to blood loss, haemolysis, chronic illness or dietary deficiencies.
- To replace deficient blood components–in bleeding and clotting disorders.
- In the case of EBT, to dilute the concentration of toxic substances in the circulation.

Red blood cell antigens and blood group antibodies

- There exist hundreds of RBC antigens in nature but few are of significant clinical importance.
- The ABO system and the Rh (Rhesus) system are the most common causes of haemolytic transfusion reactions.
- Other significant systems include the Kell, Duffy and Kidd systems, and less commonly, the Lutherian, Lewis, P and MNS systems.
- Individuals not having a particular blood group antigen either have naturally occurring antibodies against it (as in the ABO system) or may produce the antibodies via immune induction (e.g. the Rh system).
- Group O individuals are universal donors because there is no antigen for the recipients' antibodies to attack. Likewise, group AB individuals are universal acceptors because they have no antibodies to react with any incoming antigens. The mode of inheritance of the ABO system is Mendelian Co-dominant for the 3 allelic genes A, B and O.
- Two genes, *Rh* D and *Rh* CE encode for the production of D, Cc and Ee antigens. The presence of Rh D antigen is what makes an individual Rhesus Positive because it induces the most severe

antibody response capable of causing severe haemolytic transfusion reaction.

Making blood safe for transfusion

- Grouping and cross-matching–determining that the blood group of the recipient and that of the donor match in terms of the ABO and the Rh systems AND testing the recipient's serum against donor RBCs.
- Screening donor blood for common blood-borne infections such as HIV, Hepatitis B and C. Depending on the locality, other infections screened for include Malaria, CMV.
- Giving only the necessary components needed.
- Careful determination of the amount needed, and the rate of transfusion.
- Giving autologous transfusion whenever possible.

Types of blood products transfused

- Whole blood–especially for acute haemorrhagic loss.
- Packed Red Cells–the treatment of choice for most transfusions to increase haematocrit.
- Leucocyte-depleted blood–reduces febrile transfusion reactions as well as WBC associated infections like CMV. Optimized by storage in SAGM solution.
- Buffy coat (Granulocyte concentrations)–used in patients with severe leucopaenia.
- Fresh Frozen Plasma–used in the non-specific replacement of clotting factors when the desired components are not available.
- Human Albumin–used as volume expanders and in severe hypo-albuminaemia.
- Pooled Human Globulin/Specific Immunoglobulin–as a source of antibodies against viral and bacterial diseases.
- Cryoprecipitate–a source of concentrated Factor VIII and Fibrinogen for the management of Haemophilia and von Willebrand disease.
- Freeze-dried specific factors–especially Factor VIII.
- Platelets–for patients with thrombocytopenia and who have a bleeding disorder.

Complications of blood transfusion

- Haemolytic Reactions:
  - ACUTE–caused by the recipient's preformed serum antibodies via complement activation, and it causes intravascular haemolysis. It is usually seen in ABO incompatibility.
  - DELAYED–caused by induced antibodies that coat the RBCs, leading to their destruction by the reticulo-endothelial system (extravascular haemolysis). This is usually seen in Rh incompatibility.
- Non-haemolytic Reactions: Due to HLA antibodies or hypersensitivity to donor plasma proteins.
- Infections–include bacterial infections, malaria, HIV, Hepatitis B and C, CMV, etc. Proper screening can prevent most of these. However, in the case of viral infections, infection can occur if the donor is within the sero-positive window period.
- Transfusion-related acute lung injury (TRALI)–most commonly seen when the donor is a multiparous woman. Presents with symptoms of pulmonary oedema due to anti-leucocyte antibodies.
- Graft versus Host reaction–In immune-compromised patients. Due to the activity of transfused live lymphocytes.
- Volume overload–when transfusion is too fast or the volume is too much.
- Hypothermia–in the rapid transfusion of chilled blood.
- Hyperkalaemia–when donated blood is too old in storage.
- Haemosiderosis–in chronic transfusions.

Clinical features

- Haemolytic Transfusion Reaction–includes fever, chills, back pain, chest pain, nausea, vomiting, jaundice, anaphylactic shock and renal failure.
- Non-Haemolytic Reactions–fever, rigor, urticaria, pruritus, dyspnoea, facial swellings.

Treatment

- Stoppage of the transfusion and sending the blood specimens for a repeat investigation.
- Anti-shock measures–IV Dextran, Plasma or Saline.
- IV Hydrocortisone.

- An Antihistamine e.g. Promethazine.
- IV Adrenaline may be needed in severe cases.

Prevention of transfusion reactions

- Avoidance of blood transfusion when possible. Treat for iron deficiency.
- Use of alternatives such as Erythropoietin, Granulocyte colony stimulating factor, Recombinant clotting factors.
- Proper screening of donor blood.
- Full cross-matching before transfusion.
- Use of leucocyte-depleted packed cells, washed RBCs to reduce exposure to WBCs and plasma proteins.
- Irradiation of the blood product for use in immune-compromised individuals.

Ethical issues

- Exist mainly in the management of the Jehovah's Witness sect which rejects all forms of blood transfusion.

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10.4 Glucose-6-Phosphate dehydrogenase deficiency

Definition

- G6PD deficiency is an inherited RBC enzyme deficiency disease that can cause both an acute induced haemolytic illness and a chronic haemolytic anaemia. The mode of inheritance is X-linked.

Epidemiology

- Occurs worldwide, affecting over 400 million individuals.
- Majorly prevalent among natives and descendants of Africa, Mediterranean regions, the Middle East and parts of Asia.
- Spread corresponds to the malaria belt.
- It affects mainly males while most heterozygous females are only carriers. Females are affected only if they are homozygous, or in lyonization of the normal X chromosome if heterozygous.
- More than 400 mutations exist but most important are G6PD A- (in Africans) and G6PD B- (in Europe/Asia).

Pathophysiology

- G6PD enzyme catalyzes the oxidation of Glucose-6-Phosphate in the Hexose Monophosphate Pathway, producing NADPH which in turn produces reduced Glutathione.
- Reduced Glutathione protects the RBCs from oxidative stress by mopping up oxygen radicals.
- Deficiency of G6PD activity therefore exposes the Red Cells to oxidative damage, causing the denaturing and precipitation of Hb (Heinz bodies), and red cell membrane damage and subsequently, intravascular haemolysis.
- Haemolytic episodes are usually self-limiting because it is the older RBCs that have deficient enzyme activity.
- Trigger factors for haemolysis include fava beans, drugs (Sulfonamides, Aminoquinolones, Vitamin K analogues, Chloramphenicol, Aspirin, etc.) and infections.

Clinical features (history)

- Jaundice in the neonatal period, especially on exposure to certain drugs or naphthalene balls.

- Pallor, yellowness of the eyes and dark urine following fever or the ingestion of implicated drugs.
- Symptoms begin 1-3 days after trigger factors.

Clinical features (physical findings)

- Anaemia, Jaundice.
- Haemoglobinuria.
- Splenomegaly.
- Heinz bodies, fragmented cells and reticulocytosis.

Diagnosis

- Peripheral blood smear (Heinz bodies and reticulocytosis).
- G6PD enzyme assay (usually less than 10% of normal activity).
- Electrophoresis (to identify the variants).

Differential diagnosis

- Haemolytic Disease of the Newborn.
- Hereditary Spherocytosis.
- Sickle Cell Anaemia.

Treatment

- Removal of trigger factors.
- Blood transfusion.
- Phototherapy and, if indicated, exchange blood transfusion in neonates.
- IVF to increase urinary output.
- Splenectomy in severe cases.

Complications/prognosis

- Patients are generally non-symptomatic if they avoid trigger factors.
- Shock, and death may occur in the G6PD B- variety after ingestion of fava beans (favism).

Prevention

- Testing for the disease in high-risk populations before giving known drugs that cause oxidative stress.

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10.5 Haemolytic Anaemias

Definition

- Haemolytic anaemias are caused by a premature and increased rate of red blood cell destruction. The haemolysis can be both intravascular and extravascular. They are marked by anaemia and reticulocytosis in the absence of bleeding.

Pathophysiology

- Increased RBC destruction and a shortened RBC lifespan cause anaemia.
- Increased bone marrow activity leads to elevated reticulocyte counts.
- Degradation of Hb leads to the increased production and excretion of Bilirubin and Urobilinogen.
- Intravascular haemolysis leads to the release of free haemoglobin into the plasma, the formation of methemalbumin and Haemoglobinuria, haemosiderinuria.

Classification

- Hereditary
  - Membrane defects–Hereditary Spherocytosis, Hereditary Elliptocytosis, Hereditary Stomatocytosis;
  - Haemoglobin abnormalities–Hb S, Hb C, Hb E, Thalassaemias;
  - Enzyme deficiencies–G6PD Deficiency, Pyruvate kinase deficiency.
- Acquired
  - Autoimmune Haemolytic Anaemia–"Warm" and "Cold" antibodies;
  - Transfusion reactions;
  - Drug induced Haemolysis;
  - Paroxysmal Nocturnal Haemoglobinuria (PNH);
  - Red cell Fragmentation Syndromes;
  - Infections–e.g. Malaria;
  - Toxins, Venom and Chemical agents related–e.g. snake-bite, copper, lead poisoning.

Clinical features

- Pallor, Jaundice, Splenomegaly.
- Dark urine–in cases of intravascular haemolysis.
- Gallstones–in severe cases, due to the deposition of Calcium bilirubinate.

Laboratory findings: Evidence of

- Increased RBC destruction–↑ Serum bilirubin, ↑ urobilinogenuria, decreased serum haptoglobin;
- Increased RBC production–Reticulocytosis, bone marrow hyperplasia;
- Damaged RBCs–fragmented cells, abnormal red cell shapes;
- Evidence of intravascular haemolysis–Haemoglobinaemia, Haemoglobinuria, haemosiderinuria, methemalbuminaemia;
- Positive Coombs test–in immune haemolysis;
- Reduced specific enzyme activity on assay;
- Diagnostic electrophoretic patterns in specific defects.

Treatment

- Blood transfusion–in severe anaemia.
- Splenectomy–to reduce the rate of red cell destruction.
- Corticosteroids–in immune-mediated cases (except in "cold" AIHA).
- Monoclonal antibodies, Immunosuppressants–in immune cases.
- Removal/Discontinuation of specific inducing agents.
- Folic acid supplementation–unless there is a malignancy.
- Iron supplements–for secondary iron deficiency.
- Vaccines/Antibiotics for post-splenectomy patients.
- Bone marrow transplant–for PNH, Haemoglobinopathies.

Some specific conditions

- See the appropriate sections for Sickle Cell Disease, Thalassaemias, Transfusion Reactions and G6PD Deficiency.

Hereditary spherocytosis

- Autosomal dominant mode of inheritance. Rarely autosomal recessive.

- Due to defects in RBC membrane proteins (Ankyrin, Band 3 and Pallidin).
- RBCs become spherical due to membrane loss with little loss of volume.
- Spherocytes are ultimately destroyed in the spleen.
- Osmotic fragility test and Fluorescent Flow analysis diagnostic.

Hereditary elliptocytosis

- Autosomal dominant inheritance. More common in West Africa.
- Defect in membrane proteins α-spectin, ß-spectin and Protein 4.1.
- Microspherocytosis, poikilocytosis and splenomegaly.
- Most often mild clinical features.

Pyruvate kinase deficiency

- Autosomal recessive inheritance.
- Deficiency leads to decreased ATP formation, leading to rigid RBCs.
- Decreased deformability of RBCs leads to splenic destruction.

Autoimmune haemolytic anaemia (AIHA)

- "Warm" Antibodies:
  - Most reactive between $35^{O}C$ and $40^{O}C$;
  - Usually involve IgG ± complements;
  - Can be Idiopathic (Primary), or Secondary i.e. in association with ITP, SLE, CLL, Lymphomas and drugs (e.g. Methyldopa).
- "Cold" Antibodies:
  - Reaction peaks at $4^{O}C$;
  - Usually involve IgM + Complements;
  - Haemolysis is aggravated by cold.

Drug-induced immune haemolytic anaemia

Three mechanisms are involved:

- Antibodies against the drug bind to the drug molecule attached to the RBC membrane e.g. Penicillin, Ampicillin;

- Complement-mediated haemolysis of RBC to which has been attached a drug-serum protein complex e.g. Quinine, Quinidine, Rifampicin;
- True autoimmune antibodies against RBC membrane proteins.

Red cell fragmentation syndromes

- Fragmentation occurs due to direct damage to RBCs through narrowed or abnormal vessels.
- Associated with artificial valves or grafts, AV malformations, HUS, DIC or TTP.

P**aroxysmal nocturnal haemoglobinuria**

- Acquired abnormality of bone marrow stem cells forming defective clones.
- The RBC membrane is deficient in Glycosyl Phosphotadyl Inositol (GPI).
- Due to the mutation of a gene in the X chromosome coding for Phosphotadyl Inositol Glycan Protein A (PIG-A), which is necessary for the production of GPI anchor.
- Affected RBCs are more prone to lysis by complements.
- Definitive treatment is a bone marrow transplant.

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10.6 Pancytopenias

Definition

- Pancytopenia refers to a reduction of the 3 main cell types in the blood, namely the erythrocytes, leucocytes and platelets.
- This is majorly as a result of bone marrow failure (Aplastic anaemia) by either the destruction or suppression of the progenitor cells, or displacement of the marrow cells by invasive malignancies like ALL, AML.
- The malignancies will be discussed in a different chapter.

Classification of aplastic anaemia

- Inherited
  - Fanconi Anaemia;
  - Dyskeratosis Congenita;
  - Schwachman-Diamond Syndrome;
  - Amegakaryotic Thrombocytopenia;
  - Familial Aplastic Anaemias;
  - Reticular Dysgenesis.
- Acquired
  - Idiopathic–forms the majority of pancytopenias;
  - Drugs/Chemical Induced–Insecticides, Chemotherapeutic drugs, Benzene, Chloramphenicol, Gold;
  - Radiation–especially in total body irradiation doses >1.5 Gy;
  - Infections–Parvovirus, EBV, CMV, Viral Hepatitis.

Pathophysiology

- In inherited cases, chromosomal abnormalities either decrease stem cell survival or hamper their regenerative function.
- Acquired cases can result from direct stem cell damage, antibody-mediated cytotoxicity, alteration of the supporting micro-environment or loss of critical growth factors.

Clinical features (history)

- Pallor with weakness, and possibly cardiac failure.
- Severe Infections–frequently of the respiratory system. Severe fungal infections also.

- Bleeding–especially mucosal, epistaxis, easy bruising, menorrhagia
- Physical abnormalities–especially in inherited cases.
- Exposure to any of the identified causative factors in acquired cases.

Clinical features (findings)

- Anaemia–normocytic, normochromic. Can also be macrocytic (↑ MCV).
- Reduced or absent reticulocytes.
- Leucopenia. Neutrophils are more affected.
- Thrombocytopenia.
- Hypoplastic or aplastic bone marrow.
- Cutaneous, skeletal and organ abnormalities associated with particular inheritable causes.
- Hb F may be increased.

Classification of severity

- Severe–any 2 of the following:
  - Neutrophils count $<0.5 \times 10^9$/L;
  - Platelets count $<20 \times 10^9$/L;
  - Reticulocytes <1%.
- Very Severe:
  - Neutrophils count $<0.2 \times 10^9$/L;
  - Severe infections.

Diagnosis

- Full Blood Count–to demonstrate pancytopenia.
- Bone marrow aspirate and Biopsy–demonstrate hypocellularity and abnormal morphology.
- Cytogenetic investigations–to identify inherited causes.
- Flow-cytometry of RBCs using anti-CD55 and anti-CD59, to rule out PNH.

Differential diagnosis

- Myelodysplastic Syndrome.
- The leukaemias.

Treatment

- Remove or treat the cause where possible.
- Blood transfusion (Leuco-depleted, irradiated products).
- Prophylactic antibiotics.
- Bone marrow/Stem cell Transplant.
- Androgens, Granulocyte-colony Stimulating Factor, Anti-leucocyte globulins, Cyclosporine, Alemtuzumab–with variable response.

Complications

- Consequences of severe anaemia.
- Consequences of severe infections.
- Evolution to PNH.
- Increased risk of Leukaemia and other malignancies.

Prognosis

- Generally poor without treatment.
- Reduced life expectancy.

Counselling

- Genetic counselling for inherited cases in terms of the pattern of inheritance and the prospect of prenatal diagnosis.

Some specific conditions

Fanconi anaemia

- Mostly an autosomal recessive mode of inheritance. 2% are X-linked.
- Variable gene mutations that all result in the failure of DNA repair and spontaneous chromosomal breakages.
- Pancytopenia is associated with birth defects (especially absent radii and horse-shoe kidney), short stature, cafe-au-lait skin lesions, malignancies (esp. AML) and endocrine problems.
- Presents between 5 and 10 years.
- More in Ashkenazi Jews and Afrikaans.
- Ultimately fatal without a Bone marrow transplant.
- Diagnosed by the Diepoxybutane (DEB) test.

Dyskeratosis congenita

- Can be X-linked, Autosomal Dominant or Autosomal Recessive.
- Chromosomal instability leads to progenitor cell reduction.
- Pancytopenia is associated with abnormal skin pigmentation, nail dystrophy, mucosal leucoplakia and a variable host of other conditions.
- Distinguished from Fanconi anaemia by a negative DEB test.

Schwachman-Diamond syndrome

- Autosomal Recessive.
- Characterized by exocrine pancreatic insufficiency, bone marrow dysfunction and physical abnormalities.
- Pancytopenia occurs in 20% of cases.
- A high propensity to develop leukaemia.

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10.7 Iron Deficiency Anaemia

Definition

- This is anaemia resulting from the reduced availability of iron for the synthesis of haemoglobin.
- It manifests as a microcytic, hypochromic anaemia.

Epidemiology

- It is the most common cause of anaemia in all parts of the world.
- Also, the most common haematological disease in children.
- It is mostly due to excessive blood loss in developed countries while it is due to inadequate nutritional intake in developing countries.

Pathophysiology

- Iron is an essential component of the haeme component of Hb.
- About 65% of total body iron is in the RBCs as Hb, 30% as storage forms (ferritin, haemosiderin) while the rest are in the transport protein transferrin, some enzymes (e.g. Monoamine oxidase) and myoglobin.
- Only about 10% of dietary iron is absorbed following ingestion.
- The ideal dietary requirement is 10-15 mg/day.
- Children require the absorption of about 1 mg of iron/day to both meet the demand of a growing RBC mass and to replace normal losses.
- Deficiency can result either from reduced intake, reduced absorption, an increased requirement or excessive loss.
- In infants on milk alone, iron stores can get depleted after the 1st 6 months of life if there is no supplementation.
- Preterms become iron deficient much earlier– in 6 weeks.
- Reduced iron availability results in:
  - Reduced iron stores–reduced ferritin;
  - Reduced transport form iron–↑ total iron binding capacity;
  - Reduced haeme formation–hypochromasia, reduced RBC volume (microcytosis) and therefore reduced oxygen carrying capacity;

- Reduced activity of iron-containing or iron-dependent enzymes–responsible for tissue changes and cognitive dysfunction.

Clinical features (history)

- History of inadequate dietary iron consumption.
- History of decreased absorption (coeliac disease, gastrectomy, gut resection).
- History of increased loss–frank or occult haemorrhage (heavy Hookworm infestation, Oesophagitis, PUD, use of Aspirin/NSAIDs or Menorrhagia or haematuria e.g. from Schistosomiasis).
- Symptoms of anaemia–fatigue, dizziness, effort intolerance, headache, palpitation.
- Poor appetite.
- Frequent infections.

Clinical features (physical findings)

- Signs of anaemia–Mucosal pallor, tachycardia, dyspnoea, cardiomegaly, congestive cardiac failure.
- Irritability, reduced attention span, cognitive changes.
- Pica, angular stomatitis.
- Koilonychia.
- Plummer-Vinson syndrome (glossitis, dysphagia, oesophageal web).

Diagnosis

- Reduced PCV, Hb.
- Microcytic, hypochromic RBCs, Pencil cells, Target cells.
- Decreased ferritin and serum iron.
- Increased TIBC, FEP and serum TfR.
- Bone marrow biopsy showing absent staining for iron (only necessary in difficult cases).

Differential diagnosis

- Thalassaemia (there is increased serum iron).
- Anaemia of chronic infection (TIBC is reduced, ↑ Ferritin).

- Sideroblastic Anaemia.
- Lead poisoning.

Treatment

- Oral iron supplementation–better absorbed in the ferrous state e.g. Ferrous sulphate–fumarate or gluconate.
- Parenteral iron–e.g. Iron Dextran. For the case where iron loss exceeds the maximum oral availability or intolerance of oral intake.
- Blood Transfusion–only in cardiac decompensation.

Complications/prognosis

- Reversal of blood changes within weeks of therapy.
- Restoration of normal store levels within 3-6 months.
- High-dose ferrous sulphate may cause gastric irritation.

Prevention/control

- Nutritional counselling towards adequate dietary iron consumption.
- Making provision for periods of increased demand–during infancy, the adolescent growth spurt, menstruating females.
- Deworming–hookworm infestation is a cause of increased loss.
- Treat for schistosomiasis if present.

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10.8 Polycythaemia

Definition

- Polycythaemia is a condition in which there is an increase in the red blood cell mass in the body.
- There could be apparent polycythaemia where there is increased haematocrit resulting from diminished plasma volume such as in dehydration or following burns injury.

Epidemiology

- Worldwide occurrence except for genetically transmitted cases which occur within particular ethnic populations.
- However more cases are reported in Europe and the USA than in Africa and Asia.
- Polycythaemia Vera is more common in those aged 60 years and above.
- Residents of high altitudes, chronic smokers and sufferers of chronic obstructive pulmonary diseases and cyanotic heart diseases are at greater risk.

Pathophysiology

- There is increased production of red blood cells, with an attendant increase in blood viscosity and total blood volume which are responsible for most of the symptoms.
- Increased uric acid produced from cell destruction is responsible for joint pain.
- The cause could be primary or could be secondary to other conditions.
- Primary–there is an intrinsic problem in the red blood cell production process in the bone marrow
  - Polycythaemia Vera (PV)–adult onset non-hereditary clonal malignancy of the bone marrow cells. Usually associated with mutation in the JAK2 gene (95% of patients);
  - Primary Familial and Congenital Polycythaemia (PFCP)–mostly an autosomal dominant mode of inheritance. Caused by a mutation in the EPOR gene.
- Secondary–caused by conditions that cause increased erythropoietin production

- Physiologic–high altitudes, diseases associated with hypoxia (Cyanotic Heart Disease, COPD, OSA, Intrauterine hypoxia);
- Non-physiologic–Renal Ca, Liver Ca, Adrenal adenoma, Cushing's syndrome, Phaeochromocytoma, Use of anabolic steroids or extraneous erythropoietin;
- Congenital causes–high affinity Hb variants (Hb Chesapeake, Hb Kempsey), 2,3-DPG Deficiency;
- Perinatal causes–Twin-twin transfusion, Foeto-maternal transfusion.

Clinical features (History)

- Often asymptomatic.
- History of Headache, Dizziness, Blurred vision.
- Diminished exercise tolerance, itching skin, joint pains.
- There may be a positive family history in cases of genetically transmissible causes.
- Maternal diabetes mellitus, Pre-eclamptic toxaemia.
- History of any of the conditions listed earlier that causes hypoxia, stimulating increased erythropoietin production.
- Chronic smoking in adolescents.

Clinical features (physical findings)

- Plethora, Dyspnoea, Hypertension.
- Splenomegaly.
- Evidence of causative conditions e.g. finger clubbing in chronic hypoxic conditions, weight loss in carcinomas.
- In neonates–respiratory distress, anorexia, cyanosis, hypoglycaemia, hyperbilirubinaemia, apnoea, seizures, necrotizing enterocolitis, renal dysfunction.
- WHO diagnostic criteria for PV
  - Major–Hb >18.5 g/dl (males), 16.5 g/dl (females) and JAK2 gene;
  - Minor–hypercellular bone marrow, reduced erythropoietin, endogenous erythroid colony formation in vitro;
  - The presence of 2 major criteria and 1 minor criterion or 1 major and 2 minor criteria are diagnostic.

Diagnosis

- Raised PCV–>48% in females, >52% in males, >65% in neonates.
- Increased RBC count, nucleated RBCs.

- Raised erythropoietin in 2^0 polycythaemias, reduced in PV.
- Raised WBC count (>12 x 10^9/L) and Platelet count (>400 x 10^9/L).
- Hypercellular bone marrow.
- Gene studies for JAK2 and EPOR mutation (in PV).
- Investigations for secondary causes.

Differential diagnosis

- Methaemoglobinaemia.
- Chronic Myelogenous Leukaemia.

Treatment

- Phlebotomy.
- In neonates, partial exchange transfusion with plasma, 5% albumin or normal saline.
- In adults at risk of cardiac complications–Hydroxyurea, Interferon α-2b, Ruxolitinib.
- Low-dose Aspirin–to reduce thrombotic complications.

Complications

- Stroke.
- Pulmonary embolism, other thrombotic phenomena.
- Haemorrhagic manifestations e.g. GI bleeding.
- Myelofibrosis.
- Acute myeloid leukaemia.

Prognosis

- Generally good in 2^0 polycythaemia with treatment of the primary condition.
- Poor in PV without treatment but fair with treatment (10-20 years' life expectancy from the time of diagnosis).

Prevention/control

- No means of prevention in primary cases.
- Prevention of primary causes in secondary cases.

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10.9 Disorders of haemostasis

Definition

- Haemostasis is the mechanism of repairing vascular damage and preventing abnormal or excessive haemorrhage after vascular injury.
- Normal haemostasis involves the blood vessels, platelets, clotting factors, coagulation inhibitors and fibrinolysis agents.

Pathophysiology

- Following vascular damage, the initial response is vascular contraction to limit blood loss.
- Platelets adhere to the damaged vascular endothelial surface and aggregate with one another to form a platelet plug.
- The clotting cascade is activated, leading to the conversion of soluble fibrinogen to insoluble fibrin, to form a clot made up of platelets enmeshed in fibrin polymers.
- Coagulation inhibitors act to limit clot formation to the site of injury.
- Fibrinolysis agents dissolve the clots at the appropriate time to restore free vascular blood flow.
- Deficiency or abnormality of any of the factors or processes mentioned above results in abnormal or excessive bleeding or thrombotic disorder.

Bleeding disorders

- Usually due to vascular or platelet disorders.
- Vascular Disorders.
- Hereditary Haemorrhagic Telangiectasia.
- Ehlers-Danlos syndrome.
- Haemangiomas.
- Henoch-Schönlein syndrome.
- Scurvy.
- Platelet Disorders.

Thrombocytopenia

- Decreased production–Viral infections (including HIV), Thrombocytopenia-Absent Radius syndrome, Trisomies 13, 18 and 21, Fanconi Anaemia, leukaemia and other causes of bone marrow suppression.
- Increased destruction–ITP, SLE, DIC, TTP, Drug-induced immune thrombocytopenic Purpura, Kasabach-Merrit syndrome.
- Massive blood transfusion (dilution).

Abnormal Platelet Function

- Bernard-Soulier syndrome.
- Glanzmann's Thrombasthenia.
- Hermansky-Pudlak syndrome.
- Gray Platelet syndrome.
- Anti-platelet Drugs.

Clotting disorders

- Factors involved in the clotting cascade are
  - Fibrinogen;
  - Prothrombin;
  - Tissue factor;
  - Factors V, VII, VIII, IX, X, XI, XII and XIII.
- The Von Willebrand Factor (VWF) is a carrier protein for factor VIII, protecting it from destruction. It also facilitates platelet adhesion to vascular endothelium.
- Factors II, VII, IX and X are vitamin K dependent factors.
- Deficiency or abnormal function of any of the above will lead to a clotting disorder.
- Von Willebrand Disease (a disorder of VWF) is the most common hereditary disorder of haemostasis.
- The most common hereditary coagulation disorders are the Haemophilias A (factor VIII deficiency) and B (factor IX deficiency).
- Deficiencies of Fibrinogen, Prothrombin, Factors V, VII, X, XI and XIII are much rarer.
- Acquired disorders of coagulation are much more common than hereditary causes and include.

- Vitamin K deficiency–reduced vitamin K-dependent factors.
- Liver disease–most clotting factors are produced in the liver.
- DIC–excessive consumption of coagulation factors and platelets.
- Haemorrhagic Disease of the Newborn–transient deficiency of vitamin K in neonates, especially the premature.
- Use of anticoagulant drugs e.g. Warfarin, Heparin.

Clinical features

- Bleeding Disorders:
  - Mucosal bleeding–gum, nose, gastrointestinal, etc.;
  - Petechial rash, ecchymoses, spontaneous purpura;
  - Persistent bleeding from cuts;
  - Prolonged bleeding time (except in vascular disorders);
  - There may be a history of use of Aspirin or similar drugs.
- Clotting Disorders:
  - Bleeding into tissues–joints, muscles, retroperitoneal spaces;
  - Life-threatening haemorrhage during surgery.

Diagnosis

- FBC–detects thrombocytopenia, and its possible cause e.g. leukaemia.
- Prolonged bleeding time.
- Platelet aggregation test, platelet adhesion assay and platelet function analysis (PFA-100).
- Coombs test for immune thrombocytopenia.

Clotting Disorders

- Thrombin Time (TT)–tests for abnormality of fibrinogen and thrombin.
- Prothrombin Time (PT)–tests for abnormality of the extrinsic pathway (factors VII, V and X) as well as fibrinogen and prothrombin.
- Activated Partial Thromboplastin Time (APTT)–tests for abnormality of the intrinsic pathway (factors II, V, VIII, IX, X, XI and XII).
- VWF level and function assay.
- Specific clotting factor assay.
- Assay for coagulation factor inhibitors.
- Family studies to determine mode of inheritance.

Treatment

- Bleeding disorders:
  - Platelet transfusion in (except in HUS and TTP);
  - Corticosteroid and immune modulators in immune mediated cases;
  - Splenectomy;
  - Bone marrow transplant;
  - Treatment of underlying conditions.
- Clotting Disorders:
  - Replacement of deficient factor;
  - Whole blood transfusion, fresh frozen plasma, cryoprecipitate where the above is not available.

Haemophilia A

- The most common clotting factor disorder.
- X-linked mode of inheritance. Almost all sufferers are male, with a generation skip.
- Some cases result from spontaneous mutation.
- Initial presentation may be post-circumcision haemorrhage or post-accidental or surgical trauma.
- Recurrent bleeding into joints, muscles and deep tissues. Serious haemorrhage after dental extraction.
- Severity is measured in terms of the percentage of normal factor VIII activity
  - <1% Severe;
  - 1% to 5% Moderate;
  - >5% Mild.
- Joint deformities are common due to recurrent haemarthrosis.
- Abnormal APTT but normal PT.
- Assay demonstrates factor VIII deficiency, the only way to distinguish it from the clinically similar factor IX deficiency (Christmas disease).
- Increased risk of HIV and Hepatitis B and C infections due to repeated blood transfusions.
- Treatment is by factor VIII replacement therapy.
- Desmopressin (DDAVP) also temporarily increases endogenous factor VIII level.

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10.10 Megaloblastic Anaemia

Definition

- This anaemia is characterized by large erythroblasts in the bone marrow as a result of delayed cell nucleus maturation. It is usually caused by either the deficiency of, or an abnormality in the metabolism of folate and Vitamin B_{12}. It can also cause defects in DNA synthesis not related to folate or Vitamin B_{12}.

Epidemiology

- Common among vegetarians and those on a poor diet due to poverty.
- Common in post GI surgical patients.
- The premature newborns (low storage) and the aged (Pernicious anaemia).

Pathophysiology

- Dietary folate is the source of Tetrahydrofolate (THF) in the cells, which is essential for the synthesis of dTMP, a precursor of dTTP required for DNA formation.
- Vitamin B_{12} is a co-enzyme for the generation of THF from methyl-THF.
- Non-availability of either vitamin results in a reduced supply of dTTP and defective DNA synthesis. The rapidly dividing cells in the bone marrow, among others are much affected, causing ineffective erythropoiesis and apoptosis–thus the anaemia with macrocytosis.
- In the conversion of methyl-THF to THF, the methionine formed is an important source of *S*-Adenosyl methionine necessary for the methylation of myelin–thus B_{12} deficiency is associated with neurological manifestations.

Causes

- Vitamin B_{12} deficiency
  - Poor dietary intake (rare in children);
  - Deficiency of Intrinsic Factor (IF) necessary for intestinal absorption;

  - Pernicious Anaemia (Autoimmune disease in adults);
  - Congenital Pernicious anaemia–rare autosomal recessive disorder;
  - Malabsorption–diarrhoea, tropical sprue, GI surgery, Achlorhydria;
  - Deficiency of vitamin transport proteins (Transcobalamin)–rare.
- Folate deficiency
  - Poor dietary intake or increased requirement e.g. in pregnancy and in chronic haemolysis (SCA, Thalassaemia Major);
  - Decreased absorption–diarrhoea, tropical sprue, GI surgery;
  - Drugs–Antifolate medications, anticonvulsants.

Clinical features (History)

- Anorexia, weight loss, diarrhea.
- Vegan diet, Anti-folate medications, Anti-convulsants.
- Auto-immune disease, pregnancy, prematurity.
- Consumption of raw fish (fish tapeworm).
- Family history (Genetically inherited causes).

Clinical features (Physical Findings)

- Pallor, glossitis, angular stomatitis, purpura.
- Blood film–oval-shaped macrocytes, hypersegmented neutrophils, leucopenia, thrombocytopenia and reduced reticulocytes.
- Hyper-cellular bone marrow with large erythroblasts.
- Bilateral peripheral neuropathy. Developmental delay, hypotonia, seizures, failure to thrive, neuro-psychiatric changes in children.
- Neural tube defects in children of deficient mothers.
- Sterility in both males and females.
- Evidence of the underlying cause.

Diagnosis

- Serum assay of Folate, and $B_{12.}$
- Red cell folate assay.
- Endoscopy to identify underlying GI causes.
- Serum assay for methylmalonic acid (for B_{12}) and homocysteine (for both folate and B_{12}) now rarely used.

Differential diagnosis

- Non-megaloblastic macrocytic anaemias.
- Liver disease.
- Myelodysplasia.
- Myeloproliferative disease.
- Alcoholism (adults).

Treatment

- Replacement therapy
  - Folate–daily oral folic acid;
  - Vitamin B_{12}–IM 1 mg injections 3 times weekly until normal serum levels are achieved then every 2-3 months. Oral forms are also available.
- Treatment of underlying pathology.

Prognosis

- Treatment reverses most clinical symptoms except spinal cord damage.

Prevention

- Dietary advice.
- Folic acid fortification of food.
- Oral folic acid supplements for chronic haemolytic disease patients and pregnant women, and for premature neonates.
- Life-long Vitamin B_{12} for total gastrectomy or ileal resection patients.

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SECTION 11

NEONATOLOGY

IBENEME, C. A.

11.1 Respiratory distress syndrome

- Respiratory distress syndrome (RDS), also known as Hyaline Membrane Disease occurs primarily in premature infants and is due to a deficiency of pulmonary surfactant in an immature lung.
- It is a condition of increasing respiratory distress commencing at or shortly after birth and increasing in severity until progressive resolution occurs among survivors, usually between the 2nd to the 4th day of life.

Epidemiology

- RDS is the major cause of morbidity and mortality in preterm infants affecting 20,000-30,000 newborn infants each year. It has been reported in all races worldwide.
- Its incidence and severity are inversely related to gestational age (GA) and birth weight, occurring in 60-80% of infants <28 weeks gestation, 15-30% of those between 32 and 36 weeks and rarely in those >37 weeks.
- The incidence is highest in preterm males or white infants (75% risk as against 40% in blacks).

Risk Factors

- These include: Prematurity, caesarean section before the onset of labour/Induction of labour, maternal diabetes mellitus, the second born of premature twins, history of a previous infant with RDS and antepartum haemorrhage.

- Others are cold stress, intrapartum asphyxia, genetic abnormality in the SP-SP-C gene and the ABC transporter-3 (ABC-3) gene that transport surfactant across the cell membrane.
- Postnatal conditions that increase the risk of RDS are pulmonary infection, pulmonary haemorrhage, meconium aspiration pneumonia and oxygen toxicity along with barotrauma to the lungs.
- Conditions that decrease the incidence of RDS include long-term intrauterine stress such as toxaemia and hypertension, Intrauterine growth retardation, Maternal narcotic exposure, the Use of antenatal steroids (glucocorticoids) and PROM.

Pathophysiology

- Surfactant is produced by type 2 pneumocytes and is present in foetal lung homogenate at 20 weeks. It appears in the amniotic fluid by 28-32 weeks.
- It reaches mature levels by 35 weeks.
- The lungs of infants with RDS are developmentally deficient in surfactant (a complex lipoprotein) which decreases surface tension in the alveolus during expiration, allowing it to remain partly expanded hence maintaining functional residual capacity.
- Its absence results in poor lung compliance and atelectasis (lung collapse).
- Atelectasis → uneven perfusion and hypoventilation → hypoxaemia, CO□ retention → Acidosis → pulmonary vasoconstriction → pulmonary hypoperfusion → epithelial/endothelial damage → plasma leak into alveoli → fibrin and necrotic cells (hyaline membrane).

Clinical features

- Infants with RDS usually appear normal at birth but within minutes to a few hours develop signs of respiratory distress: grunting, intercostal and subcostal recessions.
- Cyanosis is often relatively unresponsive to oxygen therapy.
- Breath sounds may be normal or diminished with crepitations.
- If the condition is inadequately treated, blood pressure may fall, cyanosis and pallor increase, and grunting decreases or disappears as the condition worsens.
- Apnoea and irregular respirations are ominous signs requiring immediate intervention.

- Signs and symptoms peak at the 3rd day, after which there is gradual improvement, marked by diuresis and better oxygenation.
- Death most often occurs at about the 2nd to 7th day.

Diagnosis

- This is made clinically and with a chest radiograph showing diffuse bilateral atelectasis causing a "Ground glass appearance" (diffuse airspace and interstitial opacities) and an air bronchogram.

Differential Diagnosis

- Aspiration syndromes, Pneumonia, Spontaneous pneumothorax, Pleural effusion, Persistent pulmonary hypertension, early onset sepsis, Transient tachypnoea of newborns, cyanotic heart disease (TAPVR).

Treatment

- Supplemental oxygen. Aim for oxygen saturation of 85-90%, $Pa0_2$ of 50-70 mmHg, $PaC0_2$ 45-65 mmHg, PH 7.2-7.35.
- Ventilation can be achieved via CPAP or endotracheal intubation and mechanical ventilation.
- Exogenous surfactant via an endotracheal tube. Repeated dosing is given every 6-12 hours for a total of 2-4 doses. Both synthetic surfactant (e.g. Exosurf) and natural surfactant (e.g. survanta (bovine)) are available.
- Other treatment modalities include inhaled nitric oxide which has decreased the need for extracorporeal membrane oxygenation (ECMO) in infants with hypoxic respiratory failure.
- Supportive care for the treatment of acidosis, hypoxia, hypothermia and hypotension.
- Others are frequent monitoring of BP, Pa0□, PaC0□, PH, Temperature, Heart rate, respiratory rate, serum bicarbonate, O□ saturation, electrolytes, glucose, PCV, using arterial catheterization.
- IV fluid and electrolyte management.
- Incubator nursing to maintain temperature.
- Trophic feeding.
- Pharmacologic therapy: use of antenatal steroids (corticosteroids) to enhance lung maturity, Vitamin A supplementation to infants <1 kg to reduce complications of RDS.

- EBT and lung transplant are also useful.

Complications

- Complications from the disease and from treatment include: septicaemia, bronchopulmonary dysplasia, patent ductus arteriosus, pulmonary haemorrhage, retinopathy of prematurity, renovascular hypertension, necrotizing enterocolitis, periventricular leukomalacia, intracranial/intraventricular haemorrhage.

Prognosis

- Antenatal steroids, postnatal surfactant use and improved modes of ventilation have resulted in low mortality from RDS (10%). Mortality increases with decreasing gestational age.
- Surfactant therapy has reduced mortality from RDS to approximately 40%, but the incidence of BPD has not been measurably affected. The outlook is much better for those weighing >1,500 g. Long-term prognosis for normal pulmonary function in most infants surviving RDS is excellent.
- Prolonged ventilation, IVH, pulmonary hypertension, cor-pulmonale and oxygen dependency beyond 1 year of life are poor prognostic signs.

Prevention

- Avoidance of unnecessary or poorly timed cesarean sections and the use of pharmacological agents to inhibit premature labour,
- In utero acceleration of maturation using glucocorticoids in mothers 48 hours before delivery. Available tests that correlate with the production of surfactant include; the lecithin-sphingomyelin ratio: if <2:1 foetal lungs may be surfactant deficient (<2.5:1 in IDM). The presence of phosphatidylglycerol (PG) usually indicates foetal lung maturity.
- The surfactant-albumin ratio, <35 indicates immature lungs, 35-55 is indeterminate and >55 indicates mature surfactant.
- Betamethasone is found to be better at preventing RDS, IVH and NEC than dexamethasone which is associated with the risk of PVL.
- Administration of surfactant immediately after birth in at risk babies.

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11.2 Neonatal Jaundice

- Jaundice is a clinical description of the yellowish discoloration of the sclera, skin and mucous membrane due to a rise in the level of serum bilirubin (hyperbilirubinaemia) which could either be unconjugated or conjugated.
- Jaundice in a newborn can be a cause for concern because unconjugated bilirubin is neurotoxic and can cause death in newborns and lifelong neurologic sequelae in infants who survive (kernicterus).

Epidemiology

- Incidence figures vary widely as researchers do not use the same definitions for significant neonatal hyperbilirubinaemia.
- Jaundice is observed during the 1st week of life in approximately 60% of term infants and 80% of preterm infants.
- In a 2003 study in the United States, 4.3% of 47,801 infants had total serum bilirubin levels in a range in which phototherapy was recommended by the 1994 American Academy of Pediatrics (AAP) guidelines.
- In Ebonyi state, South East Nigeria two hundred and thirty-seven (17.25%) out of 1374 neonatal admissions were due to neonatal jaundice.

Bilirubin metabolism

- Haeme from haemoglobin is oxidized by haemeoxygenase to bilverdin, which is reduced to bilirubin by biliverdin reductase.
- Bilirubin is transported to liver cells for conjugation bound to serum albumin. Certain drugs, such as sulphonamides or free fatty acids can displace bilirubin from albumin.
- This free bilirubin can cross the blood-brain barrier, leading to neurotoxicity (bilirubin encephalopathy).
- Bilirubin conjugation by glucuronyl transferase transforms a water-insoluble (indirect) bilirubin molecule into a water-soluble conjugated (direct) molecule which allows it to be excreted into the bile and eliminated from the body in stool.

Aetiopathogenesis

Physiological hyperbilirubinaemia

- Without specific abnormality of bilirubin metabolism, the serum unconjugated bilirubin (UCB) level of most newborn infants rises in the 1st week of life.
- This is attributed to increased RBC mass and decreased RBC survival, increased enterohepatic circulation and defective conjugation.
- If the following occur, it is no longer physiological hyperbilirubinaemia, instead non-physiologic should be considered: onset of jaundice in the 1st 24 hours of life, a rate of rise of serum bilirubin (SBR) of >0.5 mg/dL/hr, a term infant with SBR >12 mg/dl, a preterm infant with SBR >14 mg/dl, jaundice persisting till 10-14 days, family history of jaundice, anaemia and splenectomy, maternal illness during pregnancy and if conjugated the fraction is >2 mg/dl.

Non-physiological/Pathological hyperbilirubinaemia

This can be due to bilirubin overproduction or impaired excretion.

- Overproduction of bilirubin
  - Blood group incompatibilities (ABO, Rh);
  - Red cell membrane defects: congenital spherocytosis, elliptocytosis, stomatocytosis;
  - Red cell enzyme deficiencies: G6PD deficiency;
  - Haemoglobinopathies: α-thalassaemia;
  - Haemolytic agents such as vitamin k, sulphonamides, naphthalene;
  - Extravasated blood: cephalhaematomas, petechiae, cerebral haemorrhages;
  - Polycythaemia;
  - Increased enterohepatic circulation: intestinal obstruction, swallowed blood.
- Impaired bilirubin excretion.
  - Metabolic and endocrine conditions such as Crigler-Najjar syndrome types I and II, prematurity, Gilbert's disease, Lucy-Driscoll syndrome, Galactosaemia, hypothyroidism;
  - Obstructive disorders such as biliary atresia, Dubin Johnson and Rotor syndrome, α-1-antitrypsin deficiency, parenteral nutrition.
- Mixed causes
  - Sepsis, intrauterine infections, hepatitis.
- Others

- Breast milk jaundice, prematurity, infants of diabetic mothers, Down syndrome.

Clinical Features

History

- Infant: History of delayed passage of meconium, caloric intake, vomiting, contact with naphthalene balls, fever, blood group, swelling on the head, high-pitched cry, abnormal movement, dark urine, pale stool, etc.
- Family: History of neonatal jaundice.
- Maternal: History of illness during pregnancy, diabetes, drug intake, blood group.
- Perinatal: History of Vacuum extraction, oxytocin-induced labour, delayed cord clamping.

Physical Examination*:*

- Level of jaundice, pallor, size for gestational age, head swelling, pallor/plethora, petechiae, hyper/hypothermia, appearance of umbilical stump, hepatosplenomegaly.

Laboratory investigations

- Serum Bilirubin (indirect, direct and free), Albumin binding capacity for bilirubin, Blood group, direct and indirect Coombs tests**,** Urinalysis (including a test for reducing substances), G-6-PD status**,** FBC, Reticulocyte count and RBC morphology**.**
- For conjugated hyperbilirubinaemia, the following may be indicated: LFT, Serum protein, ESR, Hepatitis-associated antigens, Alpha 1-anti-trypsin concentration, liver biopsy, and amino acid screening.

Treatment

- Phototherapy.
- Exchange blood transfusion (EBT).
- Others include Phenobarbitone which increases bilirubin conjugation, IVIG to inhibit haemolysis, oral agar to decrease enterohepatic circulation, and metalloprotoporphyrins to inhibit haeme oxygenase (experimental).
- Treat underlying causes: antibiotics for sepsis, surgery if indicated.

- Ursodeoxycholic acid.

Complications

- Acute Bilirubin Encephalopathy and Kernicterus, anaemia.
- Complications of phototherapy and EBT.

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11.3 Neonatal Sepsis

- Neonatal sepsis is defined as systemic bacterial infection or positive blood culture in the first month of life. It may be described as a clinical syndrome of bacteraemia with systemic signs and symptoms of infection in the first four weeks of life.
- Infections in the newborn contribute significantly to neonatal morbidity and mortality.

Epidemiology

- Sepsis accounts for about one-quarter of neonatal deaths in Nigeria. Incidence varies from region to region, centre to centre and from time to time within the same centre. In addition, the prevalent pathogens as well as their antibiotic sensitivity patterns vary from one period to another.
- The reasons for the variations are not fully understood but prevalent practices, observance of strict aseptic techniques and the index of suspicion may all play a role.
- Incidence: <5/1000 live births in developed countries of Europe and North America.
- In Nigeria prevalence rates have increased from <10/1000 live births in the 1970s and early 1980s to 20-30/1000 live births afterwards.
- Incidence rates are higher in preterm and low birth weight babies.
- Risk factors to sepsis include maternal and foetal factors such as maternal UTI, prolonged rupture of foetal membranes, chorioamnionitis, labour and delivery practices, prematurity, asphyxia with resuscitation, congenital malformations, nursery practices and male sex.

Classification

- Early-onset sepsis: birth to 7 days of life (a greater percentage occurs within 72 hours).
  - Group B streptococcus (GBS), coagulase negative staphylococcus epidermidis, Escherichia coli, Haemophilus influenza, Listeria monocytogenes are mainly the implicated organisms acquired from the mother transplacentally or during delivery.

- Late-onset sepsis: >7-28 days of life due to organisms from the environment: the community or the health facility.
  - Implicated organisms are mainly Staphylococcus aureus and Pseudomonas aeruginosa.

Pathophysiology

- It usually begins with infection and progresses through SIRS, severe sepsis, septic shock and multiple organ dysfunctions.
- Numerous host factor immunoincompetences predispose the newborn especially the premature infant to sepsis.
- These factors involve all levels of host defences, including cellular immunity, humoral immunity and barrier function. These include deficiencies of complement factor 9 and fibronectin, inefficient bacterial opsonization and neutrophil chemotaxis.

Clinical features

- Non-specific and non-localizing features which can be rapidly progressive and demand a high index of suspicion. These include fever/hypothermia, poor suck, irritability, high pitch cry, lethargy, respiratory distress, tachycardia, abdominal distension, jaundice, diarrhoea, vomiting, cyanosis, sclerema, bleeding, apnoea and shock.
- Other localizable systemic signs are a bulging anterior fontanel, hypertonia, seizures, pustules, cellulitis and abscess sites, swollen, tender joints, a discharging or offensive umbilical cord.

Diagnosis/investigations

- Cultures of blood, CSF, urine, body fluids, catheters and intravenous lines.
- Antigen detection with counter immunoelectrophoresis and latex agglutination.
- Polymerase chain reaction.
- Chest radiograph if indicated.
- Acute Phase Reactants: Indirect indicators of sepsis such as
  - Elevated Micro Erythrocyte sedimentation rate (mESR);
  - Abnormal WBC count, Neutropenia/neutrophilia. Morphologic changes in neutrophils (toxic granulations, Dohle bodies) are suggestive;

- Band (Immature): Total Neutrophil ratio: a raised immature to total neutrophil ratio (I:T >0.2) is about 85% sensitive and specific particularly for early onset sepsis;
- Elevated C-reactive protein, procalcitonin, haptoglobulin and fibrinogen;
- Inflammatory cytokines: Interleukin-6, Interleukin-8, Tumour necrotic factor.

Treatment

- Because mortality from untreated sepsis can be as high as 50%, most clinicians will initiate treatment while awaiting culture results.
- Factors determining the selection of antibiotic therapy in the newborn will include the nursery flora, antimicrobial susceptibility patterns, antibiotic pharmacokinetics in newborn infants and maternal factors.
- Empirical antimicrobials include:
  - Early onset sepsis: Penicillin (ampicillin or penicillin G) + aminoglycoside (gentamicin), Clindamycin or metronidazole in a suspected anaerobe (foul-smelling amniotic fluid);
  - Late onset (community source): Ampicillin + gentamicin or cefotaxime;
  - Late onset (nosocomial): Vancomycin + gentamicin (amikacin or 3rd generation cephalosporin for resistance to gentamicin), Vancomycin + ceftazidime if Pseudomonas is suspected;
  - Once sensitivity is determined, the most appropriate antibiotic should be selected.
- Duration of Rx: 7-10 days or 5-7 days after a clinical response has occurred. For meningitis (14-21 days for GBS and 21 days for Gram negative or 14 days after CSF sterilization).
- Adjuvants:
  - Intravenous fluids for hydration and electrolytes;
  - Ventilatory support and intensive care management;
  - Total parenteral nutrition;
  - Inotropes;
  - Exchange blood transfusion;
  - Immunotherapy
    - Intravenous Immunoglobulin;
    - Human monoclonal IgM Antibody Granulocyte transfusion;
    - Complement infusion;

- Fibronectin administration;
- Recombinant human Granulocyte CSF;
- Granulocyte-Macrophage stimulating factor.

Prevention

- Selective intrapartum chemoprophylaxis to reduce vertical transmission of GBS. Aggressive management of suspected maternal chorioamnionitis.
- Adherence to precautions with all patient contact, avoiding nursery crowding and limiting the nurse to patient ratios, strict compliance with hand washing, decreasing the number of venipuncture and the duration of catheters, providing education and feedback to nursery personnel.

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11.4 Perinatal Asphyxia

- Perinatal asphyxia is a condition in the foetus or newborn when there is reduced oxygen saturation (hypoxia) and increased acid in the blood (acidaemia) from carbon dioxide retention and lactic acid accumulation.
- It is characterized by multisystemic manifestations due to hypoxic damage to body organs.
- It is a medical emergency therefore aggressive management should be instituted once risk and aetiological factors are noted.

Epidemiology

- International incidence has been reported to be 2-6/1000 term births (de Hannet et al., 2006). The rate is higher in developing countries.
- In Nigeria, it is reported as the leading cause of neonatal morbidity and mortality where it accounted for about 10 to 60% of neonatal deaths.

Pathophysiology

- In utero, oxygenated blood from the placenta is diverted away from the lungs due to increased vascular resistance.
- At birth, with the first breath, the alveoli expand and are kept patent by the help of surfactant.
- A decrease in pulmonary vascular tension causes blood to flow into the lung for oxygenation.
- Therefore, anything that will compromise these steps will lead to a ventilation/perfusion mis-match, hypoxaemia and consequent asphyxia.
- With decreased tissue oxygenation, primary apnoea occurs followed by a gasping phase.
- If there is no resuscitation, secondary apnoea follows associated with hypoxaemia.
- Tissue perfusion decreases and blood is shunted away from the lungs, skin, liver, gastrointestinal tract and kidneys to the brain, heart and adrenals.
- Anaerobic metabolism generates lactic acid, inorganic phosphate, excitatory amino acids particularly glutamate, free radicals and

nitric oxide which accumulate in the damaged tissues. Severe asphyxia ultimately leads to tissue damage and multi organ failure.

Aetiology/Predisposing factors

- Maternal factors: Maternal illnesses such as pneumonia, hypertension, heart failure and anaemia. Others include drugs such as narcotics.
- Placental causes: Placenta insufficiency, placenta previa, placenta abruption.
- Foetal factors: Post maturity, meconium stained liquor, abnormal lie, cord prolapse and developmental problems.

Clinical manifestations

- Central nervous system: the most affected and including features of hypoxic ischaemic encephalopathy stages I, II and III, cerebral oedema and brain death.
- Respiratory system: type 2 respiratory distress syndrome (due to reduced surfactant), persistent pulmonary hyperplasia.
- Cardiovascular system: left ventricular dysfunction, tricuspid incompetence, patent ductus arteriosus, cardiogenic shock.
- Gastrointestinal tract: necrotizing enterocolitis and liver dysfunction.
- Genitourinary system: there is bladder atony, acute tubular necrosis, acute cortical necrosis.
- Haematopoietic system: bone marrow suppression, DIC.
- Metabolic: hypoglycaemia, hyperglycaemia, hypocalcaemia, acidosis, SIADH.
- Others are Adrenal haemorrhages and subcutaneous necrosis.

Management

- Early detection and prompt intervention may alter the outcome.
- Adequate preparations should be made for an anticipated infant that will need resuscitation.
- Obstetricians should notify the Neonatologist of any high-risk pregnancy well in advance of the delivery.

Early ante-partum detection can be done through:

- Prenatal diagnosis of congenital malformations; Foetal scalp blood sampling for blood gases; Foetal movement monitoring; Non-stress test; Contraction stress test; Doppler ultrasonography of foetal umbilical artery blood flow; partum foetal assessment of the foetal heart rate (baseline heart rate is 110-160) and uterine activity.

Post-partum assessment of the infant

- The APGAR scoring system at the 1st and 5th minutes of birth.
  - The Apgar score helps in the evaluation and decision regarding resuscitation measures. It assesses the appearance, pulse rate, respiratory rate, activity and grimace. Each sign is evaluated and scores 0 to 2 assigned. The 1st minute Apgar score correlates with umbilical cord blood pH and is an index of Intrapartum depression. It does not correlate with the outcome. Apgar scores beyond 1 minute are reflective of the infant's changing condition and the adequacy of resuscitative efforts. The Apgar score of 0-3 at the 5th minute is regarded as severe asphyxia.
- Resuscitation in the delivery room.
  - Adequate preparations should be made for all high-risk pregnancies. Once the infant is born, the ABCD of resuscitation should be initiated. Tactile stimulation, suction of the airway, ventilation using a bag and mask, cardiac compression, oxygen delivery, endotracheal intubation with ventilator support, intravenous adrenaline and intravenous fluid should be started depending on severity.
- Once stabilized, the infant should be monitored for seizures, hypo or hyperglycaemia and signs of raised intracranial pressure and should be treated accordingly.
- Blood pressure, heart rate, respiratory rate and urine output should also be monitored.
- Selective cerebral or whole body (systemic) cooling.
- Investigations include: S/E/U/Cr, calcium and magnesium, complete blood count, EEG, MRI of the brain, cranial CT scan.

Prognosis/complications

- This depends on the severity of asphyxia: It ranges from complete recovery to death.
- Infants with blood pH <6.7 at birth have a poor prognosis and severe neurodevelopmental problems which include cerebral palsy,

seizure disorder, mental retardation, learning disabilities, neurological deficits such as hearing and visual problems and attention deficit hyperactive disorders.

Prevention

- Proper health education of women of child bearing age.
- Proper antenatal care and delivery in centres with good neonatal resuscitative facilities.
- Early antenatal detection of high-risk pregnancies and foetal wellbeing compromises.

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11.5 Congenital Malformations

- Congenital malformations are single or multiple defects in the morphogenesis of organs or body districts, identifiable at birth or during intrauterine life. They may result in long-term disability, with a significant impact on individuals, families and healthcare systems due to the resources needed for multidisciplinary assistance.

Epidemiology

- The global prevalence rate is 2-3%. It is estimated that 10% of paediatric hospital admissions have known genetic conditions, 18% have congenital defects of unknown aetiology while 40% of paediatric surgical admissions are due to congenital malformations.
- It is estimated that each year 270,000 newborns die during the first 28 days of life from congenital malformations, with an estimated 3.2 million birth defect-related disabilities.
- In Nigeria, Obu et al. reported a prevalence of 2.8% among neonatal admissions.
- Race: Birth defects seem to occur more in Negroid than Caucasian infants.
- Studies have shown that twins are about 4 times more likely to have congenital malformations than singletons.
- In Nigeria, the majority of defects involve the central nervous and musculoskeletal systems with few urogenital, respiratory and gastrointestinal affectations. Spina bifida, meningocele, hydrocephaly, talipes and polydactyly, were among the most prevalent. Other less prevalent defects include ambiguous external genitalia, undescended testes, imperforate anus and congenital hernia.

Classification

- Congenital malformations can be classified based on a number of defects into:
  - Isolated single defects;
  - Multiple anomalies.
- Single primary defects can be classified by the nature of the presumed cause of the defect:

  - Malformation: a primary structural defect arising from a localized error in morphogenesis, resulting in the abnormal formation of a tissue or organ;
  - Dysplasia: an abnormal organization of cells into tissues;
  - Deformation: an alteration in shape or structure of a structure or organ that has differentiated normally;
  - Disruption: a structural defect resulting from the destruction of a structure or organ that had formed normally before the insult.
- Malformation and dysplasia affect the intrinsic structure and cut across a wide range of defects which can be monogenetic (Achondroplasia) or chromosomal (Trisomies, Prader Willi syndrome) in aetiology.
- It can also be from nutritional deficiency (Neural tube defects) or of teratogenic origin (Foetal alcohol syndrome).
- Deformation and disruption are secondary effects that result from forces generated that are extrinsic to the affected tissue or organ.
- When several malformations occur in a single individual, they are classified as:
  - Syndrome: a pattern of multiple anomalies that are related by pathophysiology and result from a common defined aetiology;
  - Sequence: consists of multiple malformations that are caused by a single event that can have many aetiologies;
  - Association: a nonrandom collection of malformations where there is an unclear relationship among the malformations such that they do not fit into the criteria for a syndrome or sequence.

Aetiopathogenesis/risk factors

- Genetic (30-40%): chromosomal abnormalities make up 6% while single gene disorders account for 25%. In 50% the cause is unknown.
- Environmental (5-10%).
- Multifactorial (20-30%).
- Early foetal life (between the 3rd and 8th week of G.A.) is a vital period of life for the normal development of organs; any insult to the foetus within this period may result in birth defects.
- Risk factors for congenital malformation include:
  - Maternal factors: poor antenatal care, an abnormally shaped uterus, reduced amniotic fluid volume, irradiation, smoking or alcohol intake, infections, poor nutritional status or medication use during pregnancy;

- Foetal factors: low birth weight;
- Consanguinity.

Diagnosis

History

- Pedigree or family history to assess the inheritance pattern.
- Perinatal history of recurrent miscarriages may be a pointer to a familial chromosomal disorder. Oligohydramnios may relate to deformation or disruption.
- Maternal exposure to teratogenic drugs/chemicals such as methyl mercury and ethanol is a potential cause of microcephaly. The natural history of the defect is important.
- Malformation syndromes caused by chromosomal aneuploidy or aneusomy and single gene pleiotropic disorders are usually static.
- In contrast, disorders that cause dysmorphic features by the mechanism of metabolic derangement (e.g. Hunter syndrome, Sanfilippo syndrome) are either mild or inapparent at birth and progress relentlessly, causing the deterioration of the patient over time.

Physical examination

- The size, structure and number of various body parts e.g. microcephaly and brachycephaly of Down syndrome. Eye position, shape and number (e.g. Hypo/hypertelorism, cyclopia).

Laboratory investigations

- Imaging: A full skeletal survey may be needed. CT, MRI, echocardiography and renal ultrasonography are helpful tools.
- Cytogenetics with Giemsa-banded peripheral leucocyte karyotype (or chromosome analysis) is the gold standard.
- A whole genome assay by an array of comparative genomic hybridization (CGH) is useful for chromosome imbalances.
- Molecular testing for mutations that cause pleiotropic developmental anomaly syndromes is available for many disorders.
- A general metabolic screen should be performed. Some metabolic abnormalities of the foetus can cause malformations, e.g. a defect in the sterol delta-7-reductase gene in Smith-Lemli-Opitz syndrome.
- These findings can be organized by their specificity into potential pathophysiologic processes.
- The features can be manually matched against those featured in the index of standard texts or a computerized database.

- Two approaches to the diagnosis of the dysmorphic child are typically employed:
  - The pattern recognition approach;
  - The systematic genetic-mechanism approach.

Counselling

- This is a very important and sensitive component of the management of a dysmorphic child.
- Much of the success of management is dependent on good counselling.
- This is aimed at enlightening the parents and addressing some of the social and medical concerns they may have.
- Parents are usually concerned about the possibility of the next baby having similar problems.
- Many of the environmental as well as genetic effects can be prevented through genetic counselling and preconception planning.

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11.6 Genetic Counselling

- The WHO defines Genetic counselling as the process through which knowledge about the genetic aspects of illnesses is shared by trained professionals with those who are at an increased risk of either having a heritable disorder or of passing it onto their unborn offspring.
- Genetic counselling provides accurate information to individuals about the realities of genetic disorders, their natural histories with their attendant impact on the paediatric population, the family and community at large as well as elucidating the risk and benefits of all options available for the management of these disorders e.g. by way of prenatal diagnosis.
- It provides adequate care for already affected children and the necessary support for individuals to cope with the decisions they make.
- In paediatric practice the parents of an affected child are usually counselled.
- However, the siblings and relatives of an affected child or an older child who is affected may also be counselled.
- Genetic counselling should be carried out by a physician, nurse, social worker or any person interested in counselling with a proper understanding of the genetic mechanisms and who is trained in counselling skills.
- The counsellor is expected to present the information in a nondirective manner.
- This process of genetic counselling can be divided into diagnostic (the actual estimation of risk) and supportive aspects.
- Genetic counselling can occur before conception (i.e. when one or both of the parents are carriers of a certain trait) through to adulthood (for adult onset genetic conditions, such as Huntington's disease or hereditary cancer syndromes).

Indications for Genetic Counselling

There are several indications for genetic counselling which include:

- Maternal age ≥35 years;
- Paternal age ≥50;
- A known or suspected hereditary disease in a patient or family;
- A previous child with or a family history of Congenital abnormality, Dysmorphology, Mental retardation, Isolated birth

defect, Metabolic disorder, Chromosome abnormality, Single-gene disorder;
- Consanguinity;
- Exposure to a teratogen during pregnancy;
- Repeated pregnancy loss or infertility;
- Abnormal foetal ultrasonography;
- Abnormal foetal karyotype.

Objectives of Genetic Counselling

- To make a precise diagnosis (if possible), explaining the cause and course of the disease and treatment options, if available.
- To reduce anxiety and guilt.
- Providing risk figures for future offspring/relatives based on genetic facts.
- To provide information about prenatal diagnostic possibilities and the risks involved.
- To help the couples make decisions by non-directive counselling.

Importance of genetic counselling in Paediatrics

- The incidence of genetic disorders is high.
- Most genetic disorders are obvious in childhood.
- These genetic disorders contribute in no small measure to paediatric morbidity and mortality.
- The majority of chronic diseases in children have an obvious genetic susceptibility.
- Due to the financial, social and economic implications of the chronicity of these genetic diseases, child abandonment has been on the increase in most developing countries.

Essentials of Genetic Counselling

- A precise diagnosis based on a careful and detailed family history, constructing a pedigree that lists the patient's relatives with their sex, age, and state of health, up to and including third degree relatives, clinical examination and diagnostic investigations.
- Gather information from hospital records about affected individuals and, in some cases, about other family members.
- Documenting prenatal, pregnancy, and delivery histories.

- Reviewing the latest available medical, laboratory, and genetic information concerning the disorder.
- Calculating the risk of recurrence based on the inheritance pattern, empiric risk figures or laboratory tests.
- Providing non-directive counselling with good communication with easy to understand language, maintaining truth and confidentiality.
- Giving the family information about support groups.
- Providing the family with information as it becomes available.

Steps to Effective Genetic Counselling

- Six steps represented by the acronym **GATHER** which stands for **G**–Greet, **A**–Ask, **T**–Tell, **H**–Help, **E**–explain and **R**–Return should be employed during a counselling session.

Basics of an ideal genetic counselling session

Counselling must include information on the following:

- The specific condition or conditions;
- Knowledge of the diagnosis of the particular condition;
- Natural history of the condition;
- Genetic aspects of the condition and recurrence risk;
- Prenatal diagnosis and prevention;
- Therapies and referral;
- Support groups and follow up.

Ethical issues

- Ethical principles which govern a counsellor include (i) Respect for autonomy or the patient's right to information; (ii) Beneficence; (iii) Non-maleficence; and (iv) Justice.
- It is therefore expected of a counsellor to present the available information to the client truthfully, completely and without bias and in a non-directive manner.

Psychosocial issues

- The client may pass through four different phases of the coping process: (i) initial shock and denial; (ii) subsequent anger and guilt; (iii) anxiety and depression; and (iv) the phase of acceptance.

- Coping with their reaction requires patience, empathy and tact on the part of the Counsellor and can be quite challenging.

Challenges of genetic counselling in Nigeria

- Paucity of health care professionals with specialized training in genetic counselling.
- Lack of resources and technological advancement for genetic testing.
- The poor keeping of hospital records making the retrieval of case notes and relevant data difficult.
- Laws and traditional beliefs prohibiting abortion even after prenatal diagnosis of a genetic defect.
- Poverty which imparts negatively on the health seeking behaviour of the people.

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11.7 Anaemia of prematurity

- Anaemia of prematurity (AOP) refers to a form of anaemia affecting preterm infants due to an exaggeration of the normal physiologic anaemia.

Epidemiology

- The risk of AOP is inversely related to gestational maturity and birth weight. About half of infants of less than 32 weeks gestation develop AOP.
- Race and sex have no influence on the incidence of AOP.

Aetiology

- Repeated phlebotomy for blood tests.
- Shortened Red blood cell (RBC) survival.
- Rapid growth.
- Physiologic effects of the transition from foetal (Low PaO_2 and Haemoglobin saturation) to neonatal life (High PaO_2 and Haemoglobin saturation).
- Vitamin E deficiency which is common in preterm infants.

Pathophysiology

- In the 8- to 10-week period immediately following birth, there is a gradual and progressive decline in Haemoglobin (Hb) concentration in both term and preterm infants.
- In term infants, the decline reaches a nadir of approximately 11 to 12 g/dl and is referred to as early anaemia.
- This normal process does not result in signs of illness and does not require any treatment.
- It is a physiologic condition believed to be related to several factors, foremost of which may be the increase in tissue oxygenation experienced at birth when switching from dependency on the placenta to dependency on the lungs for oxygen exchange.
- Other factors thought to contribute to the postnatal decline in Hb include rapid body growth, shortened RBC lifespan, and low blood erythropoietin (EPO) levels.
- Even in the absence of iatrogenic laboratory phlebotomy loss, preterm infants experience more rapid and severe decreases in Hb

levels than term infants (often to 7 to 8 g/dl), with the lowest levels observed among the smallest, least mature infants.

- It is uncertain whether the postnatal fall in haemoglobin level experienced by preterm infants is merely an exaggerated, albeit physiologic, form of the early anaemia observed among term infants or a pathologic condition (e.g., inadequate protein, iron, and vitamin intakes).
- Likely the anaemia of prematurity represents several mechanisms occurring simultaneously, with some being physiologic and others pathologic.

Clinical Features

- Some preterm infants seem to tolerate Hb levels of 6 to 7 g/dl without apparent difficulty; others do not.
- Because the consequences of anaemia on tissue oxygenation are so diverse, it can be difficult to document such effects definitively as pathologic.
- Some studies have reported that Hb levels of 6 to 8 g/dl in preterm infants are associated with poor weight gain, feeding problems, decreased activity, apnoea, pathologically increased heart and respiratory rates, and increased oxygen consumption.

Laboratory Investigation

- Haemoglobin levels <7-10 g/dl.
- Reticulocyte and erythropoietin levels are decreased.

Treatment

- Blood transfusion: Packed RBC transfusion of 10-20 ml/kg is given at a rate of 2-3 mls/kg/hr.
- Recombinant human erythropoietin (rHuEPO) is given at a dose of 100-500 units/kg/dose every 1-2 days for 10-21 days. The response to rHuEPO takes up to 8 days to 2 weeks and the higher dosages lead to higher Hb.
- Iron therapy: Oral iron at a dose of 3-6 mg/kg/day in 1-3 divided doses.

Prevention

- Reduction of blood loss during phlebotomy.
- Laboratory blood testing using bedside devices (point-of-care testing) reduces blood loss.
- In very low birth weight preterm infants, delayed clamping of the umbilical cord with the infant held below the level of the placenta may enhance placental infant transfusion and reduce neonatal transfusion needs.

Prognosis

- AOP spontaneously resolves within 3-6 months of birth in many preterms. However, in some cases medical intervention is required.

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11.8 ABO incompatibility

- ABO incompatibility has been the most common cause of haemolytic disease of the newborn (HDN) since the introduction of Rh immune globulin but, however, results in a milder disease than Rh incompatibility.
- About 15% of live births are at risk of ABO incompatibility with only 0.3-2.2% manifesting the disease.

Epidemiology

- ABO incompatibility is more common in blacks. There is no known gender predilection.
- It occurs in 20-25% of pregnancies but HDN develops in only 10% of such offspring.
- The incidence varies from place to place.
- In Zambia, Kapasa found an incidence of 49% with only 3.5% having HDN.
- In South West Nigeria, Oseni and colleagues found an incidence of ABO incompatibility to be 38% while Ella et al. in Northern Nigeria found the incidence of ABO HDN to be <10%.

Pathogenesis

- The cause is the reaction of maternal anti-A or anti-B antibodies to the A or B antigen on the red blood cells of the foetus or newborn causing haemolysis.
- It is usually seen only in type A or B infants born to type O mothers because these mothers, though having naturally occurring antibodies of the IgM class, can make anti-A or anti-B antibodies of the immunoglobulin G (IgG) class, which cross the placenta.
- However, mothers of type A or B usually make anti-A or anti-B antibodies of the immunoglobulin M (IgM) class, which do not cross the placenta.
- There are some modulating factors to ABO incompatibility;
    - Foetal red blood cell (RBC) surface A and B antigens are not fully developed during gestation and thus there are smaller numbers of antigenic sites on foetal RBC;
    - ABO antigens are expressed on many foetal cells thus limiting the amount of IgG antibodies available to attack foetal RBCs.

- Low antigenicity of the ABO factors in the foetus and newborn infant may account for the low incidence of severe ABO haemolytic disease.

Clinical features

- Approximately 50% of cases occur in firstborn infants.
- Most cases are mild, rarely it may become severe and symptoms and signs of kernicterus develop rapidly.
- Jaundice may be the only clinical manifestation and appears within the first 24 hours of life.
- Pallor is not present and hydrops foetalis is extremely rare.
- The liver and spleen may be mildly enlarged.

Diagnosis

- This is based on the presence of ABO incompatibility through blood grouping, a weak to moderate positive direct Coombs test result and spherocytes in the blood smear which may suggest the presence of hereditary spherocytosis.
- Hyperbilirubinaemia is present. Unconjugated serum bilirubin may be as high as 20 mg/dl or more.
- Haemoglobin level is usually normal but may be as low as 10-12 g/dl.
- Reticulocytes may be increased to 10-15% with polychromasia and increased nucleated RBCs.

Treatment

- Phototherapy may be effective in lowering serum bilirubin levels.
- Exchange blood transfusion with type O blood of the same Rh type as the infant is done in rare severe cases.
- IV gamma globulin to reduce haemolysis can be considered.
- Some infants may require transfusion of packed RBCs at several weeks of age because of slowly progressive anaemia.

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11.9 Rhesus Incompatibility

- Rhesus (Rh) incompatibility is a condition that occurs when a woman with the Rh negative blood type is exposed to Rh positive blood cells, leading to the development of the Rhesus antibody and sensitization.
- The Rh factor is a red blood cell surface antigen.
- The Rhesus antigen system consists of C, D and E antigens. More than 90% of cases are due to the "D" antigen.
- Despite the introduction and widespread use of RhD immunoglobulin, for the prevention of haemolytic disease of the newborn, Rh isoimmunization remains a significant problem in perinatology.

Epidemiology

- Rhesus isoimmunization is three times more common in Caucasians than in Blacks.
- Incidence has been noted to be generally low due to the following reasons
  - About 55% of Rh positive fathers are heterozygous and thus may have Rh negative offspring;
  - Foetal to maternal transfusion occurs in only about 50% of pregnant women;
  - Variability in the capacity of Rh negative women to form antibodies even after an adequate antigen challenge.
- In Iraq, a frequency of 4.5% was noted in 2nd pregnancies. This progressively increased to 45.4% in 5th pregnancies.
- In 2000, a review of US birth certificates showed that 6.8% of live births are complicated by Rhesus sensitization.
- In Southeast Nigeria, Okeke et al. found a prevalence of rhesus negativity among pregnant women to be 4.5%.
- Only 16-17% of Rh negative women exposed to Rh-positive foetal blood develop Rh antibodies (become alloimmunized) if anti-D immunoglobulin is not administered.

Pathogenesis

- When Rh positive blood is infused into an Rh-negative woman (usually >1 ml) through the transfusion of Rh positive blood, foetomaternal haemorrhage in pregnancy, spontaneous or induced

abortions, abdominal trauma, invasive obstetric procedures or normal delivery; antibody formation against the D-antigen may be induced in the unsensitized mother.
- Once sensitization has taken place, smaller doses of antigen are needed to stimulate a significant rise in antibody titre.
- The IgM antibody is formed initially but is later replaced by the IgG antibody that readily crosses the placenta thus causing the various clinical manifestations.

Clinical manifestations

- A wide spectrum of haemolytic disease occurs in affected infants.
- Severity may range from only laboratory evidence of mild haemolysis to severe anaemia with compensatory hyperplasia of the erythropoietic tissue leading to massive hepatosplenomegaly. Anaemia results in pallor, cardiac decompensation (cardiomegaly and respiratory distress), anarsaca and circulatory collapse.
- Hydrops foetalis–defined as excessive abnormal fluid in two or more foetal compartments (skin, pleural, pericardial, placenta, peritoneum, skin or amniotic fluid) frequently results in death in utero or shortly after birth. Hydrops is related to hepatic dysfunction (which results in reduced albumin concentration), and heart failure (oedema and ascites).
- Birth asphyxia (possibly secondary to pulmonary oedema, bilateral pleural effusion), purpura or petechial haemorrhages (due to reduced platelets or DIC) may be noted.
- Jaundice is generally evident on the 1st day of life and the risk of kernicterus is greater compared to non-haemolytic causes of hyperbilirubinaemia.
- Hypoglycaemia is present and results from hyperinsulinism and hypertrophy of pancreatic islet cells.

Diagnosis

- Diagnosis requires a demonstration of Rh blood group incompatibility and the corresponding antibody bound to the infant's RBCs.

Antenatal diagnosis

- History suggestive of possible sensitization.
- Maternal titre of IgG antibody for the D antigen at 12-16 weeks, 28-32 weeks, and 36 weeks.

- Ultrasound revealing organ enlargement and bowel oedema suggests hydrops.
- Peak systolic middle cerebral artery Doppler velocity to detect foetal anaemia.
- Amniocentesis to assess for bilirubin in the amniotic fluid.
- Kleihauer-Betke's test for the measurement of foetal RBC in maternal blood.

Postnatal diagnosis

Immediately after birth, cord blood should be collected and examined for:

- Blood group and Rhesus type, cross-match with the donor blood. The direct antiglobulin (Coombs) test is positive;
- Full blood count will usually show reduced haematocrit, increased reticulocyte count, thrombocytopenia in most cases, normal or elevated total WBC. A peripheral blood smear typically shows polychromasia and a marked increase in nucleated RBCs;
- Serum direct and total bilirubin. Baseline values are usually obtained and serial monitoring is done. A cord blood bilirubin >4 mg/dl indicates severe isoimmunization. Albumin concentrations and blood glucose level are checked.

Treatment

- Goals include preventing intrauterine death from severe anaemia and avoiding neurotoxicity from hyperbilirubinaemia.
- In utero transfusion of packed cells has improved the survival of severely affected foetuses.
- Fresh group O, Rh negative blood cross-matched against the mother's serum should be available for exchange transfusion in live newborns.
- For those with milder forms of anaemia and hyperbilirubinaemia, transfusion of compatible RBCs and phototherapy respectively may suffice.
- IV IG at a dose of 0.5-1 g/kg in a single or multiple dose has been advocated.

Prevention

- The anti-D globulin given to Rh negative mothers at 28-32 weeks and within 72 hours after birth, miscarriage, ectopic pregnancy or abortions protects against sensitization.

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11.10 Neonatal Screening

- Neonatal screening is a public health program designed to screen infants following birth for treatable conditions which may not be clinically evident in the newborn period.
- Some of these conditions only become detectable when irreversible damage has been done, while others manifest as sudden death.
- It looks for developmental, genetic and metabolic disorders in newborns to allow intervention before symptoms develop.
- Screening programs are run by state or national governing bodies to detect these disorders.
- Each year, millions of babies in the United States are routinely screened, using a few drops of blood from their heels for certain genetic, endocrine and metabolic disorders and are also tested for hearing loss, prior to discharge from a hospital or birthing centre.
- Neonatal screening tests do not diagnose illnesses but show which babies need additional testing to confirm or rule out a disease.
- Most of these tests measure metabolites and enzyme activity in whole blood collected in special filter paper.

Historical Background

- Robert Guthrie is credited for pioneering the earliest screening for phenylketonuria in the United States in the late 1960s. Phenylketonuria is a metabolic condition in which the inability to degrade the essential amino acid phenylalanine can cause irreversible mental retardation unless detected early.
- Congenital hypothyroidism was widely added in the 1970s. Guthrie and colleagues further developed bacterial inhibition assays for the detection of maple syrup urine disease and classic galactosaemia. Cystic fibrosis screening started in 1981.
- The development of tandem mass spectrometry screening in the early 1990s led to a large expansion of potentially detectable congenital metabolic diseases that can be identified by characteristic patterns of amino acids and acylcarnitines. SCID was added in 2008.

Neonatal Screening Criteria

- There are usually some criteria that screening programs should meet before being used as a public health measure for early neonatal screening:
- Having an acceptable treatment protocol in place that changes the outcome of patients diagnosed early.
- Having an understanding of the condition's natural history.
- Having an understanding about who will be treated as a patient.
- A screening test that is reliable for both affected and unaffected patients and is acceptable to the public.
- The American College of Medical Genetics recommends a uniform panel of disease that all infants born in every state should be screened for. Prior to this, babies born in different states had received different levels of screening.
- Since the "Newborn Screening Saves Lives Act of 2007" was signed into law by President George Bush, there has been increased awareness among parents, health professionals, and the public on testing newborns to identify certain disorders.
- Other developed economies have followed a similar path, however, developing countries like ours are yet to enact the enabling law to enhance newborn screening.

Disorders that can be detected with neonatal screening and their techniques

- Newborn screening tests are most commonly done from whole blood samples collected on specially designed filter paper. Each sample is attached to a form with information about the neonate and his/her parents. Samples are best taken after 24 hours to 7 days of life.
- Some disorders that can be detected include amino acid metabolic disorders, urea cycle disorders, biotinidase deficiency, HIV, congenital adrenal hyperplasia, galactosaemia, Duchenne muscular dystrophy, glucose 6 phosphate dehydrogenase deficiency, Lysosomal disorders like Gauchers, Pompes disease, organic acid metabolic disorders like propionic acidaemias, sickle cell disease and other haemoglobinopathies.
- Tandem mass spectrometry is a technically advanced method where many compounds are initially separated by molecular weight. It identifies characteristic patterns of amino acids and acylcarnitines from a single dried blood spot.

- Results however can be complicated by prematurity and neonatal illnesses which have effects on blood metabolites. A number of false positive results are therefore obtained.
- It also helps to screen for other fatty acid oxidation disorders like medium chain acyl co A dehydrogenase deficiency which can actually cause Sudden Infant Death Syndrome (SIDS).
- Endocrinopathies like Congenital Adrenal Hyperplasia are detected by elevated 17 hydroxyprogesterone using enzyme linked immunosorbent assay (ELISA).
- Congenital hypothyroidism is detected by measuring thyroxine (T4) and TSH levels.
- Haemoglobinopathies are detected by isoelectric focusing which reveals abnormal patterns showing many abnormal types of haemoglobin.
- Screening for cystic fibrosis (CF) is by measuring immunoreactive trypsinogen in a dried blood spot because measuring the concentration of sodium and chloride in sweat is not possible in the first week of life.
- For Duchenne muscular dystrophy, creatine kinase levels are elevated.
- Neonatal screening for SCID is not applied worldwide because immunologists and stem cell transplants are needed, which are scarce. The test involves detecting T cell excision circles using real time PCR.
- Urine samples are collected on the 21st day of life. Maple syrup urine disease can be detected using this method.
- Audiometry and pulse oximetry are also employed to detect a congenital hearing defect and congenital heart defects respectively.

Limitations

Every disease to be screened has to meet the criteria outlined earlier.

- Unavailability of treatment as seen in haemoglobinopathies especially in developing countries could hinder screening programs.
- Lack of screening materials in resource-poor countries.
- Policy and enabling laws are not on the ground to enhance newborn screening.
- Public awareness, sociocultural and religious inclinations make screening difficult.

- It is argued that mass spectrometry (MS) is very expensive and time consuming and only gives screening and not confirmatory results (done by enzyme assay, DNA tests).
- Effective follow up and treatment may not be available and false positive results may cause some psychological trauma to parents at a time they are supposed to be bonding with their babies.

Conclusion

- Newborn screening identifies conditions that can affect a child's long-term health or survival. Early detection, diagnosis and intervention can prevent death or disability and enable children to reach their full potential.

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SECTION 12

ENDOCRINOLOGY

IBEKWE, M.

12.1 Evaluation of a child for the presence of an endocrine disorder

Introduction

- The endocrine system consists of several glands, all in different parts of the body that secrete hormones. This system regulates growth and development and the maintenance of constants of the internal milieu.
- The endocrine system is controlled by the higher centres–mostly by the pituitary and the hypothalamus. Hormones are regulated in a feedback loop, so that the production of a hormone is controlled by its effect.
- In evaluating the possibility of an endocrine disorder, first and foremost a good history and physical examination are very important.

History

- The customary paediatric pattern of the history-taking method is used; however in suspecting an endocrine problem emphasis is laid on the following:
- Pregnancy and delivery, gestational age, medications taken by the mother, any complications and birth weight;
- Condition immediately after delivery such as Apgar scores, jaundice, developmental assessment, any complications like the use of oxygen support, treatment of hypoglycaemia and electrolyte imbalance;
- Developmental history should include the developmental milestones;

- Family history should include: if there is a polygamous/ monogamous setting, the father's occupation and the mother's educational attainment, the number of siblings, their sex and age including their height and weight, any sibling deaths and cause of death, the height and weight of the parents.
- Ask about age at menarche of the mother and the age the father had voice breaking or started shaving.
- The social life and interaction of the patient; school performance and friends.
- The dietary history will be included if the child eats an appropriate balanced diet for his/her age. If exclusive breastfeeding was done and how long breast feeding lasted.
- If the child has an aversion to feeding or is selective of certain foods.
- Enquire about past medical conditions like surgeries, medication, hospitalization, and if there are head injuries.
- The physical activity of the patient, if he/she has physical play or watches TV. The number of hours spent watching TV per day for obese children.

Physical Examination

- This is done using the standard methods however emphasis will be placed on the following:
- Anthropometry–infants should be weighed naked and children with minimal clothing using accurately calibrated scales. Weight is recorded to the nearest 0.1 kg.
- Height is measured to the last completed millimetre, supine length is for children under 2 years or those unable to stand using an infant measuring board.
- Standing height is done for older children using a stadiometer.
- The height and weight values should be plotted on reference standard charts such as the WHO centile.
- Also, the use of the estimated average height or weight can be employed using the formulae available.
- The body mass index (BMI) should be derived from weight and height = weight in kg ÷ height in m^2.
- Determination of the arm span and upper-to-lower segment ratio is useful in evaluating those with short stature (achondroplasia, delayed puberty, hypogonadism).

- In suspicion of syndromes it is important to check the HEENT–the head, eyes, ears, nose and throat. Look for midline defects like cleft lip or palate, a central incisor might point to hypopituitarism.
- Examine for voice change and the presence of beards.
- Examine the neck for goitre checking for changes in size, nodules, tenderness and bruit.
- Check for Acanthosis nigricans at the back of the neck.
- Assessment for the development of secondary sexual characteristics.
- Examine the breast and pubic hair for girls.
- For boys, it is the pubic hair and genital development. The genital examination of boys includes the stretched penile length/width and the testicular volume using a disposable ruler and the orchidometer respectively.
- The changes observed in pubertal development are graded according to the Tanner staging method.
- In a musculoskeletal examination–for skin, check for colour, café au lait spots noting the shape, type and number.
- Hair distribution, amount and changes, the presence of striae and fat distribution.
- Check for limb deformity such as Madelung deformity in short stature.
- Others include the presence of oedema.
- Assess for the presence of lymph nodes, assess visual fields and check for sense of smell especially for boys with delayed puberty to rule out Kallman's syndrome.
- Perform the Chvostek or the Trousseau sign to exclude hypocalcaemia.
- Bedside urinalysis can be done checking for glucose level or ketones in assessment for diabetes mellitus.

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12.2 Hypoglycaemia

Definition

- Plasma glucose conc. ≤40 mg/dL (2.22 mM) regardless of age.
- Physiologically, hypoglycaemia is said to occur when glucose delivery is inadequate to meet glucose demand and can occur over a range of glucose concentrations.
- In healthy individuals, maintenance of a normal plasma glucose concentration depends upon:
  - A normal endocrine system;
  - Functionally intact enzymes for glycogenolysis, glycogen synthesis, glycolysis, gluconeogenesis;
  - An adequate supply of endogenous fat, glycogen, and potential gluconeogenic substrates (e.g., amino acids, glycerol, and lactate).

Glucose homeostasis

- Gestation; maternal glucose is transported across the placenta to meet a substantial proportion of the energy needs of the foetus.
- At birth with the clamping of the umbilical cord, the infant is challenged to control his blood glucose concentration which reaches a nadir at the first 2 hours following birth.
- However, by four to six hours of life, in most infants, the plasma glucose concentration is stabilized or is increasing.
- Insulin secretion plays a central role in glucose homeostasis and is affected by a number of factors, the most important of which is the plasma glucose concentration.
- Other hormones involved in glucose homeostasis include glucagon, growth hormone, cortisol, and catecholamines.

Symptoms of hypoglycaemia

- It varies with age:

Neonate	Older child
Autonomic	Autonomic
Pallor	Anxiety
Sweating	Palpitations
Tachypnoea	Tremor
Neuroglycopaenic	Neuroglycopaenic

Jitteriness	Hunger and abdominal pains
Apnoea	Nausea and vomiting
Hypotonia	Headache
Feeding problems	Weakness and dizziness
Irritability	Blurred vision
Abnormal cry	Irritability
Convulsions	Confusion
Coma	Convulsions
	Coma

Management of hypoglycaemia

Immediate management

- The immediate management of the infant or child with hypoglycaemia involves **obtaining critical blood samples and administering parenteral glucose.**
- In critical blood samples, obtain venous blood, about 5-10 mls using fluoride bottles, or heparin bottles.
- Quickly transport to the lab for investigations.
- Blood tests done include: plasma glucose, FFA, lactate, growth hormone, c-peptide, insulin, and cortisol.
- Others are: electrolytes, LFT, metabolic screening, toxicology screening.
- Normalize blood glucose by administering intravenously 2 ml/kg of 10% Dextrose water IV push, given slowly at 2-3 mls/min repeated as needed.

Causes of Hypoglycaemia

- Hormone Deficiencies (15%): Growth hormone deficiency, Cortisol Insufficiency.
- Hormone excess (hyperinsulinaemia), B cell hyperplasia (neisidioblastosis), B cell adenoma, Beckwith-Wiedemann syndrome.
- Metabolic diseases (inborn errors of metabolism).
- Insulin excess as seen in Adenoma.
- Exogenous insulin.
- Ingestions of alcohol.
- Oral hypoglycaemics.

Diagnostic clues will include

- Short stature as seen in growth hormone deficiency.
- Midline defects and micropenis are seen in pituitary problems.
- Poor weight-gain as seen in Cortisol deficiency.
- Adrenal defects present with Pigmentations and Ambiguous genitalia.

History

- The history in a hypoglycaemic child should include a thorough exploration of the past medical history (including perinatal history, seizure disorders), details of the acute event as well as previous episodes, and family history.
- Age at the onset of symptoms?
- Inborn errors of metabolism and congenital hormone deficiencies usually present in the neonatal period or the first two years of life.
- Dietary history. Was the child in the fed or fasting condition at the time of hypoglycaemia?
- Do symptoms worsen with the ingestion of milk, galactose, protein?
- Any ingestion of alcohol, spirits?
- Intake of oral drugs like aspirin, quinine.
- Family history. Some inborn errors of metabolism, and hormonal problems run in families, hyperinsulinism.

Physical exams

- Check the height and weight status. Also check for:
- Midline facial defects (e.g., a single central incisor, optic nerve hypoplasia, cleft lip or palate) and microphallus or undescended testicles in boys may indicate hypopituitarism and/or growth hormone deficiency.
- Macrosomia, hepatosplenomegaly, and umbilical hernia may indicate Beckwith-Wiedemann syndrome.
- Whereas hepatosplenomegaly and hypotonia may indicate a glycogen storage disease, defects in gluconeogenesis, galactosaemia, or hereditary fructose intolerance.

Laboratory investigations

- Samples for studies must be obtained when the patient actually is hypoglycaemic.
- Endocrine evaluation: this will include urine and serum ketones, insulin and c-peptide levels, cortisol and growth hormone.
- Metabolic disease evaluation will include electrolytes, glucose, lactate and ammonia.

Long-term management

- Once diagnosis of the underlying cause has been made specific additional therapy can be instituted.

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12.3 Diabetes Mellitus

Definition

- Diabetes mellitus can be defined as a group of metabolic diseases of multiple aetiologies, characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both.
- Diabetes mellitus is the most common endocrine disease in childhood and adolescence.
- The American Diabetes Association (ADA) 28 and the World Health Organization (WHO)[3] expert committee on the classification and diagnosis of diabetes have recommended an aetiological classification of diabetes which includes:
  - Type 1 diabetes mellitus which results from β-cell destruction usually leading to absolute insulin deficiency due to immune mediated beta cell destruction and idiopathic beta cell destruction;
  - Type 2 diabetes mellitus resulting from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance;
  - Other specific types which include those due to genetic defects of β-cell function and insulin action, diseases of the exocrine pancreas, endocrinopathies, drug- or chemical-induced, infections;
  - Gestational diabetes, uncommon forms of immune-mediated diabetes, and other genetic syndromes sometimes associated with diabetes;
  - Neonatal diabetes mellitus.

Type I diabetes

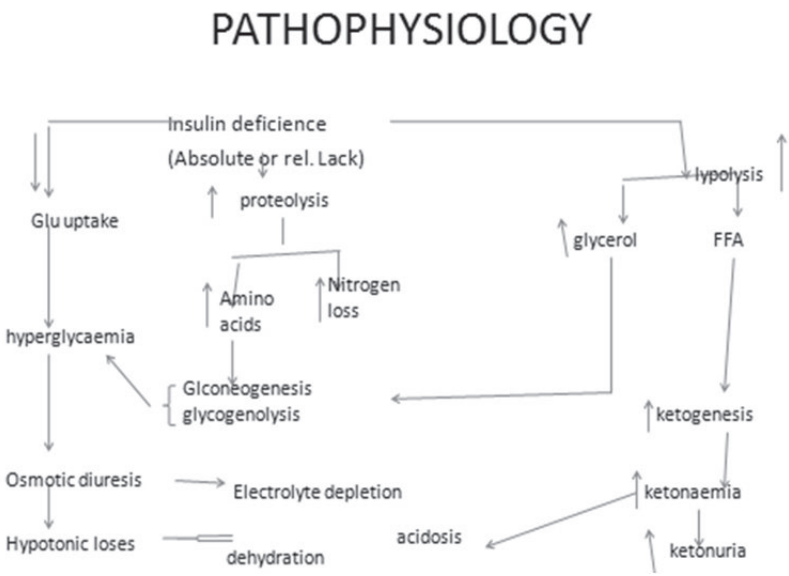
- It is the major type of diabetes in youth and accounts for over 85% of all diabetes in children and adolescents.
- It is characterized by the destruction of pancreatic beta cells, culminating in absolute insulin deficiency.
- This lack of insulin leads to hyperglycaemia and manifests with acute onset of the classic symptoms of diabetes which include: polyuria, polydipsia, polyphagia, weight loss, lethargy and if not diagnosed and treated, leads to death from ketoacidosis (which is a state of metabolic dysregulation characterized by nausea, vomiting

abdominal pain, Kussmaul breathing and altered states of consciousness).
- Therefore, in this patient there is dependence on exogenous insulin to prevent ketosis and preserve life.

Epidemiology/Aetiopathogenesis

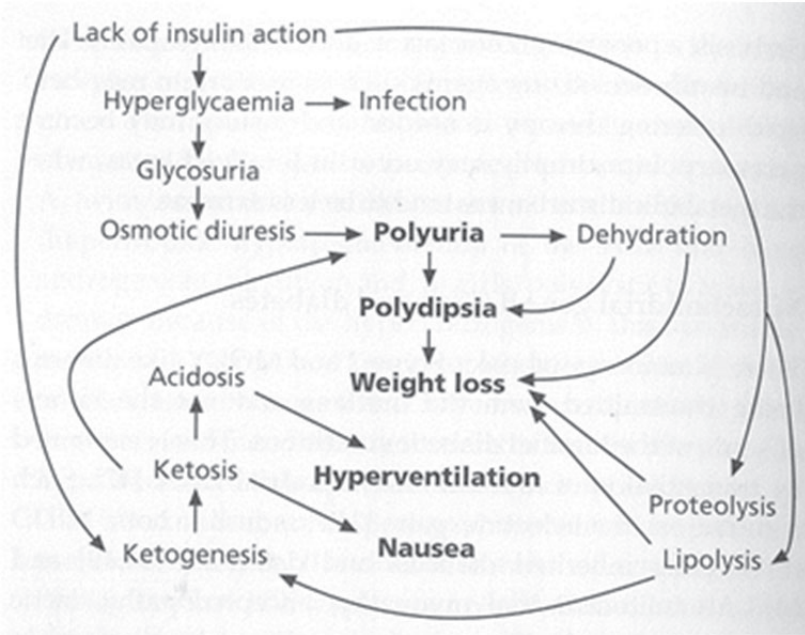
- Age and gender–age of presentation of childhood onset type 1 diabetes has a bimodal distribution with one peak at 4 to 6 years of age and a second in early puberty (10 to 14 years of age).
- The incidence of childhood type 1 diabetes varies worldwide, ranging from 0.1 to 37 per 100,000 children younger than the age of 15 years.
- In the United States, the reported incidence is 15 to 17 per 100,000 children.
- Type 1 diabetes mellitus is due to an autoimmune reaction directed against the pancreatic beta cells.
- It is a chronic, T cell-mediated autoimmune disease that results in the destruction of the pancreatic islets.
- What does this mean? An individual inherits a combination of genes that determines their risk.
- This genetic predisposition is then triggered or dampened by environmental factors.
- Diabetic genetic predisposition to Type 1 DM is mostly related to human leukocyte antigens (HLAs) coded on chromosome 6.
- In African people, Type 1 diabetes mellitus is associated with HLA susceptibility loci particularly HLA-DR3, HLA-DR4, and HLA-DR3/DR4 heterozygosity, similar to white populations.
- Environmental factors influence the expression of Type 1 diabetes mellitus in genetically susceptible individuals.
- They appear to trigger an immune response that ultimately causes the destruction of the insulin-producing pancreatic beta cells.
- These environmental factors include infectious agents, dietary factors, environmental toxins and sanitation.
- Infectious agents include viral infections like mumps, rubella and Coxsackie B.
- Dietary factors such as the early introduction of cow's milk, the ingestion of smoked food, and vitamin D deficiency.

- When a genetically susceptible individual is exposed to these environmental factors it may trigger the production of autoantibodies.
- The autoantibodies primarily associated with Type 1 diabetes mellitus include insulin autoantibodies (IAA)–islet cell antibodies, glutamic acid decarboxylase, (ICA512 (IA-2), GAD) and zinc transporter.



Symptoms of uncontrolled diabetes

- The classic symptoms due to hyperglycaemia include **polyuria** (including also **nocturia, secondary enuresis**).
- As glucose is unable to move into the cells, a system of body starvation occurs.
- The patient is **lethargic**. There is increased **weight loss** despite **increased appetite**.
- There is **dehydration** with resultant **increased thirst,** due to on-going osmotic diuresis.
- If left untreated, it can progress to a state of emergency known as diabetic ketoacidosis or death.



Diagnosis

- Fasting plasma glucose ≥126 mg/dL (7 mmol/L). Fasting is defined as no caloric intake for at least eight hours.
- Symptoms of hyperglycaemia and a random venous plasma glucose ≥200 mg/dL (11.1 mmol/L).
- Glycated haemoglobin (A1C) ≥ 6.5 per cent (using an assay that is certified by the National Glycohaemoglobin Standardization Program).

Treatment

- Optimal treatment is to restore insulin in a physiological way through the administration of exogenous insulin.
- Successful management of children with diabetes includes the balancing of strict glycaemic control, which reduces the risk of long-term sequelae, and avoidance of severe hypoglycaemia, which is more likely with stricter control.

- Insulin therapy comes in a regimen of "Fixed mixture, Basal bolus or Insulin pumps".
- Regular follow-up visits should be established with the diabetes management team and the entire family/parents of the diabetic child.
- Thorough education and counselling are of paramount importance in diabetic management as the condition is a chronic lifelong disease.
- The classical triad, "Insulin, Food and Physical activity" are essential for optimal glycaemic control in children and adolescents with type 1 diabetes mellitus.
- Blood glucose monitoring with the use of meters is an essential component of the management of type 1 diabetes mellitus.

Diabetes complications

- Emergency complications of diabetes include Diabetic ketoacidosis and Hypoglycaemia.

Hypoglycaemia

- This is the most frequent complication of Type 1 diabetes mellitus and severe prolonged hypoglycaemia may cause permanent CNS damage, particularly in young children (<6 years).
- Its presentation may be symptomatic or asymptomatic ("Hypoglycaemic unawareness").
- According to the Diabetes Control and Complications Trial (DCCT); in a diabetic patient hypoglycaemia is said to occur when the blood glucose levels are less than 4.0 mmol/l (less than 70 mg/dl) with simultaneous symptoms of hypoglycaemia.
- Symptoms of hypoglycaemia are classified according to those associated with peripheral (autonomic) effects like hunger, trembling, pallor, sweating, palpitations and those associated with low cerebral glucose (neuroglycopenia–40-60 mg%) like impaired thinking, mood changes, tiredness, convulsions, and coma.

Treatment

- The goal of treatment is to restore blood sugar back to normal and prevent convulsion and be conscious of overtreatment.

- It involves the administration of glucose through the use of fast-acting sugars such as a cube of sugar or 100 ml of soft drinks.
- Repeat after 10-15 minutes if no response.
- As symptoms improve, give the patient his next meal; or
- If the patient is not responding to the above measures and becomes unconscious–an injection of glucagon (0.5 to 1.0 mg subcut).

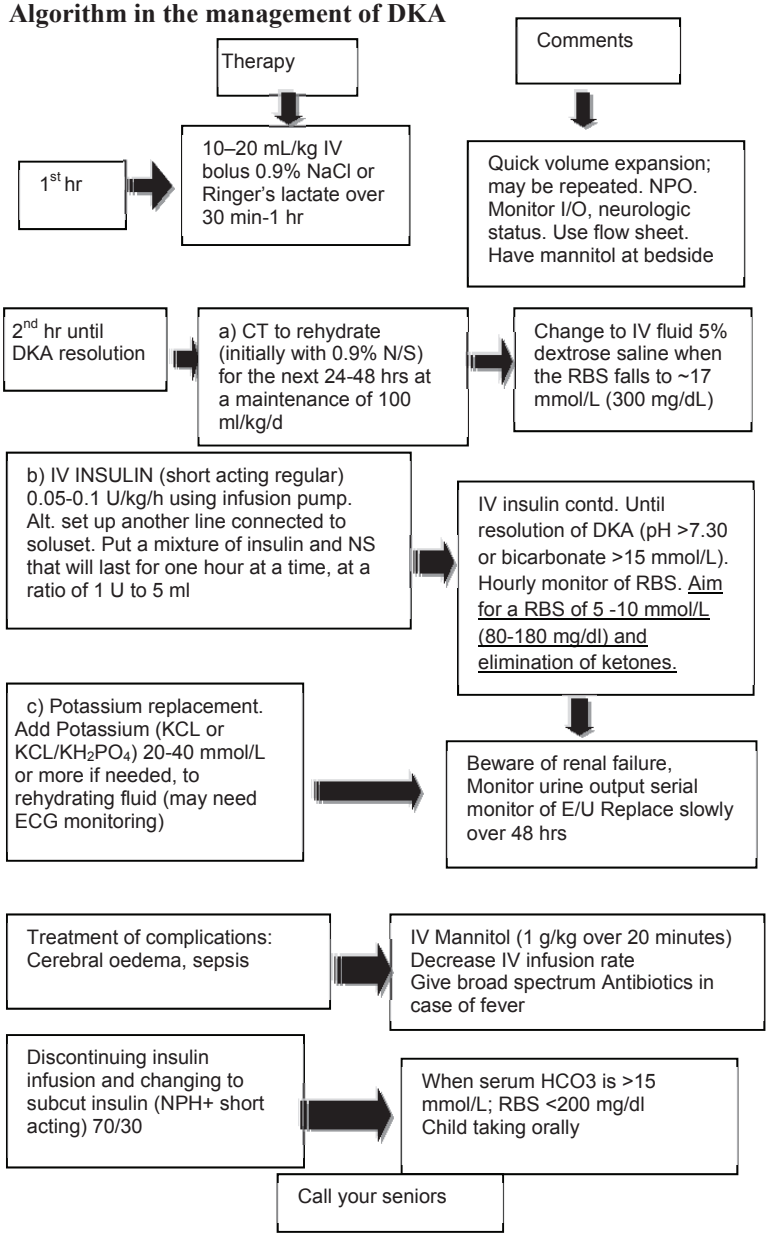
Diabetic ketoacidosis (DKA)

- Diabetic ketoacidosis is an acute decompensation characterized by a triad of hyperglycaemia, metabolic acidosis and ketonaemia, resulting from insufficient insulin action.
- DKA can occur in undiagnosed type 1 diabetes or in a known diabetic who defaults in the insulin regimen. Features of DK include: Hyperglycaemia (BG 11.1 mmol/l or 200 mg/dl), Dehydration (usually up to 10%), Ketonuria (>+), pH <7.3, Bicarbonate <15 mmol/l, Heavy glycosuria (>55 mmol/l, +++).
- Clinical features include: Dehydration, shock, acidosis, electrolyte abnormality, an altered level of consciousness.
- DKA can be classified in terms of severity based on acidosis into:
  - mild = pH <7.30 or bicarb <15 mmol/L;
  - moderate = pH <7.20 or bicarb <10 mmol/L;
  - severe = pH <7.10 or bicarb <5 mmol/L.
- Aims of therapy:
  - *1st* Correction of shock;
  - *2nd* Correction of dehydration;
  - *3rd* Correction of hyperglycaemia;
  - *4th* Correction of deficits in electrolytes;
  - *5th* Treatment of sepsis;
  - *6th* Treatments of complications (cerebral oedema).

Correction of shock

- Treat shock first with 0.9% Saline or Ringers-Lactate boluses. If necessary give O_2 by nasal prongs or a facial mask (correct shock rapidly but correct dehydration slowly).
- Cerebral oedema may occur during treatment of DKA usually 4 to 12 h after initiation of therapy. It presents as headache, decreased consciousness, bradycardia, pupil abnormalities, decorticate posturing.
- Treatment is to reduce the rate of fluid administration and give mannitol IV 0.25 to 1 g/kg IV over 20 min.

Algorithm in the management of DKA



Long-term Complications of Diabetes

- Microvascular and macrovascular complications of diabetes in general are related to the duration of the disease and the degree of blood sugar control.
- They include retinopathy, nephropathy, skin lipoatrophy and lipohypertrophy, obesity, Neuropathy, etc. The DCCT demonstrated that tight control with blood sugar close to normal will decrease the development of these complications and even reverse them.
- HbA1c levels reflect the average blood glucose level over time of a diabetic patient. The DCCT has shown that the HbA1c levels correlate with the risk of diabetic complication and the risk of hypoglycaemia.

Honeymoon

- This is a period of resumed insulin production and improved control seen mostly in children with type1 diabetes.
- It is a time of temporary remission and some may even not require insulin for months. This period does not define a cure.

Type 2 diabetes

- Type 2 diabetes is the more common form of diabetes but usually seen in older people. It is as a result of insulin-resistance and/or relative insulin deficiency.
- Over 85% of cases are associated with overweight. The incidence is rising among children as a result of the rising incidence of obesity in younger children. Unlike in type 1 diabetes there is history of a relative with diabetes in 74-100% of cases.

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12.4 Diabetes Insipidus

Definition

- Diabetes insipidus (DI) is a clinical condition whereby there is an inability to release adequate arginine vasopressin (AVP) or its action in the face of increased serum osmolality.
- This disorder of vasopressin secretion and its action in the kidney can lead to clinically important derangements in water and sodium homeostasis.

Physiology

- Arginine vasopressin, otherwise known as antidiuretic hormone (ADH) is a nonapeptide hormone produced by the cells of paraventricular and supraoptic nuclei of the hypothalamus.
- The neurons of these nuclei terminate at the posterior Pituitary. An osmotic detector is located close to the supraoptic nuclei so that in the face of increased osmolality, vasopressin will be released which will in turn stimulate the collecting ducts of the kidneys to retain water. Vasopressin acts through G protein via V2 receptors located at the collecting duct.

Pathophysiology

- Diabetes insipidus results when there is passage of a large volume of urine (diabetes) that is hypotonic, dilute, and tasteless (insipid).
- When there is failure of release of vasopressin from the posterior pituitary it will result in ***central DI***.
- A situation of failure of the collecting ducts to respond to the presence of vasopressin will result to ***nephrogenic DI***.
- A situation of habitual excessive water intake can lead to psychogenic polydipsia and resultant ***functional nephrogenic DI.***

Normal blood osmolality

- Blood osmolality ranges between 280 and 290 mOsm/kg H_2O. The major osmotically active constituents of blood are sodium, chloride, and glucose (with insulin deficiency).
- Therefore, vasopressin secretion occurs when the blood osmolality rises.
- Two mechanisms work to maintain the water balance in the body– namely Vasopressin secretion which stimulates water reabsorption

by the kidney preventing water loss and the thirst mechanism which stimulates water ingestion, thereby restoring previous water loss.

Causes of central DI

Genetic	Congenital	Acquired
AVP Gene mutation **Autosomal dominant** Mutations in the AVP–NPII gene. Symptoms: first decade of life, usually before 7 years of age **Autosomal recessive** Single mutation in the AVP–NPII. Asymptomatic for the first year or more of life. **Wolfram syndrome**	**Midline craniofacial defects** **Septo-optic dysplasia** The most frequent defect characterized by hypoplasia of the optic nerves with other midline cerebral anomalies and pituitary hormone deficiencies. **Holoprosencephalic syndromes** **Agenesis of the pituitary**	**Neoplasms** Craniopharyngioma Germinoma, Pinealoma Leukaemia/lymphoma Inflammatory/infiltrative Langerhans cell histiocytosis Systemic lupus erythematosus Neurosarcoidosis Lymphocytic neurohypophysitis **Infectious** Meningitis, Encephalitis Congenital infection **Traumatic injury** CNS surgery, Head trauma, Hypoxic injury **Idiopathic** **Pregnancy** (increased vasopresinase

Causes of Nephrogenic DI

Genetic	Acquired
X-linked recessive (AVP-V2 receptor) Autosomal recessive (AQP-2) Autosomal dominant (AQP-2) Genetic causes are more common and more severe in children than acquired	**Drugs:** Lithium, Foscarnet, Demeclocycline **Metabolic:** Hyperglycaemia Hypercalcaemia, Hypokalaemia Protein malnutrition **Renal** Chronic renal failure, Ischaemic injury Impaired medullary function **Outflow obstruction**

Diagnosis

- The diagnosis of DI is established when there is history of the passage of a large volume of diluted and hypotonic urine (>30 ml/kg/day), with urine osmolality <300 mOsm/kg and specific gravity <1.010. The serum osmolality is >300 mOsm/kg and serum sodium Na + >145/meq/l.
- ***Water deprivation test:*** After establishing the history of polydipsia and polyuria the patient should undergo a water deprivation test. The patient is deprived of water for 8 hours and then urine and serum osmolality are assessed. If serum osmolality is above 300 and urine osmolality is below 600, the patient has DI. Proceed to the vasopressin response phase.
- To distinguish between central DI and Nephrogenic DI, vasopressin response is done after the vasopressin response phase:
  - *A twofold increase in urine osmolality indicates CDI;
  - *An increase of less than twofold in urine osmolality is consistent with NDI.

Treatment

Central DI

- Treatment of CDI is usually lifelong. Management involves fluid therapy. The patient takes enough water according to need because with intact thirst and free access to water, an individual with DI will drink sufficient to maintain normal serum osmolality and high-normal serum sodium**.**
- Drug therapy involves the use of dDAVP (desmopressin). Desmopressin [desamino-d-arginine vasopressin; dDAVP] is the synthetic analogue that is more potent and has a longer half-life then the endogenous vasopressin.
- It is given to relieve the symptoms of polyuria and polydipsia, the treatment of choice is administration by subcutaneous injection, nasal solution or orally.
- Oral dDAVP is highly effective and safe in children in doses of 50-600 mcg (0.05-0.6 mg) every 8-12 hours.

Nephrogenic DI

- Treatment of Nephrogenic DI will involve removing the underlying disorder or drug. Foods with the highest ratio of calorie content to osmotic load should be used to maximize growth and minimize the urine volume required to excrete solute.

- Thiazide diuretics in combination with amiloride or indomethacin are the most useful pharmacological agents.
- Thiazides enhances the Na excretion at the expense of water.

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12.5 Thyroid Disorders

Physiology

- Thyroid hormones are produced by the thyroid gland. The thyroid gland is the first endocrine gland to develop.
- As early as the 3rd week of intrauterine life, the thyroid originates from the floor of the primitive pharynx.
- Through its connection by the thyroglossal duct, it migrates downwards and by the 7th week it arrives at its definitive position as a bilobed shaped gland in front of the trachea, inferior to the cricoid cartilage in the anterior lower neck.
- By 12 weeks the foetal thyroid gland has started synthesizing hormones.
- Iodine is an essential micronutrient almost exclusively utilized by the thyroid gland in the synthesis of thyroid hormones.
- Iodine is found in relative abundance in marine plants and animals and certain mineral deposits.
- Iodine deficiency affects thyroid hormone biosynthesis and can lead to hypothyroidism.
- If the deficiency occurred during a critical period such as in early life, it will result in permanent neurologic damage.

Function and control of thyroid hormones

- The main function of the thyroid gland is to synthesize the thyroid hormones–triiodothyronine (T3) and tetraiodothyronine or thyroxine (T4).
- The functional unit of the thyroid gland is the thyroid follicle.
- Thyroid hormones increase oxygen consumption, stimulate protein synthesis, influence growth and differentiation, and affect carbohydrate, lipid, and vitamin metabolism.
- Thyroid hormones are essential for brain maturation and for brain function throughout life.
- Thyroid function is under hypothalamic-pituitary control, thus thyroid hormones are produced by the thyroid gland in response to the stimulation of Thyroid stimulating hormone (TSH) produced by the anterior pituitary.
- TSH is in turn regulated by the hypothalamic peptide, thyrotropin releasing hormone (TRH) synthesized from the hypothalamus.

- The function of the entire complex is modified by the availability of the thyroid hormones in a typical negative feedback manner.

Disorders of thyroid function

- An enlargement of the thyroid gland is a goitre and the patient may be hypothyroid, euthyroid or hyperthyroid.

Hypothyroidism

- Hypothyroidism results from the deficient production of thyroid hormone or a defect in thyroid hormone receptor activity.
- The disorder may be manifested from birth or acquired. Hypothyroidism seen at birth is called congenital hypothyroidism. The prevalence of congenital hypothyroidism is 1/4,000 infants worldwide.
- Thyroid hormones are essential for the development of the brain and the nervous system of the foetus and during the first 3 years of life.
- Lack of sufficient thyroid hormones during this period results in mental retardation and other neurological sequelae.
- Common aetiologies of congenital hypothyroidism include thyroid dysgenesis, thyroid dyshormonogenesis, hypothalamic pituitary abnormalities, iodine deficiency thyroid hormone unresponsiveness.
- Most neonates with congenital hypothyroidism appear clinically normal at birth. When signs and symptoms initially present, they are nonspecific, making clinical detection difficult and often delayed.
- Routine newborn screening has been instituted in most developed countries to detect congenital hypothyroidism early and offer early treatment in order to prevent permanent neurologic damage.

Clinical signs of neonatal (congenital) hypothyroidism include

Dry skin	Prolonged jaundice
Lethargy	Constipation
Poor feeding	Hoarse cry
Macroglossia	Sleepiness
Enlarged post. Fontanel	Hypothermia
Umbilical hernia	

Acquired hypothyroidism

- It can occur at any age, and frequency increases with age.
- A differential diagnosis of "acquired" hypothyroidism in early childhood is congenital hypothyroidism not detected in the newborn period.
- This is particularly likely for partial thyroid dysgenesis or dyshormonogenesis that is compensated by gland hypertrophy for a variable period of time.
- Other causes of acquired hypothyroidism are autoimmune thyroiditis and thyroid dysfunction, secondary to thyroid/ hypothalamic/pituitary destruction from chemotherapy, radiotherapy, iron or other infiltrative processes.
- ***Hashimoto thyroiditis*** (or chronic lymphocytic thyroiditis or autoimmune thyroid disease) is responsible for the majority of cases of acquired hypothyroidism.
- The most sensitive clinical sign of hypothyroidism in the growing child is growth retardation.
- Decreases in linear and bone growth are characteristics of hypothyroidism and the examination of bone films and the growth curve can be extremely helpful in timing the onset of hypothyroidism.
- Manifestations of hypothyroidism do not generally differ by the gender of the affected individual (other than menstrual irregularities which can occur in women with hypothyroidism).
- The prevalence of thyroid diseases (autoimmune and sporadic dysgenesis) is much greater in females (2:1 ratio for thyroid dysgenesis–3-5:1 for thyroiditis).

Laboratory investigation for hypothyroidism include

FT4	TSH
T3	Iodine
Thyroid ultrasound	Anti-thyroglobulin antibody

Treatment

- Levothyroxine is the treatment of choice for congenital hypothyroidism; its long half-life allows daily dosing and no

consequences of an occasional missed dose. For term newborns: 10-15 µg/kg/day.

- Levothyroxine is also the treatment of choice for acquired hypothyroidism in a variable dose, depending on age and weight:
  - 0-3 months, 8-12 µg/kg/day;
  - 3-6 months, 7-10;
  - 6-12 months, 6-8;
  - 1-5 years, 4-6;
  - 6-12 years, 3-5;
  - >12 years, 2-4.

Hyperthyroidism

- This is as a result of excessive levels of circulating free thyroid hormones. Graves' disease accounts for the majority (80%) of cases.
- It is an autoimmune disease that may co-exist with Hashimoto's thyroiditis.
- Other causes of hyperthyroidism include, Neonatal thyrotoxicosis, Hashimoto's thyroiditis (~1%), selective T4 resistance, autonomous nodules (~2%) TSH-dependent hyperthyroidism.

Signs of thyrotoxicosis

- These include goitre exophthalmos, restlessness, increased appetite, weight loss, tremor, hands transpiration, warmth-intolerance.
- Lab investigations are the same as above.

Treatment options

- Antithyroid drugs: PTU (propylthiouracil) or methimazole, propranolol (Propranolol 1 mg/kg/day is added to control signs of sympathetic overactivity), Block-replacement–at least 1 year. Block and treat (with thyroxine). Remission: 25%; Side effects minor: 5-10%; major: 2-5%.
- Surgery: total or near total thyroidectomy. Complication–morbidity is seen in 2-5% (<1% in experienced hands), hypothyroidism: seen in 50% the first year. Relapse seen in 10-15%.
- Radioiodine Therapy. This is the administration of radioactive iodine.

Neonatal hyperthyroidism

- This is seen in an infant born to a mother with Graves' disease. It is acquired from transplacental thyroid-stimulatory immunoglobulin (TSI) made by the mother. At birth, they may present with high mortality, heart rhythm disturbances, decompensation cordis exophthalmos, goitre.
- Treatment: by the use of propranolol 2-3 mg/kg/d in divided doses.
- Anti-thyroid drugs: methimazole, iodide.
- Late consequences include craniosynostosis, psychomotor retardation.

Thyroid Neoplasia

- Solitary or multiple thyroid nodules are very rare in childhood.
- Over 50% of isolated thyroid nodules are cysts or benign adenomas, 30-40% are malignant. Of the malignant nodules >90% are papillary or follicular. Toxic nodules are rare.

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12.6 Growth and Development

Definition

- ***Growth*** is the increase in body size both in weight and height. It is a general indicator of the state of a child's health.
- ***Growth monitoring*** is the measurement of the increase in body size over a period of time.
- ***Growth assessment*** is an essential component of paediatric health surveillance and the most powerful tool in growth assessment is the growth chart.
- Measurements of growth provide a sensitive indication of health in childhood. Changes in growth rates provide an early and sensitive pointer to health problems.
- Growth evaluation involves frequent measurement of the following parameters
  - Weight, Height;
  - Head circumference, BMI;
  - Body proportions;
  - Height velocity;
  - Target height.
- Measurement must be frequent, accurate and reliable, by trained personnel, with appropriate equipment and plotted on the correct growth charts.
- Height is measured with a stadiometer, but for children below 2 years recumbent length is measured using an Infantometer or measuring board.
- Normal phases of growth include the periods–Foetal, Infancy, Childhood and Puberty
  - **Infancy (0-1 year)** is the period with the highest growth velocity. It represents the part of postnatal linear growth which seems to be independent of the Growth Hormone;
  - Growth in the infancy period is nutrition dependent;
  - **Childhood growth phase** (2 years to puberty) is under hormonal control–GH-IGF1, Thyroid hormone, Insulin;
  - **The Pubertal phase** is under hormonal control which includes the gonadotrophins, gonadal steroids in addition to the above listed childhood hormones.

Years	Normal Height velocity (Cm/yr)
1 yr	25 cm
2 yrs	10 cm
3-4 yrs	7 cm
5-7 yrs	6 cm
7 to puberty	5 cm
puberty	10.3 cm

Requirements for normal human growth include:

- Adequate nutrition;
- Normal hormonal actions;
- Absence of chronic disease;
- Emotional stability, a secure family environment;
- The absence of defects impairing cellular and bone growth.

Formulae for Approximate Average Height and Weight of Normal Infants and Children

Weight	Kilograms
At birth	3.25
3-12 months	$\frac{\text{Age (mo)} + 9}{2}$
1-6 yr	Age (yr) × 2 + 8
7-12 yrs	$\frac{\text{Age (yr) x 7-5}}{2}$
Height	**Centimetres**
At birth	50
At 1 yr	75
2-12 yrs	age (yr) × 6 + 77

- **Puberty**–This is the transition period from the sexually immature state to the potentially fertile stage during which secondary sexual characteristics appear.
- The changes of puberty occur because of orderly, sequential changes in endocrine activity.
- The physical changes of puberty in individuals are defined by the **Tanner stages**.
- For females–It is Breast development and pubic hair.
- For Males–It is external Genitalia and pubic hair.
- It is staged from stage I (Preadolescent stage) to stage V (full adult maturity).

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12.7 Abnormal Growth

Introduction

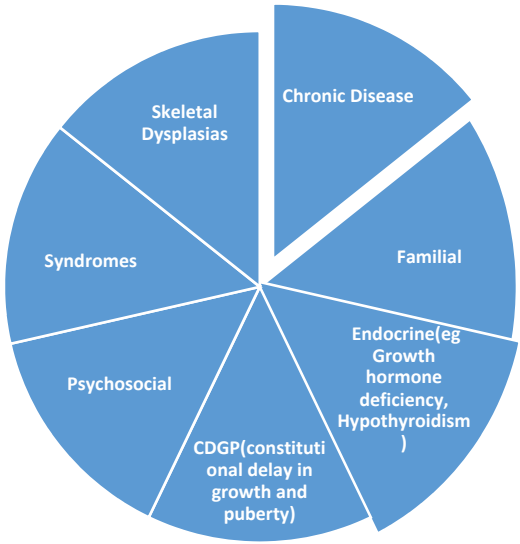
- Normal growth will depend on:
  - Adequate nutrition;
  - A stimulating environment;
  - Normal hormone function;
  - The absence of chronic disease.

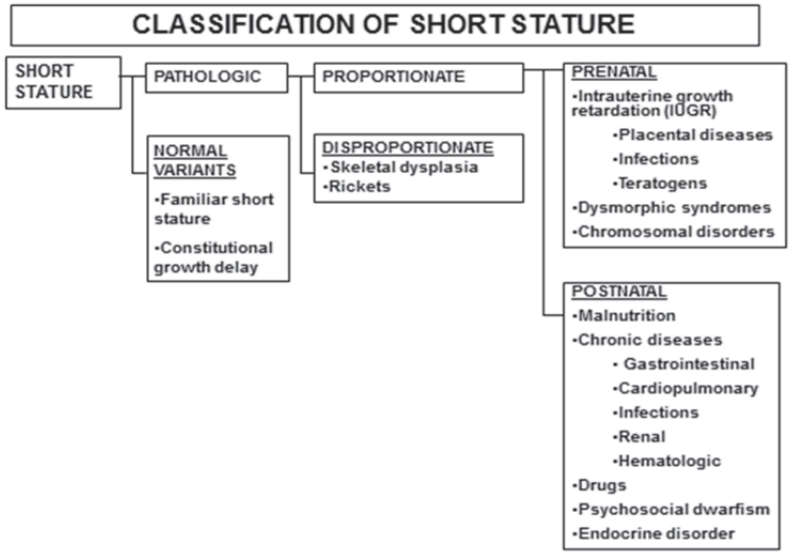
Abnormal patterns of growth

- Growth can be slowed or accelerated by a variety of conditions.
- Changes in growth may be the first sign of a pathologic condition (e.g., malnutrition, inflammatory bowel disease, hypercortisolism, thyroid dysfunction).
- Abnormal patterns include;
- Poor weight gain;
- Obesity;
- Short stature;
- Tall stature;
- Microcephaly and macrocephaly;
- Short stature is probably the most common complaint that brings a child to the paediatric endocrinologist;

In short stature

- This is relative and needs to be defined according to the growth performance of a given population and reference charts relevant to it.
- Height which is <2.5 SD (below the 0.4th centile); should be evaluated for short stature.





Syndromes with short stature include

- Down Syndrome, Silver-Russell, Turner, Noonan, Foetal alcohol, Prader-Willi, and Congenital rubella.

Tall Stature

- Tall stature can result from an intrinsic defect in bone and/or connective tissue often of genetic origin. Growth is frequently disproportionate and dysmorphic features are common.
- It can result in a secondary growth disorder such as hormonal disturbances.
- It could be idiopathic tall stature–includes familial or constitutional tall stature: tall stature becomes evident at 3-4 years of age.
- Familial tall stature is the most common cause of tall stature. Although the primary and secondary growth disorders are less common, genetic factors play a role in several of them.

Syndromes associated with tall stature

Chromosomal defect	**Overgrowth syndromes**
Klinefelter's syndrome	Beckwith-Wiedemann syndrome
XXY, XYY syndromes	Hyperinsulinism
Short stature Homeo SHOX excess	Soto's syndrome
Tall stature of endocrine origin	Weaver's syndrome
GH secreting pituitary tumour	Marshall-Smith syndrome
Precocious puberty	Marfan syndrome
Hyperthyroidism	Homocysteinuria
ACTH resistance	
Androgen insensitivity	
Oestrogen deficiency	

Clinical Evaluation of Abnormal growth

- Assess parental heights!
- Midparental Height.
- Weight Measurement in Children.
- Height Measurement in Children.
- Weight for Height Age.
- Look for Dysmorphic features in Congenital disorders.
- Upper to Lower Segment Ratio and arm span.

Laboratory investigation

Specific

- Growth Hormone Level, Thyroid Stimulating Hormone (TSH).
- Amino acid screen (Homocysteinuria).
- Chromosome Karyotype (Klinefelter Syndrome).
- 17-Hydroxyprogesterone (Congenital Adrenal Hyperplasia).
- Glucose (Beckwith-Wiedemann).
- Androgen and Oestrogen levels (Precocious Puberty).
- Imaging–Bone age X-ray.

Others

- Marfan syndrome–cardiac/ophthalmic.
- Homocysteinuria–Metabolic tests in urine or plasma are carried out for the diagnosis.
- Beckwith-Wiedemann syndrome–USS of internal organs, specifically the kidneys.

Treatment

- Identify the underlying cause and treat accordingly.
- Note: Short stature can pose significant psychosocial problems for most children or adults.
- Some short children and adolescents feel insecure, have low self-esteem, are introverted, withdrawn, depressed, socially isolated, anxious, aggressive and immature. They may be bullied and have difficulty adjusting at school. These problems need to be recognized so that the child and family can receive appropriate psychological support.

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12.8 Evaluation of Growth

Introduction

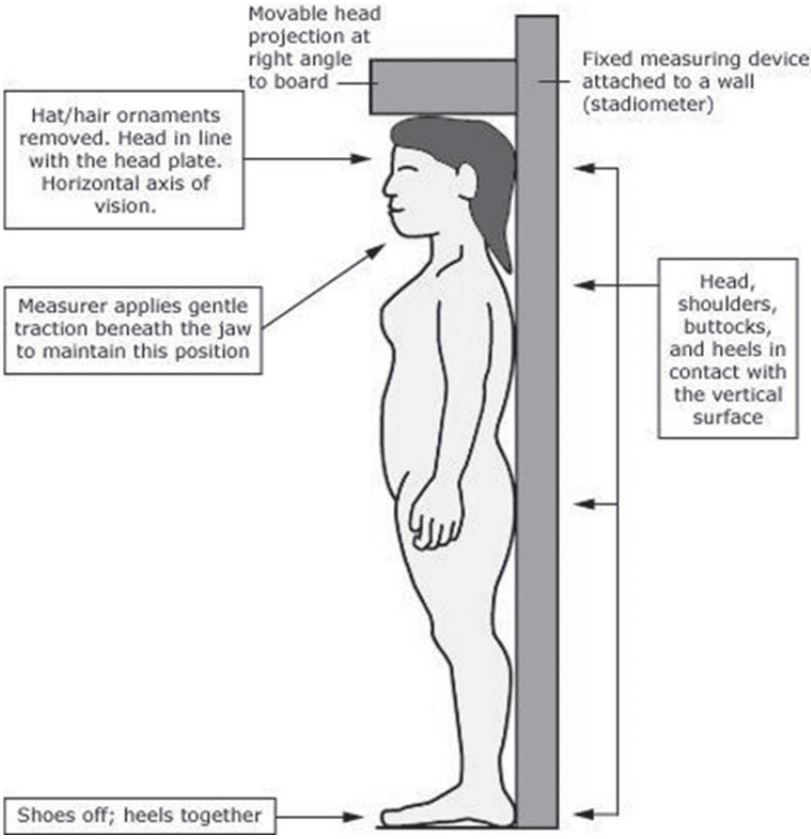
- Growth is a general indication of a child's health; its evaluation can be used to assess the state of health of a child.
- The growth pattern of a child may herald the onset of both endocrine and non-endocrine systemic diseases or a state of malnutrition or may mean health and general wellbeing.

History and physical examination

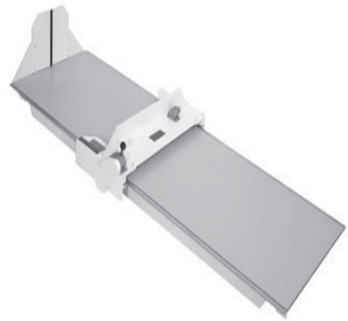
- Growth evaluation begins with good history taking. In the history, it is important to note the:
- Duration of the presenting complaint such as short stature,
- Past history of chronic illness, syndromes, or pituitary lesions,
- Dietary history,
- Medication use such as corticosteroid treatment.
- Antenatal details such as toxic exposures at pregnancy, difficulties of delivery, degree of prematurity,
- Birth details like gestation at birth, birth weight and length,
- Age at menarche including that of parents,
- Family history. Mother's and father's height. Family history of growth disorders,
- Family social class.

Physical examinations–Growth measurement

- This involves anthropometry. It is important to note that after measurements are obtained, they must be displayed graphically on a growth chart.
- Therefore, the most powerful tool in growth assessment is the growth chart.
- **Height**–failing to measure a child on the first visit is a serious mistake that limits further assessment of the wellbeing of the child.
- Measurement must be accurate.
- It can be done as standing height for children more than 2 years or as recumbent length for those aged 2 years and below.
- The Harpenden stadiometer is used to measure standing height.



- The recumbent length is done using the Harpenden measuring table.
- Its main component is a rigid, horizontal backboard with legs.
- It has a rigid, fixed headboard and a rigid, free-moving footboard which moves back and forth on miniature ball bearing rollers.
- The readout is in millimetres and located on the footboard.



- **Weight** measurement is done using the Bassinet weighing scale for infants and the standing scale for older children.

Figure 12.8.3 Bassinet weighing scale

Figure 12.8.4 Standing weighing scale

- H**ead circumference:** is measured using a flexible tape. It is measured as the maximal occipito-frontal circumference.
- Therefore, the examiner stands facing the lateral side of the subject.
- The non-stretch tape should encircle the head above the ears, midway between the eyebrows and the hairline and over the occipital prominence at the back of the head.

Figure 12.8.5 Measurement of head circumference

Growth charts

- A child's measurements are plotted on a growth centile chart, so comparisons can be made with a reference population.
- There are several growth charts available like the CDC, WHO and Nigerian growth charts.
- The CDC reflects the USA population while the WHO made an input of the different world populations in its production.
- While the CDC growth charts can be used continuously from ages 2-19, the WHO growth charts only provide information on children up to 5 years of age.

- The Nigerian chart is being produced using Nigerian children from the ages of 4 to 16 years.
- In the construction of charts the measurements are derived from a reference sample that shows a Bell-shape or Gaussian distribution also conventionally described as normal distribution.
- This is a function that tells the probability that any real observation will fall between any two real limits or real numbers, as the curve approaches zero on either side.

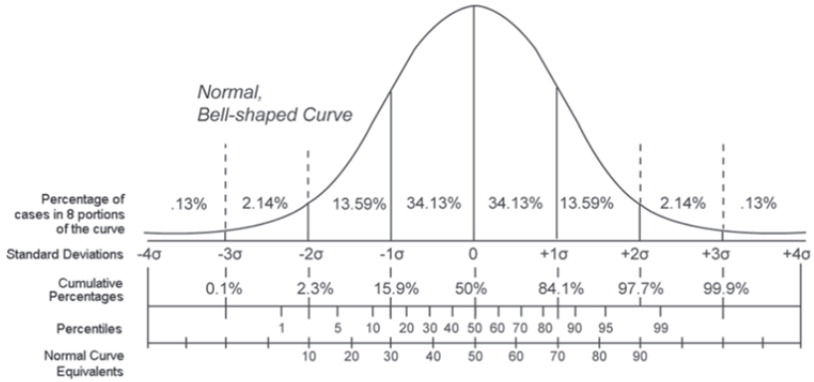
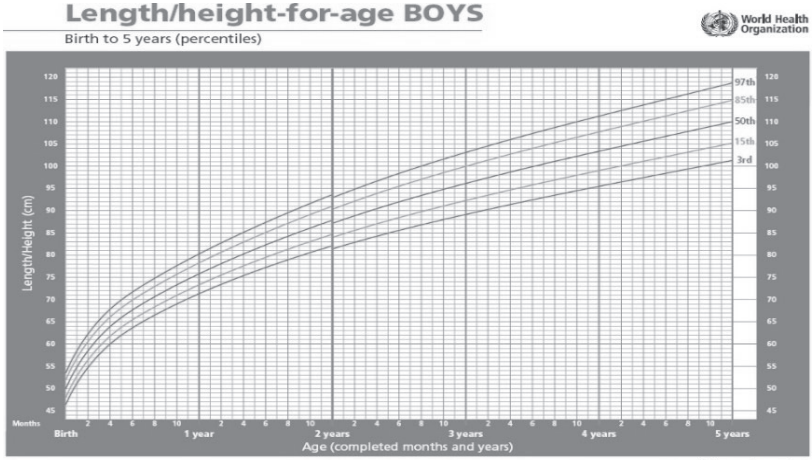
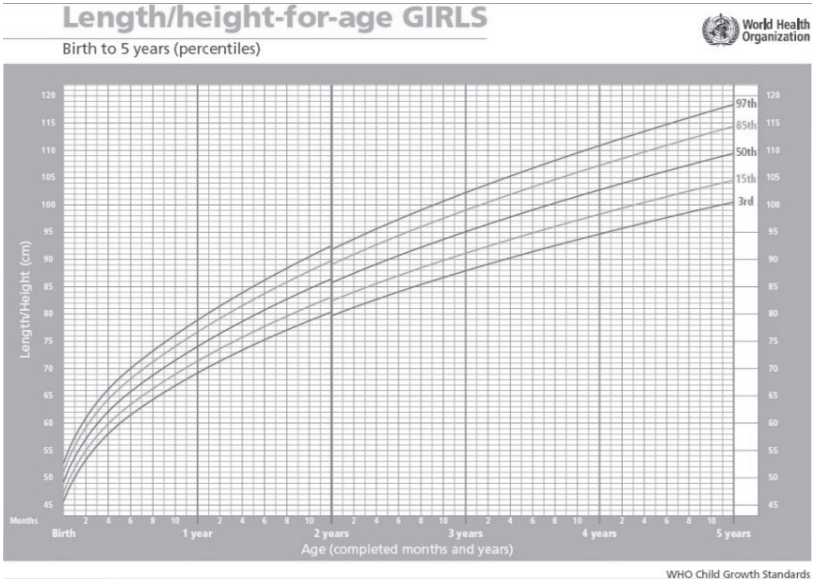


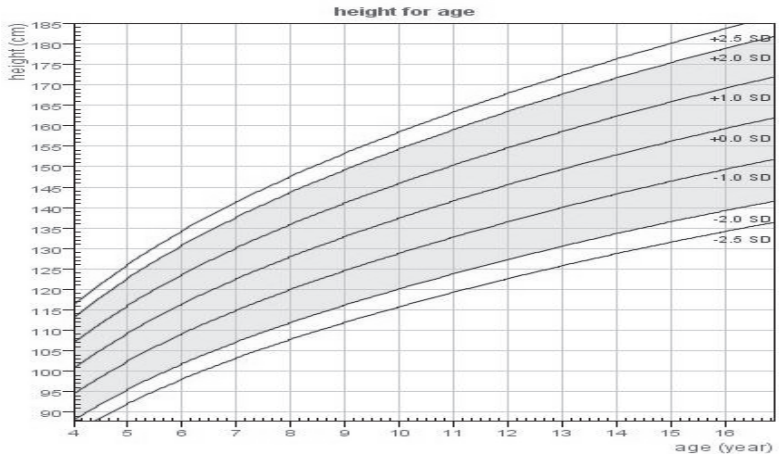
Figure 12.8.6 Centiles and standard deviations. Bell-shaped

Shore H. Accurate RMM-Based Approximations for the CDF of the Normal Distribution". *Communications in Statistics – Theory and Methods* 2005*;* 34: 507–513

- The corresponding centile and standard deviation will be:
  - 50° centile 0 SD;
  - 25°-75° centile ± 0.66 SD;
  - 10°-90° centile ± 1.28 SD;
  - 5°-95° centile ± 1.65 SD;
  - 3°-97° centile ± 1.88 SD.
- Gender specific growth charts for height, weight, head circumference, body mass index are used in the clinics. Blue colour charts are for males while pink colour are for females e.g.

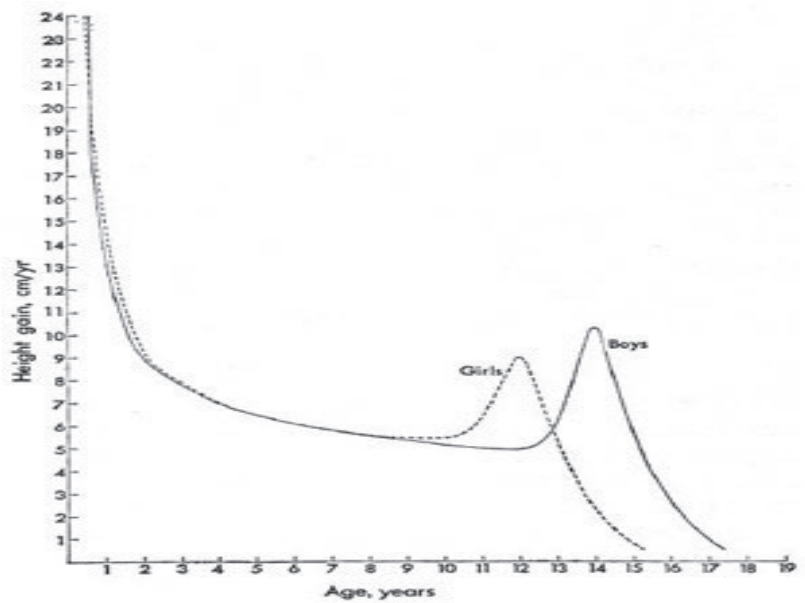






(http://www.cdc.gov/growthcharts/who_charts.htm)

- Growth velocity: this represents the change in measurement per year on the vertical axis and age on the horizontal.



(http://dx.doi.org/10.5124/jkma.2009.52.3.211)

- There are two peaks in the growth velocity curve, the infancy and adolescent periods.
- However, the infancy period represents the period with the highest growth velocity.

Normal height velocity

Year	cm/year
1	25
2	10
3-4	7
5-7	6
7-puberty	5
Puberty	10.3

Target Height

- This is calculated from the Mid Parental Height (MPH) ± 8 cm.
- Mid parental Height is an indicator of a child's growth potential based on the genetic background:
- MPH is calculated as the average of the mother's (M) height and the corrected father's (F) height.
- Parents' heights are plotted on the right-hand side on growth charts

MPH: Boys = $\frac{(M + F) + 13}{2}$

Girls = $\frac{(M + F) - 13}{2}$

Target Height = MPH ± 8

Bone age

- This is used to assess the skeletal maturity and growth potential.
- The bone age is determined by a radiograph of the left hand and wrist as compared with the standards in the Greulich and Pyle atlas.

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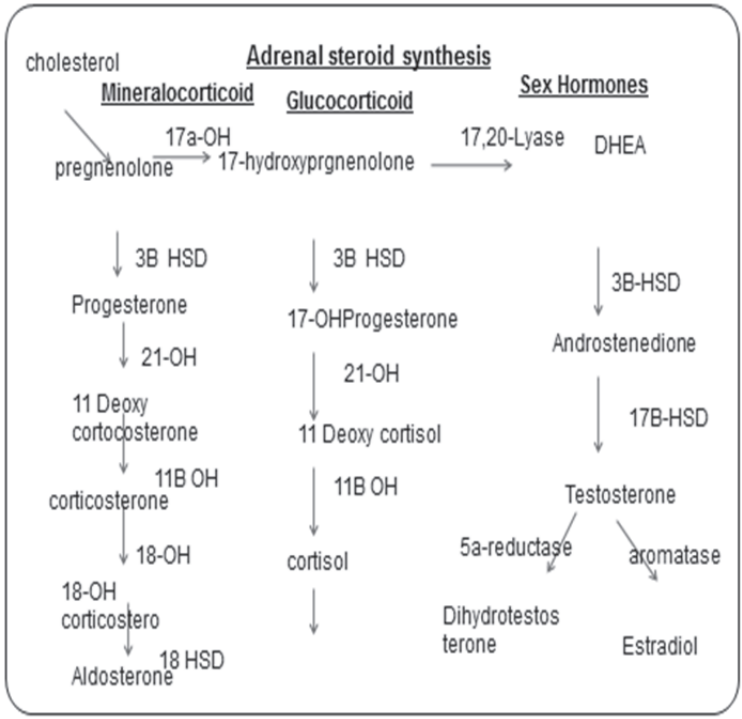
12.9 Congenital adrenal hyperplasia

Definition

- Congenital adrenal hyperplasia is a family of autosomal recessive adrenal hyperplasia (CAH) disorders of adrenal steroidogenesis.
- There is impaired cortisol synthesis, as a result of cortisol deficiency which increases the secretion of ACTH, and in turn leads to adrenocortical hyperplasia and overproduction of precursors.
- The clinical manifestations of the different disorders are due to the diminished production of cortisol and, depending upon the site of the block, decreased or increased production of mineralocorticoids and androgens.

- **Figure 12.9.1 Adrenal Steroid Biosynthesis**



(http://www.clinchem.org/content/56/8/1245.full)

- Defective conversion of 17-hydroxyprogesterone to 11-deoxycortisol accounts for more than 95 per cent of cases of congenital adrenal hyperplasia.
- This conversion is mediated by 21-hydroxylase.
- 21-hydroxylase deficiency is the most common inherited disorder.
- The 21-hydroxylase gene–the CYP21A2 gene is inherited in an autosomal recessive manner. Incidence is 1:10,000 births.
- Depending on the spectrum of inheritance it could be classic or non-classic. The classic form is severe accounting for 75% of all the forms and presents as the salt-wasting form or simple virilising.
- Excessive androgen production is the hallmark of CAH. Approximately 75% of affected infants have the salt-losing form, whereas 25% have the simple virilising form of the disorder.
- In the severe classic form, genital ambiguity is present in affected female infants.
- Affected females are virilised and may present in the newborn with ambiguous genitalia.
- The genitalia of males are unaffected by the excess adrenal androgens.
- These problems typically first develop in affected infants at about 2 weeks of age.
- However, even in severely virilised females, the internal genitalia are still normal.
- Boys present as neonates with a salt-losing adrenal crisis (hyponatraemia, hyperkalaemia, and failure to thrive) or as toddlers with signs of puberty (non-salt-losing form).

Clinical features	**Laboratory investigations**	**Laboratory Features**	**Management**
Ambiguous genitalia	Serum electrolyte	Hyponatraemia	Rehydration with normal saline. 20 mL/kg bolus of 0.9% normal saline. Repeated boluses may be needed
Altered sensorium/ unresponsiveness	Blood glucose measurement	Hyperkalaemia	IV Hydrocortisone 100 mg/m^2/day

Poor feeding/ weak suck	CBC	Hypoglycaemia	Fludrocortisone 150 mg/m^2/day
Dry mucous membranes	17 hydroxy progesterone	Metabolic acidosis	
Vomiting		Hypothermia	Replacement with Tab hydrocortisone, in three divided doses of 10 to 20 mg/m^2 per day. In 2-3 divided doses for life
Hyperpigmentation	Pelvic Ultrasound	Hypotension	6 monthly Monitoring of growth velocity and 17OHP profile
Decreased activity/ fatigue	Karyotype	Dehydration	Annual bone age estimation
		Lack of weight gain	Virilised girls will later require surgical correction

Table 12.9.1 Clinical features and Management

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12.10 Disorders of bone and mineral metabolism

Introduction

- The skeleton is an active endocrine organ and has the largest reservoir for two important minerals–calcium and phosphorus.
- 99% of calcium stores and 85% of phosphorus stores in the body are found in the bones.
- The skeletal system is very important as it provides mechanical support to the body and also protects vulnerable organs in the rib cage, skull and pelvis.

Calcium

- Calcium functions include neuromuscular excitability in muscle and nerve function including myocardial contractility and it also plays a key role in the clotting system and skeletal integrity.
- The normal dietary requirement is 500-800 mg daily in prepuberty and up to 1200-1500 mg daily at puberty and for adults 1000 mg daily.
- Sources of calcium include milk and milk products, fish, and some leafy vegetables.
- Calcium in the body exists as 50% ionized, 40% protein-bound and 10% as complexed calcium.
- Total serum calcium is 2.1-2.6 mmol/l[1,2].
- Serum calcium is regulated within close limits by several hormones that balance gastrointestinal intake with urinary and faecal losses.
- Therefore, the skeleton serves as a reservoir for calcium so that calcium may be mobilized when needed or stored when necessary.

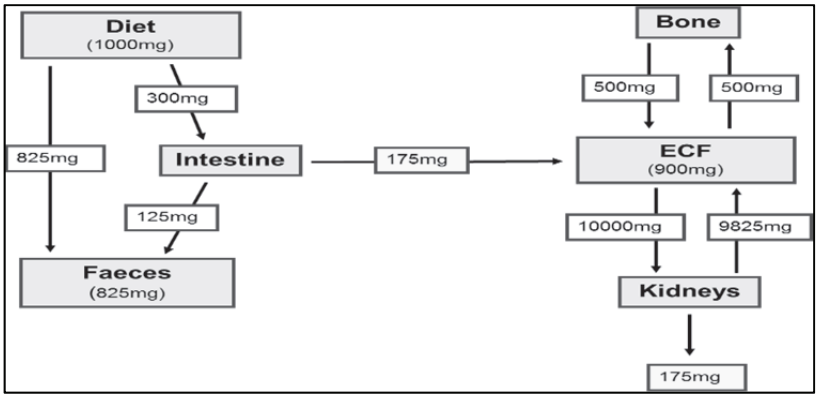

Figure 12.10.1 Calcium Balance

- Calcium absorption takes place in the duodenum, jejunum and ileum and its absorption is under hormonal control.
- Calcium absorption is a function of an active transport across the lumen and is controlled by 1,25(OH)2D. Calcium is excreted from the kidneys.

Phosphate

- About 85% of phosphate in the body is in the bone and it functions as a component in ATP.
- The daily dietary requirement is between 500 and 1200 mg and normal values are age dependent, in children it is 1.28-2.00 mmol/l and phosphate is excreted via the kidneys.

Factors involved in calcium homeostasis

- These include Parathyroid Hormone, Vitamin D, Calcium Sensing Receptor, Calcitonin.

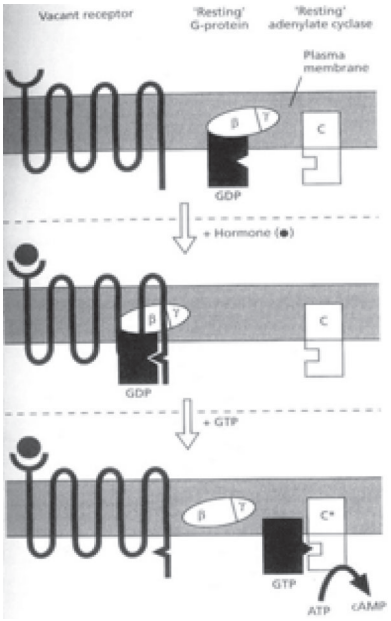

Figure 12.10.2 The G protein receptors

The G protein receptors-Peptide hormone act through specific cell membrane receptors called G protein coupled receptors or serpentine receptors.

- Upon the binding of the peptide hormone on these receptors, it leads to the activation of adenylyl cyclase with the subsequent phosphorylation of molecules and the generation of a second messenger known as cAMP.
- This in turn causes a cascade of events that ultimately leads to the metabolic action predicted by the presence of the hormone on the receptor (e.g. PTH, ACTH, LH, FSH, TSH, GnRH, GHRH, Glucagon).

Parathyroid Hormone (PTH)

- It is synthesized by the chief cells in the 4 parathyroid glands.
- It is stored in vesicles and its release is stimulated by a fall in plasma calcium within seconds.

- Parathyroid hormone exerts its function by its effect on the receptors (G protein receptors) located chiefly in the kidneys, intestines and bone.
- It causes increased calcium reabsorption of the distal tubules.
- It increases phosphate excretion by inhibiting reabsorption and stimulates the 1α-hydroxylase in the 1,25(OH)2D synthesis.
- Its action in bone is to increase the release of calcium and phosphate.
- In the intestine PTH indirectly through its action on Vit D increases calcium reabsorption.

Vitamin D

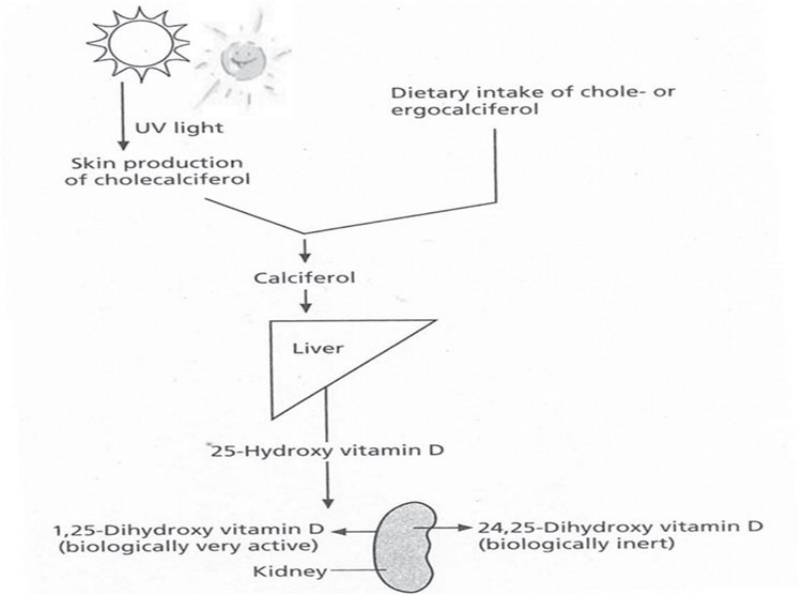

Figure 12.10.3 Vitamin D metabolism

- Vitamin D (Cholecalciferol or Vit D3) can be derived from the diet or from plants and fungi (Ergocalceferol or Vit D2). The main source of Vit D is sunshine.
- Vitamin D3 (Cholecalciferol)–produced in the skin of man and animals from the action of UVB radiation (270-300 nm) on cholesterol in the dermis–7 dehydrocholesterol.

- Vitamin D3 in the liver is then hydroxylated to 25(OH) cholecalciferol (calcidol). This is the main circulating hormone. It is measured in ng/ml or nmol/l and can be used to determine deficiency or excess.
- The main biologically active hormone is the 1,25 dihydroxycholecalciferol (Calcitriol)–synthesized in the kidney (pmol/l).
- Through the action of the PTH hormone on 1a hydroxylase in the kidney cells, 25(OH) Vit D is converted to 1,25 dihydroxycholecalciferols (1,25(OH)2 Vit D3 or Calcitriol)–it is the main biologically active hormone (pmol/l).
- 1,25(OH)2 Vit D3 in the kidney acts on the bone by stimulating osteoblast activity leading to bone mineralization. It increases calcium and phosphate reabsorption in the intestine and inhibits 1a Hydroxylase activity increasing calcium and phosphate reabsorption from the kidneys.

Calcium Sensing Receptor

- There are cell surface receptors present on: Parathyroid chief cells, the renal tubule and the C-cells of the thyroid. Their main function is to act as the "Calciostat" by regulating: PTH and Calcitonin secretion.

Calcitonin

- This is produced by C-cells of the thyroid gland and has no clear function in calcium homeostasis in humans.

Hypocalcaemia in Childhood

- Hypocalcaemia is as a result of a decrease in ionized calcium leading to neuromuscular irritability and may manifest clinically with; convulsions, tetany, stridor, paraesthaesia–hands and feet.
- The deficiency may be elicited using Trousseau's sign and Chvostek's sign.
- Causes of hypocalcaemia include;
  - PTH disorder
    - ✓ Reduced PTH secretion;
    - ✓ Impaired PTH action.
  - Vitamin D disorder

- ✓ Vitamin D deficiency;
- ✓ Impaired Vitamin D metabolism;
- ✓ Impaired renal function.
- o Abnormality of Calcium
- ✓ Sensing Receptor.

PTH Disorder

- Reduced PTH secretion leads to hypoparathyroidism and can be congenital e.g. as an isolated case or in association with abnormalities in Di George syndrome, deafness and renal dysplasia.
- It can be acquired as seen in cases of iron overload, autoimmune disorders and post thyroid surgery.
- Impaired PTH secretion is seen in individuals with resistance to PTH and leads to pseudohypoparathyroidism.
- This is a situation of hypocalcaemia with high PTH due to an abnormality of the PTH G protein coupled receptor.
- It makes the PTH receptor unresponsive. Phenotypically it presents as Albright hereditary osteodystrophy, which consists of mental retardation, short stature, short neck, round face, obesity, short 4th metacarpals/metatarsals.

Vitamin D Disorder (Rickets)

- Vit D deficiency usually presents with rickets. Rickets is due to poor mineralization of newly formed matrix (growth plates and bone).
- There is normal/low plasma calcium, low/normal phosphate with raised alkaline phosphatase.
- Rickets is a condition of inadequate deposition of mineral (a salt of calcium and phosphate known as calcium hydroxyapatite) on the growth plate. If this happens on cortical or trabecular bone it is called osteomalacia.
- This condition impacts adversely on the mechanical support and mineral reservoir function of the skeleton.
- Causes of rickets. Rickets can result from a deficiency of calcium/phosphate or from a deficiency or an interruption in the supply, metabolism or utilization of Vitamin D.
- This is also known as nutritional rickets and is the most common cause of rickets.

- Rickets causes an increase in PTH secretion, which causes bone turnover and elevated serum alkaline phosphate activity.
- Rickets occurs during growing periods causing an abnormal form of long bones, ribs and skull, while osteomalacia occurs when growth ceases and leads to fracture risks.
- Causes of Vit D deficiency include:
  - Problems with Vitamin D synthesis–latitude, atmospheric pollution, clothing, melanin pigmentation, sunlight exposure;
  - Impaired Vitamin D intake–prolonged exclusive breast feeding, maternal vitamin D deficiency, unusual diets;
  - Defects in Vitamin D metabolism–low calcium intake, intestinal calcium absorption and genetic variation.
- Plasma 25 Hydroxyvitamin D–is the accepted marker for Vit D and values >20 ng/ml (50 nmol/l) are accepted as normal.
- Clinically rickets presents with bowed legs (toddler or early childhood), knock knees (older child), delayed walking, short stature, hypocalcaemia–convulsions and tetany, fracture, dental abscesses, coincidental x-ray findings.

An investigation of rickets will include:

- ***Blood investigations***: Calcium, Phosphate, Alk Phos, Creatinine, LFTs, Serum PTH, 25OH Vitamin D.
- ***Urine investigations***: Calcium, Phosphate, Creatinine, Calculation of TRP and TmPO4/GFR, X-Ray, Wrist and Knee.
- Radiologic features of rickets as seen at the metaphyseal ends of bone on a plain x-ray will show cupping, fraying, splaying and flaying of the metaphyses. There is increased translucency of the bone.
- Prevention of Nutritional rickets will include sunlight exposure, food fortification and Vit D supplements.
- The global consensus on nutritional rickets states that; “Vit D 400 IU given per day is adequate to prevent rickets in infants.”
- We recommend this dose for all infants in the first year of life and beyond this age for all children with risk factors for vitamin D deficiency.
- Vitamin D supplementation should be provided to children with factors or conditions that affect the synthesis or intake of vitamin D.
- Vitamin D supplementation should be provided to all children with documented asymptomatic vitamin D deficiency.”

Vitamin D treatment regimes

Country	Age	Daily dosing regime	High dose regime
USA	< 1 month 1-12 months > 12 months	1000iu 1000-5000iu > 5000iu For 8-12 weeks	100,000 – 600,000iu over 1 to 5 days
Australia	< 1 month 1 -12 months > 12 months	1000iu 3,000iu 5,000iu for 12 weeks	Not advised 300,000iu 500,000iu over 1 to 7 days
UK	0-6 months 6 months – 12 yrs > 12 yrs	3,000iu 6,000iu 10,000iu for 8 -12 weeks	 Not advised 300,000iu

- In the treatment of nutritional rickets, the recommended route is oral treatment which gives a more rapid restoration of 25OHD levels than i.m. treatment.
- Daily oral treatment should be given for 12 weeks with some children requiring longer.
- Oral calcium either as a dietary intake or supplements providing 500 mg daily should be routinely used with vitamin D in treatment.
- For daily treatment or prevention vitamins D2 and D3 are equally effective.
- If single large doses are used vitamin D3 is recommended as it has a longer half-life.

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12.11 Disorders of sex development

Introduction

- Normal gonadal differentiation and sex development depend on the meticulous choreography and synchrony of a network of genes, transcription factors and hormones. Disturbance of this intricate network results in disorders of sex development (DSDs).
- The term DSD is defined as congenital conditions in which the development of chromosomal, gonadal or anatomic sex is atypical.
- Approximately 1 in 4000 infants is born with a DSD.

Programme for sexual development

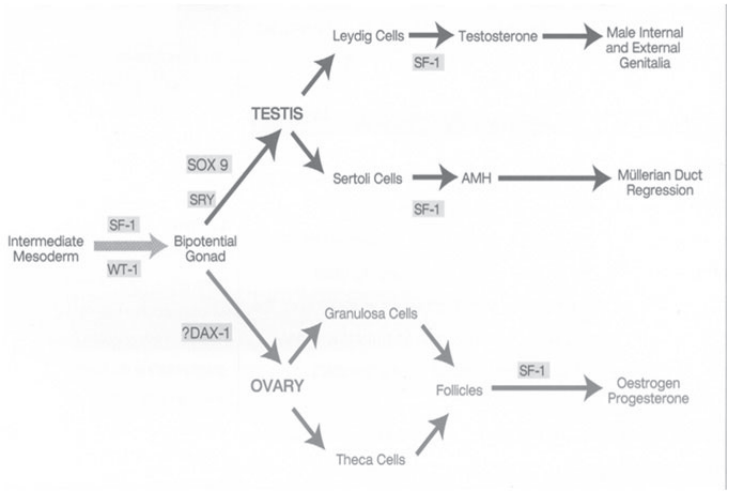
- **Genetic sex** determination occurs during the process of fertilization and refers to the composition of the sex chromosomes of the individual at the cellular level.
- Hence 46, XX is genetically female while 46, XY is genetically male.
- **Gonadal sex** determination on the other hand refers to the process through which bipotential embryonic gonadal tissue develops into testis or ovary.
- A unique feature of the developing gonad is its ability to differentiate into an ovary or a testis.
- Current theories postulate that the default programme generates an ovary.
- The genetic locus primarily responsible for this binary switch is the sex-determining region on the Y (SRY) gene on the Y chromosome.
- Sexual differentiation refers to the process through which the male or female phenotype develops gonads from intermediate mesoderm.
- Urogenital ridges appear at 4-6 weeks as a paired outgrowth of the coelomic epithelium.
- Under the influence of certain genes (SRY, WT1, GATA4, Chromebox homolog 2 (CBX2), SF1, EMX2 and LIM1) the bipotential gonads develop from the urogenital ridges.

- **Phenotypic sex:** The steroid metabolism that occurs in the gonads through the conversion of cholesterol to androgens also has enzymes that function in the adrenal gland.
- Defects in these enzymes may lead to a gonadal defect and or adrenal dysfunction.
- Phenotypic sexual development involves the internal ducts and the external genital appearance.

Molecular events in Gonadal Development

- These two areas may develop in alternative directions depending on the effectiveness of the androgens.
- Testosterone produced by the foetal Leydig cell is the active hormone in Woolfian duct differentiation and stabilization (responsible for vas deference, seminal vesicles and ejaculatory ducts).
- The most potent form of testosterone is produced after its conversion to dihydrotestosterone (DHT) by the action of 5α reductase enzyme.
- DHT is responsible for the development of the urogenital sinus and male external genitalia (prostate, prostatic utricle, scrotum, male-type urethra and the glans penis).

Presentation of DSD



- In the African setting the safe delivery of a newborn baby is usually accompanied by a question about the sex of the child, but when the external genitalia of a baby cannot be assigned as boy or girl it is often referred to as ambiguous genitalia and brings anxiety to family members.
- To the clinician, it is considered as a biological and psychosocial emergency.
- In 1-in-4500 births, the genital anatomy is so abnormal that it is not possible to decide the sex of the baby.

Clinical Features in a Neonate Suggesting Sexual Ambiguity

- Ambiguous external genitalia.
- Masses palpable in the labia majora or inguinal canal in a female.
- Hypospadias with uni- or bilateral cryptorchidism.
- Bilateral cryptorchidism.
- Salt-losing crisis after a few days.
- Micropenis.

Different forms (Nomenclature) of DSD include

- 46, XX DSD, 46, XY DSD Ovotesticular DSD, 46, XX testicular DSD and 46, XY complete gonadal dysgenesis.
- ***46XX DSD***: this is a case of a virilised female. There is the presence of foetal androgens. Causes include: Congenital adrenal hyperplasia: 21α, 11ß, 3β.
- Maternal androgens, Iatrogenic Foetal Virilization, Associated with congenital malformations, Unexplained, Simulation by Local Lesions.
- ***46XY DSD***: This is an undervirilized male. Causes may include–
  - (1) Impaired Leydig Cell Activity as seen in Inborn errors of testosterone biosynthesis, Leydig cell hypoplasia;
  - (2) Impaired Peripheral Androgen Metabolism as seen in 5α-Reductase deficiency, Androgen receptor defects, Post-receptor resistance;
  - 3) Others associated with congenital anomalies, Iatrogenic, Persistent Mullerian structures.
- ***Ovotesticular DSD***:
  - A very rare condition, characterized by the presence of ovarian and testicular tissue (testis + ovary, or ovotestis, true hermaphroditism) in the same individual;
  - External genitalia show varying degrees of ambiguity;

- Genetically the majority of cases are XX, a much smaller proportion are XY, and the remainder are mosaics**.**

Clinical approach to ambiguous genitalia

- The need to assign a sex to a newborn is a medical/psychological emergency and should involve a multi-disciplinary team: a Paediatric endocrinologist (Head of team), Paediatric urologist, Psychologist, and the Parents.

History

- A careful family history is very important, and may elucidate other affected family members, e.g. Salt loss, ambiguous genitalia with autosomal recessive (AR) inheritance (especially important in consanguinous families) will point to CAH.
- Aunties/sisters on the mother's side with absent menstruation/ infertility (X-linked inheritance).

Physical examination

- The presence of palpable gonads will likely be due to testes but may not be normal. An ovary may be present in an inguinal hernia.
- The presence of a dysmorphic appearance can be seen in Turner's in XO/XY.
- Features of systemic illness (lethargy, dehydration, fever, hypotension) will suggest adrenocortical insufficiency.
- The presence of pigmentation will point to an increased ACTH level and suggests CAH.
- Absence of a uterus will indicate the presence of AMH (from foetal testis) seen in androgen insensitivity syndrome (AIS).

Investigations

- This will include:
  - Karyotype;
  - Hormonal measurements (basal/stimulated) in blood and/or urine;
  - Ultrasound of pelvis: presence of uterus, ovaries, vagina;
  - Genitograph.

Counselling

- The clinician should: Be prepared to discuss all the results openly and be careful about the terminology used.

- State very clearly what is the recommended sex of rearing, with reasons.
- Listen to the parents' views carefully.
- Avoid referring to the baby as "it"; say "your baby". Start using the baby's given name and the word "he" or "she" as soon as the sex of rearing has been decided.
- Ask all staff to follow suit.

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12.12 Normal puberty

Introduction

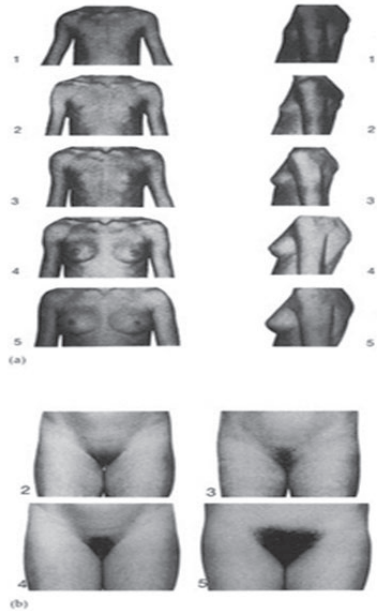
- Puberty is the stage of development during which children attain adult secondary sexual characteristics and reproductive capability. It is a transition from the sexually immature to the sexually mature stage.
- There is a complex cascade of hormonal signals that trigger puberty and regulate its progress. The changes of puberty occur because of orderly, sequential changes in endocrine activity.

Normal puberty

- The normal age of onset of puberty in North America is 9-14 years in boys, while in girls it is 8-13 years. Certain genetic, environmental, nutritional and life conditions have been shown to have a contributory influence on the timing of puberty.
- Although the precise trigger of puberty is unknown, however, at the onset of puberty, kisspeptin, a hypothalamic neuronal peptide is secreted, which in turn stimulates the gonadotropin-releasing hormone (GNRH) from the hypothalamus.
- The physical changes of puberty in individuals are defined by the Tanner stages.
- It assesses–breast development and pubic hair for females while in males it assesses external genitalia and pubic hair.
- ***Girls*****:** Pubertal development in girls begins with breast budding, then pubic hair. The onset of the growth spurt occurs with breast budding and menarche occurs at the end of puberty.
- ***Boys*****:** This starts by testicular and genital enlargement, then pubic hair. Although initial onset of puberty is similar to that of girls, the growth spurt occurs around mid-puberty, later than in girls.

Pubertal Stages

Girls: breast development



Stage B1: Preadolescent. Elevation of the papilla only.

Stage B2: Breast buds are palpable with enlargement of the areola.

Stage B3: Further enlargement and elevation of the breast and areola, with no separation of their contours.

Stage B4: Projection of the areola and papilla to form a secondary mound above the level of the breast.

Stage B5: Mature stage, projection of the papilla alone due to the recession of the areola.

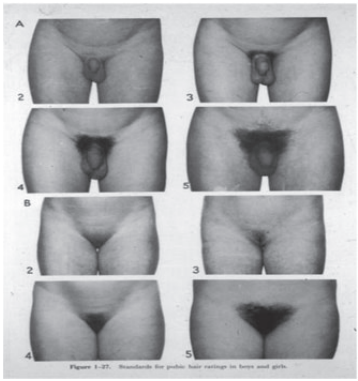
Girls Stage PH1: Preadolescent. No pubic hair.

Stage PH2: Sparse growth of slightly pigmented downy hair chiefly along the labia.

Stage PH3: Hair is darker, coarser and more curled, spreading sparsely over the junction of the pubes.

Stage PH4: Thick adult-type hair, but not spread to the medial surface of the thighs.

Stage PH5: Adult-type hair is distributed in the classic inverse triangle.



Boys Stage P1: Preadolescent. No pubic hair.

Stage P2: Sparse growth of slightly pigmented downy hair chiefly at the base of the penis.

Stage P3: Hair is darker, coarser and more curled, spreading sparsely over the junction of the pubes.

Stage P4: Hair is adult in type, but not spread to thighs.

Stage P5: Adult-type hair and spread to the medial thighs.

Boys: Testicular and Genital enlargement

Stage G1: Preadolescent. The testes, scrotum and penis are the size as in early childhood.

Stage G2: The testes have enlarged more than 2.5 cm in diameter. The skin of the scrotum reddens and there are changes in texture. Little or no enlargement of the penis.

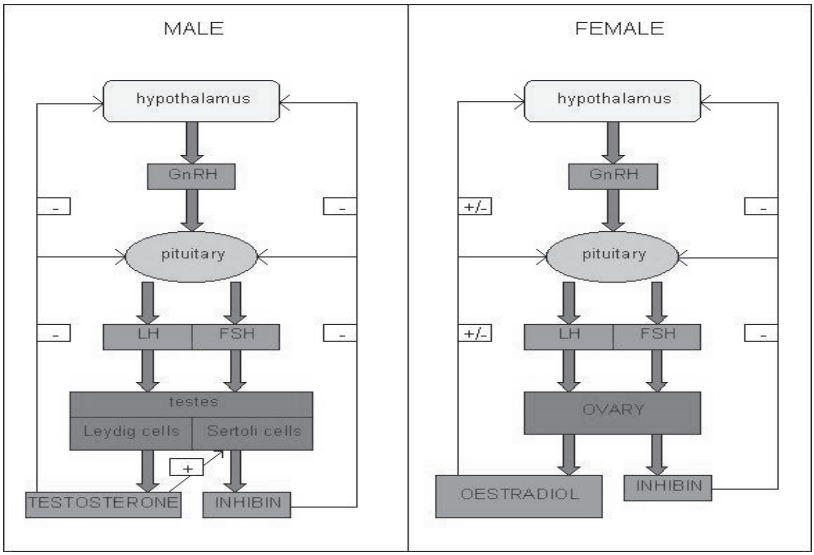
Stage G3: The penis grows in width and length. There is further growth of the testes and scrotum.

Orchidometer: for the measurement of testicular volume

Stage 4: The penis further enlarges and the testes are larger with a darker scrotal skin colour.

Stage 5: Genitalia are adult in size and shape.

Normal puberty hormones



- **Hypothalamus: GnRH (LHRH).** The gonadotropin-releasing hormone controls the release of the luteinizing hormone and follicle stimulating hormone (LH & FSH) from the anterior pituitary gland and this is the most important regulatory mechanism for sexual maturation and fertility.

- **Pituitary Gonadotropins: (LH & FSH)** The gonadotropins activate the production of sex steroids from the testes and ovaries.
- Follicle stimulating hormone (FSH): stimulates testes and ovaries to produce sperm and ova, while Luteinizing hormone (LH): releases sex hormones from the testes and ovaries–testosterone and oestradiol respectively.
- **Androgens ("Male-Type" Hormones).** These are produced in both sexes and are responsible for virilization (including pubic hair). They are produced by both gonads and adrenals. The predominant androgen from the gonads is testosterone, although androstenedione and dihydro-testosterone are also androgenic.
- **Oestrogen ("Female-Type" Hormone)**. This is responsible for breast development. Produced in gonads, it can also be produced by peripheral conversion of androgens in fat tissue.

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12.13 Pubertal disorders

Precocious puberty

- This is the onset of secondary sexual characteristics before the age of 8 years in girls, and 9 years in boys (-3 SD below the mean). Also, Menarche before 9 years of age (-4 SD).
- The Lawson Wilkins Pediatric Endocrine Society (LWPES) recommended that evaluation for a pathologic cause of precocious puberty be reserved for white girls who have breast and/or pubic hair development before seven years of age and black American girls before six years of age.
- ***Features of precocious puberty***–patients present with features of pubertal changes, tall stature (esp. in relation to parental heights), rapid growth rate, advanced skeletal maturation (advanced bone age).
- They also present with evidence of sex-steroid production: greasy skin and hair, acne, body odour, mood swings.
- The consequence of this is that children will present with rapid growth and progress to maturation and early epiphyseal fusion at an early age with a resultant final short adult height.

Causes of precocious puberty

CENTRALLY MEDIATE (**Gonadotropin dependent** or central precocious puberty (CPP)
- Idiopathic
- Secondary: Tumours, (hamartoma, optic glioma hydrocephalus, trauma, abuse.

Gonadotrophin Independent Precocious Puberty
- Primary cause is in the gonads e.g. tumours, ovarian cyst, McCune-Albright syndrome
- Testotoxicosis

Virilization (Gonadotropin independent precocious puberty)
- Adrenarche
- Congenital adrenal hyperplasia
- Cushing's disease, Adrenal tumours

Abnormal Patterns of Gonadotrophin Secretion
- Premature thelarche & thelarche variant
- Hypothyroidism

- ***In gonadotropin dependent, precocious puberty*** (GDPP or central precocious puberty)–this is caused by premature activation of the hypothalamus-pituitary-gonadal axis.
- Pubertal events progress in the normal sequence. The majority of cases are idiopathic, and most (90%) are girls.
- ***In gonadotropin Independent Precocious puberty*** (GIPP or peripheral precocious puberty). It is caused by excess secretion of sex hormones (oestrogens or androgens) derived either from the gonads or adrenals.
- It is independent of gonadotropin-releasing hormone (GnRH) and gonadotropin stimulation. It is more common in boys than girls.
- In abnormal Patterns of Gonadotropin Secretion (**Incomplete precocious puberty**)–There is early development of secondary sexual characteristics and usually it is a variant of normal puberty.
- Children with premature thelarche and premature adrenarche have incomplete preciosity. It is transient, puberty occurs at the usual time, and growth velocity is usually normal. Bone age is not advanced and final height is also normal.
- However, close monitoring is needed, as a significant number of these children will develop GDPP.

Approach to management of precocious puberty

- History: Age at presentation, progression, growth, and the development of other features. Examination will include height, pubertal staging (Tanner staging), signs of virilization/feminization and other features like a skin exam (McCune-Albright). Investigation will include–a hormonal profile e.g.: LH/FSH (LHRH test), oestradiol, testosterone and other androgens (blood or urine), TFT.
- Radiological investigation for: bone age, pelvic ultrasound, other scans (head, adrenal).
- Treatment: this is directed at the cause and treating the underlying disease conditions e.g. in CPP–treatment with GnRH agonists (Leuprorelin, Goserelin, Triptorelin).
- These drugs are GnRH analogues that act by binding to the anterior pituitary receptors causing down-regulation and desensitization of the pituitary.
- The pituitary gonadotrophs are subjected to prolonged rather than physiological pulsatile GnRH levels.

Delayed puberty

- Puberty is delayed if the early signs of puberty are absent at an age when most other children are relatively advanced in puberty.
- In North America and the UK, the lack of breast development by the age of 13 years in girls and the lack of testicular enlargement by 14 years in boys suggest delayed puberty.
- ***Causes of delayed puberty*** can be classified into central and peripheral.
- ***Central–***–In the presence of an intact Hypothalomo-pituitary axis (HP)–Constitutional delay in growth and puberty (CDGP), chronic disease, poor nutrition, psychosocial deprivation, steroid therapy, hypothyroidism.
- In Impaired HP-axis–tumours are adjacent to the HP axis (cranio, optic glioma, germinoma),
- Congenital anomalies (hypopituitarism, septo-optic hypoplasia), irradiation and trauma,
- GnRH/LH/FSH deficiency (including Kallmann, Prader-Willi, Laurence-Moon-Bardet-Biedl syndrome).
- ***Peripheral causes***–In male-bilateral testicular damage (cryptorchidism, torsion).
- Syndromes associated with cryptorchidism (Noonan, Prader-Willi, Laurence-Moon-Bardet-Biedl syndrome).
- In female intersex disorders e.g. androgen insensitivity syndrome (AIS), polycystic ovarian syndrome, toxic damage (thalassaemia, galactosaemia).
- In both sexes–gonadal dysgenesis [female; Turner syndrome (45XO), male; Klinefelter syndrome (47XXY)] and irradiation/ chemotherapy.

Approach to management in delayed puberty

- ***History***: take a good history paying attention to the growth pattern, a systemic review about general health including neurological symptoms, sense of smell, nutritional history, past medical/surgical history.
- Any long-term therapy–chemotherapy, radiotherapy, family history, development history (the presence of a learning difficulty, behaviour problems). History of undescended testis.
- **In physical examination**–Do the anthropometry, Tanner staging body habitus, signs of chronic illness, check for signs of

dysmorphic features, other diseases (thyroid, CNS, inflammation), neurological (sense of smell, visual fields, other cranial nerve lesions, etc.), hernia repairs or scars. The presence of gynaecomastia, external genitalia appearance: stretched penile length (micropenis), imperforate hymen.

- **An investigation will include**–Basal gonadotropins (LH, FSH), sex steroid levels: oestradiol in girls, early morning testosterone in boys, prolactin, thyroid function test, coeliac screen, FBC, ESR, LFT, bone chemistry, bone age, pelvic or testicular ultrasound, testicular biopsy, CT scan/MRI, karyotyping.
- **Treatment**–This involves treating the underlying cause in chronic systemic diseases.
- In Constitutional delay in growth and puberty–reassurance and counselling are given, however short-term treatment with testosterone or oestrogens for 3 to 6 months occasionally is required if the patient is psychologically stressed.
- Other forms of treatment are given depending on the cause such as hormonal replacement therapy–Males, monthly IM Testosterone, oral testosterone, dermatological preparations (patches and gels) give promising results. Oral Oxandrolone (synthetic androgen) daily.
- Hormonal replacement therapy–Females.
- Constitutional delay in growth and puberty (CDGP) is the most common cause of delayed puberty in both boys and girls. It is more common in boys than girls (7:1).
- Diagnosis is based on: History of long-standing/borderline short stature during childhood, poor growth from ~11 years of age, delayed puberty, delayed bone age; often there is a positive family history, the absence of other causes to account for delayed puberty. Treatment is mainly reassurance and counselling.

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SECTION 13

PREVENTIVE PAEDIATRICS

TAGBO, B.

13.1 Primary Healthcare and Child Survival

Introduction

- 1977–WHO declaration of health for all by the year 2000 and beyond.
- 1978–Alma Ata declaration >> PHC.
- PHC–"Essential health care, based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families in the community by means acceptable to them, through their full participation and at a cost that the community and family can afford to maintain at every stage of their development in a spirit of Self-determination."
- It forms an integral part both of the country's health system, of which it is the central function and main focus, and of the overall social and economic development of the community.
- "It is the first level of contact of individuals, the family and community with the national health system bringing health care as close as possible to where people live and work, and constitutes the first element of a continuing health care process"–*World Health Organization 1978. Declaration of Alma Ata.*
- 1948–WHO defined health as "A state of complete physical, mental and social well-being and not merely the absence of Disease or deformity."
- The PHC objective is to reach everyone especially those in greatest need.
- UNICEF developed the Child Survival and Development Revolution (CSDR) as a means of achieving PHC.

- Initially–4 high impact interventions (Child Survival Strategies) Growth monitoring, ORT, Breast feeding and Immunization **(GOBI)**.
- Then–7 Strategies **(GOBIFFF)** where the 3Fs are Female education, Family planning and Food supplementation.
- Then–11 Strategies **(GOBIFFFEETH)** OR **[GOBIF^3 E^{2}TH]**.
- E^{2}TH–Essential drugs, Environmental sanitation, Treatment of common ailments and injuries, Health education.
- Integration into the existing health system is fundamental.

Elements of PHC

- The ultimate goal of primary health care is better health for all. The WHO has identified five key elements to achieve that goal:
- reducing exclusion and social disparities in health (universal coverage reforms);
- organizing health services around people's needs and expectations (service delivery reforms);
- integrating health into all sectors (public policy reforms);
- pursuing collaborative models of policy dialogue (leadership reforms); and
- increasing stakeholder participation.

Characteristics of PHC

- Targeted at the most vulnerable.
- Reach them at the community where they are.
- Made simple enough yet very effective.
- Low cost.
- Sustainable.
- Full involvement of the community.

Components of PHC

- Health promotion (Health education).
- Promotion of food supply and proper nutrition.
- Adequate supply of safe water and basic sanitation.
- Maternal and child healthcare service including family planning.
- Immunization against common childhood diseases.
- Treatment of common minor ailments and injuries.

- Provision of essential drugs and supplies.
- Promotion of a programme on mental health.
- Promotion of a programme on oral health–Nigeria.

Problems of PHC

Poor funding

- Donor driven.
- Lack of sustainability.
- No community participation.
- Lack of ownership of the programme e.g. EBF.
- Central governance.
- Poor accountability.
- Lack of leadership and coordination.

Poor referral system

- Inadequate functional and accessible secondary care.
- Distance.
- Transport.
- Road infrastructure.
- Communication.
- Cultural inhibitions.

Poor staffing

- Poor motivation.
- Rural deprived environment.
- Poor supervision.
- Inappropriate staff deployment.
- Poor infrastructure at the PHC facility.

Lack of community participation

- Sustainability.
- Accountability.
- Functionality.

Poor political will

- No perceived tangible benefit.
- Poor awareness.
- Lack of advocacy.

Nigeria

- In Nigeria, the LG is responsible for the provision of PHC.
- However, there is a Federal NPHCDA responsible for policy-making and supervision.
- Because the PHC has not received attention from LG,
- The Federal Government has gone beyond its mandate to provide some support especially infrastructure.
- This however, has not been optimal due to the fact that the Federal Government is too centralized with poor accountability.
- HCs are often sited in areas too far away from where the people live (>5 km) often due to political reasons.

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13.2 Introductory Vaccinology

What is vaccinology?

- The science or methodology of developing a vaccine, testing it, producing it in large quantities and utilizing it to protect against diseases.

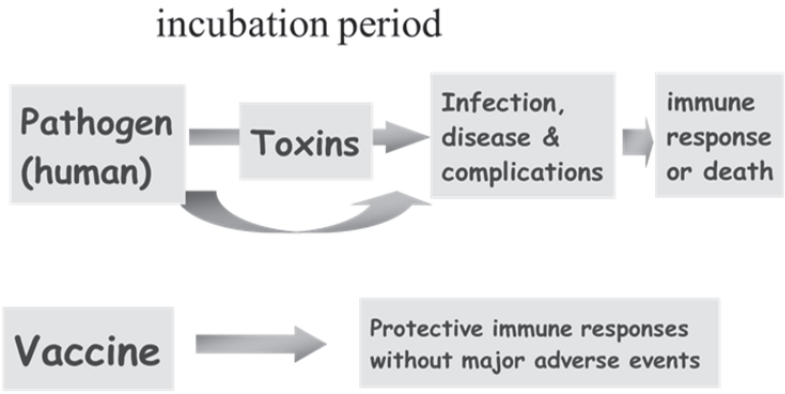
Vaccinology involves

- Product development and GMP.
- Deployment of the vaccine for the best outcomes.
- Provision of appropriate vaccine-related healthcare infrastructure.
- Provision of strong disease surveillance.

Vaccinology is therefore a combination of

- Microbiology, Virology, Immunology, Epidemiology, Preventive Paediatrics, Infectious diseases and Preventive Medicine.

Battle for survival!



Innate & adaptive immunity

- Innate immunity–the first line of defence, present from birth, non-specific.

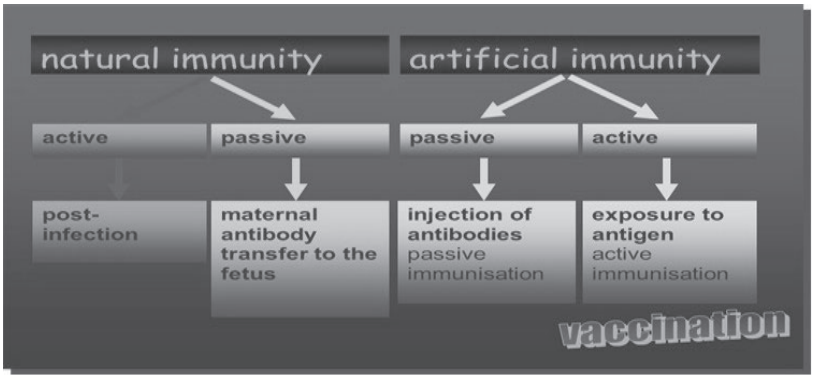
- Adaptive immunity–the second line of defence, learned, specific.

Immune response mechanisms

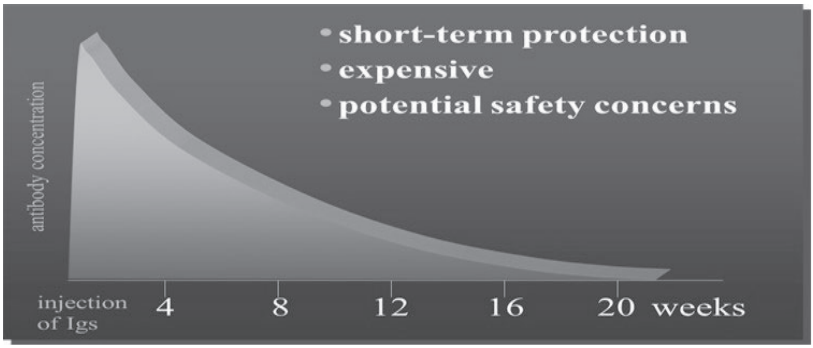
Cell-mediated
- Proliferation of specialised cells.
- Directed against intra-cellular pathogens.
- Mediated by T lymphocytes.

Antibody-mediated
- Generation of specialised proteins or antibodies.
- Directed against circulating antigens/pathogens.
- Mediated by B lymphocytes +/- T lymphocytes help.

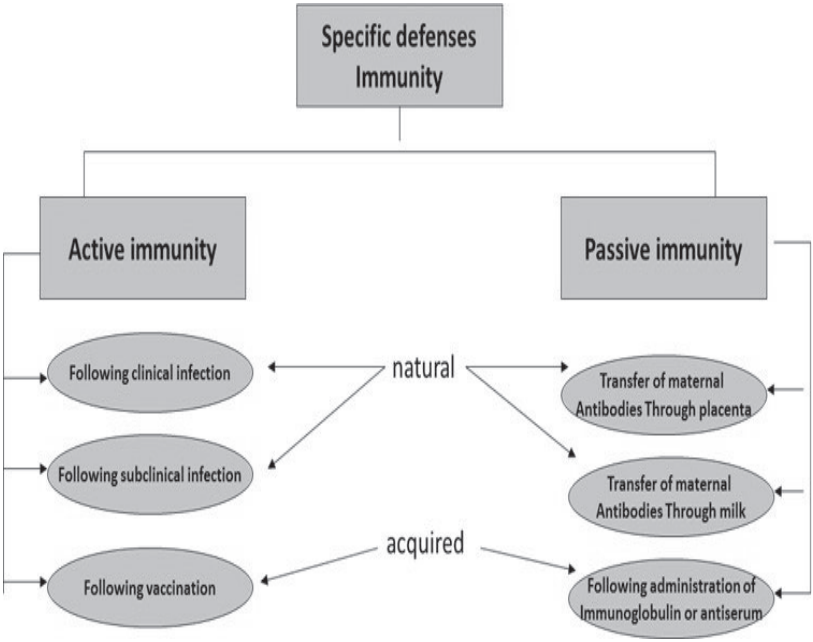
Passive & active immunity



Passive immunisation



Immunity



What is a vaccine?

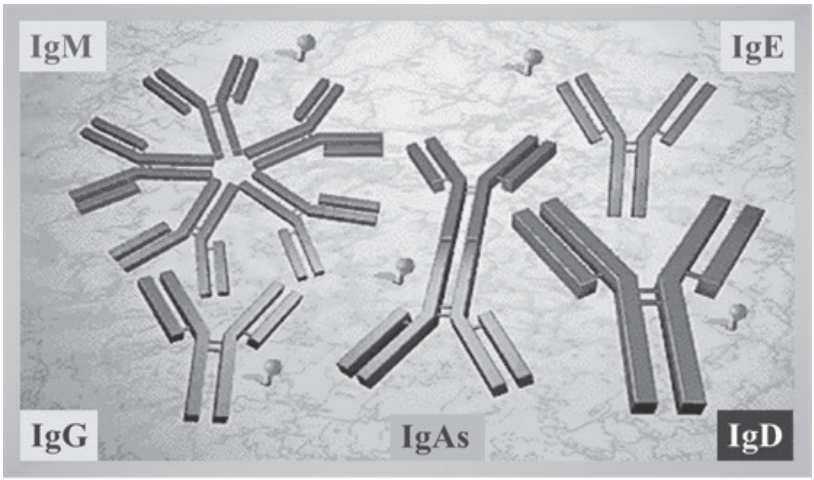
- An inactivated or attenuated pathogen or, a component of a pathogen that when administered to the host, stimulates a protective response of the cells in the immune system.
- A vaccine is immunogenic (antigenic) but not pathogenic.

Herd Protective Effects of Vaccines

- Are demonstrated by a protective impact of a vaccine in a population that exceeds an impact expected on the basis of:
  - The proportion of the population vaccinated and the protective efficacy of the vaccine.
- Can result from:
  - Transmission of a live vaccine from the vaccinee to a neighbouring non-vaccinee ("herd immunity");

- Reduction of transmission of the target pathogen in a population in which a proportion become immune due to vaccination with either a live or an inactivated vaccine ("herd protection").

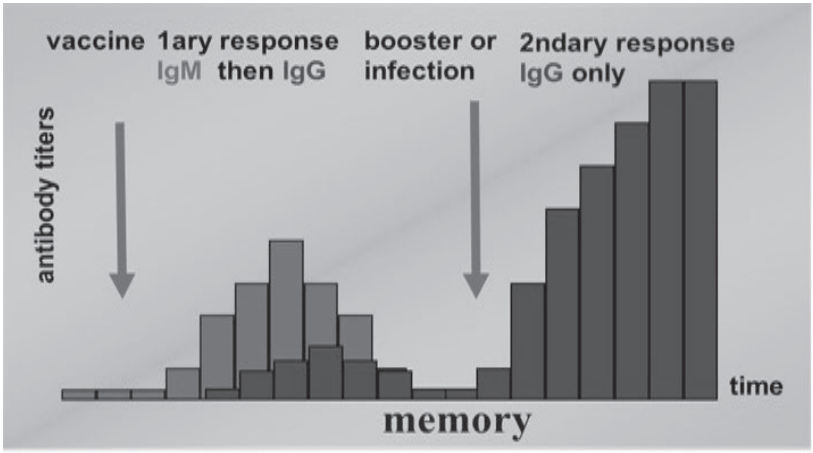
5 classes of antibodies



Principle of vaccination

- The purpose of vaccination is to produce an antigen-specific immune response against a virulent infectious agent without actually causing disease.
- It was first scientifically demonstrated famously by Edward Jenner in the late 1700s
  - He inoculated a young boy with cowpox virus material, less-virulent than the deadly smallpox virus;
  - When the boy was subsequently inoculated with fully virulent material from a smallpox lesion, the child did not develop the disease
- Vaccines effect their immune protection primarily by the stimulation of B lymphocytes, rarely CD4 and CD8.

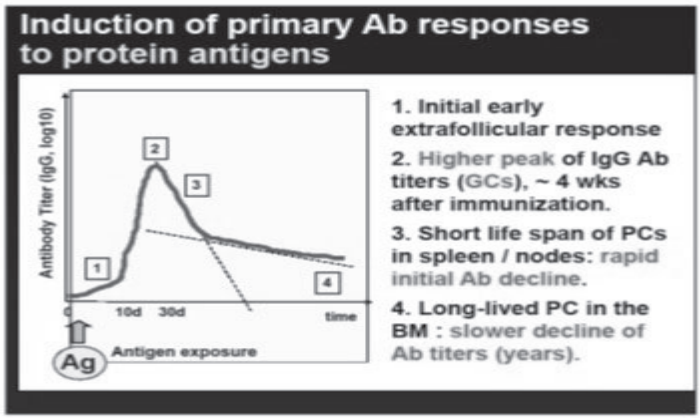
Principle of vaccination

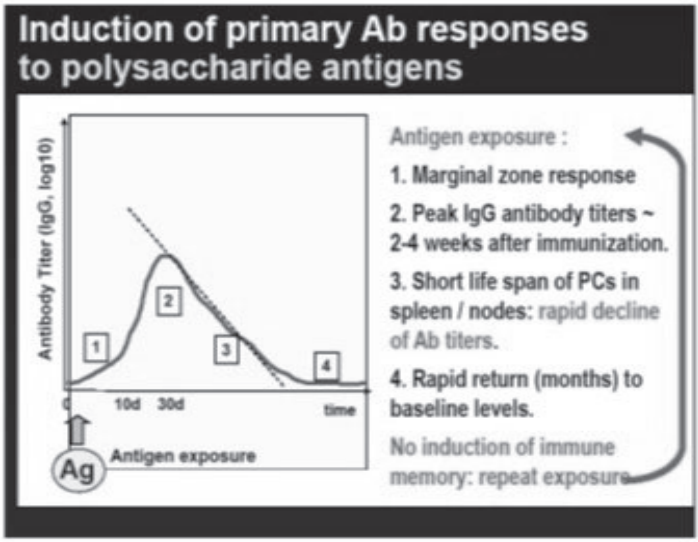


Types of vaccines

- Live vaccines (attenuated), Inactivated (killed vaccines), Toxoids, Polysaccharide and polypeptide (cellular fraction or sub-unit) vaccines, DNA (recombinant) vaccines.

Vaccination scheduling





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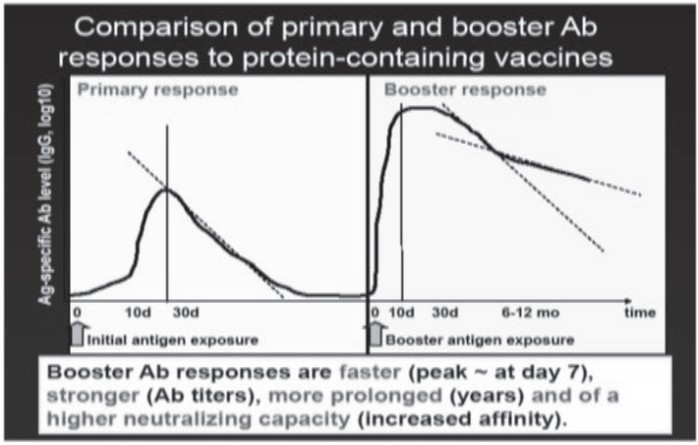


Determinant of duration of Ab responses in healthy individuals

- Type of vaccine.
- Interval b/w primary doses.
- Interval before boosting.
- Age at immunization.

Qualities of an ideal vaccine

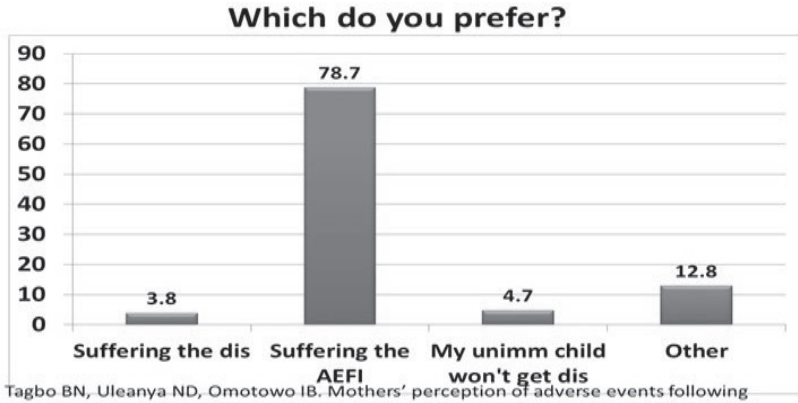
- Affordable & accessible.
- Acceptable reactogenicity profile.
- Long-lasting protection.
- Immunogenic and protective.
- Stable in field use.
- Can be integrated into EPI.
- No frequent boosters required.

How Vaccines differ from drugs

- Given to healthy people, high safety required.
- Larger governmental role.
- Low efficacy unacceptable.
- Often used in infants.
- Given once or a few times.
- Manufacturing is the larger part of the cost.

- High regulatory and quality control burden and it is supposed to be
- Cheap.

Attitude to vaccines



Tagbo BN, Uleanya ND, Omotowo IB. Mothers' perception of adverse events following routine immunization. J Vaccines Vaccin 2013: 4: 202. doi: 10.4172/2157-7560.1000202

The Road to Vaccine Development

Academic

1. Identify the mechanism of natural protection.
2. Isolate the antigen(s) responsible for the protection.
3. Show in animals that the vaccine protects.
4. Find the best formulation of the antigen.

Industry

5. Increase the yield and purity of the vaccine.
6. Show the safety of the vaccine in animals.
7. Produce a lot under GMP.
8. Perform Phases 1, 2, 3, 4 of the clinical trial.

Phases of Vaccine Development

- Preclinical–Yield, Animal safety and Immunogenicity.
- Phase 1–Safety and Immunogenicity (10-100).
- Phase 2–Dose, Schedule, Safety, Immunogenicity (100-1000).
- Phase 3–Efficacy, Safety (10,000-70,000), Consistency.
- Phase 4–Safety (100,000-1,000,000).

Minimal Timing of Vaccine Development

- Preclinical 2 years
- Phase 1 1 year
- Phase 2 2-3 years
- Phase 3 3 years
- Licensing 1 year

Ten years minimum, 15 years median

- Phase 4 3 years

Other aspects of vaccinology will be discussed in the following few sections.

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13.3. Routine Immunization, Target Diseases and Schedule

Introduction

- Immunization prevents between 2 and 3 million deaths every year.
- Global measles mortality has declined by 74%.
- Polio cases have decreased by over 99%.
- Immunization provides an opportunity to deliver other life-saving measures.

Definition

- It refers to a procedure that increases an individual's level of immunity against a particular infectious agent or toxin.

Explanation

- The process of protecting an individual against communicable diseases by injecting weakened or killed infectious organisms or part of their structure into the body to cause the immune system to produce antibodies against the organism without causing the full-blown disease.
- Immunization is the process by which an individual's immune system becomes fortified against an agent (known as the immunogen).

WHO

- Immunization is the process whereby a person is made immune or resistant to an infectious disease, typically by the administration of a vaccine.
- Vaccines stimulate the body's own immune system to protect the person against subsequent infection or disease.
- An organism is treated so that it loses its pathogenicity while maintaining immunogenicity.
- Pathogenicity = ability to cause disease.
- Immunogenicity = ability to stimulate/increase immunity.

Vaccination Vs Immunization

- Vaccination = introducing vaccines into an individual.
- Immunization = protection against the disease.

Routine Immunization (RI)

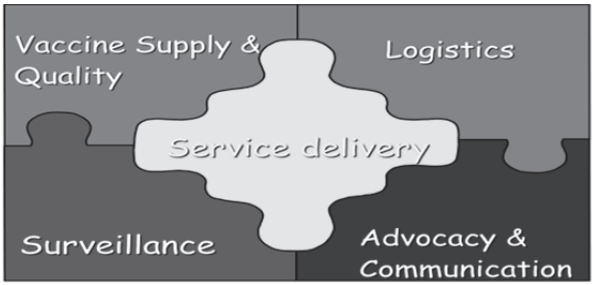
- This refers to immunization given to eligible age groups of children (<1 year) and Women of Childbearing Age (WCBA) during regular visits to the Health Facility.
- The **GOAL** is to reduce morbidity and mortality due to vaccine preventable disease through the provision of potent vaccines, technical, cold chain and logistics to States and LGAs.
- The **TARGET** is to control vaccine preventable diseases through the use of vaccines.

To reduce the disease burden due to VPDs a minimum vaccination coverage of 80% is desired.

Elements of RI

- Vaccines Supply.
- Logistics/Cold Chain.
- Service Delivery.
- Data/Records Management.
- Advocacy/Social mobilization/Communication.
- Surveillance, Monitoring & Supervision.
- Co-ordination and collaboration.

WHO's Approach: Components of the routine immunization system



Strategies for RI service provision

- Fixed Post: Regular Vaccination at the Health Post on specific days as scheduled.

- OUTREACH: Service Delivery to Clients who cannot get to the Health Facility. Could be done monthly.
- Service delivery to people living in remote areas. This has a high resource implication.

RI target diseases in Nigeria

- Tuberculosis
- Diphtheria
- Pertussis
- Tetanus
- Poliomyelitis
- Measles
- Yellow fever
- Hepatitis B
- Haemophilus influenza b (Hib)
- Pneumococcal disease
- Cerebrospinal meningitis^
- Rotavirus*
- Human papilloma virus*
- Malaria*
- *^Not on a routine basis *in the pipeline*

National RI Target Diseases and their causes

NPI Target Disease	Causative organisms	Transmission
Tuberculosis	Mycobacterium Tuberculosis	Droplet infection
Poliomyelitis	Polio Virus	Faeco-oral infection
Diphtheria	Corynebacterium Diphtheriae	Droplet infection
Pertussis (whooping cough)	Bordetella Pertussis	Droplet infection
Tetanus	Clostridium Tetani	Infected and unsterilized instruments

Hepatitis B	Hepatitis B virus	Through infected blood and blood products
Yellow Fever	Yellow Fever Virus	From the bite of infected mosquitoes
Measles	Measles Virus	Droplet infection
Meningitis	Neisseria Meningitidis	Overcrowding, hot weather
Haemophilus influenzae b	Haemophilus influenzae b	Overcrowding, nasal carriers
Pneumococcal disease	Strep Pneumococcus	Overcrowding, nasal carriers
Rotavirus	Rotavirus	Faeco-oral
Human papilloma virus	Human papilloma virus	Sexual
Malaria	Plasmodium	Mosquito bite

National Routine Immunization schedule (by disease/vaccine)

NPI Target Disease	**Period of Administration**
Tuberculosis/BCG	At birth
Poliomyelitis/OPV	At birth, 6, 10 & 14 weeks
Poliomyelitis/IPV	At 14 weeks
Pentavalent (DPT, HBV, Hib)	6, 10 & 14 weeks
PCV	6, 10 & 14 weeks
Rotavirus disease/RV	6 & 10 weeks
Hepatitis B/HBV	At birth
Yellow Fever	9 months
Measles	9 months
Meningitis^	12 months

Nigerian national routine immunization schedule (by age)

Age	Antigens (vaccines) given
Birth	BCG, OPV_0, $HepB_0$
6 weeks	OPV_1, $Pentavalent_1$, PCV_1, $Rota_1$
10 weeks	OPV_2, $Pentavalent_2$, PCV_2, $Rota_2$
14 weeks	OPV_3, IPV, $Pentavalent_3$, PCV_3
9 months	Measles, Yellow Fever

Vaccines and their administration

Contact	Minimum target age	Type of vaccine	Dosage	Route	Site
1st	At birth	HBV,	0.5 ml	Intramuscular	Outer thigh Upper left arm
		BCG,	0.05 ml	Intradermal	
		OPV_0	2 drops	Oral	
2nd	At 6 weeks	$Penta_1$	0.5 ml	Intramuscular	Left outer thigh
		OPV_1	2 drops	Oral	
		PCV_1	0.5 ml	Intramuscular	Right outer thigh
		$Rota_1$	1 ml	Oral	
3rd	At 10 weeks	$Penta_2$	0.5 ml	Intramuscular	Left outer thigh
		OPV_2	2 drops	Oral	
		PCV_2	0.5 ml	Intramuscular	Right outer thigh
		$Rota_2$	1 ml	Oral	

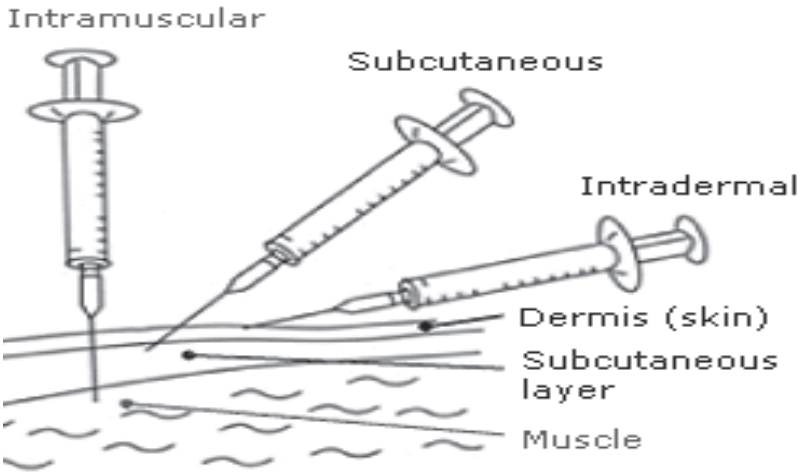
4th	At 14 weeks	Penta$_3$	0.5 ml	Intramuscular	Left outer thigh
		OPV$_3$	2 drops	Oral	
		PCV$_3$	0.5 ml	Intramuscular	Right outer thigh^
		IPV	0.5 ml	Intramuscular	Right outer thigh^
5th	9-12 months	MV	0.5 ml	Subcutaneous	Upper left arm
		YF	0.5 ml	Subcutaneous	Upper right arm

^At least 2.5 cm apart (about 2 finger-breadths apart)

Tetanus toxoid for women of childbearing age

Dose	When to give	%age protect-tion	Duration of protection
TT-1	At 1st contact or as early as possible in pregnancy	NIL	None
TT-2	At least 4 weeks after TT-1	80	3 years
TT-3	At least 6 months after TT-2 or during subsequent pregnancy	95	5 years
TT-4	At least one year after TT-3 or at subsequent pregnancy	99	10 years
TT-5	At least one year after TT-4 or during subsequent pregnancy	99	For life

Routes of vaccine administration



Vitamin A

- Not a vaccine, but a micronutrient that is usually given along with vaccines to infants and pregnant women.
- Essential for growth and development; strengthening the immune system, limiting the severity of illness and increasing the chances of curability.
- Deficiency causes reduced resistance to infection, blindness in children and anaemia.
- Prevention is by consuming enough vitamin A rich food in addition to taking vitamin A drops (Vitamin A supplementation).
- Vitamin A supplementation during RI and SIAs (e.g. During NIPDs) is one of the quickest and least expensive ways of reaching a large number of children in high risk groups.

Vitamin A dosage & schedule (2 doses given for 6-59 months at 6 month intervals)

Age Group	Dose to be given	Amount of Vitamin A	
		If 100,000 IU (blue) Capsule is given:	If 200,000 IU (red) capsule Is given:
6 -11 months	100,000 IU	All drops in one blue capsule	Half of the drops in one red capsule (4 drops)
12 - 59 months	200,000 IU	All drops in two blue capsules	All drops in one red capsule. (8 drops).

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13.4. Routine Vaccines

BCG Vaccine

- Bacillus Calmette Guerin.
- Protects against tuberculosis.
- Comes in powdered form.
- Must be reconstituted before use.
- Reconstituted vaccine is even more sensitive to heat than the powder and therefore must be used within 6 hours or discarded.
- Wrapped in foil or paper to protect it from light.
- Stored with the diluents at 0-8^{0}C.
- Given at birth or as soon as possible.
- One dose of 0.05 ml for <1 year and 0.1 m for >1 year given intradermally in the upper left arm.
- Do not rub or apply anything to the injection site.
- Side effects
  - A small sore for 2 weeks, and it will leave a small scar;
  - Swollen glands–refer to the doctor;
  - Abscess–refer to the doctor.
- Not given to children with clinical AIDS.

Hepatitis B Vaccine

- Protects against Hepatitis B.
- Comes in a cloudy liquid in a vial or a prefilled syringe.
- Does not have to be reconstituted.
- Must be mixed by shaking before administration.
- May come as a combination vaccine.
- Stored at 0-8^{0}C.
- Both heat- and freeze-sensitive.
- Given at birth, 6, 14 weeks.
- 0.5 ml at the outer part of the thigh, intramuscular.
- Side effects–mild fever–Paracetamol.

Oral Polio Vaccine (OPV)

- Protects against 3 types of virus that cause poliomyelitis.
- Liquid that comes in small plastic bottles that work like droppers or glass vials with droppers in a separate plastic bag.

- Since 1996, OPV vials supplied by WHO/UNICEF have had vaccine vial monitor (VVM) attached.
- It tells the health worker whether the vaccine is safe for use.
- Stored at 0-8^{0}C.
- Damaged by heat.
- Not harmed by freezing.
- Given at birth, 6, 10 and 14 weeks.
- The interval between doses must be at least 4 weeks.
- The dose is 2 drops.
- In the case of diarrhoea, give OPV as usual, then a 5th dose 4 weeks after last dose.
- Dropped in the mouth (Oral).
- Most of the time, no adverse events.
- Rarely paralysis (VAPP, cVDPVs).

Pentavalent vaccine

- Consists of:
  - Diphtheria toxoid;
  - Pertussis vaccine;
  - Tetanus toxoid;
  - Hepatitis B vaccine;
  - Haemophilus influenzae b vaccine.
- It comes in two separate formulations:
  1. Liquid;
  2. Liquid + lyophilized version (lyophilized means freeze dried).
- The Liquid + the Lyophilized version of the pentavalent vaccine comes in two separate vials.
  - One vial is liquid and contains DPT–hepatitis B vaccine (used as a diluent);
  - The other vial contains lyophilized (freeze-dried) Hib vaccine.
- Like the measles vaccine, the lyophilized pentavalent vaccine has to be mixed (reconstituted) before use.
- Stored at 0-8^{0}C.
- Diphtheria and Tetanus toxoids are damaged by freezing (do not freeze).
- Given at 6, 10 and 14 weeks.
- An interval between doses not less than 4 weeks.
- Do not give Pentavalent vaccine to children >3-5 years with a severe reaction to the previous dose.

- Instead give Td, Hep-B, Hib.
- The dose is 0.5 ml.
- Site–outer thigh, Intramuscular (IM)-never in the buttocks.
- Side effects may include:
  - About 25% of patients report pain, mild redness, swelling and soreness at the injection site;
  - Rarely, a fever may develop which should subside within 48 hours;
  - Paracetamol may be given to reduce symptoms;
  - Abscess–antibiotics +/- Incision & Drainage (I & D);
  - Serious side effects (e.g. anaphylactic shock) may occur, though these are extremely rare**.**

Inactivated Polio Vaccine (IPV)

- Prevents poliomyelitis.
- Comes in liquid form.
- Stored at 0-8^{0}C, freeze, heat and light sensitive (DO NOT FREEZE).
- Given intramuscularly on the outer thigh for infants, the dose is 0.5 ml.
- The primary series consists of 2-3 doses at least 4 weeks apart.
- However, in OPV-only countries, WHO has recommended the additional minimum of one dose of IPV preferably at 14 weeks.
- Side effects–redness, pain, swelling, fever, vomiting, anaphylactic reaction.

Measles vaccine

- Prevents measles.
- Comes in powdered form.
- Must be reconstituted before use and discarded after 6 hours.
- Stored at 0-8^{0}C.
- Not damaged by freezing.
- Given at 9 months or as soon as possible after 9 months, regardless of whether the child has had measles or not.
- Given subcutaneously at the upper left arm.
- Side effects–mild fever one week later, give paracetamol.
- Mild rash may appear–no treatment.

Yellow fever vaccine

- Prevents yellow fever.
- Comes in powdered form and must be reconstituted before use.
- Discard reconstituted vaccine after 6 hours.
- Stored at 0-8^{0}C.
- Given at 9 months.
- Not given before 6 months.
- Not given to children with clinical AIDS.
- The dose is 0.5 ml, subcutaneous, at the upper right arm.
- Side effects–fever, mild muscle/joint pain, treatment is paracetamol.

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13.5. Cold Chain System and Logistics

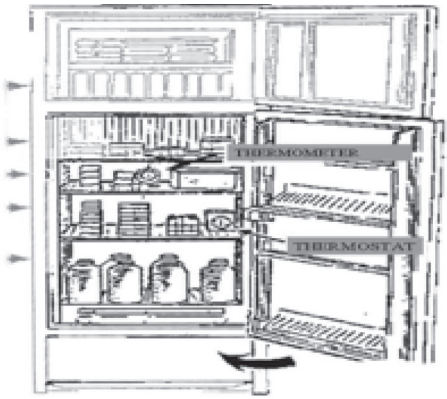
Introduction

- The "cold chain" is a system of storing and transporting vaccines at recommended temperatures from the point of manufacture to the point of use.
- That is, the role of the cold chain is to maintain the potency of vaccines.
- There is also a concept called the "reverse cold chain", which is a system of storing and transporting samples at recommended temperatures from the point of collection to the laboratory.
- The system used for keeping and distributing vaccines in good condition (potency) **is called the cold chain.**
- The cold chain consists of a series of storage and transport links, all designated to keep measles vaccine within an acceptable range until it reaches the user.
- **Two Types of Cold Chain Options**
- **"Slow cold chain":** Equips or provides each immunization unit with equipment for a long vaccine storage duration;
- **"Fast cold chain":** Provides the means of transport for frequent supplies to the immunization units.
- **Cold Chain Equipment**: Cold or Freezer rooms, freezers, refrigerators, cold boxes, and sometimes refrigerated trucks for transportation, Refrigerators with freezing compartments, ice-lined refrigerators, cold boxes and vaccine carriers, ice packs, power generating sets.

Storing Vaccines in the refrigerator

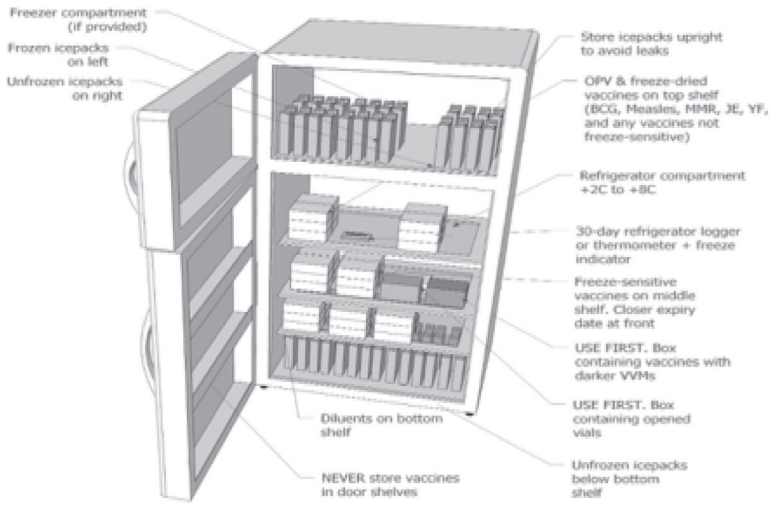
How to arrange vaccines in the refrigerator:

- Top: Ice packs;
- Shelf 1: Live viral vaccines (OPV, Measles);
- Shelf 2: Penta, TT, Hep B, BCG, IPV on the lower shelves away from the freezer space;
- The diluent next to its vaccine or clearly marked.



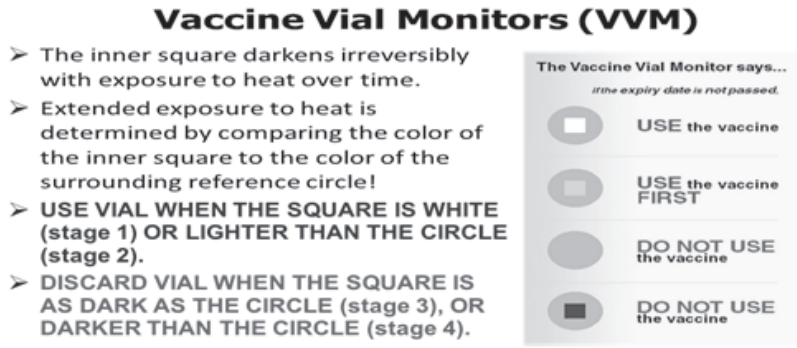
NPHCDA. Immunization training module for inactivated polio vaccine marked introduction in Nigeria 2015

Vaccine and diluent arrangement in a front-opening domestic, gas or kerosene vaccine refrigerator



WHO. Immunization in practice. Module 2: The vaccine cold chain. WHO/IVB/04.06

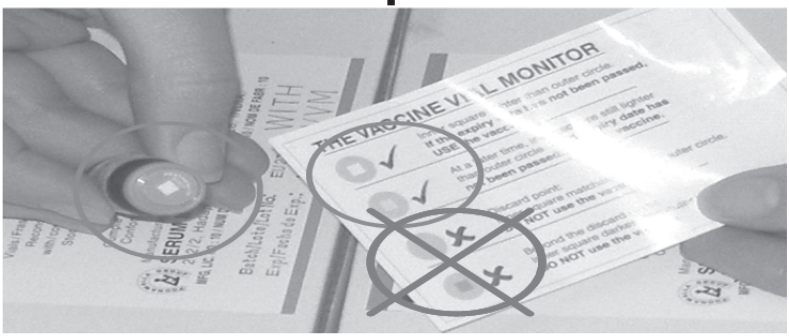
- **Maintenance of the cold chain requires vaccines and diluents to be:**
- **Collected** from the manufacturer or an airport as soon as they arrive and stored at a temperature of 2 to 8 degrees;
- **Transported** at a temperature between 2ºC and 8ºC from the airport and from one store to another;
- **Stored** at the correct temperature in primary/central and intermediate vaccine stores and in the health facility, -15ºC up to 2ºC-8ºC;
- **Transported** at a temperature between 2ºC and 8ºC to vaccination posts and during mobile activities;
- **Kept** at a temperature between the 2ºC and 8ºC range during immunization sessions; **and** during the return to health facilities from vaccination posts.



Check for vaccine safety

- Ensure the vaccine and diluents have labels, ensure the expiry date has not passed and ensure the VVM stage is not at the discard point.
- The VVM for reconstituted vaccines like measles is on top of the vial (on the cap).

VVM on top of Measles vaccine vial



- For liquid vaccines, the VVM is on the side label and the Multi-dose vial policy applies.
- Cold boxes when lined with frozen ice packs can store vaccines for 2-7 days, used for short-term storage at the health facility level.
- Vaccine carriers lined with frozen ice packs can store vaccines for a maximum of 24-48 hours.
- The duration of cold life is affected by the frequency of opening the cold box or vaccine carrier.

Multi-dose vial policy (MDVP)

This policy says you can re-use opened liquid vaccine vials if:

- The VVM has not passed the discard point, the expiry date has not passed and you have maintained aseptic conditions.

Ice Packs

- Ice Packs are flat plastic bottles that are filled with water and frozen.
- They are used to keep vaccines and diluents cool inside the vaccine carrier or cold box.
- The number of ice packs varies according to the model of the vaccine carrier.
- Gio-style: the preferred model for routine sessions, has space for 4 ice packs of size 0.4 ml.

Temperature range for vaccine storage

Type of vaccine	National store MAX 6 Months	Provincial store MAX 3 months	District store MAX 1 month	Service level MAX 1 month
OPV	-15°C to -25°C	-15°C to -25°C	+2°C to 8°C	+2°C to 8°C
BCG, Measles, MR, MMR, YF, Hib FD	WHO no longer recommends that freeze-dried vaccines be stored at –20°C. Storing them at –20°C is not harmful but it is unnecessary. Instead, these vaccines should be kept in refrigeration and transported at +2° to +8°C.		+2°C to 8°C	+2°C to 8°C
HepB, DTP-HepB Hib liquid, DTP, DT, TT, Td	+2°C to 8°C	+2°C to 8°C	+2°C to 8°C	+2°C to 8°C
HepB, DTP-HepB Hib liquid, DTP, DT, TT, Td	•NEVER freeze •Where space permits store diluents at +2°C and +8°C •When packaged with vaccine store diluents at +2°C and +8°C			+2°C to 8°C

WHO Recommended vaccines storage temperature

	Primary vaccine store Up to 6 Months	Intermediate vaccine store		Health centre Up to one month	Health post Up to one month
		Region- up to 3 months	District- up to one month		
OPV	-15°C to -25°C		+2°C to +8°C		
BCG	2°C to +8°C (-15°C to -25°C also possible)				
Measles, MR, MMR					
YF					
Hib freeze-dried					
Meningococcal A&C					
HepB	+2°C to +8°C Never Freeze !				
IPV					
DT, DTP, DTP Hep B					
Hib liquid					
Td					
TT					

OPTIMIZE PATH World Health Organization

THE SHAKE TEST

- The shake test is carried out whenever you suspect that a freeze-sensitive vaccine has frozen and then thawed.
- Below is the WHO protocol for conducting the shake test.

What is the Shake Test?

- The Shake Test is used to check whether freeze-sensitive vaccines have been damaged by exposure to temperatures below 0°C. After it has thawed, a vial of vaccine that has been frozen no longer has the appearance of a cloudy liquid, but tends to form flakes that settle at the bottom of the vial.
- The Shake Test requires two vials of the same vaccine from the same manufacture and with the same batch number. One of these is a vial that you suspect has been frozen and the other is a vial that you have deliberately frozen solid overnight. Allow the frozen test vial to melt completely, shake the two vials in the same hand, place them side-by-side and watch the contents settle. If the suspect vial settles at the same speed as the frozen vial you know that it has been frozen. If it settles more slowly, it has **not** been frozen.

When is the Shake Test needed?

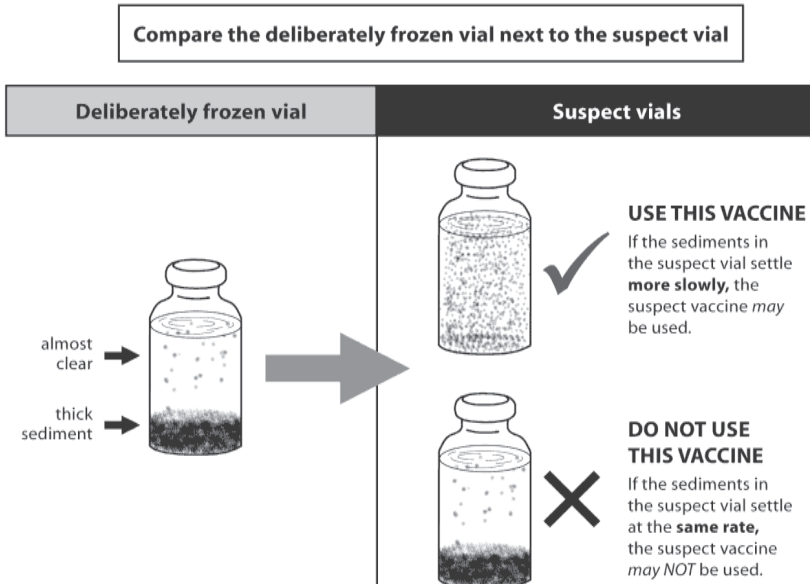
- If a freeze indicator is activated, or temperature recordings show negative temperatures, freeze-sensitive vaccines may have been damaged. If this occurs, notify your supervisor. If s/he decides to proceed, carry out the Shake Test on a sample of the freeze-sensitive vaccines.

How is the Shake Test done?

- The Shake Test protocol is shown below.

Notes: 1) **This protocol must not be altered**: there is only one correct way to conduct a Shake Test. 2) The test procedure described below should be repeated with all suspect batches. In the case of international arrivals, the shake test should be conducted on a random sample of vaccine. However, if there is more than one lot in the shipment, the random sample must include a vial taken from each and every lot.
1. Take a vial of vaccine of the same type and batch number as the vaccine you want to test, and made by the same manufacturer.
2. Clearly mark the vial as "FROZEN."
3. Freeze the vial in a freezer or the freezing compartment of a refrigerator until the contents are completely solid.

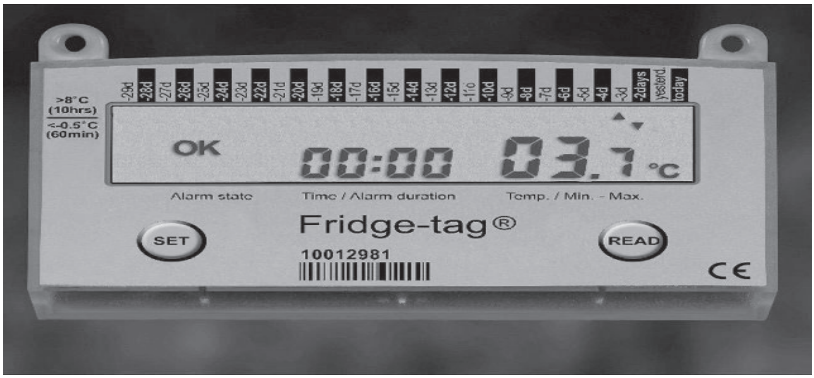
<table>
<tr><td colspan="2">4. Let it thaw. Do NOT heat it!</td></tr>
<tr><td colspan="2">5. Take your “TEST” vial from the batch that you suspect has been frozen.</td></tr>
<tr><td colspan="2">6. Hold the “FROZEN” vial and the “TEST” vial together in one hand.</td></tr>
<tr><td colspan="2">7. Shake both vials vigorously for 10-15 seconds.</td></tr>
<tr><td colspan="2">8. Place both vials on a flat surface side-by-side and start continuous observation of the vials until the test is finished.
(NOTE: If the vials have large labels that conceal the vial contents, turn both vials upside down and observe sedimentation in the neck of the vial.)</td></tr>
<tr><td colspan="2">Use an adequate source of light to compare the sedimentation rates between vials. If,</td></tr>
<tr><td>9. The TEST vial sediments more slowly than the FROZEN vial, THEN,</td><td>10. Sedimentation is similar in both vials OR the TEST vial sediments faster than the FROZEN vial THEN,</td></tr>
<tr><td>11. Use the vaccine batch.</td><td>11. <u>Vaccine damaged</u>: Notify your supervisor. Set aside all affected vaccine in a container marked “DAMAGED VACCINE FOR DISPOSAL–DO NOT USE’’</td></tr>
<tr><td rowspan="2"></td><td>12. Discard all the affected vaccine once you have received permission to do so.</td></tr>
<tr><td>13. Fill in the Loss/Adjustment Form.</td></tr>
</table>



WHO. Immunization in practice. Module 2: The vaccine cold chain. WHO/IVB/04.06

Note: The shake test is not effective for determining if IPV has been frozen. If you suspect a vial has frozen, discard.

That is why it must be stored in the middle shelf of a standing refrigerator or in a basket in the top layer of a chest refrigerator but never in a freezer or the top shelf of a standing fridge. You can also use a fridge tag for continuous temperature monitoring of the refrigerator which usually records and also alarms whenever the temperature reaches the minimum or maximum set temperature for a set period of time.



WHO EPELA plus 2013

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13.6. Communication and Advocacy for Immunization

Communication

Definition

- The act or process of using words, sounds, signs, expressions, gestures or behaviours to express or exchange information or to express your ideas, thoughts, feelings, etc., to someone else.
- The process of sending and receiving messages through verbal or nonverbal means–speech (oral communication), writing (written communication), signs, signals, or behaviour.
- A two-way process of reaching mutual understanding, in which participants not only exchange (encode-decode) information, news, ideas and feelings but also create and share meaning.

Qualities of effective communication

- Friendliness–warmth, concern, politeness, encouragement.
- Simplicity–simple language, short, clear.
- Timeliness–relevant to the client's needs.
- Truthfulness–only facts, correct misconceptions.
- Good listening–eye contact, good body gestures like smiling, nodding, and paying attention.
- Client communication must address
  - The mother's or caregivers' concerns;
  - What vaccines were given;
  - Expected adverse events;
  - The next visit;
  - What vaccines to receive at the next visit;
  - Care of the immunization card and always visit the health facility with the immunization card.

Interpersonal communication skills (IPC)

What is IPC?

- IPC refers to inter-personal communication.
- It involves two or more persons.
- It is face to face communication that involves talking, listening, and allowing the other person or persons to respond and to ask questions and for clarifications.

- IPC recognizes the importance of the caregiver. It is useful for encouraging the caregiver to complete immunization for all eligible children.

Basic IPC Skills

- Be polite, friendly and caring.
- Speak simply and directly in the local language.
- Listen to and understand the caregiver's concerns and questions.
- Give relevant answers to any concerns and questions no matter how they sound.
- Respectfully correct inaccurate information.
- Tell them that there could be a reaction but it is rare.
- Thank them for their patience and interest.

Handling Rumours

- Determine the magnitude of the rumour–the type, source, persons or organization spreading the rumour.
- Probe factors, individuals and motives behind it.
- Engage the source of the rumour and give them the opportunity to be part of the solution.
- Involve key stakeholders in addressing the rumour and implement an agreed response, including messages.
- Engage the media to disseminate appropriate messages to address the rumour.

Advocacy

Definition

- Advocacy can be described as any effort to influence policy and decision-makers, to fight for social change, to transform public perceptions and attitudes, to modify behaviours, or to mobilize human and financial resources. In your efforts to improve immunization and child health, advocacy might encompass all these definitions in one form or another.

Steps

- Gather information/data.
- Build a plan.
- Create messages and materials.
- Build partnerships.
- Engage policy and decision-makers.
- Inform and involve the public.
- Work with mass media.
- Monitor and evaluate.

Characteristics of an Advocate

- Researches the issue.
- Believes in the issue.
- Gives real-life examples.
- Plans for small changes.
- Is passionate and persistent.
- Takes advantage of opportunities.
- Is a good negotiator.
- Is hard to intimidate.
- Stays focused on the issues.

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13.7. Disease Surveillance

Definition

- Public Health Surveillance is the ongoing systematic collection, analysis, interpretation, and dissemination of health data.
- *This is a mechanism that public health agencies use to monitor the health of their communities. Its purpose is to provide a factual basis from which agencies can appropriately set priorities, plan programs, and take action to promote and protect the public's health*.
- The ongoing systematic collection and analysis of data and the provision of information which leads to action being taken to prevent and control a disease, usually one of an infectious nature.
- **Why was it called "surveillance"?** It is the close observation of exposed persons to identify the onset of disease. The definition changed in the 1950s.

What are the key elements of public health surveillance?

- Ongoing.
- Systematic.
- Collection, collation, analysis, interpretation, and *dissemination.*
- Data regarding a health-related event.
- For *use* in public health *action* to reduce morbidity and mortality and to improve health.

Vaccine preventable disease surveillance strategies

- National, sub-national, hospital sentinel.
- Active versus passive.
- Reporting: Case-based versus aggregated.
- Examples: Polio, Measles, New vaccines.

Before vaccine introduction

- Demonstrate the disease burden.
- Justification to introduce vaccines.
- Establish system to measure vaccine impact.
- Identify circulating strains.

After vaccine introduction

- Monitor the vaccination program impact.
- Monitor any change in circulating strains: needs strong laboratory support.
- Platform to evaluate safety.

Sentinel:

- Easier, cheaper.
- Likely good lab.
- Better quality data (active vs. passive).
- Monitor trends over time.
- More severe cases, so not representative of all disease.

National

- More expensive, harder.
- Transport samples to the lab.
- All disease in the country (mild, severe).
- Monitor trends over time.
- Identify outbreaks, epidemics.

New vaccine surveillance sites in Nigeria

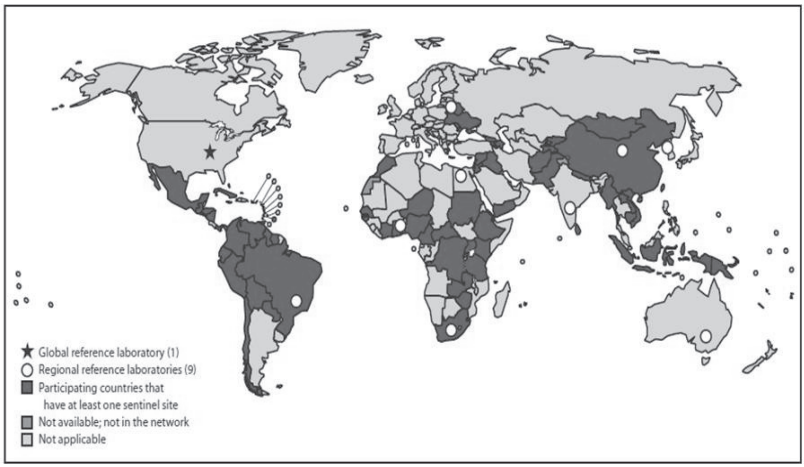
- **Rotavirus surveillance**
- Institute of Child Health, University of Nigeria Teaching Hospital in collaboration with the Department of Paediatrics & Microbiology UNTH Enugu, Enugu State University Teaching Hospital, Enugu and Mother of Christ Specialist Hospital, Enugu, Enugu State.
- University of Ilorin Teaching Hospital, Kwara State.
- *About to commence–University of Benin Teaching Hospital (Edo State).*
- **Paediatric Bacterial Meningitis (PBM-Hib, Pneumococcus, Neisseria)**
  - Institute of Child Health, University of Nigeria Teaching Hospital, Enugu.
  - Lagos University Teaching Hospital, Lagos State.
  - University of Ilorin Teaching Hospital, Kwara State.

- University of Benin Teaching Hospital, Benin, Edo State.
- Abubakar Tafawa Balewa University Teaching Hospital ATBUTH, Bauchi state

- National Measles & Polio surveillance, ongoing with 2 WHO accredited labs at University College Hospital, Ibadan and University of Maiduguri Teaching Hospital
- Nigeria is part of a WHO global new vaccine surveillance network and each site reports data monthly to the WHO African Regional office which in turn, reports to the global office for collation, analysis, interpretation and feedback to countries for action.
- As at December 2014, the network includes 88 Sentinel Hospital Sites/Laboratories), 18 National Laboratories, nine Regional Reference Laboratories (RRL), and one Global Reference Laboratory (GRL).

Reporting countries and countries with sentinel sites meeting inclusion criteria–World Health Organization, Global Rotavirus Surveillance Network, 2011–2012

Centers for Disease Control and Prevention. WHO Global Rotavirus Surveillance Network: A Strategic Review of the First 5 Years, 2008-2012. Morbidity and Mortality Weekly Report (MMWR) July 25, 2014 63(29): 634-7.



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13.8. School health

What is School health?

- There is no single best definition because school health has to be tailored to meet the needs of the particular state, community and school.
- It is concerned with the early detection of health and social problems in schoolchildren and their subsequent treatment and surveillance.
- According to the CDC, Coordinated School Health is a systematic approach to improving the health and well-being of all students so they can fully participate and be successful in school.
- The process involves bringing together school administrators, teachers, other staff, students, families, and community members to assess health needs; set priorities; and plan, implement, and evaluate all health-related activities.
- Coordinated School Health typically integrates health promotion efforts across eight interrelated components that already exist to some extent in most schools.

Components of school health

- Health education.
- Physical education.
- Health services.
- Nutrition services.
- Counselling, psychological, and social services.
- Staff health promotion.
- Family and community involvement.
- Healthy and safe environment.

Health Education

- Addresses all dimensions of health.
- Develops knowledge, attitudes, and skills.
- Tailored to each grade level.
- Motivates students.

Physical Education

- Promotes lifelong physical activity.
- Develops basic movement skills.
- Develops physical fitness.
- Enhances social and emotional ability.

School Health Services

- Preventative Services.
- Education.
- Emergency Care.
- Referral.
- Management of acute and chronic conditions.

School Meals and Nutrition Services

- Integration of:
- Nutrition Education;
- Nutritious and appealing meals;
- An environment that promotes healthy dietary behaviours;
- Food Safety;
- Gardening.

School Counselling/Social Services

- Cognitive
- Emotional
- Behavioural
- Social Needs

} Individuals/Groups/Families

Healthy School Environment

- Provides a safe physical plant, as well as a healthy and supportive environment that fosters learning.
- Physical Climate.
- Emotional Climate.
- Social Climate.

Teacher/Staff Wellness

- Staff Activities:
- Assessment;
- Education;
- Fitness;
- Staff serve as role models.

Family/Community

- Develop partnerships among schools, families and community groups.
- Individuals will share and maximize resources and expertise in addressing the development of healthy children, youth, and their families.
- A closer working relationship between parents and schools.
- Parents, businesses and community groups, and schools can form powerful coalitions to address the health needs of students.

How does school health enhance academic success?

- The reading and math scores of 3rd and 4th grade students who received comprehensive health education were significantly higher than those who did not receive it.
- Students with poor nutrition and low levels of physical activity are more likely to be absent and tardy.
- School nutrition services can improve students' scores on standardized tests.
- Physical activity among adolescents is consistently related to higher levels of self-esteem and lower levels of anxiety and stress.
- Intensive PE programs have positive effects on academic achievement even when time for PE is taken from the academic day:
- Increased concentration;
- Improved math, reading, and writing scores;
- Reduced disruptive behaviours.
- Schools with school-based health centres report:
- Increased school attendance;
- Decreased drop-outs and suspensions;
- Higher graduation rates.

School health situation in Nigeria

In Nigeria, there is a government policy in place (2006) but the gap between policy and implementation is very huge.

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13.9. Growth monitoring

Growth

- A normal, healthy child grows at a genetically predetermined rate and this can be affected by an imbalance in nutrient intake.
- Growth is a dynamic process defined as an increase in the physical size of the body as a whole or any of its parts associated with an increase in cell number and/or cell size.
- It reflects changes in absolute size, mass and body composition.
- Growth in childhood and adolescence is the most sensitive indicator of well-being. Normal growth only occurs if a child is healthy, adequately nourished and emotionally secure.
- Factors that affect growth in the first 2 years include: birth weight and gestational age; nutrition; genetic background (family height, ethnicity, etc.) and social factors.
- Growth in those aged 2-18 years is affected by endocrine factors, the timing of puberty, nutrition and well-being.
- Children's growth should be monitored regularly in the well-child clinic without waiting for them to fall ill. Whenever a faltering in growth is observed, appropriate measures should be taken to identify and address the problems responsible.
- Growth assessment requires accurate measurements with good, regularly calibrated equipment. Measurements must be made by a trained measurer and the measurements should be accurately plotted on a centile chart.

Why Monitor Growth?

- Growth is the most sensitive indicator of health.
- Normal growth only occurs if a child is healthy.
- Growth assessment is an essential part of the examination or investigation of any child.
- It allows an objective detection of growth disorders at the population level at the earliest opportunity.
- Early identification and treatment improve the outcome.
- Identify under or over nutrition.

What does a growth chart measure?

- Length-for-age.
- Weight-for-age.
- Weight-for-length.
- Head circumference-for-age: information about brain development.

Issues in Measurement

- Accuracy of Results.
- Instrument Variation.
- Observer Variation.
- Subject Variation.

Minimizing Error

- Careful measurements by trained personnel.
- A standardized measuring and recording technique.
- Accurate well-positioned equipment.
- Appropriate equipment that is well maintained and calibrated regularly.
- Consider growth data in the overall clinical context of the child and not in isolation.
- Careful plotting on centile charts and interpretation.
- Disease-specific or sub-population growth charts are available for many conditions such as Down syndrome and sickle cell disease.

Growth charts

CDC/NCHS (2000) http://www.cdc.gov/growthcharts/

- 5 cross-sectional nationally representative surveys between 1963 and1995.
- Sex-specific
  - Weight-for-age;
  - Length-for-age;
  - Weight-for-length;
  - Head circumference-for-age.
- Choice between outer limits at the 3rd and 97th percentiles, or the 5th and 95th.

WHO (2006) http://www.who.int/childgrowth/en

- Data from Brazil, Ghana, India, Norway, Oman and the USA.
- Multiethnic, affluent.

- Exclusive breastfeeding to 4 months.
- Solids according to recommendations to 6 months.
- Continued breastfeeding to 12 months.
- Sex-specific
  - Weight-for-age,
  - Length-for-age,
  - Weight-for-length,
  - Head circumference-for-age,
  - On the WHO site: BMI, other measurements.
- Outer limits at the 2nd and 98th percentiles.

Differences between the WHO and CDC infant charts

- The WHO mean > the CDC mean, birth to 6 months.
- "Healthy breastfed infants track weight-for-age along WHO but falter on CDC."
- On the CDC chart, children appear heavier and shorter.
- On the WHO chart, children appear taller.
- WHO charts:
  - A higher estimate of overweight;
  - Lower estimates of underweight, undernutrition.

Note that: the 2nd and 98th percentiles on WHO correspond to the 5th and 95th on CDC.

Failure to Thrive (Failure to Grow)

- Failure to gain weight or grow at expected rates
  - Weight-for-age <5th percentile;
  - Weight-for-length <5th percentile;
  - Decreased growth velocity (a decrease over 2 SD over 3-6 months).
- Inadequate intake
  - Not enough food offered: Food insecurity, a lack of knowledge of the child's needs;
  - Not enough food consumed: Oral-motor dysfunction, behavioural feeding problems, chronic ill-health, Emesis.
- Malabsorption.
- Increased metabolic demand.

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13.10. Introduction to infant and young child feeding

WHO/UNICEF global strategy for infant and young child feeding

- The goal is to improve the survival, growth and development of children during the first years of life through the protection, promotion and support of early and exclusive breastfeeding for 6 months, followed by continued breastfeeding for up to 2 years or longer with age-appropriate, complementary feeding (www.who.int).
- Developed by WHO and UNICEF to revitalize world attention on the impact that feeding practices have on infants and young children.
- Malnutrition has been responsible, directly or indirectly, for over 50% of the 10.6 million deaths annually among children <5 years.
- Over two-thirds of these deaths occur in the first year of life.

Policy initiatives

- International Code of Marketing of Breast-milk Substitutes (1981).
- The Innocenti Declaration (1990).
- The Baby-friendly Hospital Initiative (1991).
- The Global Strategy for Infant and Young Child Feeding (2002).

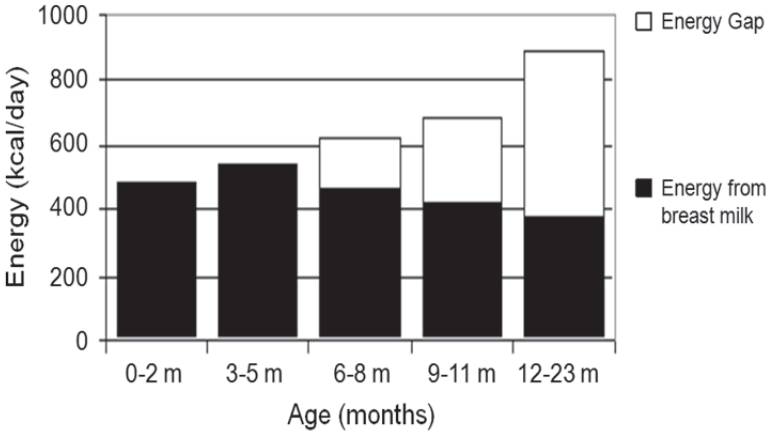
Exclusive breastfeeding

- Breastfeeding provides ideal food for the healthy growth and development of infants.
- Infants should be exclusively breastfed for the first six months of life.

Complementary feeds

- After six months, all babies require complementary foods while breastfeeding continues for up to two years of age or beyond.
- Complementary (family foods and liquids) feeds should be:
  - Timely, adequate, safe and properly fed to meet nutritional needs.

Energy required by age and the amount supplied from breast milk



The optimal infant and young child feeding recommendation

Exclusive breastfeeding 0-<6 months

- Only breastmilk, no other liquids or solids, not even water, with the exception of necessary vitamins, mineral supplements or medicines.

Complementary feeding 6-<24 months old

- Support for continued breastfeeding for 2 years or beyond.
- Introduce safe and appropriate complementary foods.
- Frequent feeding, adequate food, appropriate texture and variety, active feeding, hygienically prepared (FATVAH).

Frequency	Frequent feeding
Amount	Adequate amounts of food
Texture	Appropriate consistency
Variety	A variety of different foods
Active	Responsive feeding
Hygiene	Hygienically prepared

Complementary feeding is more than just interactive/responsive feeding

Feeding in exceptionally difficult circumstances

- Emergency situations.
- Malnourished children.
- Low-birth-weight and premature babies.
- Infants of HIV-infected mothers.
- Orphans.
- Adolescent mothers.

WHO recommendations on infant feeding and HIV (2010)

- If the HIV status of the mother is unknown or she is HIV negative then exclusive breastfeeding for the first six months, followed by continued breastfeeding for 2 years or beyond, with the introduction of safe and appropriate complementary feeding.
- Where the HIV status of an individual mother is unknown or she is HIV negative, then the recommended feeding practices are the same optimal feeding practices as for the general population, irrespective of the prevalence of HIV in the population.
- This offers the best chance of child survival.
- If the mother is HIV-infected and on ARVs then exclusive breastfeeding for the first six months, followed by continued breastfeeding for at least 1 year, with the introduction of safe and appropriate complementary feeding unless replacement feeding is acceptable, feasible, affordable, sustainable and safe (AFASS).

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SECTION 14

EMERGENCY PAEDIATRICS

14.1 Upper airway obstruction (Ndu, I. K.)

- Upper airway obstruction (UAO) is a life-threatening emergency that requires prompt diagnosis and treatment. It involves obstruction up to the epiglottis and aryepiglottic folds. It interferes primarily with inspiration.

Causes

- Foreign body aspiration, Chemical burns.
- Epiglottitis, Tracheomalacia.
- Croup.
- Trauma, Peritonsillar abscess.
- Retropharyngeal abscess.

Symptoms include

- Characteristic croupy or brassy cough;
- Stridor, irritability;
- Altered sensorium, choking;
- Difficulty breathing;
- Unconsciousness, cyanosis.

Assessment

- A harsh, barking or brassy cough in a febrile, irritable but healthy child suggests croup.
- The absence of cough, stridor with low-pitched expiratory rhonchi and drooling suggest epiglottitis.
- Sudden onset in an otherwise well child with coughing, choking and aphonia suggests an inhaled foreign body.

- Swelling of face and tongue, wheeze or urticarial rash suggests anaphylaxis.
- High Fever, hyperextension of the neck, dysphagia and the pooling of secretions in the throat suggest retropharyngeal/peritonsillar abscess.
- A toxic child with a markedly tender trachea suggests bacterial tracheitis.
- Pre-existing stridor in an infant suggests congenital abnormality e.g. laryngomalacia, haemangioma/subglottic stenosis.

Investigations

This usually presents as an emergency but the clinician should quickly do the following:

- Bronchoscopy;
- Laryngoscopy: (with caution because it often precipitates the need for intubation);
- X-rays (the "steeple sign" for croup, the "inverted thumb sign" for epiglottitis);
- Blood can be drawn for culture and complete blood count;
- Pulse oximetry.

Treatment

- Oxygen may be given while awaiting definitive diagnosis/ treatment.
- Treat the underlying cause.
- Use intravenous fluids, antibiotics and nebulization as required.
- Consider the need for an advanced airway.
- For foreign body aspiration, such as a piece of food, abdominal thrusts, back slaps or chest thrusts can be lifesaving.

Complications

- Brain damage.
- Respiratory failure.
- Death.

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14.2 Asthma (Ndu, I. K.)

Introduction

- Asthma is a common chronic inflammatory airway disease characterized by variable and recurring symptoms, reversible airflow obstruction and bronchospasm.
- The airway obstruction is diffused and distributed unevenly, causing some alveoli to be over ventilated while others are under ventilated. This uneven distribution of ventilation creates a ventilation-perfusion mismatch and subsequent hypoxaemia.

Epidemiology

- Age: 30% before 1 year; 80-90% before 4-5 years.
- Current Global Initiative for Asthma (GINA) guidelines reported that the prevalence of asthma is estimated to be 1% to 18%.
- In the United States, the number of asthmatics has leapt by over 60% since the early 1980s.
- African values: Ethiopia 9.1%, Kenya 15.8%, Nigeria 13.0%, South Africa 20.3%; and French-speaking regions: Algeria 8.7%, Morocco 10.4%, and Tunisia 11.9%.
- Risk factors: Gender, genetics, Atopy, Environmental factors, Cigarette smoke, Obesity, Black race, LBW, Poverty.

Aetiology

- Autonomic, Immunologic, Infectious, Endocrine, Psychologic.

Classification of asthma by level of control

- Asthma control is the degree to which the goals of therapy are met (e.g., prevent symptoms/exacerbations; maintain normal lung function and activity levels).
- Components of control are impairment and risk i.e. assessment of the control of clinical manifestations and the control of expected future risk.
- The level of control of clinical manifestations classifies asthma into controlled, partially controlled and uncontrolled asthma.
- The control of expected future risk such as exacerbations, rapid decline in lung function and side effects of treatment.

Classification of asthma by severity

- Asthma severity is the intrinsic intensity of the disease process and dictates which step to initiate treatment.
- Clinical manifestations classify the severity of asthma into intermittent and mild, moderate or severe persistent asthma.

Pathophysiology

- Airflow limitation: bronchoconstriction, airway oedema, airway hyper-responsiveness, airway remodelling.
- Airway inflammation: the interplay of inflammatory cells and inflammatory mediators.

Pathogenesis

- Interplay between two major factors–host factors (innate immunity, genetics, sex) and environmental exposures (allergens, respiratory infections, tobacco smoke) that occur at a crucial time in the development of the immune system.

Clinical features–history

- Nocturnal cough, cough with exercise and cold air.
- Persistent cough following ARI.
- Cough with exposure to animals, pollen, cigarette smoke.
- Recurrent episodes relieved by beta agonists.
- Features suggestive of atopy, positive family and social history.

Clinical features–physical findings

- Dyspnoea, Prolonged expiratory phase, Rhonchi, Silent chest.

Diagnosis

- Clinical grounds: medical history, physical exam, pulse oximetry.
- Pulmonary function tests: *Lung function tests* may be done before and after taking a bronchodilator, a metacholine challenge or a provocative test.
- Laboratory evaluation: arterial blood gas measurements, imaging studies, nitric oxide test and allergy testing.

Differential diagnosis

- Foreign body, Bronchiolitis, Endobronchial tuberculosis.
- Gastroesophageal reflux, Congestive heart failure.

Treatment

Four components of asthma care:

- Component 1: develop patient/family/doctor relationships;
- Component 2: identify and reduce exposure to risk factors;
- Component 3: assess, treat and monitor asthma;
- Component 4: manage asthma exacerbations (administration steroids, aerosolized $ß_2$ agonist drugs and ipratropium bromide).

Complications

- Death, Atelectasis, Poor sleep, School or work absenteeism.
- Side effects of medications, Permanent change in lung function.

Prognosis

- There is no cure for asthma, although symptoms sometimes improve over time. With proper self-management and medical treatment, most people with asthma can lead normal lives.

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14.3 Febrile convulsion (Ndu, I. K., Chinawa, J.)

Definition

- Brief, generalized tonic-clonic seizure associated with a febrile illness, but without any CNS infection or neurologic cause.

Epidemiology

- Incidence: 3-5% of children. More common in males.
- Age: Traditionally said to occur between 6 months and 5 years, but this has been modified by the National Institutes of Health to between three months and five years of age.

Aetiology

- There is convincing evidence for a genetic basis for febrile seizures, with 24%–40% of patients reporting a positive family history.
- There is a higher concordance rate among monozygotic than dizygotic twins.
- Susceptibility foci have been identified on chromosomes 2, 5, 6, 8, 18 and 19.

Classification

- Febrile seizures are classified as either simple or complex.

Simple febrile seizures have the following features:

- They are brief (lasting less than 15 minutes) and resolve spontaneously;
- They typically occur as isolated events and not more than once in 24 hours;
- They are characterized by generalized convulsions of the body.

Complex febrile seizures have one or more of the following features:

- They are prolonged (greater than 15 minutes) and may not resolve spontaneously;
- They occur more than once in 24 hours during a febrile illness;
- There is focal convulsion of one side of the body.

Pathophysiology

- The pathophysiology of febrile seizures is incompletely understood. The role of activation of the cytokine network is presently being studied.
- It is possible that circulating toxins and immune reaction products modulate neuronal excitability thus lowering the seizure threshold.

Clinical features–history

- A history of the cause of fever (e.g., viral illnesses) should be elucidated.

Clinical features–physical findings

- The underlying cause for the fever should be sought.
- A careful physical examination often reveals otitis media, pharyngitis, or a viral exanthem.
- Serial evaluations of the patient's neurologic status are essential.

Diagnosis

- Can be made on clinical grounds.
- Provocative aetiologies such as electrolyte imbalance and primary neurological insults (meningitis or encephalitis) must be excluded.

Differential diagnosis

- Meningitis, encephalitis, sepsis, epilepsy.

Treatment

- Airway management, high-flow oxygen, supportive care, and anticonvulsants as necessary.
- Patients who are postictal should receive supportive care and antipyretics as appropriate.

Prognosis

- After a first simple febrile seizure, approximately 30% of children will have a recurrence, 50% after the second episode up to 5 years.

Recurrence risk factors include:

- Family history of febrile seizures;
- Onset of simple febrile seizures at less than 12 months of age;
- Temperature at less than 40^0C;
- Risk of epilepsy: 2%.

Epilepsy risk factors include:

- Family history of epilepsy;
- Occurrence of complex febrile seizures;
- Occurrence of multiple simple febrile seizures;
- Onset of simple febrile seizures at less than 12 months of age.

Management

- Counselling.
- Reassure parents about the benign nature of events.
- Timely use of antipyretics.
- Prophylactic anticonvulsant is not indicated.

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14.4 Shock (Ndu, I, K., Chinawam, J.)

Definition

- Shock is the clinical expression of circulatory failure that results in inadequate cellular oxygen utilization. It is a life-threatening medical emergency,

Epidemiology

- The incidence/prevalence of shock is currently unknown.
- However, all types of shock carry a very high mortality.

Classification of shock and different aetiologies

- Hypovolaemic shock: haemorrhage, severe burns, vomiting, diarrhoea, urinary tract losses.
- Cardiogenic shock: myocarditis and valvular heart disease.
- Obstructive shock: cardiac tamponade, massive pulmonary embolism, tension pneumothorax.
- Distributive shock: Septic shock, anaphylactic shock, neurogenic shock, adrenal crisis.

Pathophysiology

- Cardiogenic shock occurs when myocardial damage reaches a point where pump function is markedly impaired.
- Obstructive shock is characterized by inadequate ventricular filling due to cardiac compression or severe obstruction to the ventricular inflow or outflow.
- Hypovolaemic shock is characterized by the loss of circulating volume.
- The characteristic feature of distributive shock is a decline in peripheral vascular resistance.

Stages of shock

- Shock can be divided into three, progressively worsening stages:
  - Compensated;
  - Progressive;
  - Irreversible shock.

Clinical features–history/physical findings

- Signs of autonomic response to low cardiac output: tachycardia, tachypnoea.
- Signs of decreased tissue perfusion: capillary refill time ≥3 seconds, cold extremities.
- Signs of major organ dysfunction: altered consciousness, acute kidney injury, DIC.

Diagnosis

- Early recognition is important.
- Basic evaluation should include metabolic panel, haemogram, arterial blood gas, electrocardiogram, and chest x-ray.

Differential diagnosis

- Hypoglycaemia.

Treatment

- Oxygen administration to meet metabolic demands.
- Emergency intravenous/intraosseous access.
- Fluid therapy: with the exception of cardiogenic shock, aggressive fluid resuscitation is usually required.
- Cardiovascular support with ionotropic or vasopressor or vasodilator agents.
- Correction of metabolic derangements.
- Antibiotics.
- Steroids for acute adrenal insufficiency.

Prognosis

- Prognosis is good with aggressive and early management.
- Mortality depends on aetiology and is as high as 50% with septic shock.

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14.5 Severe anaemia (Ndu, I. K.)

Definition

- Anaemia is a condition in which the number of red blood cells (and consequently their oxygen carrying capacity) is insufficient to meet the body's physiologic needs.
- Specific physiologic needs vary with a person's age, gender, residential elevation above sea level (altitude), smoking behaviour, and different stages of pregnancy.
- Anaemia is classified as mild, moderate or severe based on the concentrations of haemoglobin in the blood. Mild anaemia corresponds to a level of haemoglobin concentration of 10.0-10.9 g/dl for pregnant women and children under the age of 5.
- Moderate anaemia corresponds to a level of 7.0-9.9 g/dl, while severe anaemia corresponds to a level less than 7.0 g/dl.

Aetiology

- Decreased RBC production: nutritional, physiologic, aplastic.
- Increased RBC destruction: membrane defects, enzyme defects, hypersplenism.
- Increased RBC losses: acute and chronic blood loss.

Epidemiology

- Racial differences are also apparent, with black children having lower normal values than white and Asian children of the same age and socioeconomic background.
- In developing nations, the prevalence of anaemia is extremely high. This is particularly true in preschool-aged children, in whom the prevalence reached as high as 90% of the sample population studied.
- In addition, the prevalence of certain hereditary forms of anaemia (e.g., thalassaemia, sickle cell disease) varies with ethnicity and, thus, with geography.

Pathophysiology

- The physiologic response to anaemia varies according to acuity and the type of insult.

- Gradual onset may allow for compensatory mechanisms to take place.
- With anaemia due to acute blood loss, a reduction in the oxygen carrying capacity occurs along with a decrease in intravascular volume, with resultant hypoxia and hypovolaemia.
- Hypovolaemia leads to hypotension, which is detected by stretch receptors in the carotid bulb, aortic arch, heart and lungs.
- These receptors transmit impulses along afferent fibres of the vagus and glossopharyngeal nerves to the medulla oblongata, cerebral cortex and pituitary gland and increase sympathetic outflow to maintain perfusion to the tissues by increasing systemic vascular resistance (SVR).

Clinical features

- Symptoms of anaemia include pallor, fatigue, lethargy, dizziness, and anorexia.
- Patients with acute and severe anaemia appear in distress, with tachycardia, tachypnoea, and hypovolaemia. Patients with chronic anaemia are typically well compensated and usually asymptomatic.
- Patients with significant anaemia often have a systolic ejection murmur. Look for signs of congestive heart failure (CHF), such as tachycardia, gallop rhythm, tachypnoea, cardiomegaly, wheezing, cough, distended neck vein, and hepatomegaly.

Diagnosis

- FBC, Reticulocyte count, Blood film.
- Coombs test (autoimmune haemolytic anaemia).
- Haemoglobin electrophoresis (haemoglobinopathies).
- Red cell enzyme studies (e.g., G-6-PD, pyruvate kinase).

Treatment

- Blood transfusions.
- Corticosteroids or other medicines that suppress the immune system.
- Erythropoietin, a medicine that helps your bone marrow make more blood cells.

- Supplements of iron, vitamin B12, folic acid, or other vitamins and minerals.

Complications

- Congestive heart failure, Hypoxia, Hypovolaemia, Shock, Seizures.

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14.6 Tension pneumothorax (Ndu, I. K., Chinawa, J.)

- Tension pneumothorax is the progressive build-up of air within the pleural space. Positive pressure ventilation may exacerbate this "one-way-valve" effect.

Epidemiology

- Tension pneumothorax is a complication in approximately 1-2% of cases of idiopathic spontaneous pneumothorax.

Etiology

The most common aetiologies are either iatrogenic or related to trauma and include:

- Trauma (blunt or penetrating and barotrauma);
- Conversion of an idiopathic, spontaneous, simple pneumothorax to a tension pneumothorax;
- Unsuccessful attempts to convert an open pneumothorax to a simple pneumothorax;
- Chest compressions during cardiopulmonary resuscitation (CPR).

Pathophysiology

- Tension pneumothorax occurs anytime that a disruption involves the visceral pleura, parietal pleura, or the tracheobronchial tree.
- This condition develops when injured tissue forms a one-way valve, allowing air inflow with inhalation into the pleural space and prohibiting air outflow.
- The volume of this nonabsorbable intrapleural air increases with each inspiration because of the one-way valve effect.
- As a result, pressure rises within the affected hemithorax.

Clinical presentations

- Sudden chest pain, Shortness of breath, Chest tightness, Easy fatigue.
- Bluish colour of the skin due to lack of oxygen.
- Rapid heart rate, Low blood pressure.
- Decreased consciousness, Rapid breathing.

- Bulging (distended) veins in the neck.

Investigations

- A chest x-ray, Arterial blood gases, Electrocardiogram.
- Tension pneumothorax primarily is a clinical diagnosis and so a high index of suspicion is paramount.

Treatment

Needle Thoracostomy

- The classical management of a tension pneumothorax is emergent chest decompression with needle thoracostomy.
- A 14-16G intravenous cannula is inserted into the second rib space in the mid-clavicular line.
- The needle is advanced until air can be aspirated into a syringe connected to the needle.
- The needle is withdrawn and the cannula is left open to air. An immediate rush of air out of the chest indicates the presence of a tension pneumothorax.
- The manoeuvre effectively converts a tension pneumothorax into a simple pneumothorax.

Chest tube placement

- The definitive treatment of traumatic pneumothorax.

Differential diagnosis

- Catamenial pneumothorax, Traumatic pneumothorax.
- Aspiration, Bacterial, Mycoplasmal, and Viral Pneumonia.
- Diaphragmatic Injuries, oesophageal spasm.
- Foreign Bodies, Trachea, Mediastinitis.
- Myocardial Ischemia, Pneumomediastinum.

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14.7 Cardiopulmonary resuscitation (Ndu, I. K.)

Definition

- CPR refers to the series of coordinated interventions designed to restore adequate ventilation and circulation in a child whose vital functions have ceased.
- It consists of skills that support or restore effective ventilation/ circulation and is the foundation of basic and advanced life support of the child in respiratory or cardiopulmonary arrest.
- Many causes of arrest in children are preventable and special efforts should be made in prevention and prehospital care to improve survival.
- Children who have delayed resuscitation or present in asystole have a poor prognosis, because hypoxaemia already will have caused extensive damage to the brain and other vital organs.

Causes of Cardiac arrest

- Cardiac arrest due to primary cardiac events is rare in children. Common causes include:
- Pulmonary: Foreign body aspiration, smoke inhalation, respiratory failure, near drowning;
- Traumatic: Motor vehicle injuries, burns, child abuse;
- Infections: Sepsis, AGE, Meningitis, pneumonia;
- Central nervous system: Seizures, Head trauma;
- Others: Anaphylaxis, Sudden infant death syndrome, poisoning.

Beginning CPR

- Recognize cardiac arrest: unresponsiveness, pulseless or pulse <60/min with poor perfusion despite oxygenation and ventilation.
- Commence CPR sequence: Compressions-Airway-Breathing.
- Compression rate: At least 100/min to a depth of at least 1/3 of the AP diameter.
- Airway: Maintain patency with Head tilt-chin lift or jaw thrust in suspected trauma. In the case of FBAO: >1 year: Heimlich manoeuvre; <1 year: back slaps or chest thrust.
- Breathing: Coordination of chest compressions and breaths: Single rescuer: 30:2 Double rescuer: 15-2.

Advanced life support

- Vascular access: Direct: IV/IO and Indirect: endotracheal, sublingual.
- Airway and ventilation, Oxygen therapy, Suction, Intubation, BVM device.

Fluid therapy

- Crystalloids, colloids, blood products.

Pharmacotherapy

- Epinephrine, vasopressin, Sodium bicarbonate, calcium, atropine, Glucose.

Electrical therapy

- Defibrillation for pulseless VT and VF.

Termination of CPR

- If there is no response after 20-30 minutes, CPR can be discontinued.

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SECTION 15:

PAEDIATRIC SYNDROMES

CHINAWA, J.

15.1 Trisomies

- Trisomies are types of numerical chromosome abnormalities that can cause certain birth defects.
- There are three specific types.

Trisomy 21 (Down's syndrome)

- Down's syndrome was named after John Langdon Down (1828-1896), who was the first physician to identify it, in 1866.

Epidemiology

- It occurs in about 1 out of every 700-900 live births worldwide. The chances of Down's increase as the woman gets older, with an incidence of about 1:85 at 40 years of age.

Pathophysiology

- There are three forms of Down's syndrome **M**osaicism is the least common type; **T**ranslocation is the 2nd most common; and **N**on-disjunction is the most common type (acronym MTN).

Clinical symptoms

- Decreased or poor muscle tone, Short neck, with excess skin at the back of the neck, flattened facial profile and nose, Small head, ears, and mouth, upward slanting eyes, White spots on the coloured part of the eye (called Brushfield spots), Clinodactyly, bradydactyly, AVC canal defect.

- **Constant features:** Hypotonia and mental retardation.

Trisomy 18 (Edwards)

- Trisomy 18 is a genetic disorder in which a person has a third copy of material from chromosome 18, instead of the usual two copies.

Pathophysiology

- It is three times more common in girls than boys. The syndrome occurs when there is extra material from chromosome 18.

Symptoms

- Clenched hands, Crossed legs, Feet with a rounded bottom (rocker-bottom feet), Low birth weight, Low-set ears, mental delay, poorly developed fingernails. Small head (microcephaly), Small jaw (micrognathia), Undescended testicles, Unusual shaped chest (pectus carinatum), ASD, PDA.

Investigations

- X-rays may show a short breast bone. Chromosome studies will show trisomy 18, partial trisomy, or translocation.

Treatment

- This depends on the patient's individual condition.

Patau syndrome (also known as **trisomy 13**)

- This is considered the 3rd most common autosomal trisomy. It is a rare chromosomal disorder in which all or a portion of chromosome 13 appears three times (trisomy) rather than twice in cells of the body.
- Patau syndrome, Down's syndrome (T21) and Edward syndrome (T18), are the only three trisomies to be compatible with extra-uterine life.

Epidemiology

- The estimated incidence is at ~1: 6000. It increases with advanced maternal age.

Clinical spectrum

- Congenital heart disease such as hypoplastic left heart syndrome (HLHS), ventricular septal defect (VSD). Hydrocephalus or microcephaly, spina bifida, abdominal wall abnormalities, genitourinary anomalies, etc.

Pathophysiology

- Three forms are known: free trisomy 13: classical form, translocation trisomy 13, mosaic trisomy 13.
- Risk factors: increased maternal age. Associations: a single umbilical artery.

Investigations

- Reduced maternal serum alpha fetoprotein (MSAFP), reduced maternal beta HCG, reduced PAPP-A.
- Radiographic features such as Antenatal ultrasound will show Polyhydramnios (more common) or oligohydramnios, evidence of IUGR, hydrops foetalis, etc.

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15.2 Prader Willi Syndrome

- A rare genetic disorder in which seven genes on chromosome 15 (q11-13) are deleted or unexpressed.

Epidemiology

- The incidence of PWS is between 1 in 25,000 and 1 in 10,000 live births.
- Prader-Willi syndrome has been reported worldwide with prevalence rate of 1 per 8000 population.
- Complications due to obesity and behavioural problems are major contributors to morbidity and mortality in individuals with Prader-Willi syndrome.
- There are racial differences in clinical presentation. In black patients, growth is less affected, the length of the hands is usually normal, and the facies are less typical.
- Differences in prevalence rates between sexes have not been reported.
- Prader-Willi syndrome is a genetic disorder with a lifelong implication.

Pathophysiology

- Prader-Willi syndrome is the first human disorder attributed to genomic imprinting.
- An imprinting centre has been identified within 15q11-13; gene expression may be regulated by DNA methylation at cytosine bases.
- Prader-Willi syndrome results from the loss of imprinted genomic material within the paternal 15q11.2-13 locus.
- Most cases of Prader-Willi syndrome are sporadic. Most manifestations of Prader-Willi syndrome are attributable to hypothalamic dysfunction.
- Three major variables could result in Prader-Willi syndrome:
- Deletion, Uniparental Disomy (UPD) and PWS by Imprinting Mutation.

Clinical features

- The symptoms of Prader-Willi syndrome are believed to be caused by the dysfunction of a portion of the brain called the hypothalamus.
- Although hypothalamic dysfunction is believed to lead to the symptoms of PWS, it is unclear how the genetic abnormality causes hypothalamic dysfunction.
- There are two generally recognized stages of the symptoms associated with PWS:

Stage 1

- In the first stage, infants with PWS are hypotonic or "floppy", with very low muscle tone. Weak cry and a poor suck reflex are typical. An inability to breastfeed.
- As these children grow older, strength and muscle tone generally improve. Motor milestones are achieved but are usually delayed.

Stage 2

- An unregulated appetite characterizes the second stage of PWS. This stage most commonly begins between the ages of 2 and 6 years old.
- Individuals with PWS lack normal hunger and satiety cues. The metabolic rate of persons with PWS is lower than normal. This could result in obesity.

Diagnosis

- A FISH (fluorescent in-situ hybridization) test identifies PWS by deletion but does not diagnose other forms of PWS.
- The methylation test does identify all types of PWS and is the preferred test for diagnosis.

Treatment

- Currently there is no cure for Prader-Willi syndrome.
- For many individuals affected by the disorder, the elimination of some of the most difficult symptoms of the syndrome like voracious appetite and obesity may improve their quality of life**.**

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15.3 Beckwith–Wiedemann Syndrome

- An overgrowth disorder which is usually present at birth characterized by an increased risk of childhood tumours and congenital anomalies.

Epidemiology

- It occurs in 1 in 14,000 births.
- There is no sex or racial predilection.
- Beckwith-Wiedemann syndrome is a congenital disorder with Wilms tumour as the most common association.
- Most children develop Wilms tumour before the age of 4 years.

Pathophysiology

- Genotypic abnormalities of the distal region of chromosome arm 11p.
- Imprinting has been associated with structural modifications of DNA near the gene, such as methylation or lack of acetylation.
- Several 11p genes are imprinted, including *p57* (a cation-independent cyclase), *IGF-2* (the gene for insulin-like growth factor-2 [IGF-2]), the gene for insulin, and *H19*.

Causes

- Unknown, but it may be genetic. Most cases are associated with a defect in chromosome number 11.

Symptoms

- Infants with Beckwith-Wiedemann syndrome (BWS) present as large for gestational age and, typically, with neonatal onset of hypoglycaemia.
- The pregnancy is usually uncomplicated. Others include
- An abdominal wall defect: umbilical hernia or omphalocele;
- Creases in ear lobes;
- Enlargement of some organs and tissues (macroglossia, large pinnae, etc.);
- Low blood sugar (hypoglycaemia);

- Poor feeding;
- Separated abdominal muscles (diastasis recti);
- Seizures;
- Undescended testicles (cryptorchidism).

Investigations

- Fasting Blood sugar.
- Chromosomal studies for abnormalities in chromosome 11.
- MRI or CT scan of the abdomen, abdominal ultrasound, Skeletal survey.
- Serum alpha fetoprotein (AFP), every three months until 8 years of age, and tumours should be treated as needed.

Treatment

- Symptomatic, no definitive treatment.

Prognosis

- Guarded.

Possible Complications

- Development of tumours.
- Feeding problems.
- Hypoglycaemia.
- Respiratory difficulties from obstruction due to a large tongue.
- Seizures.

Prevention

- There is no known prevention for Beckwith-Wiedemann syndrome. Genetic counselling may be of value for families who would like to have additional children.

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15.4 Crouzon Syndrome

- Craniofacial dysarthrosis, Craniofacial Dysostosis or Craniofacial dysostosis syndrome.
- It is a genetic disorder known as a branchial arch syndrome.
- This affects the first branchial arch, which is the precursor of the maxilla and mandible.

Epidemiology

- Currently estimated to occur in 1 in 25,000 people in the general population.
- Associations with mutations in the genes of FGFR2 and FGFR3 have been identified.
- Crouzon syndrome is autosomal dominant.
- High intracranial pressure caused by disproportion between craniostenosis and brain growing may lead to death.
- Race is not noted as a predisposing factor.

Pathophysiology

- Dysplasias of the skeleton are caused by the malformations of the mesenchyme and ectoderm.
- Mutation of the gene (locus 10q26) for fibroblast growth factor receptor 2 (*FGFR2*) could be responsible for Crouzon syndrome.
- Moreover, the mutation in the transmembrane region of *FGFR3* (locus 4p16.3) is also implicated.

Clinical features

- Bony face deformity is observed at birth, followed with time by other factors of the syndrome.
- Headache for those who can complain.
- Convulsions often occur; mental retardation is frequently observed.
- Coronal and sagittal sutures are obliterated; fontanels remain not obliterated and pulsating for a long time.
- Lateral and anteroposterior flattening of the acrocranium.
- The anteroposterior diameter is smaller than the transverse diameter.
- The forehead is high and wide.

- Wide face and hypoplastic maxilla producing pseudoprognathism.
- The upper lip is shortened and sometimes cleaved.
- Progressing optic nerve atrophy leads to vision impairment because of the intracranial hypertension.
- Hearing impairment.
- Malocclusion, malposed teeth, hypsistaphylia (narrow/high-arched palate), rhinolalia, and dysphasia are noted (as depicted below).

Treatment

- Surgical.

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15.5 Pierre Robin Syndrome

- Pierre Robin syndrome, also called Pierre Robin malformation, Pierre Robin sequence, Pierre Robin anomaly or Pierre Robin anomalad.
- A congenital condition of facial abnormalities in humans characterized by cleft palate, micrognathia and glossoptosis.
- The male-to-female ratio is 1:1.

Aetiology

- Autosomal recessive inheritance is possible. An X-linked variant also does occur involving cardiac malformations and clubfeet.

Pathophysiology

- Three pathophysiological theories are propounded.
- ***The mechanical theory:*** The initial event, mandibular hypoplasia, occurs between the 7th and 11th week of gestation. This keeps the tongue high in the oral cavity, causing a cleft in the palate by preventing the closure of the palatal shelves.
- Oligohydramnios could play a role in the aetiology.
- ***The neurological maturation theory:*** A delay in neurological maturation has been implicated.
- ***The rhombencephalic dysneurulation theory:*** Here, the motor and regulatory organization of the rhombencephalus is related to a major problem of ontogenesis.

Symptoms

- Cardiovascular findings: pulmonary stenosis, patent ductus arteriosus, patent foramen ovale, atrial septal defect, and pulmonary hypertension.
- Musculoskeletal system: Syndactyly, dysplastic phalanges, polydactyly, clinodactyly, hyperextensible joints, and oligodactyly in the upper limbs, foot anomalies (clubfeet, metatarsus adductus), femoral malformations (coxa varus or valgus, short femur), hip anomalies (flexure contractures, congenital dislocation), anomalies of the knee (genu valgus, synchondrosis), and tibial abnormalities.
- Vertebral column deformities include scoliosis, kyphosis, lordosis, vertebral dysplasia, sacral agenesis, and coccygeal sinus.

- Central nervous system (CNS): defects such as language delay, epilepsy, neurodevelopmental delay, hypotonia, and hydrocephalus may occur.
- Genitourinary defects may include undescended testes, hydronephrosis, and hydrocele.

Associated syndromes and conditions include

- Stickler syndrome, trisomy 11q syndrome, trisomy 18 syndrome.
- Velocardiofacial (Shprintzen) syndrome.
- Deletion 4q syndrome.
- Rheumatoid arthropathy.
- Hypochondroplasia.
- Möbius syndrome.
- CHARGE association.

Management

- Conservative measures.
- Surgical: Tracheostomy remains the most widely used technique, subperiosteal release of the floor of the mouth, glossopexy, Mandibular lengthening.

Complications

- Breathing difficulties, especially when the child sleeps.
- Choking episodes.
- Congestive heart failure.
- Death.
- Feeding difficulties.
- Low blood oxygen and brain damage (due to difficulty breathing).
- Pulmonary hypertension.

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15.6 Treacher Collins Syndrome

- Also known as Treacher Collins–Franceschetti syndrome or mandibulofacial dysostosis.
- Very rare and inherited by autosomal dominant fashion.
- Characterized by craniofacial deformities, such as absent cheekbones, downward slanting eyes, micrognathia, conductive hearing loss, underdeveloped zygoma, drooping part of the lateral lower eyelids, and malformed or absent ears.

Diagnosis

- Both clinical and radiographic.

Clinical

- Based on OMEN criteria (namely O; orbital asymmetry, M; mandibular hypoplasia, E; auricular deformity, N; nerve development and S; soft-tissue disease).

Radiographic

- CT scan, dental X ray, etc.

Differential diagnosis

- Acrofacial dysostoses.
- Nager Syndrome.
- Miller Syndrome.
- The oculoauriculovertebral spectrum.
- Hemifacial Microsomia.
- Goldenhar Syndrome.

Treatment

- A multidisciplinary approach.

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SECTION 16:

BASIC PAEDIATRIC PROCEDURES

CHINAWA, J.

16.1 Venipuncture

Introduction

Venipuncture is the act of puncturing the vein for the purpose of adding a substance or removing blood.

Materials

1. Safety Needles; 22G or less.
2. Butterfly needles; 21G or less.
3. Syringes.
4. Blood Collection Tubes.
5. Tourniquets. Latex-free tourniquets are available.
6. Antiseptic. Individually packaged 70% isopropyl alcohol wipes.
7. 2 x 2 Gauze or cotton balls.
8. Sharps disposal containers.

Precautions

1. Observe universal (standard) safety precautions.
2. Wash hands in warm running water.
3. Gloves are to be worn during all phlebotomies and changed between patient collections.
4. A lab coat or gown must be worn during blood collection procedures.
5. Needles and hubs are single use and are disposed of in an appropriate “sharps” container as one unit.
6. Contaminated surfaces must be cleaned properly.

Procedure

- Select the proper size needle and attach it to the syringe or Vacutainer hub.
- Position the draw site for best visualization.
- Apply the tourniquet 3-4 inches above the selected puncture site.
- Prepare the patient's arm or the site using a spirit swab.
- Grasp the patient's arm firmly using your thumb to draw the skin taut and anchor the vein, at a 15-30 degree angle with the skin, into the lumen of the vein.
- If the patient complains of "shooting, electric-like pain, or tingling or numbness proximal or distal to the puncture site," the needle should be **removed immediately**.
- If the blood does not begin to flow, reposition the needle by gently moving the needle either backwards or forwards in the arm.
- After you have attempted to reposition the needle and are still not successful, remove the tourniquet, remove the needle and begin the process with a new site.
- When the collection is complete, remove the tourniquet and place gauze over the venipuncture site.
- Apply adequate pressure to the puncture site to stop the bleeding and avoid the formation of a haematoma.

Sites to avoid:

- Burns or surgery sites.
- Haematoma.
- Intravenous therapy/Blood Transfusions.
- Oedematous extremities.
- Sites with noticeable skin conditions, such as eczema or infection.

Complications

- Venospasm.
- Haematoma.
- Air embolism.
- Overhydration.
- Non-running Iv infusion.
- Local complications: Extravascular drug administration.
- Interatrial drug administration.

- Drug related complications: Nausea and vomiting.
  - Allergy.
  - Laryngospasm.
- Complications that arise from administering the drugs themselves.

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16.2 Venous Cut down

Introduction

- Venous cut down is a procedure in which venous access is obtained by cutting through skin and soft tissues, exposing a peripheral vein and cannulating it.

Objective:

- Venous cut down is indicated when peripheral veins in the upper extremities are difficult to access because of obesity vascular collapse or frequent vein puncture (thrombosis).

Materials needed

- Wash your hands well and sterile gloves (universal).
- Povidone Iodine paint.
- Sterile drape.
- Scalpel.
- 23-gauge needle.
- Appropriate size venous catheters depending on the patient.
- Intravenous infusion.
- 5 ml syringes.
- Artery forceps.
- Silk sutures.
- Nylon suture.
- 0.5 or 1% xylocaine.
- Tourniquet.

Indications

As an alternative to venipuncture in critically ill patients in need of vascular access and in whom venipuncture may be difficult. Examples: shock, small children, sclerosed veins of intravenous drug abusers.

Contraindications

- **Absolute:** When less invasive options exist for venous access.

- **Relative:** Bleeding diathesis, Overlying skin infection and Immunocompromised patients.

Complications

- Infection: Thrombophlebitis, Vein stripping, local bleeding, Catheter occlusion or dislodgment.

Procedure

- The skin is cleaned, draped, and anaesthetized.
- The greater saphenous or antecubital vein is identified on the surface, a full-thickness transverse skin incision is made, and 2 cm of the vein are freed from the surrounding structures. **(Locate the vein 1 cm anterior and 1 cm superior to the medial malleolus.)**
- The vessel is tied and closed distally, the proximal portion is transected and gently dilated, and a cannula is introduced through the site and secured in place with a more proximal ligature around the vein and cannula.
- An intravenous line is connected to the cannula to complete the procedure.

Usual sites

- Saphenous vein.
- Antecubital vein at the elbow: (the same procedure with the saphenous venous cut down except for the location: At the antecubital area (anterior elbow) which lies about 2 to 3 cm above and medial to the epicondyle.

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16.3 Peripheral venous cannulation

Introduction

The veins of choice for catheterization include the cephalic or basilic veins, followed by the dorsal hand venous network.

Preparation and site selection

- Select a site where the vein is long straight and accessible ensuring it is not on the antecubital fossa or near a bony prominence.
- Wash hands and prepare the equipment needed.
- Extend the limb and apply a tourniquet.
- Palpate the selected vein and thoroughly clean the site with an alcohol swab.

Equipment list

- Nonsterile gloves.
- Tourniquet.
- Antiseptic solution (2% chlorhexidine in 70% isopropyl alcohol).
- Local anaesthetic solution.
- 1-ml syringe with a 30-G needle.
- 2 × 2 gauze.
- Venous access device.
- Vacuum collection tubes and adaptor (see the image below).
- Saline or heparin lock.
- Saline or heparin solution.
- Transparent dressing.
- Paper tape.

Principles of the procedure

- Put on disposable gloves.
- Remove the cannula cover and loosen the introducer from the cannula.
- Anchor the vein by holding the surrounding skin taut using your non-dominant hand.
- Insert the cannula at an angle of 5-10 degrees.

- Observe the flashback of blood in the cannula chamber. Level off the cannula and advance a few millimetres into the vein.
- Withdraw the introducer by approximately 5 mm. Advance the cannula further into the vein, observing for the continued flashback of blood along the cannula.
- Release the tourniquet. Apply firm pressure over the vein at the distal end of the cannula and then withdraw.
- Attach an extension set or sterile bung to the end of the cannula.
- Flush the cannula with 5 mls of sterile saline and then apply a sterile transparent dressing.

Indications

The main indications for the insertion of a peripheral venous cannula are:

- Administration of intravenous medicines.
- Transfusions of blood or blood components.
- Maintenance or correction of hydration levels if unable to tolerate oral fluids.
- Potential venous access.

Contraindications

- The presence of injury or damage (e.g. fracture, Cerebrovascular accident, oedema, lymphadenopathy, thrombosis caused by multiple attempts of cannulating or venipuncture).
- The presence of infection as suggested by inflammation, phlebitis, cellulitis.
- Veins which are mobile or tortuous, or sited near a bony prominence.
- If intravenous therapy is predicted to be long-term.
- Continuous infusions or therapies which are vesicant or have a pH of <5 or >9 (Hadaway, 2010).

Complications

- Pain.
- Failure to access the vein.
- Blood stops flowing into the flashback chamber.
- Difficulty advancing the catheter over the needle and into the vein.

- Difficulty flushing after the catheter was placed in a vein.
- Arterial puncture.
- Thrombophlebitis.
- Peripheral nerve palsy.
- Compartment syndrome.
- Skin and soft tissue necrosis.

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16.4 Umbilical catheterization

Introduction

- Umbilical vein catheterization is a life-saving procedure in neonates who require vascular access and resuscitation.
- The umbilical vein is patent and viable for cannulation until approximately 1 week after birth.

Indications

- Central venous access in neonates in the first 14 days of life.
- Administration of medication, parenteral nutrition and IV fluids.
- Exchange or partial exchange transfusion.
- Central venous pressure monitoring.
- Frequent blood sampling in unstable patients without arterial access.

Contraindications

- Abdominal surgery requiring an incision above the umbilicus.
- Infection: Omphalitis, Necrotizing Enterocolitis, Peritonitis.
- Abdominal wall defect: Omphalocele, Gastroschisis, Umbilical fistula.

Materials Required

- Personal protective equipment (i.e., sterile gown, gloves, mask).
- Sterile drapes.
- Umbilical catheter, 3.5F or 5F (see the images below). 5F umbilical catheter. Note the proximal attachment for the stopcock. Close-up of umbilical catheter.
- Iris forceps without teeth, Small clamps, Scalpel, Scissors, Needle holder.
- Silk suture (3-0) or umbilical tape.
- Intravenous tubing and 3-way stopcock.

Procedure

- A radiant warmer should be provided, and the patient should be connected to a cardiac monitor. Necessary equipment includes the following:
- The infant's abdomen and cord are cleaned with alcohol. The area is then draped so that only the cord is exposed.
- Tie a piece of umbilical tape around the base of the umbilical cord tightly enough to minimize blood loss but loosely enough so that the catheter can be passed easily through the vessel.
- Using a scalpel, the cord is cut cleanly 1.0 cm from the skin.
- The cord is stabilized with forceps or a haemostat, and the vessels are identified. The single, large, thin-walled oval vein can readily be distinguished from the two smaller, thick-walled round arteries.
- The arteries are usually constricted, so that the lumens appear pin-point in size.
- Grasping the catheter with forceps or between the thumb and forefinger, the catheter can be inserted into the lumen of the dilated vein. Supporting the stump is usually necessary. Once the catheter has been inserted, it may encounter resistance at the level of the anterior abdominal wall or at the bladder. This resistance can usually be overcome by the application of gentle, steady pressure.
- Observe both legs for evidence of blanching, cyanosis or mottling. If a "blue leg" develops (presumably from vasospasm), the catheter should be removed or carefully observed for a short period of time to allow for resolution of the impaired circulation.
- A purse-string suture is placed around the umbilicus taking care not to puncture the catheter after its placement.

N/B

- It is expedient that the length of the catheter insertion is estimated based on the shoulder-to-umbilicus length.
- Alternatively, the shoulder-to-umbilicus length may be multiplied by 0.6 to determine a length that leaves the tip of the catheter above the diaphragm but below the right atrium.
- In an emergency resuscitation, the catheter is best advanced only 1-2 cm beyond the point at which good blood return is obtained.

Complications

- Infection.
- Haemorrhage.

- Vessel perforation.
- Creation of a false luminal tract.
- Hepatic abscess or necrosis.
- Air embolism.
- Catheter tip embolism.
- Portal venous thrombosis.
- Dysrhythmia and pericardial tamponade or perforation (if the catheter is advanced to the heart).

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16.5 Exchange blood transfusion

Introduction

- Exchange transfusion is a medical procedure where a patient's blood is removed via a catheter and replaced with an IV transfusion of plasma or donor blood.

Indications

1. Alloimmune haemolytic disease of the newborn.
2. Significant unconjugated hyperbilirubinaemia.
3. Severe anaemia.
4. Antibodies in maternal autoimmune disease.
5. Polycythaemia.
6. Severe disturbances of body chemistry.
7. Sickle cell disease (SCD).

Materials Needed

- 3-way taps; 5 ml syringe; 10 ml syringe.
- Small sterile plastic drape; Large sterile plastic drape.
- Large sterile drape; Small sterile fenestrated drape.
- EDTA, Heparin and coagulation tubes.
- Blood gas syringes; Heparin ampoules (50 IU in 5 mls).
- Normal saline; Calcium gluconate ampoules.
- Exchange transfusion recording chart.

Procedure

Push-pull method

- The procedure takes 90-120 minutes. The volume in/volume out balance should not exceed 5% of the infant's blood volume. Thumb rule: 5 ml aliquots for a pre-term baby (<2000 gms); 10 ml for a term baby (or >2000 gms).
- Connect 2 three-way taps and a syringe.
- Connect the filtered line from the blood pack to the proximal three-way tap (tap 1–closer to the infant).
- Attach the line to the waste bag to the distal three-way tap (tap 2–closer to the syringe) for closed disposal of the withdrawn blood.

- Prime the set-up system from the blood pack and ensure a set-up free of air bubbles.
- Connect the set-up to the primary lumen of the umbilical venous catheter–ensure tap 1 is turned off to the blood pack and tap 2 is turned off to the waste disposal bag.
- Withdraw the first aliquot slowly, announce the volume (x-mls) "out", the nurse records it.
- Collect baseline blood samples from this volume.
- Fill the syringe for a replacement from the blood pack via tap 1.
- Infuse the desired amount and announce the volume (x-mls) "in", the nurse records it.
- The following "out" is sent to the disposal bag via tap 2.
- Volumes "in" and "out" are repeated sequentially (approximately one minute for each action) and recorded each time by the nurse on the flow sheet including running totals.
- The nurse announces the running total every 100 mls.

Isovolumetric method

- Connect a syringe for the withdrawal process (the size appropriate to pre-determined aliquot volumes) to a three-way tap.
- Attach the waste bag to the remaining site on the three-way tap for closed disposal of withdrawn blood.
- Connect to the umbilical arterial catheter (or peripheral arterial line).
- Prime the set-up system (via the blood filter) from the blood pack through the infusion pump and ensure the lines are free of air bubbles.
- Place the blood line into the blood warmer at a set temperature of 37 degrees.
- Connect the set-up to the umbilical venous catheter. Add an additional three-way tap to the set-up for FFP/Albumin infusion if required.
- Set up the infusion of FFP/Albumin via the syringe driver for infusion if required.
- Commence the infusion at the corresponding time to the initiation of the first withdrawal process.
- Withdraw the first aliquot slowly, announce the volume (x-mls) "out", the nurse records it.
- Collect baseline blood samples from this volume.

- Repeat the sequence, at all times ensuring that the volume being removed is kept at the exact pace of the volume being supplied via the infusing pump.

Complications

- **Complications from catheter placement:** Gut perforation, peritonitis, cardiac arrhythmias, necrotizing enterocolitis.
- **Complications from EBT:** Hypovolaemia, electrolyte imbalance, acid-base imbalance.
- **Complications from blood transfusion:** Transmission of infection, transfusion reaction, thromboembolic episodes.

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16.6 Lumbar puncture

Introduction

- Quincke performed the first lumbar puncture (LP) in 1891 to relieve increased intracranial pressure in children with tuberculous meningitis.

Materials needed

- Usually a prepackaged commercial kit containing: a 20-gauge spinal needle, syringes and needles (22 and 25 gauge) for spinal anaesthesia, a manometer with a stopcock, sterile drapes, gauzes and local anaesthetic.

Technique

- ***Preparation***–An LP can be performed with the patient in the lateral recumbent position (preferred because it allows accurate measurement of the opening pressure) or sitting upright (especially in infants).
- The highest points of the iliac crests should be identified by inspection and confirmed by palpation; an imaginary line joining these crests is a guide to the fourth lumbar vertebrae.
- The subarachnoid space must be entered below the level of spinal cord termination. Any of the interspaces between L3-L4 and L5-S1 can be used for the lumbar puncture in children. The spine should be flexed maximally to increase spacing between spinous processes.
- The overlying skin should be cleaned with methylated spirit or povidone-iodine or chlorhexidine (0.5 per cent in alcohol 70 per cent); the antiseptic should be allowed to dry before the procedure is begun.
- After the skin is cleaned and allowed to dry, a sterile drape with an opening over the lumbar spine is placed on the patient.
- After, local anaesthesia is injected into the lumbar area. The spinal needle may be advanced slowly, angling slightly towards the head, as if aiming towards the umbilicus.
- Once CSF appears and begins to flow through the needle, the patient should be instructed to slowly straighten or extend the legs to allow the free flow of CSF within the subarachnoid space.

Imaging guidance

- Fluoroscopic guidance for LP may be required if attempts without imaging are unsuccessful. This is also suggested for patients who are obese or have difficult anatomy because of prior spine surgery or other reasons.

Indications

- Suspected meningitis or encephalitis.
- Suspected subarachnoid haemorrhage, only if the CT scan is normal.
- Diagnosing or ruling out sepsis in the neonatal period.
- Other indications include the diagnostic work-up of certain malignancies, seizures, metabolic disorders and other neurological conditions (e.g. MS, GBS).
- Idiopathic intracranial hypertension (pseudo tumor cerebri).
- Normal pressure hydrocephalus.

Contraindications:

- Although there are no absolute contraindications to performing the procedure, caution should be used in patients with:
- Coma.
- Suspected raised intracranial pressure.
- Cardiovascular compromise.
- Respiratory compromise.
- Suspected cerebral herniation.
- Coagulopathy/thrombocytopenia.
- Local infection at the lumbar puncture site.
- Vertebral anomalies.

Complications

- Postural puncture headache (relatively common).
- Local back pain.
- Infection.
- Spinal haematoma.
- Subarachnoid epidermal cyst.
- Apnoea.

- Transient limp or parasthaesias.
- Transient ocular palsy.
- Cerebral herniation.

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16.7 Diagnostic set: contents and uses

Introduction

- A diagnostic set is a set of medical instruments used to examine the eyes, ears, nose, and throat. The set may consist of a single instrument with configurable parts which can be used for all four functions.

Contents

- Ophthalmoscope.
- Otoscope (auroscope).
- Convertible rechargeable handle.
- Converter ring.
- Recharging battery.
- Charging transformer.
- Carry case.
- Metallic spatula.
- **Ophthalmoscope:** It is used to detect and evaluate disease of the retina or optic discs.
- **Auroscope (Otoscope):** To detect disease of the tympanic membrane, and external auditory meatus.
- **Fibre Optic Nasal Illuminator:** It facilitates easy nasal examinations. The head can be detached and the illuminator used to examine the throat.
- **Metallic spatula:** It can be used to depress the tongue to examine the tonsils and pharyngeal fauces.
- NB: Not used in acute epiglottis.
- **Carry case:** This is used to carry or cover the instrument in the case.

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Diagnostic sets obtainable from *www.wow.com/Medical+Diagnostic+Kit.* Accessed on 20 May 2014.

SECTION 17

COMMON PAEDIATRIC FORMULAE, REFERENCE STANDARDS AND ACRONYMS

TAGBO, B. AND CHINAWA, J.

17.1 Formulae

Table 3. Estimated Fluid Deficit		
Severity	**Infants (weight <10 kg)**	**Children (weight >10 kg)**
Mild dehydration	5% or 50 mL/kg	3% or 30 mL/kg
Moderate dehydration	10% or 100 mL/kg	6% or 60 mL/kg
Severe dehydration	15% or 150 mL/kg	9% or 90 mL/kg

- **Osmolarity** is a measure of the osmoles of solute per litre of solution (referring to the number of solute particles per litre of solution). A capital letter M is used to abbreviate units of mol/L.
- **Osmolality** is a measure of the moles (or osmoles) of solute per kilogram of solvent (referring to the number of solute particles per kg of water) expressed as mol/kg, molal, or m.

Normal maintenance fluid

For the first 10 Kg allow	100 ml/kg/day
plus, 2nd 10 Kg allow	50 ml/kg/day
plus, for any >20 Kg allow	20 ml/kg/day
Water–normal requirements	
Skin losses	= 30 cc/100 Cal/day
Pulmonary losses	= 15 cc/100 Cal/day
Insensible water loss (IWL)*	= 45 cc/100 Cal/day

**losses from the skin and lungs but does not include sweat*

Sources of Unusual Loss	Concentration of Electrolytes (mEq/L)			
	Na^+	K^+	Cl^-	HCO_3^-
Gastric	140	15	155	0
Small Bowel (ileostomy)	140	15	115	40
Diarrhoea (non-secretory)	40	40	40	40

Type of Dehydration	Water volume (mls)	Na^+ (mmol/kg)	K^+ (mmol/L)
Isonatraemic	100-120	8-10	8-10
Hypernatraemic	100-120	2-4	0-4
Hyponatraemic	100-120	10-12	8-10

Caloric requirement

- Newborn: 120-150 Kcal/Kg/day, decreases with age to
- 1-5 years: 100-90 Kcal/Kg/day.
- If fever is present for a large part of the day the estimated caloric expenditure is increased by: 12% for each 1° above 37^O.

Blood transfusion

- Fresh frozen plasma (FFP) =10-15 ml/Kg.
- Pack cell = 12 mls/kg.
- Sedimented cells = 15 mls/kg.
- Whole blood = 20 mls/kg.
- Plasma exchange = 10 mls/kg.
- Saline exchange or plasma exchange = [observed-expected/expected] wgt × 65.
- Transfusing a paediatric patient with 4 ml/Kg of blood will increase the Hb by 1 g/dl (transfusing 1 unit of blood in an adult will raise Hb by 1g/dl or HCT by 3%).

Estimated blood volume (EBV) by age

Age	Blood Volume (mL/kg)
• Premature infant	100
• Full-term neonate	85
• Older infant	70-75
• >12 months	70-75

Estimated volume per unit of blood products is as follows:

- Packed red blood cells (PRBCs): 300 mL/unit.
- Whole blood: 450-500 mL/unit.
- Fresh frozen plasma (FFP): 250-300 mL/unit.
- Platelets: 40-50 mL/unit.
- Cryoprecipitate: 10-12 mL/unit.
- Volume of PRBCs to be transfused = desired HCT – present HCT* x EBV.

HCT of PRBC (average 60%–70%).
**HCT of whole blood 40%–45%.*

Weight Gain

- Neonate: Growth here is mainly in terms of weight not necessarily length.
- Birth: 2.5 kg; 45 cm.
- Weight drops by 10% before the end of 1 week.
- It starts increasing again by 30 kg per day.
- Infants: weight gain of 30 grams per day continues till the end of the second month.
- Then 20 grams per day from the third to the sixth month.
- There is a doubling of birth weight at 5 months, which tipples at 1 year.
- 2 years to 5 years (weight): 240 grams/month.
- 6-12 years (weight): 3 kg/year.

Weight Estimate

- 0-3 months: n (age in days) – 10 x 30g + Birth weight.
- 3-12 months: n + 9/2.
- 1-6 years: 2n + 8.
- 7 years-12 years**:** 7n - 5/2.

Length Gain

- 3.5 cm/month:1st three months of life.
- 2 cm/month: 4th-6th months of life.
- 1.5 cm/month: 7-9 months.
- 1.2 cm/month: 10-12 months.
- Average of 2 cm/month.

Height gain/year

- 1st year: 25 cm.
- 2nd year: 12 cm.
- 3rd year till puberty: 6 cm/year.
- Growth spurt during puberty (usually about 2 years duration):
- Girls 6-11 cm/year;
- Boys 7-12 cm/year.

Height Estimate: 6n + 77 (From 1 to 12 years)

Occipitofrontal Circumference

- 2, 2, 2, 1, 1, 1, 0.5, 0.5, 0.5, 0.5 cm (per month for the 1st year).
- 0.25 (cm/month for the second year).
- 2-5 years: 0.25 cm/month.
- 6-12 years: 0.5 cm/yr.

Body mass index (BMI): Weight (kg)/Height (metres^2)

- Underweight: <5th centile.
- Normal: 5th to <85th centile.
- Overweight: 85th to <95th centile.
- Obesity: ≥95th centile.

The Ponderal Index (PI):

- P= Weight/height^3.

Urine volume:

- **Normal:** 1-4 mls/kg/hr. **Polyuria:** >4 mls/kg/day. **Oliguria:** <1 ml/kg/hr.

Blood pressure

- Blood Pressure estimate: x + 90/x + 55 (x = years).

- Normal blood pressure: <90th centile for age, sex and height.
- Prehypertension: BP between the 90th and 95th centile.
- Prehypertension in adolescents: BP ≥120/80 mmHg, even if this figure is <90th centile.
- Hypertension: Systolic BP and/diastolic BP ≥95th centile and should be staged.
- Stage 1 (95th centile to the 99th centile plus 5 mm Hg).
- Stage 2 (>99th centile plus 5 mm Hg).

Glomerular filtration rate (GFR) New Schwartz formula:

- GFR (mL/min/1.73m^2) = (K × Height in cm)/Creatinine in mg/dL, where: K = constant 0.413.
- GFR for males and females aged 2-12 years old is 133.0 ± 27.0.
- For males aged 13-21 years old it is 140.0 ± 30.0.
- For females 13-21 years of age it is 126.0 ± 26.0.

Conversion from conventional to SI units

Conventional unit = SI unit multiplied by a factor; SI unit = Conventional unit divided by a factor.

Compound	Conventional unit (US)	Factor	SI unit
Glucose	mg/dl	0.0555	mmol/l
Cholesterol	mg/dl	0.0259	mmol/L
Creatinine	mg/dl	88.4	μmol/L
Creatinine clearance	ml/min	0.0167	ml/s
Urea nitrogen	mg/dl	0.357	mmol/L
Potassium	mEq/L	1.0	mmol/L
Sodium	mEq/L	1.0	mmol/L
Osmolality	mOsm/kg	1.0	mmol/kg
Protein, total	g/dl	10	g/L

Adapted from the Society for Biomedical Diabetes Research, SI unit conversion calculator, 2014

17.2 Reference standards

Anthropometric indicators of nutritional status in the under fives

- Stunting–low height-for-age, Wasting–low weight-for-height.
- Underweight–low weight-for-age.
- The Z-score classification of these indicators is most widely used.

	≥ -2SD	<-2SD to -3SD	<3SD
Underweight (weight-for-age)	Normal	Moderate	Severe
Wasting (weight-for-height)	Normal	Moderate	Severe
Stunting (height-for-age)	Normal	Moderate	Severe
Overweight (<10 yrs) = weight-for-height of +2SD			
BMI for age (wt/ht^2) 5-19 yrs			
>1SD (25 kg/m^2 at 19 yrs)	>2SD (30 kg/m^2 at 19 yrs)	<-2SD	<-3SD
Overweight	Obesity	Thinness	Severe thinness
BMI percentile			

Comparison of percentiles and Z-scores in anthropometry

Percentiles	Z-score
0.2nd	–3
2.3rd	–2
2.5th	–1.96
5th	–1.64
15th	–1.04
16th	–1
50th (median)	0
84th	+1
85th	+1.04
95th	+1.64
97.5th	+1.96
97.7th	+2
99.8th	+3

MUAC

Measurement	Nutritional Status
>13.5 cm	Normal
12.5-13.5 cm	At risk of acute malnutrition
11-<12.5 cm	Moderate acute malnutrition
<11 cm	Severe acute malnutrition

The 1995 WHO growth reference: use of percentiles and Z-scores

Outcomes	Anthropometric measures and cut points	Indication of growth/nutrition problems
Infants and children (<10 years)		
Stunting	HAZ <–2 Z score, or <3rd percentile	Chronic malnutrition
Wasting/thinness	WHZ <–2 Z score, or <3rd percentile	Acute malnutrition, current malnutrition
Overweight	WHZ >2 Z score	Overweight
Adolescents (> =10 years)		
Stunting	HAZ <–2, or <3rd percentile	Chronic malnutrition
Thinness	BMI-for-age <5th percentile	Underweight
At risk of overweight	BMI-for-age 85th-<95th percentile	Overweight
Obese	BMI-for-age ≥95th percentile and triceps and subscapular skinfold thickness-for-age ≥90th percentiles	Obesity

Classification of Hypertension in Children and Adolescents

Class	SBP or DBP Percentile
Normal	<90th percentile
Prehypertension	≥90th percentile to <95th percentile, or if BP exceeds 120/80 even if below the 90th percentile up to <95th percentile
Stage 1 hypertension	95th percentile to the 99th percentile plus <5 mmHg
Stage 2 hypertension	99th percentile plus ≥5 mmHg

- Osmolarity = 1.86 Na + (Glucose/18) + (BUN/2.8) + 9 (or) 1.91 Na + (Glucose/15) + (BUN/2.25).

Normal Values of Arterial Blood Gas

pH	7.35-7.45
$[HCO_3^-]$	20-28 mEq/L
P_{CO_2}	35-45 mm Hg

- The Henderson-Hasselbalch equation, emphasizes the relationship between the pCO_2, the bicarbonate concentration, and the hydrogen ion concentration: $[H^+] = 24 \times pCO_2/[HCO_3^-]$.
- The anion gap = $([Na^+] + [K^+]) - ([Cl^-] + [HCO_3^-])$: (with potassium).

$= [Na^+] - ([Cl^-] + [HCO_3^-]) = -16$ mEq/L: (without potassium).

Haemoglobin

Age	Males (g/dL)	Females (g/dL)
Newborn	14.7–18.6	12.7–18.3
6 months to 2 years	10.3–12.4	10.4–12.4
2-6 years	10.5–12.7	10.7–12.7
6-12 years	11.0–13.3	10.9–13.3
12-18 years	11.5–14.8	11.2–13.6
18 years	10.9–15.7	10.7–13

Platelet count value 10^3/L (L = mm^3)

Age	Males	Females
Newborn	164-351	234-346
1-2 months	275-567	295-615
2-6 months	275-566	288-598
6months to 2 years	219-452	229-465
2-6 years	204-405	204-402
6-12 years	194-364	183-369
12-18 years	165-332	185-335
18 years	143-320	171-326

White blood cell count values 10^3/µL (10^9/L or 1000/mm^3 or 10^3/mm^3)

Age	Males	Females
New-borns	6.8-13.3	8.0-14.3
6 months–2 years	6.2-14.5	6.4-15.0
2–6 years	5.3-11.5	5.3-11.5
6-12 years	4.5-10.5	4.7-10.3
12-18 years	4.5-10.0	4.8-10.1
18 years	4.4-10.2	4.9-10.0

Blood Serum Chemistry–Normal Values.

Constituent Electrolytes	Typical Normal Range
Bicarbonate: (total)	18-30 mEq/L
Calcium: (total)	9-11 mg/dL; 4.5-5.5 mEq/L
Chloride:	98-106 mEq/L
Magnesium:	1.8-3.6 mg/dL; 1.5-3.0 mEq/L
Phosphorus: Adults	3-4.5 mg/dL; 1.8-2.3 mEq/L
Children	4-6.5 mg/dL; 2.3-3.8 mEq/L
Potassium:	3.5-5.5 mEq/L
Sodium:	135-147 mEq/

Table 5. Composition of standard and reduced Osmolarity ORS solutions

	Standard ORS solution	Reduced Osmolarity ORS WHO Solution
	(mEq or mmol/l)	(mEq or mmol/l)
Glucose	111	75
Sodium	90	75
Chloride	80	65
Potassium	20	20
Citrate	10	10
Osmolarity	311	245

Prematurity Definition

- Preterm: a birth date before 37 completed weeks of gestation.
- Gestational age: the time elapsed between the first day of the last menstrual period and the day of delivery.
- Number of weeks preterm: 40 weeks minus the gestational age.
- Chronological age: the time elapsed since birth.
- Postmenstrual age: gestational age plus the chronological age in weeks.
- Corrected age: chronological age minus the number of weeks preterm (RCPCH, 2011).

Birthweight Definition

- Birthweight is the first weight of the newborn obtained after birth (ideally within one hour of delivery).
- Low birthweight (LBW) <2500 g.
- Very low birthweight (VLBW) <1500 g.
- Extremely low birthweight (ELBW) <1000 g.

(UNICEF & WHO, 2004).

Glasgow Coma Scale

Best Eye Opening	Adult/Child	Infant	Score
	Spontaneous	Spontaneous	4
	To speech	To speech	3
	To pain	To pain	2
	No response	No response	1
Best Verbal response	Oriented to time, place, person	Coos and babbles	5
	Confused/ disoriented	Irritable cries	4
	Inappropriate words	Cries to pain	3
	Incomprehensible sounds	Moans to pain	2
	No response	No response	1
Best motor response	Obeys commands	Moves spontaneously	6
	Localizes to pain	Withdraws to touch	5
	Withdraws to pain	Withdraws to pain	4
	Flexion to pain	Flexion to pain	3
	Extension to pain	Extension to pain	2
	No response	No response	1

Interpretation

Coma level	**GC Score**
Best response	15
Comatose	≤8
Totally unresponsive	3
Injury level	
Mild injury	13-15
Moderate injury	9-12
Severe injury	3-8

MATURATIONAL ASSESSMENT OF GESTATIONAL AGE (New Ballard Score)

NAME _____ SEX _____
HOSPITAL NO. _____ BIRTH WEIGHT _____
RACE _____ LENGTH _____
DATE/TIME OF BIRTH _____ HEAD CIRC. _____
DATE/TIME OF EXAM _____ EXAMINER _____
AGE WHEN EXAMINED _____
APGAR SCORE: 1 MINUTE _____ 5 MINUTES _____ 10 MINUTES _____

NEUROMUSCULAR MATURITY

NEUROMUSCULAR MATURITY SIGN	SCORE -1	0	1	2	3	4	5	RECORD SCORE HERE
POSTURE								
SQUARE WINDOW (Wrist)	 >90°	 90°	 60°	 45°	 30°	 0°		
ARM RECOIL		 180°	 140–180°	 110–140°	 90–110°	 <90°		
POPLITEAL ANGLE	 180°	 160°	 140°	 120°	 100°	 90°	 <90°	
SCARF SIGN								
HEEL TO EAR								
							TOTAL NEUROMUSCULAR MATURITY SCORE	

SCORE
Neuromuscular _____
Physical _____
Total _____

MATURITY RATING

SCORE	WEEKS
-10	20
-5	22
0	24
5	26
10	28
15	30
20	32
25	34
30	36
35	38
40	40
45	42
50	44

GESTATIONAL AGE (weeks)
By dates _____
By ultrasound _____
By exam _____

PHYSICAL MATURITY

PHYSICAL MATURITY SIGN	SCORE -1	0	1	2	3	4	5	RECORD SCORE HERE
SKIN	sticky friable transparent	gelatinous red translucent	smooth pink visible veins	superficial peeling & / or rash, few veins	cracking pale areas rare veins	parchment deep cracking no vessels	leathery cracked wrinkled	
LANUGO	none	sparse	abundant	thinning	bald areas	mostly bald		
PLANTAR SURFACE	heel-toe 40–50 mm: -1 < 40 mm: -2	>50 mm no crease	faint red marks	anterior transverse crease only	creases ant. 2/3	creases over entire sole		
BREAST	imperceptible	barely perceptible	flat areola no bud	stippled areola 1–2 mm bud	raised areola 3–4 mm bud	full areola 5–10 mm bud		
EYE / EAR	lids fused loosely: -1 tightly: -2	lids open pinna flat stays folded	sl. curved pinna; soft; slow recoil	well-curved pinna; soft but ready recoil	formed & firm instant recoil	thick cartilage ear stiff		
GENITALS (Male)	scrotum flat, smooth	scrotum empty faint rugae	testes in upper canal rare rugae	testes descending few rugae	testes down good rugae	testes pendulous deep rugae		
GENITALS (Female)	clitoris prominent & labia flat	prominent clitoris & small labia minora	prominent clitoris & enlarging minora	majora & minora equally prominent	majora large minora small	majora cover clitoris & minora		
							TOTAL PHYSICAL MATURITY SCORE	

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Composition of Intravenous Fluids (Based on 1-litre bags)

Type	Na^+	K^+	Ca^{2+}	HCO_3^-	Osm	Comments
Plasma	140	4.5	2.3	26	290	=
Saline 0.45%	77	0	0	0	154	"half" saline
Saline 0.9%	154	0	0	0	308	"normal" saline
Saline 0.9% + 20 mmol KCl	154	20	0	0	348	
Saline 0.9% + 40 mmol KCl	154	40	0	0	388	
Glucose 5%	0	0	0	0	277	50g glu/L
Glucose 5% + 20 mmol KCl	0	20	0	0	317	50g glu/ L
Glucose 5% + 40 mmol KCl	0	40	0	0	357	0
Glucose 10%	0	0	0	0	556	100g glu/ L
Glucose 50%	0	0	0	0	2777	25 g/50 ml; irritant
Glucose 4% Saline 0.18%	31	0	0	0	284	40 g glucose per litre
Glucose 5% Saline 0.45%	77	0	0	0	431	0
Hartmann's solution	131	5	2.0	29	278	0
Ringer's lactate	130	4	1.4	28	273	0
Plasmalyte 148 and 5% glucose	140	5	0	29	294	with 5% glucose

Constituents of Standard vs. Low Osmolarity ORS

Reduced Osmolarity ORS	Reduced Osmolarity (mmol/litre)	Standard ORS solution (mmol/litre)
Sodium	75	90
Chloride	65	80
Glucose, anhydrous	75	111
Potassium	20	20
Citrate	10	10
Total Osmolarity	245	311

The LATCH Scoring System			
Score	**2**	**1**	**0**
Latch	Grasps breast, tongue down, lips flanged, rhythmic sucking	Repeated attempts, hold nipple in mouth, stimulate to suck	Too sleepy or reluctant; no latch achieved
Audible swallo-wing	Spontaneous and intermittent < 24 hrs; spontaneous and frequent > 24 hrs	A few with stimulation	None
Type of nipple	Everted	Flat	Inverted
Comfort	Soft, tender	Filling, reddened/small blisters, bruises; mild/moderate discomfort	Engorged, cracked bleeding, large blisters or bruises, severe discomfort
Hold (position -ing)	No assistance from staff; mother able to position/hold infant	Minimal assist (i.e., elevate head of bed; place pillows for support) teach one side; mother does other; staff holds and then mother takes over	Full assist (staff holds infant at breast)

Characteristics of Commonly Used Tools for Breastfeeding Assessment and Documentation					
Characteristic	Lactation Assessment Tool LAT	LATCH	Infant Breastfeeding Assessment Tool IBFAT	Systematic Assessment of the Infant at the Breast SAIB	Mother-Baby Assessment MBA
Scored by	Assessor	Mother or nurse	Mother or nurse	Nurse	Nurse
Time frame	Progressive: beginning to ending	Static	Progressive: beginning to ending	Any point in the feeding	Progressive: beginning to ending
Scoring	Compares assessed findings with optimal	Expect increase in scores	Use mean of scores	Yes/no	Use best of scores
Assesses	Pre-feeding, latching and sucking dynamics	Latch on, audible swallowing, nipple comfort, help needed with positioning	Signalling, rooting, suckling	Alignment, areolar grasp, areolar compression, audible swallowing	Readiness, position, latch on, milk transfer outcome

Clinical Findings of Dehydration			
Symptom/Sign	**Mild Dehydration**	**Moderate Dehydration**	**Severe Dehydration**
Level of consciousness	Alert	Restless/irritable or Lethargic	Obtunded/drowsy, floppy
Capillary refill*	2 s	2-4 s	>4 s, cool limbs
Mucous membranes/Tongue	Normal (moist)	Dry	Parched, cracked
Thirst	Drinks normally	Thirsty, drinks eagerly	Unable to drink
Tears	Normal	Decreased	Absent
Heart rate	Slightly increased	Increased	Very increased
Respiratory rate/pattern*	Normal	Increased	Increased and hyperpnoea
Blood pressure	Normal	Normal, but orthostatic	Decreased
Pulse	Normal	Thready	Faint or impalpable
Skin turgor*	Normal	Slow	Tenting
Fontanel	Normal	Depressed	Sunken
Eyes	Normal	Sunken	Very sunken
Urine output	Decreased	Oliguria	Oliguria/anuria
[+]Best indicators of hydration status. Author Lennox H Huang, MD, FAAP			

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SECTION 18

COMMON ORTHOPAEDIC PROBLEMS IN CHILDHOOD

EKUMANKAMA

18.1 Talipes equinovarus

Introduction

- Talipes equinovarus is a congenital club foot deformity (Congenital Talipes equinovarus–CTEV).
- An affected baby is born with one or both feet twisted into an abnormal shape.
- Acquired TEV e.g. from post-polio palsy can also occur in children.

Epidemiology

- The incidence is 1-2 per 1000 live births; the male to female ratio is 2:1.
- It is bilateral in 30-50% of cases.
- Sporadic cases are common; some are familial in occurrence.
- There is a 30% chance of occurrence in a subsequent sibling, if one child is affected.

Pathology

- The aetiology of CTEV is unknown.
- Conflicting theories on the pathogenesis abound, including:
- A neuromuscular origin e.g. its association with Spina bifida;
- Tight packaging in utero e.g. Oligohydramnios;
- A germ defect in the Talus causing plantar flexion/inversion with subsequent medial soft tissue contracture.

- The components of CTEV include: Ankle equinous, hindfoot varus, forefoot adduction, cavus, and hypotrophic calf.

Classification

- Intrinsic type–rigid, such as seen in AMC, Spina bifida.
- Extrinsic type–flexible and mild, often postural in origin.

Clinical features: history

- Foot deformity at birth.
- Other associated deformities.
- Family history of a similar problem among the siblings.
- Antenatal/natal history on risk factors.

Physical findings

- Look for ankle equinous, heel varus, midfoot adduction, cavus, deep creases on the midfoot and heel.
- Compare with the normal foot.
- Talar prominence is felt and correction of the deformity attempted, noting foot flexibility.
- Associated deformities: on the back, hip (CHD), other sites.

Left-sided unilateral clubfoot at FETHA clinic

Diagnosis

- Diagnosis is clinical.
- X-ray of the foot is useful in monitoring severity/progress of treatment.
- Lines are drawn on the radiograph to measure various angles.
- Prenatal ultrasound enables in-utero diagnosis.

Differential diagnosis

- Tibial Hemimelia and Acquired clubfoot e.g. polio.

Treatment

- **AIM:** To restore a plantigrade, supple, painless and functional foot.
- Options:
- **Non-operative treatment:** This is the mainstay of treatment.
- It is started in the 1st week of life, using the Ponseti casting technique.
- Serial manipulation and Pop casting, applied from groin to toe with the knee flexed.
- Correction is sequential: cavus, adduction, varus before Equinous for 5 to 6 weeks.
- Achilles tenotomy if equinous is not fully corrected.
- Ankle foot orthosis is worn for 2-3 years to maintain correction.

Operative treatment

- Indicated in failed conservative treatment, rigid CTEV, Resistant and neglected cases.
- Soft tissue release with elongation of the Achilles tendon is done.
- Bony osteotomies for an older child from 4 years of age.

Complications

- Functional disability, Rocker-bottom deformity, Pressure-sores and wound breakdown/recurrence.

Prognosis

- Good if diagnosed and treated early.
- Flexible type as well as post-casting bracing.

Prevention

- The cause is unknown, a reduction of risk factors e.g. smoking during pregnancy.

Counselling

- To elicit the cooperation of parents during treatment.

- Antenatal counselling following ultrasound diagnosis (in advanced countries).

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18.2 Polydactyly

- Polydactyly is a congenital anomaly characterized by extra digits in the hand or foot.
- It may be either isolated or part of a complex genetic syndrome (Autosomal Dominant).

Epidemiology

- It is common. Incidence varies with the digit involved.

Classification: 3 main categories:

- Type 1 pre-axial–Duplication of the thumb.
- Type 2 central–Duplication of the index, long or ring fingers.
- Type 3 post-axial–Little finger duplication.
- Pre-axial: this is more common among whites/Asians.
- Central: this is rare and usually associated with syndactyly.
- Post-axial: this is the most common type in blacks.
- Classified into 3 types on the basis of the bony or soft tissue component.
- Type 1 involves soft tissue alone.

Pathophysiology

- The cause is unknown.
- It results from malformations in mesenchyme growth and differentiation.
- Heritable genetic mutations may occur in some cases.

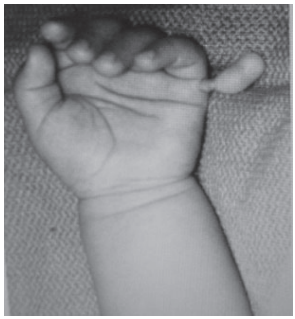
Fig 1 Postaxial polydactyl

Clinical features

History:

- More than 5 digits are seen at birth.
- Syndactyly or other anomalies may be noted.
- Pain is usually absent.

Physical examination

- Look for the involved digit and note its size.
- A narrow stalk of tissue may connect it to the adjoining finger.
- Syndactyly may be present.

- Feel for consistency; it may have a bony or soft tissue attachment.
- Other sites may reveal associated anomalies.
- Post-axial polydactyl (L) hand (Figure 1).
- (Picture from Lovell and Winter's *Paediatric Orthopaedics*).

Diagnosis

- This is mainly clinical.
- X-rays of the hand or foot help to determine if the lesion is simple or completely bony.
- Simple types have only a soft tissue attachment.
- 2-D Echocardiography or Abdominal ultrasound is needed only if other congenital anomalies exist.

Differential diagnosis

- Polydactyly is associated with specific syndromes e.g. Dandy Walker syndrome.

Treatment

- The aim is to achieve cosmetic improvement and better function.
- An X-ray is necessary to visualize any bony component.
- Parental counselling on prognosis is also important.

Options:

- The use of ligatures or a vascular clip around the base leading to ischaemia.
- Indicated mostly for small finger (or toe) duplication with a narrow stalk.
- Done with or without local anaesthesia.
- Usually when the child is less than 4 months.
- Surgical excision:
- Commonly for thumb or central digit duplication.
- Complex reconstructive procedures may be required.
- The timing for surgery is often around 1 year of age.

Complications

- If left untreated, there is difficulty in fitting shoes (foot polydactyly).

- Ridicule from peers.
- Following surgery: Wound infection, angular deformity, scar contracture and joint stiffness.

Prognosis

- Best in small finger duplication with a narrow stalk.
- Worse in thumb or central types.
- Early recognition and treatment improve the outcome.

Prevention

- Genetic counselling after the prenatal ultrasound diagnosis as in the case of Triphalangeal thumb (three instead of two phalanges) which can be inherited.

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18.3 Syndactyly

Introduction

- Syndactyly is a condition in which there is webbing of two or more fingers or toes.
- It is the most common congenital anomaly of the hand.
- Most cases are sporadic in occurrence; others are part of a syndrome.

Epidemiology

- The occurrence is 1 in 2000 births.
- It is bilateral in half of the patients.
- Boys are more frequently affected than girls.

Pathophysiology

- The cause is unknown.
- There is a failure of separation of the digital rays in utero.
- Digital separation starts distally and proceeds proximally at 5 to 8 weeks of gestation.
- If separation fails to occur or ends prematurely syndactyly results.

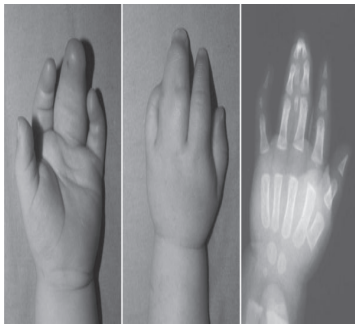
Classification

- This is based on clinical and x ray findings:
- A complete syndactyly–if the web extends over the entire length of the digits.
- An incomplete syndactyly–if the fingers are joined to a point proximal to the finger tips.
- Simple syndactyly–the digits are joined only by skin or other soft tissue.
- Complex syndactyly–there is osseous connection between the digits.
- Acrosyndactyly–webbing of the tips of the digits.
- Syndactyly associated anomalies include: Poland syndrome and Apert syndrome.

Clinical features

History:

- The 3rd web space is most commonly affected.
- The 4th, 2nd and 1st in diminishing frequency.
- Functional impairment of the digit.
- Toe syndactyly and any associated syndromes.



Syndactyly in a child (simple type) picture from Campbell's Orthopaedics

Physical examination:

- The involved digits; size and length.
- Compare with a contra-lateral hand.
- Partial or complete.
- Soft tissue or bony union.
- Function of digits/associated deformities.

Diagnosis:

- Plain x-rays help to exclude complex types.
- This is important for surgical reconstruction.

Treatment

Options include:

- No treatment if the syndactyly does not extend beyond the PIP joint.
- This will not limit function.
- Surgical reconstruction:
- Indicated for cosmetic and functional reasons.
- Timing is 12 to 18 months.
- For the border digits (1st and 4th webs) 6-12 months is preferred.
- This is because the longer digit may develop a flexion contracture/angulation.
- Zigzag incisions are used.

Differential diagnosis

- Some of the rare syndromes associated with syndactyly.

Complications

- Cosmetic blemish.
- Impairment of independent function of the affected digits.
- Flexion contracture/angulation.
- Surgery-related sequelae including circulatory damage.

Prognosis

- Simple and incomplete types have a better prognosis.

Prevention

- This is difficult since there is no known aetiology.

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18.4 Ingrowing toe nail

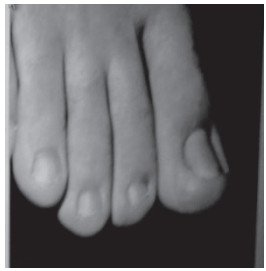
- A painful condition of the toe in which the sharp edge of the nail is embedded in the nail fold.
- Also known as embedded toe nail or onychocryptosis.

Epidemiology

- The big toe is commonly affected; although any toe can be involved.
- It is rare in people who do not wear shoes.
- Adults and adolescents are more affected than children.

Pathophysiology

- Extrinsic pressure such as a tight-fitting shoe causes the nail fold to push into the sharp edge of the nail leading to the skin breaking.
- Skin bacterial/fungal flora enter the wound.
- Serous or abscess discharge and later.
- An inflammatory process ensues.
- Granulation tissue formation.



Ingrown toenail
(Campbell Orthopaedics)

Clinical features

History: Pain/swelling of the big toe

- Serous or pussy discharge;
- An ulcer beneath the nail fold.

Physical findings

- General examination to exclude fever/anaemia (not usually present);
- Erythema, swelling and tenderness of the affected toe;
- Embedded nail (Fig. 1), discharge or granulation tissue.

Diagnosis

- This is clinical.
- PCV and urinalysis if surgical treatment is required.

- Wound swab–M/C/S.
- Plain X-ray to exclude chronic osteomyelitis or fracture.

Differential diagnosis

- Nail bed injuries.
- Bunion.
- Candidiasis.
- Cellulitis.
- Herpetic whitlow.

Treatment

- Insert pledgets of cotton beneath the nail edge.
- This is done daily for 2 weeks.
- Cut the nail square instead of round.
- Applicable in the early inflammation stage.
- If an abscess or granulation tissue forms: Antibiotics/Tetanus prophylaxis, remove the nail partially or completely.
- Part of the nail's germinal layer is destroyed.
- To prevent recurrence.

Complications

- Recurrence.
- Chronic osteomyelitis.
- Upward-turned nail-bed and pulp after nail excision.

Prognosis

- Good in the early stage.

Prevention

- Present early for treatment.
- Careful nail trimming.
- Use of shoes with a roomy toe-box.
- Keep the feet clean and dry.

Counselling

- Avoid tight shoes.

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18.5 Genu Varum (Bow-legged)

- Genu varum is the outward bending of the knee with the distal leg directed medially.
- It is a common knee deformity in children.
- It can be physiologic or pathologic.
- The pathological type may be due to:
- Blount's disease (Tibia vara), persistent physiologic varus, Rickets, physeal injury.
- Skeletal dysplasia e.g. Achondroplasia.

Pathophysiology

- The ***physiologic*** type–a normal growth and developmental occurrence.
- Seen from birth to 2 years. It usually corrects spontaneously.

Blount's disease:

- A progressive bow-leg deformity.
- Associated with alteration in endochondral ossification.
- Affects the posteromedial part of the proximal tibial epiphyses (physes/metaphyses are also involved).
- Obese children who walk early are more affected.
- More common in Negros.

Rickets:

- The bony manifestation of disordered calcium/phosphorous metabolism (vit. D deficiency).
- Asteroid (newly formed bone) is not mineralized.
- Bone softens and is prone to bowing.
- Inadequate intake, absorption, and utilization are the cause.

Skeletal dysplasia:

- Abnormal development/ossification of cartilage.

The limb is short and misshaped.

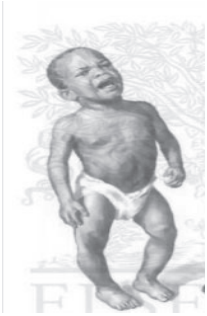
Clinical features: History: (a child with bow-leg deformity)

- Bowing at 0-2 years–physiologic genu varum.
- If after 2 years it is progressive with no history of injury–Blount's disease.
- Inadequate dietary intake of calcium /vit. D/exposure to sunlight–Rickets.
- Dwarfism/family history of misshapen limbs or skull–bone dysplasia.

Clinical features:

Physical findings

- A well-nourished infant with symmetrical/ bilateral bowing–physiologic.
- Bowing with lateral tibial thrust/internal tibial torsion–Blount's.
- A goniometer is used to measure the femoro-tibial angle.
- Skull bossing, Rickety Rosary, expanded wrists, knees and ankles–Rickets.
- Limb deformity, short stature ± abnormal skull shape–bone dysplasia.



Physiologic genu varum. Netter's *Atlas of Orthopaedics Anatomy*

Diagnosis

- Serum calcium–low or normal in Rickets.
- Phosphorous–low, Alkaline Phosphatase–high.
- Plain x-ray shows cupping of bone metaphysis, osteopenia, bowing.
- Metaphyseal beaking, epiphyseal depression in Blount's.

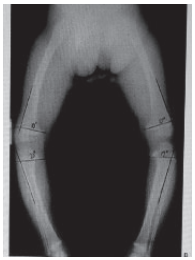


Figure 2. X-ray of a child with genu varum

Differential diagnosis

- Malunited tibia/femur fractures.
- Other causes of genu varum.

Treatment

- Depends on the cause: Physiologic varum–no treatment.
- Rickets–vitamin D (400-2000 I U), calcium tablets.
- Corrective osteotomy in persistent deformities.
- Blount's/other causes–do corrective osteotomy.

Complications

- Waddling gait if the deformity is untreated.
- Osteoarthritis in adulthood, recurrence after surgery.

Prognosis

- Worse in late presentation.

Prevention/control

- Dietary (vitamin D-rich) e.g. milk, egg yolk, fish.
- Exposure to sunlight, prompt hospital presentation.

Counselling

- Reassurance if varus is physiological.
- Awareness of risk factors.

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18.6 Genu valgum

- Genu valgum implies an inward bending of one or both knees (knock knees) with the ankles far apart so the knees knock together in walking.

Epidemiology

- Common in children aged 3-4 years.
- The physiologic type is often implicated.
- Spontaneous correction is usual by 5-8 years.
- Pathological type can be bilateral or unilateral.

Pathophysiology

- The pathologic type is seen in:
- Rickets (vitamin D deficient or Resistant types).
- Skeletal dysplasia e.g. multiple epiphyseal dysplasia.
- Physeal injury.
- Congenital dislocation of the patella.

Clinical features: History

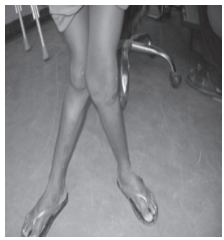
- Valgum knee, if below 4 years and bilateral–physiologic.
- Diet lacking in vitamin D–rickets.
- Injury or joint infection–physeal destruction.
- Family history of short stature/deformities–bone dysplasia.

Clinical features: physical findings

- General appearance: nutritional status/body habitus.
- Tibio-femoral angle–usually more in valgus.
- Intermalleolar distance–more than 8 cm.
- Medial ligamentous laxity.
- A knock-knee on one side with a bow on the other (wind-swept deformity).
- Other findings specific to the aetiology. Genu valgum–seen at the clinic.

Diagnosis

- Diagnosis is clinical.
- For confirmation,
- Serum calcium, phosphorous, alkaline phosphatase in metabolic bone diseases (rickets);
- Plain x-ray, standing (AP, and Lateral views);
- Shows physeal widening/metaphyseal cupping in rickets;
- Epiphyseal distortion in bone dysplasia;
- Severity/tibio-femoral angle is noted.



Bilateral genu valgum (seen at the Orthopaedic clinic)

Differential diagnosis

- These include the congenital and acquired causes above.

Treatment

- This depends on the cause.
- Oral vitamin D and calcium (or phosphorous in Hypophosphataemic rickets).
- Hemi-epiphysodesis.
- Corrective osteotomy.

Complications

- Gait anomalies/patella dislocation.
- Early-onset osteoarthritis.
- Common peroneal nerve injury post-surgery.
- Recurrence.

Prognosis

- Good in physiological valgum.
- Prior correction of deficient nutrients before surgery.
- Early presentation.

Prevention

- Adequate dietary intake of vitamin D.
- Exposure to sunlight.

Counselling

- Knowledge of the risk factors.
- Treatment options including lengthening procedures for short stature.

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18.7 Septic arthritis

Introduction

- Septic arthritis is an infection of the joint due to bacterial invasion.
- It is also referred to as Suppurative Arthritis (pyoarthritis) or infectious arthritis.
- Osteomyelitis and septic Arthritis may occur simultaneously in children.

Epidemiology

- It is most common in children and rare in adults.
- Host factors determine the type of bacteria involved.
- Predisposing factors include local trauma, immune compromise and debilitating diseases e.g. Diabetes.
- Weight-bearing lower limb joints, e.g. knee and hip, are more commonly affected.

Pathophysiology

- Joint infection follows a haematogenous route.
- Direct spread from an adjacent bone abscess may occur.
- Bacteria lodges on the synovium; this evokes an acute inflammatory response.
- Fluid exudation with the release of enzymes and toxins by leucocytes, bacteria and synovial cells leads to articular cartilage damage/joint destruction.

Bacteriology

- The age of the patient is related to the causative bacteria.
- Staphylococcus aureus is the most common.
- Haemophilus influenza may be implicated in children aged 1-4 years.

Clinical features

***History**:*

- Varies according to the age group involved.

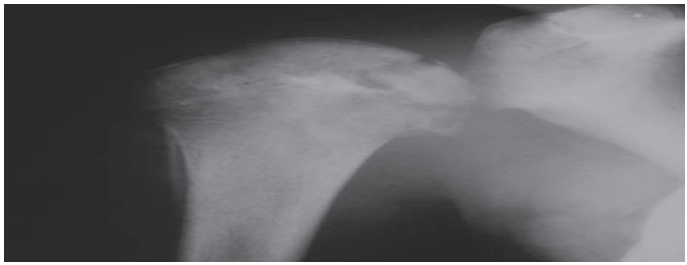
- Neonates and infants may not complain of pain.
- Features of septicaemia with irritability, fever, a refusal to eat should be noted.
- Children–fever, joint pain, pseudoparesis.

Physical findings:

- An irritable neonate, ill-looking, rapid pulse and febrile (occasionally), a site of infection in the ear, nose or skin may be found. Pseudoparesis is usually present.
- Children–acutely ill-looking, swelling, warmth, tenderness and pseudoparesis of the limb.

Diagnosis

- Joint aspiration (arthrocentesis) is done to reveal any pus or turbid fluid.
- Gram stain, M/C/S and synovial fluid analysis for the choice of antibiotics.
- Full blood count/ESR indicates Hb status and the presence of infection.
- Genotype to screen for SCD.
- Urinalysis to exclude Diabetes.
- X-ray of involved joint–comparing it with the unaffected joint.
- Normal findings initially but shows soft tissue swelling, the widening of joint space.
- Later x-rays may show joint narrowing, destruction or associated osteomyelitis.
- Magnetic resonance imaging or ultrasonography are useful.



AP view of the shoulder showing humeral head subchondral Erosions/sclerosis with periosteal reaction in late presentation of Septic Arthritis (From Lourdes Nunez–Atahualpa et al., Medscape May 12, 2016)

Differential diagnosis:

- Acute osteomyelitis may coexist with septic arthritis.
- Trauma resulting in synovitis or haemarthrosis.
- Sickle cell disease.
- Other forms of infection around the pelvis e.g. psoas abscess.

Treatment

- Principles include: adequate drainage of the joint.
- Antibiotics to kill the pathogens.
- Splinting of the limb to prevent deformity.
- Joint aspirate is obtained for investigations.
- Empirical antibiotics are commenced (intravenous initially and later oral).
- IV fluid resuscitation/correction of anaemia.
- Open drainage of the joint under anaesthesia.
- Splinting of the limb with a pop cast or skin traction.

Post-operative care

- Antibiotics are continued for another 2-3 weeks or more.
- Active movement is commenced gradually if the clinical response is good.
- Adequate analgesics are given.

Complications/prognosis

- Prognosis is worse in late presentation (after 4 days).
- In children less than 6 months (epiphysis largely cartilaginous).
- Concomitant osteomyelitis and hip joint involvement.
- Complications include:
- Subluxation or dislocation;
- Osteomyelitis;
- Retarded growth/joint deformity.

Prevention

- Treat pre-existing infections to avert bacteraemia.
- Prompt diagnosis and treatment.

Counselling

- Caregivers on risk factors and the need for early presentation.

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18.8 Blount's disease

Introduction

- A bow-leg deformity in children.
- Due to disordered growth in the medial part of the proximal tibia epiphysis.
- Progressive in nature.
- Unlike normal physiological bowing.

Epidemiology

- Bilateral (80%), or unilateral.
- Predisposing factors:
- Race–common in blacks and Scandinavians.
- Age at walking–early walkers are more involved.
- Obese (overweight) children.
- Genetic factor–Positive family history.

Pathophysiology

- The exact cause is unknown.
- The Heuter-Volkmann principle:
- Compressive force across the medial tibial metaphysis, leads to
- Growth retardation (altered endochondral ossification),
- Varus/internal rotation and later shortening of the limb.

Classification

- Early onset–below 8 years.
- Late onset–8 years and above.

Clinical features

***History*:**

- Progressive bowleg deformity.
- Painless in infantile type; no trauma or infection.
- Leg-length discrepancy.
- Positive family history.

***Physical findings*:**

- General appearance–often normal.
- Bilateral or unilateral bowing.
- Internal tibial torsion.
- Tibio-femoral angle >5^{o} to 7^{o}.
- Intercondylar distance >6 cm.
- Check other sites to exclude rickets, bone dysplasias.

Diagnosis

- Plain x-ray (standing) AP/Lateral, from hip to ankle preferably.
- Fragmentation/beaking–proximal medial Tibial physes.
- Medial epiphyseal wedging.
- Fusion (Langenskioid grade VI) of the physes.
- A femoro-tibial or varus angle using a goniometer.
- A metaphyseo-diaphyseal angle–drawn on the x-ray if >11^{o}, Blount's more likely than physiologic bowing.

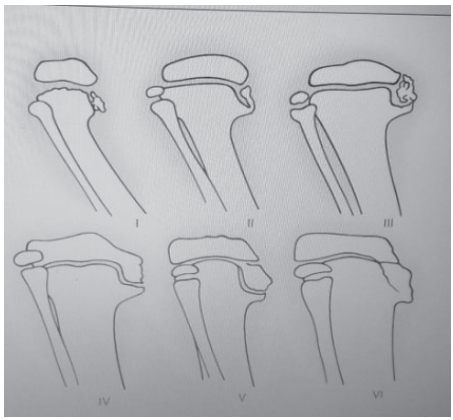

Diagram of X-ray features of Blount's (Campbell's *Orthopaedics*)

Differential diagnosis

- Physiological bowing–resolves spontaneously.
- Metabolic bone diseases e.g. rickets.
- Skeletal dysplasia.
- Infection/trauma to proximal tibia physis.

Treatment

- Depends on age/severity.
- Bracing or observation for early grades in those aged <3 years.
- Corrective osteotomy–definitive treatment.

Complications

- Cosmetic blemish.
- Limb shortening/gait anomaly.
- Problems associated with surgery:
- Common peroneal nerve injury,
- Compartment syndrome,
- Recurrence.

Prognosis

- The infantile type is better than the adolescent type.
- A poor outcome in the advanced stages.

Prevention

- Weight reduction in an overweight child may be helpful.

Counselling

- Early presentation for treatment is advised.

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APPENDIX

Abbreviations

2, 3 DPG-2, 3-Diphosphoglycerate

ACS–Acute Chest Syndrome

ADEM–Acute disseminated encephalomyelitis

AFASS–acceptable, feasible, affordable, sustainable and safe

AGE–acute gastro-enteritis

AICD–Automatic Implantable Cardioverter Defibrillator

AIHA–Auto-immune Haemolytic Anaemia

AMC–Arthrogryposis multiplex congenita

AOP–Anaemia of prematurity

AV–Artero-venous

BPD–Bronchopulmonary dysplasia

BVM–Bag valve and mask

CGH–Comparative Genomic Hybridization

CHD–Congenital Hip dysplasia

CHF–Congestive heart failure

GOBIFFFEETH OR [GOBIF^{3}E^{2}TH]–Child survival strategies– Growth monitoring, ORT, Breast feeding, Immunization, Female education, Family planning, Food supplementation, Essential drugs, Environmental sanitation, Treatment of common ailments and injuries, Health education

COG–Children oncology Group

CPS–Complex partial seizures

CVD–Cardiovascular disease

DARC–Duff antigen receptor for chemokines

DBP–Diastolic blood pressure

DCM–Dilated Cardiomyopathy

DDAV–Desamino D-Arginyl Vasopressin

DDD–Dense deposit disease

DHAP–Dexamethasone, high dose cytarabine (Ara-c), cisplatin

DMSA–Dimercaptosuccinic acid

DNAse B–Deoxyribonulease B

dRNA–Double-stranded ribonucleic acid

ds-DNA–Double-stranded DNA

dTMP–-deoxy-Thymine monophosphate

DTR–Deep tendon reflex

dTTP–deoxy-Thymine triphosphate

EBV–Estimated blood volume

EFE–Endocardial Fibroelastosis

EM–Erythema multiforme

EMF–Endomyocardial Fibrosis

EN–Epidermal Necrolysis

Epo–Erythropoietin

EPOCH–Etoposide, vincristine, doxorubicin, cyclophosphamide, prednisolone

EPOR gene–Erythropoietin Receptor Gene

FAP–Functional abdominal pain

FBAO–Foreign body airway obstruction

FBG–Fasting Blood Glucose

FEP–Free Erythrocyte protoporphyrins

G cells–Gastrin secreting cells.

GBS–Group B Streptococcus

GERD–Gastroesophageal reflux disease

GN–Glomerulonephritis

GRL–Global reference laboratory

HC–Health centre

HDV–Hepatitis d virus

Hib–Haemophilus influenzae b

HPF–High power field

HPLC–High Performance Liquid Chromatography

HSE–Herpes simplex encephalitis

IBS–Irritable bowel syndrome

IDM–Infant of diabetic mother
IEF–Iso-Electric Focusing
IF–Intrinsic factor
INPC–International Neuroblastoma pathology committee
INRG–International Neuroblastoma Risk Group
INRGSS–International Neuroblastoma Risk Group Staging system
INSS–International Neuroblastoma staging system
IO–Intra-osseous
IOTF–International Obesity Task Force
IPC–Interpersonal communication skills
ITP–Idiopathic Thrombocytopenic Purpura
IVIG–Intravenous immunoglobulin
JAK2–Janus Kinase 2
LE–Leucocyte esterase
LG–Local Government
LMN–Lower motor neuron
LRTI–Lower respiratory tract infection
LV EMF–Left Ventricular Endomyocardial Fibrosis
LVAD–Left Ventricular Assist Devise
MALT–Mucosa-associated lymphoid tissue
MAP–Mean arterial pressure
MDVP–Multi-dose vial policy
mESR–Micro Erythrocyte sedimentation rate
MGRS–Multicentre Growth Reference Study
MIBG–Metaiodobenzyl guanidine
MMN–Multiple micronutrient
MS–Mass spectrometry
NAFLD–Non-alcoholic fatty liver disease
NIPDs–National immunization plus days
NPHCDA–National Primary Health Care Development Agency
NTD–Neural tube defect
NTHi–Nontypable haemophilus influenza

NWTSG–National Wilms tumour study group
OP–Operation
PA–Pulmonary Artery
$PaCO_2$–Partial pressure of Carbon IV oxide
PAGE–Polyacrylamide gel electrophoresis
PaO_2–Partial pressure of Oxygen
PCV–Pneumococcal conjugate vaccine
PDGF–Platelet derived growth factor
PEG–Polyethylene glycol
PET–Positron emission tomography
PFCP–Primary Familial and Congenital Polycythemia
PFO–Patent foramen ovale
PNH–Paroxysmal Nocturnal Haemoglobinuria
PPI–Proton pump inhibitors
PRBCs–Packed red blood cells
PV–Polycythemia Vera
RAS–Reticular activating system
RB–Retinoblastoma
RBF–Renal blood flow
RI–Routine immunization
RMS–Rhabdomyosarcoma
ROD–Renal osteodystrophy
RV EMF–Right Ventricular Endomyocardial Fibrosis
SAGM–Saline-Adenine-Glucose-Mannitol
SaO_2–Percentage oxygen saturation of arterial blood
SAS–Subarachnoid space
SBP–Systolic blood pressure
SBR–Serum Bilirubin
SCID–Severe combined immunodeficiency
SCORTEN–SCORe of Toxic Epidermal Necrolysis
SCr–Serum creatinine
SCU–Severe childhood undernutrition

SE–Status epilepticus

SIAs–Supplementary immunization activities

SIOP–International Society of Paediatric Oncology

SIRS–Systemic inflammatory response syndrome

SJS–Stevens-Johnson Syndrome

SNGFR–Single nephron glomerular filtration rate

SPS–Simple partial seizures

TfR–Transferrin Binding Receptors

TGF–Transforming growth factor

THF–Tetrahydrofolate

TIBC–Total Iron Binding Capacity

TMA–Thrombotic microangiopathy

TNF–Tumour Necrosis Factor

TRALI–Transfusion Related Acute Lung Injury

TSG–Tumour suppressor gene

UAO–Upper airway obstruction

UCB–Unconjugated Bilirubin

UMN–Upper motor neuron

VEGF–Vascular endothelial growth factor

VF–Ventricular fibrillation

VT–Ventricular tachycardia

VVM–Vaccine vial monitor

VWF–Von Willebrand Factor

VZV-Varicella-zoster virus

VZVE–Varicella zoster virus encephalitis

WAGR–Wilms tumour, aniridia, genitourinary malformation, mental retard

WCBA–Women of child bearing age

WT–Wilms tumour

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