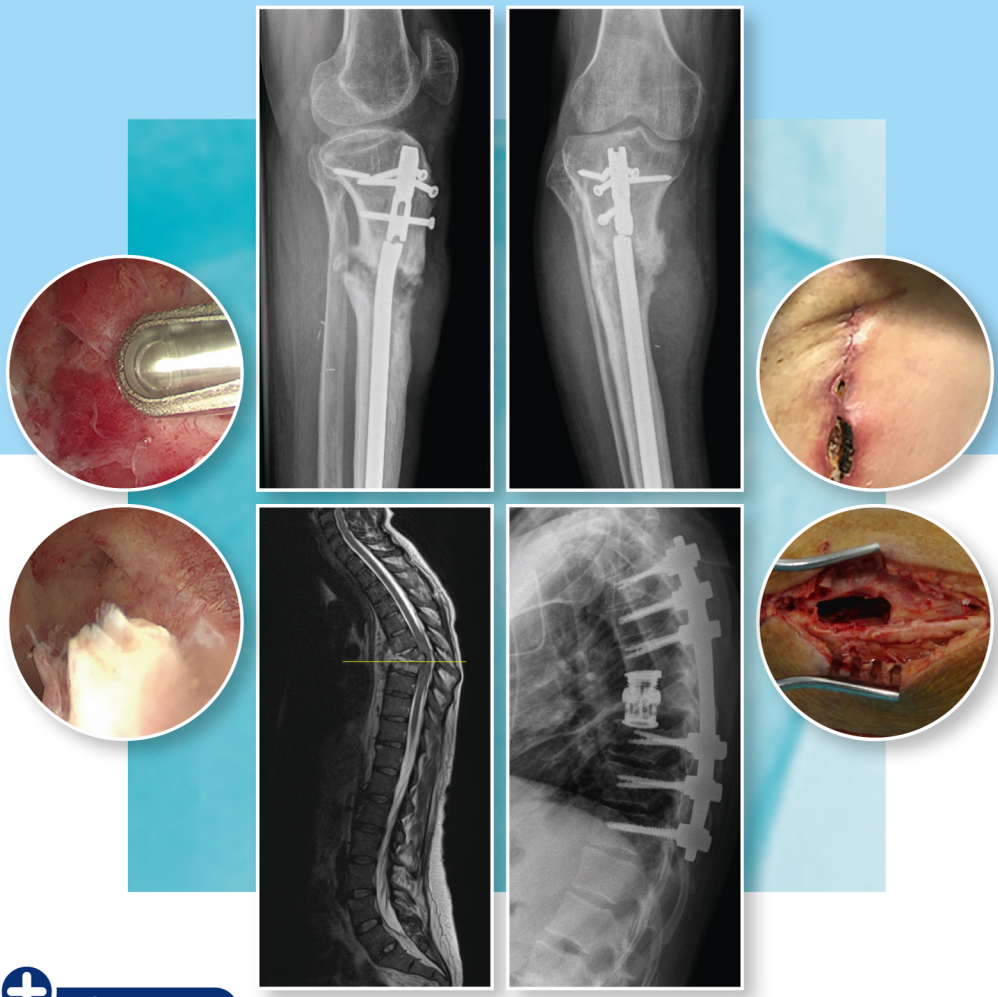
Management of Orthopaedic Infections

A Practical Guide

Antonia F. Chen



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A Practical Guide

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First and foremost, I would like to dedicate this book to my mother, Jean F. Lian, who has taught me and raised me to become the woman that I am. My dedication, work ethic, and drive have all come from her, and I am eternally grateful for everything that she has done for me.

Secondly, I would like to dedicate this book to my sister and friend, Victoria Chen Norland, who has encouraged and supported me throughout the years.

Thirdly, I would like to dedicate this to my father, Bor-Kuan Chen, who taught me a love for science and scientific writing.

And finally, I would like to dedicate this book to my mentors, friends, and colleagues who have contributed to this book, and those with whom I love sharing and growing together in the field of orthopaedics.

Antonia F. Chen, MD, MBA

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Foreword

Infections that afflict patients who undergo orthopaedic procedures are as devastating today as they were half a century ago. In spite of new antibiotics and innovative surgical techniques, bacterial infections seem to stay one step ahead of clinicians to bring additional pain and suffering to patients. Modern orthopaedic surgery has made tremendous strides in helping those with musculoskeletal disorders return to a quality of life that they seek, and we clinicians have at our disposal, tremendous new innovative technology to help our patients. However, this new thrust in innovation is often accompanied by more sophisticated implants and longer surgical times, which seem to be an ideal environment for the opportunistic bacteria to wreak havoc. In spite of minimally invasive techniques that seem to mitigate some of the risks, infections still seem to somehow sneak into arthroscopic portals or other tubular access channels. Infections today are just as devastating to the patient and surgeon as they were in previous generations, especially with the ever-changing bacterial DNA which seems to dodge the barrage of new wave antibiotics that we clinicians throw at it.

In *Management of Orthopaedic Infections: A Practical Guide* edited by Antonia Chen, MD, MBA, all of the major topics that are critically important for surgeons treating such infections are covered in a very pragmatic way, which provides clinicians a useful blueprint for treatment. Introductory chapters on general principles of microbial detection and the use of various antibiotics lay the foundation for diagnosis and medical treatment, but chapters in the principles of surgical irrigation and debridement as well as orthopaedic dressing management provide very useful and evidence-based practical guidelines for both young and experienced orthopaedic surgeons in all subspecialties. The book then turns to specific nuances of the sub-specialties that affect patients differently and provides *Practical Tips* and guidelines for optimizing treatment success.

Management of Orthopaedic Infections: A Practical Guide is a resource that all orthopaedic surgeons as well as other subspecialists will find very useful for quick reference and guidelines for treating orthopaedic infections. Infections will never go away, so we clinicians have to maintain our vigil and constantly look for improved techniques and better drugs to fight this ever-present danger that lurks around our patients.

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Preface

Orthopaedic infections are devastating complications that can occur after any procedure and affect all aspects of orthopaedic surgery. At some point in our careers, we are likely to encounter an orthopaedic infection and it is imperative that we diagnose and treat it effectively.

The purpose of this pocket guidebook is to provide *practical* tips on how to determine and manage the most common orthopaedic infections, including osteomyelitis, septic joint, periprosthetic joint infection, open fractures and infected nonunions, spine infections, and graft infections. Other applicable information includes the most common organisms found in orthopaedics and antimicrobials used to treat them, culture and molecular methods to improve organism determination, different formulations of antibiotics used to treat orthopaedic infections, various irrigation solutions to use during surgery, and dressings that can be used to prevent and address orthopaedic infections.

This useful guide will provide information that orthopaedic surgeons can regularly apply to their practices while managing difficult orthopaedic infections. This book provides hands-on knowledge with step-by-step guides on how to treat these infections. Multiple tables are provided to serve as quick references for easy access to information needed to manage the care of patients with orthopaedic infections. Additionally, notable figures help illustrate important concepts and extensive references are listed to provide published literature from which one can gain further knowledge.

Although orthopaedic infections have occurred throughout history, our means of diagnosing and treating these infections have improved over time, and effectively battling orthopaedic infections can make a difference in patient care. The practical tips and tricks from each chapter of this book can potentially enhance our care of patients with orthopaedic infections, and pave the way to orthopaedic infections becoming never events.

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1 Detection of Microbes in Orthopaedic Infections

Michael Henry, Andy O. Miller, and Barry D. Brause

Abstract

A very broad range of microorganisms cause orthopaedic infections. Modern diagnosis depends on traditional culture techniques, which remain in common use, and on molecular testing, which is advancing rapidly as a field. Advances in culture-based techniques include modifications in specimen collection, incubation, and identification. Identification of pathogens through detection and analysis of microbial nucleic acids, without culturing the organism, is the focus of molecular microbiologic diagnostics. A variety of polymerase chain reaction (PCR) tests can identify single or multiple pathogens in a single PCR reaction. 16S PCR uses conserved DNA sequences to identify a very broad array of pathogens. Newer techniques (next-generation sequencing) avoid the limitations of PCR and can detect an even broader, theoretically unlimited range of pathogens by sequencing all of the nucleic acids in entire samples. The place for these technologies in orthopaedics is evolving. While anecdotal reports and some studies show molecular diagnostics' advantages over culture, traditional cultures still remain the most accessible, affordable, and reliable in most clinical scenarios. However, further improvements are likely to alter the landscape of microbial diagnosis of orthopaedic infections.

Keywords: Osteomyelitis, prosthetic joint infection, bacteria, microbiology, biofilm, PCR, next-generation sequencing

Practical Tips

- When obtaining cultures, one should take specimens of deep tissue and fluid prior to antibiotic administration; swabs and samples of draining sinuses or postoperative wounds have low culture yield.
- It is ideal to obtain three to five cultures at a time using separate surgical instruments.
- Samples should be transported in blood-culture bottles and enriched media to the lab in under 2 hours, and these cultures should be grown on both solid and liquid media culture. Gram stains are not recommended.
- The optimal incubation period for anaerobic cultures is 14 days to increase culture yield.
- Molecular techniques that improve organism identification include polymerase chain reaction (PCR) to identify single or multiple pathogens or 16S conserved DNA sequences, or next-generation sequencing to detect an even broader range of pathogens.

1.1 Introduction

There is a broad range of microorganisms that cause orthopaedic infections. Many microbiologic diagnostic techniques are available to identify these pathogens. Pathogen

identification has traditionally been performed with standardized laboratory culture and biochemical analytic techniques, many of which have been in use for over a century. The increasing sophistication and availability of molecular microbiologic techniques have the potential to transform the way organisms are identified. They hold promise in augmenting the sensitivity of traditional techniques, shortening the time required to identify an organism, and broadening the spectrum of pathogens to include those that have been difficult to isolate in culture. Molecular technology remains less widely available, more expensive, and sometimes more difficult to interpret. In addition, many of these tests are laboratory-derived single-center assays, and lack of standardization can lead to varying accuracy between the performing laboratories.

Traditional culture-based techniques remain the backbone of orthopaedic infection diagnosis. Much scholarship has gone into improving and streamlining these well-established methods. Active areas of study to maximize the sensitivity of these tests without sacrificing specificity have included: specimen acquisition, specimen number, biofilm culture methods, incubation techniques, improvements in culture media, and duration of incubation.

1.2 Culture-Based Microbiology

Orthopaedic infections can develop in native bone or synovium, or can involve orthopaedic hardware, tissue grafts, or other foreign bodies. The most commonly encountered orthopaedic infections are osteomyelitis and septic arthritis. As with infections at other sites in the body, the specific organisms one expects to encounter in each patient is dictated by many host factors. Being able to anticipate which organisms to expect allows the clinician to better provide an optimal approach to the microbiology workup and to understand the limitations of each technique. The overwhelming majority of orthopaedic infections develop via hematogenous spread, via extension to bone from a contiguous site or via direct inoculation in the setting of trauma or surgery. The range of potential pathogens varies greatly as a result of a number of host and environmental factors. Differences in age, immune status, as well as an array of comorbidities, such as diabetes, peripheral vascular disease, and hemoglobinopathies, can all inform which organisms are more likely to be encountered. The most salient variable dictating which organisms will be the cause of infection is the presence or absence of orthopaedic hardware or other foreign material. The presence of orthopaedic hardware creates an area of focal immunodeficiency, as immune effectors such as leukocytes and antibody are often unable to function in close proximity to foreign surfaces. In addition, orthopaedic hardware, which often has large surface areas, permits the development of chronic bacterial biofilms. This allows many generally nonpathogenic organisms to cause infection.

Recent guidelines published by the Infectious Diseases Society of America (IDSA) and American Society for Microbiology (ASM) outline the optimal approach to obtaining and processing tissue specimens for culture, including bone and joint tissue.[1] Regardless of the type of infection, the use of swabs to obtain specimens is strongly discouraged in almost all situations.[2,3,4] Swabs hold an extremely small volume of specimen and are prone to picking up extraneous organisms. The winding fibers that make up the bulb also entrap organisms, preventing efficient release when the swab is used to inoculate liquid or solid media.[5] This further reduces an already limited yield. Draining sinus tracts or postoperative wounds is an inviting target for swab cultures, but repeated demonstrations have shown the inaccuracy of superficial cultures for delineating the pathogens in deep infection.[6,7,8] Instead, cultures of deep tissue and fluids

from the site of the infection are the most valuable specimens to submit for culture to more readily establish the microbiological diagnosis.

The IDSA/ASM guidelines also recommend that specimens be acquired prior to the administration of antibiotic. Once a specimen is collected it should be kept at room temperature and transported to the lab in under 2 hours. Extended transport time decreases the population of viable organisms, which can delay or prevent their recovery in the microbiology lab.[9] Once the specimen arrives in the lab, there are no widely accepted standards for the microbiologic workup for orthopaedic infections.[10] In general, the basic protocols for culturing bone and prosthetic hardware once the specimen arrives in the microbiology lab are modeled on the techniques and protocols that have been refined over decades to process blood cultures. Direct examination can be performed, typically a Gram stain. If the pathogen is present in sufficient quantity, Gram staining can provide immediate visual detection of a wide array, but not all, organisms that typically cause orthopaedic infection. However, Gram staining rarely yields a pathogen in nonpurulent orthopaedic infections, and many institutions no longer recommend its routine use in this setting. Clinical specimens are then processed and inoculated onto solid agar media and into liquid media (broth), followed by incubation for aerobic and anaerobic bacteria (and also mycobacteria and fungi if desired). Often several different media are employed, enriched with nutrients or otherwise modified to identify a specific type or range of microorganisms. When microbial growth is noted in the initial cultures, it undergoes further testing to identify the organism and its antimicrobial susceptibility profile. This may be done through manual or automated methods, via the analysis of a wide variety of the characteristics of the organism including growth characteristics, morphology, and biochemical and metabolic characteristics. Antimicrobial sensitivity is performed with disk diffusion or dilution methods. Much of this analysis is now automated.

In addition to being plated onto solid media, liquid media culture is typically performed as well. These cultures frequently include thioglycolate or similar solutions and are designed to support anaerobic bacterial growth. Liquid media is also able to support the recovery of smaller quantities of inoculated microorganism and may be more sensitive than solid media. The use of more sensitive media comes at the expense of an increased rate of isolating contaminants. Detected growth in liquid media is plated onto solid media (sub-cultured) before further analysis of the isolate can be completed.

Because longer incubation duration increases the isolation rate of nonspecific contaminants, the standard incubation time for blood cultures is 5 days; the incubation period for bacteria in tissue cultures and body fluid is variable from lab to lab but is usually between 2 and 5 days.[11] Some microbiology labs, both academic and commercial, incubate tissue (including bone and synovial fluid) culture for only 48 to 72 hours. As discussed below, the optimal incubation duration can greatly extend beyond 5 days, depending on the organism and clinical scenario.

1.2.1 Limitations of Culture-Based Microbiology

The majority of the bacteria that routinely cause orthopaedic infection can be grown in culture using standard media. However, recovering these bacteria in the setting of an orthopaedic infection can be a frustrating experience even in an experienced microbiology lab. For example, the cultures from 10 to 50% of orthopaedic prosthesis infections, with results varying on the population under study, fail to recover any organisms.[12] The concordance between preoperative aspirate cultures and intraoperative tissue culture in

chronic prosthetic joint infection (PJI) has been reported at 60%.[13] Several characteristics inherent to orthopaedic infections reduce the efficacy of traditional culture techniques. The most important factor may be the presence of biofilm.

1.2.2 Detection of Microbes in Biofilm

Traditional culture techniques are optimized for recovering bacteria in their active growth phase (planktonic growth). However, many orthopaedic infections, particularly those that are chronic or associated with hardware, persist due to the presence of a biofilm. The formation of biofilm is induced by specific conditions hostile to planktonic growth, and marked by significant changes in gene expression, allowing the microorganisms to attach to solid, preferentially inert, surfaces or dead tissue, forming microcolonies.[14] As the biofilm matures, bacteria secrete a complex mixture of polysaccharides, DNA, and protein,[15] allowing the microcolonies to aggregate, to become enmeshed in a complex extracellular matrix, and to develop into complex and functionally heterogenous communities. This increases the ability of the colony to survive regardless of the type of metabolic stress encountered. The extracellular matrix (aka slime, glycocalyx) resists the effects of antibodies, oxidative stress, host immune cells, and many chemical and enzymatic detergents,[16] and provides a structural framework within which bacteria can remain mechanically sheltered. While most culture-based techniques are optimized for bacteria in planktonic growth phase, most organisms within a biofilm are in stationary growth phase. The dramatic differences in phenotype greatly hinder the sensitivity of traditional culture methods.

1.2.3 Infections with Atypical Organisms

Traditional culture techniques can also fail in the setting of a wide array of less common causes of infection that are difficult or impossible to identify in this manner. Many of these bacteria, such as *Cutibacterium acnes*, *Brucella* spp., and nutritional variant streptococci are more indolent, requiring a prolonged incubation period and/or have specific nutritional requirements not met by standard enriched culture media.[17,18] *C. acnes* can require up to 14 days of anaerobic incubation to be detected; *Brucella* spp. can require up to 4 weeks.[19] Other causes of orthopaedic infections such as *Neisseria gonorrhoeae* require specialized handling and specific environmental conditions to enhance growth in culture.[20] Lyme arthritis is caused by *Borrelia burgdorferi*, which cannot be cultured in routine clinical labs.[21] Mycobacteria and fungi are also uncommon, but important, causes of orthopaedic infection.[17] Some fungi, such as *Candida* species, grow readily in standard bacterial culture media. Otherwise, almost all these organisms require specifically tailored culture media to support their growth; the duration of incubation for these organisms is often many weeks. To diagnose many fungal or mycobacterial infections, or to detect the wide range of bacteria that grow poorly with traditional culture methods, a high index of suspicion is required. In order to grow these organisms in culture, appropriate tests need to be specifically requested when submitting tissue or body fluid for culture.

To improve the yield of orthopaedic fluid and tissue culture, many adaptations and variations of the standard microbiologic approach have been evaluated for their ability to maximize the sensitivity of the cultures while avoiding a loss of specificity. Targets of study include improvements in the methodology of specimen collection and variations on the laboratory testing parameters, including the tissue preparation, duration

of incubations, as well as the use of enhanced and/or more selective media. Over the past decade there have been dramatic advances in molecular diagnostic techniques, including PCR sequencing, and matrix-assisted laser desorption ionization time-of-flight (MALDI-TOF) mass spectrometry, allowing for the identification of many organisms that have proven difficult to isolate and identify by traditional culture-based techniques. These advances in culture technique are an active area of study in both septic arthritis and osteoarthritis, but because of the high burden of biofilm-driven infections, the majority of investigation has centered on orthopaedic hardware infection.

1.2.4 Orthopaedic Hardware Infections

The presence of hardware, such as prosthetic joint or fracture-fixation hardware, can complicate any attempt to establish a microbiologic diagnosis. From a technical standpoint, the common causes of hardware-related infection, staphylococcal and streptococcal species, enteric gram-negative bacilli, and *Enterococcus*, can be easily recovered in the microbiology lab. However, the rate of culture-negative workups can be substantial, exceeding 20 to 25% in some series.[22,23] Methods to maximize the sensitivity of culture-based diagnostics of orthopaedic hardware infection without sacrificing specificity have been an active area of research for the past several decades. While some researchers have focused on spinal and fracture-fixation hardware infections, PJIs have been the main focus of inquiry.

Hardware Infections: Number of Cultures

Sending multiple cultures from the site of infected orthopaedic hardware, especially when there is concern for a low virulence or fastidious organism, improves the likelihood of a successful microbiologic diagnosis. Obtaining multiple specimens increases the overall yield of the cultures and can also aid in differentiating whether a cultured organism is a pathogen or a contaminant. Bacteria making up the normal skin flora can be asymptomatically introduced to the site of orthopaedic hardware at the time of surgery, only to present with infection months to years later. Often these subacute and chronic orthopaedic hardware infections can present without systemic or even local signs of infection or inflammation or may only come to attention after they have led to mechanical loosening, fracture nonunion, or other forms of hardware failure. Determining whether an isolated organism is the cause of infection or is merely a contaminant based on a single specimen can be very difficult.

Several early studies underscored the importance of obtaining multiple cultures in patients with PJIs. A 1981 prospective study of 63 infected and 30 uninfected patients found that collection of five cultures allowed for the investigators to differentiate infection from contamination, concluding the growth in “one or two of five biopsy samples was a strong indication of contamination, while growth in all five biopsies strongly correlated with the presence of an infection.”[24] A much larger prospective trial published in 1998 found, through mathematical modeling, that the optimal number of culture specimens to send is five to six and that finding the same organism in at least three of the specimens strongly correlates with the presence of infection.[25] This observation was corroborated in a 2016 prospective, multicenter study enrolling 264 patients with suspected infection, using patients as their own controls. Using a random-sampling method, repeated 1,000 times per case, the authors found that obtaining four separate specimens and inoculating them on three distinct culture media to be equivalent to

obtaining five specimens. This reduction in specimens required was a result of leveraging newer methodologies, including specimen preparation, choice of culture media, and duration of incubation, underscoring the many factors that can impact on the yield of orthopaedic intraoperative cultures.[26] Peel et al, in 2016, reported that the greatest accuracy of diagnosis was observed when four tissue cultures were performed. However, when directly inoculating tissue specimens into blood culture bottles, the optimal number of tissue specimens required decreased, without sacrificing sensitivity, to three specimens.[27]

Hardware Infection: Sample Acquisition

Separate surgical instruments should ideally be used to collect intraoperative tissue specimens. Swab cultures, whether taken intraoperatively or preoperatively (such as from a draining sinus), have been repeatedly shown to be less sensitive and less specific than deep tissue culture; as a result, the use of swab cultures in the orthopaedic setting is strongly discouraged.[2,3] Cultures should be taken prior to any extensive debridement, suctioning, or electrocautery.[2,4] Which type of tissue has the highest diagnostic value is unclear. Expert guidelines recommend the surgeon take tissue cultures from the "most suspicious" areas[28] and target "visibly inflamed or abnormal tissue"[2] and in the setting of infected fracture fixation hardware, tissue from the "site of perceived infection," including "necrotic bone, site of pseudarthrosis or nonunion or the surrounding deep tissue bed,"[4] whether it be synovial tissue, periprosthetic tissue including the bone–implant interface and periprosthesic membrane, or the orthopaedic implant component. In spite of the extensive literature evaluating the microbiologic workup of orthopaedic hardware infection, very little of it has focused on comparing sites of tissue acquisition.[29] The periprosthetic membrane/bone–implant interface has been touted by some to have a higher rate of culture positivity as compared to neosynovium by some authors,[30,31] while others have found no difference.[29] Bone cultures were found to be of low diagnostic yield in one study.[32]

Hardware Infection: Use of Blood Culture Bottles and Enriched Media

The direct inoculation of both synovial fluid and intraoperative tissue into blood culture bottles has been shown to improve the sensitivity of the cultures without a rise in false positive results.[33,34] The observation that blood culture bottles for synovial fluid could improve the yield and isolate more fastidious organisms was first made in the 1980s, although hypothesized much earlier.[35] This technique was later adopted for prosthetic joint synovial fluid cultures. Small retrospective studies in the 2000s reported increased sensitivity,[33] reporting significant improvements with the recovery of anaerobes when compared to traditional cultures, as well as faster recovery of microorganisms.[36] These findings were confirmed in a prospective study using automated blood culture systems.[37] Recent work by Peel et al found the use of a semi-automated method of tissue culture using blood culture bottles improved the sensitivity for tissue cultures without an increase in false positives, as well as shortening the time to positivity.[34] Why blood culture bottles outperform traditional culture techniques is not entirely understood, although several mechanisms have been proposed.[33,38] The large volume of media in blood culture broth dilutes the host inflammatory cells that are present within the synovial fluid inoculated into the bottle; the presence of these

inflammatory cells can inhibit of bacterial growth. In addition, the use of blood culture bottles allows for a larger volume of synovial fluid to be cultured in a single culture, as compared to the volume of synovial fluid that can be plated on to solid media. Also, lytic agents present in blood culture bottles allow phagocytized organisms to be released from white blood cells. From a practical standpoint, the use of blood culture bottles also allows the lab to use automatic culture systems, which reduces contact with the environment and diminishes exposure to aerobic conditions. A recent workflow analysis at a referral center for revision arthroplasty reported that the use of blood culture bottles for tissue culture reduced cost and labor time when compared to conventional methods.[39] The routine use of blood culture bottles for synovial fluid and intraoperative tissue culture is strongly advocated.[2] There has been little formal study of the role blood culture bottles for infected fracture-related hardware and spinal instrumentation.

Other than the use of blood culture bottles, exceptionally little research has been done comparing the effect of different culture media. The only prospective evaluation of culture media (including blood culture bottles) involved 178 patients and found the sensitivities of blood culture bottles (87%) and two other enriched media, cooked meat broth (83%), and fastidious anaerobic broth (57%) to be superior to traditional direct plating method (39%).[37]

Hardware Infection: Sample Preparation

The inability to reliably culture biofilm bacteria in biofilm is a major impediment to establish the presence of infection. Simply scraping infected hardware has been shown to be a very ineffective method to dislodge biofilm.[40] Several methods to either mechanically or chemically disrupt biofilm in pursuit of establishing a microbiologic diagnosis have been reported. In a study of 92 patients, the process of bead milling tissue (the use of very small glass, ceramic, or steel beads to homogenize tissue that is difficult to process with standard techniques) prior to culturing was reported to have a higher documentation rate (83.7%) than standard techniques (53.2%).[41] In a study of 770 patients, researchers using dithiothreitol to chemically disrupt biofilm was found to improve the yield of microbiological diagnosis.[42] The overall clinical experience with these methods is very limited. The most promising tool to disrupt biofilm for diagnostic purposes is sonication.

Sonication

Sonication uses ultrasound energy to disrupt biofilm on retrieved hardware via cavitation.[43] A range of protocols have been studied, but the general approach is consistent.[44,45,46] The prosthetic device is collected into a large, sterile container and after the addition of a diluent, the container is vortexed. Vortexing increases the concentration of air bubbles, augmenting cavitation.[44] The container is then placed in an ultrasound bath and the sonicate fluid is collected and cultured in the same manner as tissue and synovial fluid cultures. In the first large study to assess the utility of sonication for the diagnosis of PJI, the sensitivity of periprosthetic tissue and sonicate fluid cultures were 61 and 78% respectively. Much of this benefit was seen in patients who had recently received antibiotics. Many follow-up studies from other medical centers have reported similar success. However, there have been a number of well-conducted studies with the opposite findings, reporting equivalent or lower sensitives of sonicate fluid culture as

compared to tissue culture, including a recent meta-analysis.[47,48] Some of the discord within the literature is likely secondary to variations both in sonication technique and methods for tissue culture. Different cutoff points for numbers of bacterial colonies to be considered positive also make it difficult to compare the literature. Using lower cut-off rates can potentially decrease the specificity of sonicate cultures by allowing for the identification of contaminant or microbial bystanders present in only very low concentrations. Another potential source of complicating the interpretation of sonicate fluid cultures is a direct result of the extracellular structure of the biofilm. Despite these issues, the body of literature supporting the use of sonicate fluid over conventional methods to increase the diagnostic yield of cultures has been expanding. Inoculating the sonicate fluid into blood culture bottles[46] or subjecting the sonicate fluid to molecular diagnostics further improves the diagnostic yield. Reflecting these findings, the most recent proceedings from International Consensus Meeting on Orthopaedic Infections regarding the use of sonication states that "sonication of the explanted orthopaedic prosthesis is a viable method for detecting pathogens, particularly in the setting of culture-negative infections."[10] Previously, the use of sonication was recommended in only limited cases. The role of sonicate fluid has primarily been studied in the setting of PJI. The use of sonicate fluid has been evaluated in fracture-related hardware infections[49] and spine hardware infections[50]; results have been mixed, and the current literature is too limited to make any firm conclusions.

Hardware Infection: Duration of Incubation

The large majority of organisms that are known to commonly cause PJIs can be identified using routine culturing methods within a few days. Prolonging the duration of incubation can in some cases increase sensitivity, but at a potential cost to the specificity. Slow growing organisms that cause late PJI are often members of the host skin flora, and are also commonly encountered culture contaminants. However, a significant minority of the bacteria, mostly *C. acnes*, that are routinely encountered during the workup for PJIs are well documented to require upwards of 7 to 14 days to be isolated.[18] Detecting an indolent organism in more than one culture in a set of cultures, and from more than one culture medium have both been correlated with an improved ability to establish the cause of infection and avoid misidentifying contaminants.[51] Concerns of an increased recovery of contaminants with an extended incubation period have not been borne out. By correlating these results with other clinical and laboratory factors, the concern for the detection of false positives can sometimes be further mitigated. For example, a retrospective study of prosthetic shoulder revision cases where *C. acnes* had grown from intraoperative cultures found that a shorter time-to-positivity of cultures for *C. acnes* correlated with the presence of infection. *C. acnes* isolates recovered with longer time-to-positivity were more often found in cases that were ultimately shown to be uninfected.[52] Current IDSA guidelines for the diagnosis and treatment of PJI advise holding anaerobic cultures routinely for at least 14 days.[28]

1.2.5 Native Bone and Joint Infections

In contrast to diagnosis of orthopaedic hardware infections, there is limited published research describing optimal methods to culture pathogens in native bone and joint infections.

Septic Arthritis

Many of the commonly encountered organisms causing septic arthritis can be readily cultured by traditional means. Routine synovial fluid cultures are positive in 70 to 90% of cases.[53] In adults, *S. aureus* makes up about 50% of cases. Streptococcal species are the next most common, including Group B and related beta-hemolytic strep (Groups A, C, F, and G), and less commonly *Streptococcus pneumoniae*. Gram-negative rods are estimated to cause 15% of cases.[54] In septic arthritis, the gram stain and cultures are of relatively high yield. A retrospective study of over 400 patients with septic arthritis found the gram stain to be positive in 50% of the cases overall.[55] The gram stain has been shown to have the highest yield in gram positive infections, upwards of 70%, and less in gram-negative septic arthritis, approximately 50%.[54] *N. gonorrhoeae*, a well-described cause of septic arthritis, only represents approximately 6% of all cases; for these infections, the gram stain is rarely helpful as it is positive only 25% of the time.[56]

Most native joint septic arthritis develops secondary to hematogenous spread, often via occult bacteremia. Blood cultures should be sent upon presentation. In one cohort of 476 possible cases of septic arthritis, blood cultures were positive in 24% of the cases where the synovial fluid culture was positive; in 9% of cases, blood cultures were positive in the setting of negative synovial cultures.[55] In a review of 94 patients who underwent arthrocentesis in the setting of acute monoarticular arthritis, the mean time to positive culture was 37 +/– 27 hours, with more than half detected within the first 24 hours.[57] Growth beyond 90 hours was not observed, leading the study authors to conclude that synovial fluid cultures can be considered negative if there is no growth after 4 days of incubation. Synovial culture negativity in the setting of a clinical suspicion of septic arthritis can suggest the presence of a fastidious organism, such as: nutritionally variant streptococci or *N. gonorrhoeae*; virtually unculturable organisms, such as *B. burgdorferi*; or noninfectious mimics (such as gout and rheumatoid arthritis). Culturing synovial fluid cultures in blood culture bottles provides increased sensitivity and specificity, as well as a decrease in the time to culture positivity over traditional agar plates, although the choice of culture technique may be less consequential in patient with an acute presentation.[58] The use of blood culture bottles markedly increases the ability to detect more fastidious organisms, such as *Kingella kingae*. The growing sophistication of molecular diagnostics has also allowed for the identification of organism difficult to isolate in the microbiology lab.

Osteomyelitis

As with septic arthritis, advances in the microbiologic diagnostics of osteomyelitis have come through the use of molecular diagnostic methods rather than optimization of culture technique. Osteomyelitis is in many ways a more complex disease than septic arthritis. While the vast majority of septic arthritis is a result of hematogenous spread, with a relatively limited array of responsible pathogens, osteomyelitis can, in addition to hematogenous spread, develop by contiguous spread from an adjacent site of infection, as a result of vascular insufficiency or via penetrating trauma, either accidental or iatrogenic. Like septic arthritis, almost all of the commonly infecting organisms can be theoretically grown using standard techniques. However, the yield of bone cultures, especially in subacute and chronic osteomyelitis, are lower than those observed with synovial fluid cultures when diagnosing septic arthritis.[59] This is largely because subacute

and chronic osteomyelitis are biofilm-driven infections. As with hardware infections, swab culture of sinus tract drainage is similarly inaccurate and misleading.[6] Likewise, Gram stains are extremely insensitive.[8]

Microbial etiology can be reliably established in acute hematogenous osteomyelitis. In a study of 250 children with acute hematogenous osteomyelitis, blood cultures were positive 40% of the time. A bone biopsy culture, obtained either by an open procedure or percutaneously with interventional radiology guidance, identified the pathogen in 82%.[60] Acute hematogenous osteomyelitis in adults, which often manifests as vertebral osteomyelitis,[61] fares similarly: blood culture positivity rates between 30 and 78% have been reported[62] and sensitivity of tissue biopsy in the setting of vertebral osteomyelitis, whether obtained percutaneously or intraoperatively, has been reported to be 70 to 91%.[61]

1.3 Molecular Techniques

Molecular techniques hold promise for the diagnosis of orthopaedic infection. Theoretical advantages of molecular techniques include the possibility of rapid microbial detection with high accuracy and low cost. To date, molecular techniques have not yet replaced microbial culture in most clinical laboratories because of real-world disadvantages including lack of specificity, lack of sensitivity, increased cost, need for local expertise, and slow turnaround time. While exceptions certainly exist, current molecular techniques still are limited in their ability to accurately assess drug resistance across the broad range of antimicrobial drugs. To date, the majority of molecular diagnostic studies on orthopaedic infection have focused on PJI. However, there may be additional particular advantages in different patient groups and diseases, including pediatrics, and including unusual and/or uncultivable organisms. This portion of the chapter will seek to summarize the current state of this field, noting that much of the current available technology is not currently in common clinical use.

1.3.1 Polymerase Chain Reaction (PCR)

Background

A variety of PCR assays have been developed for pathogen detection in PJI and other orthopaedic infection, with varying characteristics, sensitivity, and specificity. PCR assays can be designed to amplify specific DNA sequences from a single species, from a panel of pathogens (multiplex PCR), or from highly conserved DNA sequences flanking more variable DNA. (16S PCR is the most common version of this technology.) Published assessments have compared PCR to conventional culture across a variety of specimen types and clinical scenarios, with variable results summarized below.

Pathogen-Specific PCR

Single Organism PCR

The potential advantages of single-organism PCR for orthopaedic infection lie in sensitivity and speed. Many of the currently developed tests aim to diagnose bacteria that grow poorly in culture.

PCR for *B. burgdorferi* is commercially available but not FDA-approved. There is encouraging data regarding its specificity.[63,64] The test may have more utility when

positive, especially when Lyme serology is concurrently positive. The significance of a positive PCR in a patient with negative serum markers for Lyme disease remains undetermined.[65] Lyme PCR may be helpful in rare reported cases of borrelial PJI, as it may represent a subset of culture-negative PJI.[66]

Assays for PCR detection of *N. gonorrhoeae* in synovial fluid have been developed[67,68,69] but are not in routine use. On the other hand, *Tropheryma whipplei*, which can cause musculoskeletal manifestations in localized Whipple's disease, is best diagnosed with a commercially available PCR.[69]

In pediatric patients where it is a normal member of the oral flora, *K. kingae* orthopaedic infections are common and cause considerable morbidity. *K. kingae* is difficult and slow to grow in culture, and PCR has remarkably improved its diagnosis.[70,71] The experience with *K. kingae* molecular testing is also suggestive of a broader general point, that single-organism PCR is often more accurate than broad-range techniques such as 16S PCR.[72]

The PJI literature is more limited with respect to single-organism PCR. A limited number of studies have sought to use PCR to assay for the presence of a single organism genus (*Staphylococcus*) with subsequent evaluation for the presence of the main genetic determinant of methicillin resistance (*mecA*). These studies[73,74,75] show single-organism PCR to vary in sensitivity, to be costly, and—because of the breadth of etiologic agents of PJI—to appear less promising for future improvements in PJI diagnosis.

Multiplex PCR

The use of pathogen panels—multiplex PCRs with paired primers for each pathogen selected in the panel—theoretically allows for rapid, inexpensive, and sensitive detection of a set of common pathogens. Complex sequencing and data processing steps required for 16S PCR and next-generation sequencing (NGS) technologies are not needed. However, only a limited scope of bacteria can be detected. Depending on the selection of organisms on any panel, organisms that both contaminate orthopaedic specimens and cause orthopaedic infection (such as *C. acnes* and coagulase-negative staphylococci) may be either under- or over-diagnosed.[76] Multiplex panels have found wide clinical use for syndromic diagnosis in upper respiratory infections[77] and gastrointestinal infections[78] but are not currently commercially available for PJI. Evaluations of panels for PJI diagnosis[79,80,81,82,83,84] have not been found to have reliably superior clinical utility compared to culture.

Multiplex PCR panels for the diagnosis of orthopaedic brucellosis and tuberculosis[85] and native joint septic arthritis[86] show promise.

16S PCR

16S PCR offers theoretical improvements compared to the above PCR techniques, because of its theoretical ability to assay simultaneously for a very broad population of microbes (that share the conserved 16S ribosomal sequence); costs and turnaround time suffer because of the need to sequence and analyze the PCR amplification product for pathogen identification. Sensitivity of 95% from sonicate fluid (compared to tissue sensitivity of 76%) was noted in one recent study.[87] Nevertheless, studies of 16S PCR for PJI pathogen identification[30,87,88 89] have to date noted variable sensitivity, not superior to culture.

A recent meta-analysis assessed PCR assays for the identification of bacteria in synovial fluid.[90] Compared to the authors' own meta-analysis from several years prior, mean

PCR sensitivity in recent studies has worsened (to the 72% range) with slightly better specificity of 94%. Hypothetical reasons include the disadvantages of multiplex panels (missing organisms not included on the panels) and 16S PCR (where sensitivity is more dependent on bacterial burden or specimen types). However, this observation remains unexplained and its significance remains unclear.

Anecdotal cases continue to suggest a role for 16S PCR in the diagnosis of PJI caused by unusual or fastidious microbes, such as *Ureaplasma*[91] or *Listeria*.[92] 16S PCR-based diagnosis of native osteoarticular infections may hasten initiation of active treatment and prevent unnecessary surgery. Results from some research groups appear clearly promising, as in spine cases.[93,94]However, similar testing was not shown to be as useful in native septic arthritis.[95] In summary, while 16S PCR is conceptually powerful, commercially available, and on occasion extremely helpful, its superiority (and convenience) in routine use, compared to traditional culture, has not been demonstrated.

1.3.2 Next-Generation Sequencing (NGS)

Rather than by detection of pathogens by growth, or by identification of short specific DNA segments, NGS methods detect microbial target sequences from within the entirety of DNA present in a clinical sample—whether human, bacterial, or others. This technology is developing rapidly within the clinical arena as a result of rapid advances in affordable DNA sequencing, although time and money still remain limiting factors. The cost-effectiveness of the technology is likely to increase as technology cost decreases, but remains dependent on the likelihood of infection in any given case.[96] Some variants of NGS include an initial 16S amplification step (to enrich for bacterial DNA). Advantages to the approach include the ability to detect a profound diversity of microbes, limited only by the diversity of the databases against which sample sequences are compared. Quality of reference databases, many of which remain proprietary and incomplete, remains a critical quality issue.

Recent studies from several laboratories illustrate the promise of NGS for PJI. Sanderson et al[97] and Ivy et al[98] studied shotgun sequencing in PJI. Studying 168 cases of knee PJI, Ivy found 90% genus concordance in culture positive cases. Seven of 60 (12%) “aseptic” cases showed potentially significant organisms. A variant technique, 16S-amplicon targeted NGS, yielded similar pathogen detection in culture-negative cases, as well as detection of multiple pathogens in others.[99] This illustrates the possibility that advanced techniques will show PJI to be complex polymicrobial infections, where culture-based techniques typically demonstrate monobacterial growth.

Improvements in automated pathogen detection from large data sets are emerging. One recent study comparing sonicate fluid culture to NGS (using a commercial detection platform, CosmosID) detected bacteria in 95% of sonicate-culture positive specimens, and in 38% of sonicate-culture negative specimens.[100] Nevertheless, prediction of staphylococcal susceptibilities was limited. In a second recent study, samples from a series of 44 revision shoulder arthroplasty patients were evaluated by NGS and culture.[101] At least one organism grew in the culture of 52% of these patients; NGS identified at least one positive specimen in 39% of patients. While *C. acnes* (57%) and coagulase-negative staphylococci (39%) were often found in cultures, NGS identified *C. acnes* in even more (71%) of infected cases; it also detected a likely false positive signal, for *Acinetobacter radioresistens*, in 35%. Considering the 13 cases deemed “definitely” or “probably” infected by predetermined clinical criteria, only 8 had agreement between culture and NGS.[101]

Molecular Detection of Orthopaedic Pathogens from Blood

Sequencing and analysis of cell-free DNA in plasma (and other specimens) with NGS techniques (otherwise known as liquid biopsy) have become important facet of care for various malignancies[102] and prenatal genetic conditions,[103] and are of increasing interest in infectious diseases.[104] Further peer-reviewed data on this exciting new approach, which could theoretically allow for noninvasive diagnosis and monitoring in orthopaedic infections, are avidly awaited.

1.4 Conclusions

A variety of techniques exist for the diagnosis of microbial pathogens in osteoarticular infections. Culture remains the gold standard in most hospital laboratories: in general, traditional culture techniques have not been replaced by molecular testing, except in specific circumstances. Studies comparing molecular diagnostics to traditional culture-based techniques have frequently noted comparable diagnostic accuracy. However, it is likely that advances in technology and decreases in cost will continue to make molecular testing more accurate and more affordable. The current landscape of microbiologic diagnosis of orthopaedic infection remains fluid and promising.

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2 Antibiotics for Orthopaedic Infections

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Abstract
Antibiotics play a critical role in the treatment of bone and joint infections. In clinical practice, antibiotics may be delivered intravenously, orally, or topically, alone or as part of a delivery mechanism. This chapter will discuss the most commonly used oral and intravenous antibiotics in orthopaedic infections, their efficacy and bioavailability, and important considerations when using these antibiotics for patient care. This chapter will additionally focus on the use of topical antibiotics and nondegradable/biodegradable carriers for antibiotic delivery, such as the use of heat-stable antibiotics in cement spacers. The information presented here is designed for use as a clinical reference to provide guidance on the care of patients with orthopaedic infections including osteomyelitis, septic joints, and periprosthetic joint infections.

Keywords: Intravenous antibiotics, oral antibiotics, topical antibiotics, heat stable antibiotics, bone and joint infections, orthopaedic infections, musculoskeletal infections, periprosthetic joint infections, antibiotic carriers, cement spacers

Practical Tips

- Antibiotics may be administered intravenously, orally, topically, and/or in combination with a carrier.
- Factors such as known or suspected organisms, bioavailability, and bone penetration may all impact antibiotic selection.
- Unique host factors such as medication allergies, drug interactions, immunocompromise, and liver/kidney function may also affect choice of antibiotic.
- A multidisciplinary approach may be beneficial for the treatment of orthopaedic infections.

2.1 Systemic Antibiotics

2.1.1 Definitions

Surgical antimicrobial prophylaxis refers to the use of antimicrobial therapy prior to surgery to prevent surgical site infection (SSI).

Preemptive therapy is when antibiotic therapy is used after microorganisms have been introduced into a wound to prevent overt infection. For example, in patients with an open fracture awaiting internal fixation, a short course of antibiotics is recommended to prevent infection.

Empiric therapy is when an antibiotic is used due to the presence of infection but prior to the identification of the causative microorganisms. In this situation, clinicians must consider the type of infection and most likely resistance pattern when designing a treatment regimen. Antibiotics should be adjusted as soon as additional culture information is available.

Targeted therapy is when antibiotic treatment is tailored to the microorganism and its antibiotic susceptibility. Targeted therapy also involves determining the duration of therapy and need for intravenous (IV) versus oral therapy depending on the type of infection.

Suppressive therapy is the use of long-term oral antibiotics to prevent symptoms of infection in patients in whom cure is not possible.

2.1.2 Antibiotic Selection and Administration

The optimal antimicrobials for surgical prophylaxis should target the most common organisms that can cause SSI, rapidly achieve bactericidal tissue levels, and have an excellent safety profile (▶ Table 2.1).[1] Cephalosporins such as cefazolin are first-line prophylaxis for orthopaedic procedures. Vancomycin should be used (in addition to, or in lieu of cefazolin) if there is a history of methicillin-resistant *Staphylococcus aureus* (MRSA). Because cefazolin is a more effective prophylactic than vancomycin against sensitive organisms and offers the addition of some gram-negative coverage, some centers recommend the use of both agents when MRSA is present, although there may be a higher nephrotoxicity risk with combination therapy, and the optimal approach in this setting is not yet clear. Either vancomycin or clindamycin can be used if there is a life-threatening penicillin and/or cephalosporin allergy.[2] Gentamicin may be added for additional gram-negative coverage, such as when there is an open fracture.[1] Penicillin may be added to prevent clostridial infection when there is fecal or soil contamination.

Antibiotic administration should be timed so that the antibiotic serum and tissue concentration is bactericidal at the time when the incision is made.[3] The optimal time

Table 2.1 Surgical prophylaxis

Clinical scenario	Antimicrobial and dose	Notes
Standard prophylaxis	Cefazolin 2 g	3 g if >120 kg; administer within 30–60 minutes of the incision; redose every 4 hours for normal renal function
Personal history of MRSA (infection or colonization)	Vancomycin 15 mg/kg (maximum dose 2 g)	Administer vancomycin starting within 2 hours of incision, optimally to be completed 1 hour prior to incision; consider addition of cefazolin to vancomycin
Serious β-lactam allergy	Vancomycin 15 mg/kg (maximum dose 2 g) or clindamycin 900 mg	Administer vancomycin starting within 2 hours of incision, optimally to be completed 1 hour prior to incision; clindamycin redosing interval: 6 hours
Desired gram-negative coverage (e.g., open fracture; environmental contamination)	Addition of gentamicin 5 mg/kg to above	Dose based on adjusted body weight if BMI >30
Soil (e.g., farm injury) or fecal contamination (*Clostridia*)	Addition of penicillin G 4 million units to above	Redose every 4 hours for normal renal function

Abbreviations: BMI, body mass index; MRSA, methicillin-resistant *Staphylococcus aureus*.

for preoperative antibiotic administration is within 60 minutes prior to the time of incision.[1] Vancomycin requires a longer administration time (over 1 to 2 hours prior to surgical incision) and this time should be taken into account when vancomycin is utilized.[1] In patients undergoing aseptic joint arthroplasty, only one perioperative antibiotic dose is necessary. There is no increased risk of subsequent surgical site or prosthetic joint infection (PJI) when a single dose is administered, as compared with multiple doses. This also applies even if allografts are used.[2,3] There is also no role for prolonged surgical antimicrobial prophylaxis due to the presence of drains.[3]

The selection of antimicrobials for empiric and targeted therapy requires consideration of multiple factors. The clinician should first consider the most likely pathogens causing the bone and joint infection, such as *Staphylococci*, *Streptococci*, and *Enterobacteriaceae*. Institutional and local antibiotic resistance patterns and changes in patterns over time should be reviewed to guide antibiotic therapy, along with prior available culture data for the specific patient. Risk factors for multidrug resistant infections should be identified, including prior history or known colonization with MRSA, residence in countries where drug resistance is more common, and patients with multiple comorbidities or a history of extensive antibiotic exposure. Patients who use intravenous drugs may be at higher risk of MRSA, *Pseudomonas aeruginosa*, and *Candida* infections. Other host factors that impact antimicrobial therapy selection include medication allergies and intolerances, renal and hepatic function that might affect antibiotic dosing, and impaired immune function, such as due to organ transplantation, chemotherapy, corticosteroid, or other immunosuppressive therapies.

The penetration of antibiotics into bone and devitalized tissue is important to consider when designing a regimen. Because of inflammation, bone penetration of antibiotics may be higher in viable infected bone with intact perfusion than in uninfected bone. Nonetheless, certain antibiotics may still require adjusted dosing strategies to ensure appropriate bone penetration. Antibiotic penetration into bony sequestrum and necrotic bone is minimal given limited to nonexistent vascular flow. Additionally, peripheral vascular disease also limits bone penetration, particularly to the lower extremities. Bone penetration of specific antibiotics is discussed in greater detail next (*Intravenous versus Oral Antibiotics*). Of note, bone penetration data does not always correlate directly with efficacy of treatment. This discrepancy results from experimental differences in antibiotic dosing, initial bone health, and timing of bone harvesting compared with the typical clinical situation.

Biofilm formation can reduce antibiotic efficacy. A biofilm is comprised of sessile microbes contained within an extracellular matrix. This extracellular membrane protects the bacteria from antibiotics, the host immune response, and environmental stressors. The readiness with which organisms attach to surfaces and form biofilms depends on a variety of factors, including the species of bacteria, the roughness and porosity of the attachment surface, and the hydrophobicity/hydrophilicity of the environment. Once established, the permeability of the biofilm is limited. Neutrophils and macrophages have limited entry and have reduced efficacy in eliminating sessile bacteria. For most antibiotics, penetration into the biofilm is also limited. The minimal inhibitory concentration (MIC) of antibiotics to treat specific free-living bacteria may not be relevant when applied to the same bacteria within biofilms. The minimum biofilm eradication concentration (MBEC) measures *in vitro* antibiotic susceptibility of microbes in biofilms. However, clinically validated parameters are not yet available.

2.1.3 Intravenous versus Oral Antibiotics

The use of IV versus oral antibiotics to treat orthopaedic infections is another area of debate. A 2013 Cochrane review of patients with chronic osteomyelitis showed no difference between oral and IV antibiotics.[4] It was noted, however, that many studies contained bias and were performed at a time when antibiotic resistance was less problematic. The recently published OVIVA (Oral versus intravenous antibiotic treatment for bone and joint infections) trial, which included 1,050 patients from 30 hospitals in England and Scotland, showed that oral antibiotic therapy was noninferior to IV antibiotic therapy for the treatment of bone and joint infections.[5] This was a parallel group, randomized, unblinded, and noninferiority trial. The primary outcome was treatment failure within 1 year of randomization. Data is otherwise limited on this topic, and practice patterns vary. A hybrid approach, with a transition to oral therapy after an initial IV course, has been used satisfactorily in some cases.

Intravenous Antibiotics

▶ Table 2.2 summarizes commonly used IV antibiotics in bone and joint infections and their bony penetration. Beta-lactam antibiotics include penicillins, cephalosporins, and carbapenems. Bone levels for most beta-lactams are only 5 to 20% of serum levels, but this is still adequate for bone levels to exceed the MIC in most cases when administered intravenously. Vancomycin is often used as a first-line treatment for MRSA and other methicillin-resistant infections, as well as in the setting of serious beta-lactam allergy. However, vancomycin is slow to reach optimal concentrations in bone, especially cortical bone. Daptomycin can be used for treating MRSA and other methicillin-resistant infections. In *in vivo* models, daptomycin has activity in osteomyelitis and can penetrate into biofilms, synovial fluid, and cancellous bone,[6,7] although clinical data evaluating these properties are more limited.

Oral Antibiotics

▶ Table 2.3 summarizes commonly used oral antibiotics in bone and joint infections and their bony penetration. The following antibiotics have excellent oral bioavailability, as they are well-absorbed and achieve excellent serum levels in bone and joint infections: clindamycin, fluoroquinolones, linezolid, metronidazole, tetracyclines, trimethoprim-sulfamethoxazole, and rifampin.

Rifampin is established for use in staphylococcal bone and joint infections in combination with another antibiotic, usually in the setting of retained hardware. Patients treated with a rifampin-based combination regimen for PJI have lower treatment failure rates than those who are not.[9] Oral bioavailability is >95% when taken on an empty stomach. The clinician should ensure that the isolated staphylococcal organisms are susceptible to rifampin before use. Rifampin can be used in patients with osteoarticular infections associated with implants, as rifampin is active against staphylococci-forming biofilms on implants. Rifampin must be used in combination with a second antibiotic to provide synergy and reduce killing time; it should never be used in monotherapy. The use of rifampin in combination also reduces the emergence of resistance. It may be added to the primary active agent once the bacterial load has been reduced (such as with surgical debridement or a period of IV therapy). The risk of resistance is highest when there is a

Table 2.2 Intravenous antibiotics for treatment including bone penetration: gram-positive infections

Drug (dose)	Typical dosing frequency (average weight/renal function)	Spectrum	Ratio of bone/serum levels, %	Comments
Agents for primarily gram-positive infections				
Oxacillin (2 g) Nafcillin (2 g)	Every 4 hours	Methicillin-susceptible staphylococci	10	Confirm susceptibility prior to treatment
Ampicillin (2 g)	Every 4–6 hours for ampicillin alone, every 6–8 hours in combination with sulbactam	Streptococci, *Cutibacterium* species, most *Enterococcus* spp.	17	Often used for targeted therapy and infections due to *Enterococcus* species
Ampicillin-Sulbactam (1.5–3 g)	Every 6–8 hours	Streptococci, methicillin-susceptible staphylococci; also active against some gram-negatives and anaerobes	12–17	Often used for empiric therapy
Cefazolin (1–2 g)	Every 8 hours	Methicillin-susceptible staphylococci, most streptococci; active against some gram-negatives	7.5–37	Tolerated better than oxacillin for methicillin-susceptible staphylococcal infections
Vancomycin (1 g)	Every 8–24 hours based on trough levels	Gram-positive bacteria, staphylococci, streptococci, *Cutibacterium* spp., *Enterococcus* spp.	5–21	Often used for empiric therapy and definitive therapy for resistant gram-positive infections
Daptomycin (6–8 mg/kg)	Every 24 hours	Gram-positive bacteria, staphylococci, streptococci, and *Enterococcus* spp.	7	Doses may need to be adjusted based on the MIC of the organism
Agents for primarily gram-negative infections				
Ceftriaxone (1–2 g)	Every 24 hours	Respiratory and GI gram-negatives, including *Haemophilus influenzae*, susceptible Enterobacteriaceae; also active against many gram-positives including streptococci	5–19	Frequently used for targeted outpatient IV therapy
Ceftazidime (1–2 g)	Every 8 hours, dosing based on severity	Susceptible respiratory gram-negatives, Enterobacteriaceae, *Pseudomonas aeruginosa*	3–27	

Table 2.2 (*Continued*) Intravenous antibiotics for treatment including bone penetration: gram-positive infections

Drug (dose)	Typical dosing frequency (average weight/renal function)	Spectrum	Ratio of bone/serum levels, %	Comments
Cefepime (1–2 g)	Every 8 hours	Similar to ceftazidime but with higher *in vitro* activity against oxacillin-susceptible staphylococci, streptococci, and resistant *Enterobacter* species	87–100	Confirm MIC of *Enterobacter* species prior to treatment; monitor for neurotoxicity especially if renal function impaired
Imipenem (500 mg to 1 g)	Every 6 hours	Similar to cefepime plus resistant gram-negative bacteria including *Enterobacter* spp. and *Pseudomonas aeruginosa*	16–48	Treatment of possible or proven multidrug-resistant gram-negative bacteria
Meropenem (500 mg)	Every 8 hours	Similar to cefepime plus resistant gram-negative bacteria including *Enterobacter* spp. and *Pseudomonas*	17	Treatment of possible or proven multidrug-resistant gram-negative bacteria
Piperacillin (2–4 g)	Every 4–6 hours	Generally used in combination with tazobactam: Streptococci, staphylococci (penicillin susceptible), *Enterobacter* spp., and *Pseudomonas aeruginosa*	5–7.5	
Piperacillin (3 g)/tazobactam (0.375 g)	Every 6 hours		20/25	

Abbreviations: GI, gastrointestinal; IV, intravenous; MIC, minimal inhibitory concentration.
Source: Adapted with permission from Spellberg and Lipsky[8] and incorporating data from Zimmerli W and Sendi P. Systemic antibiotics. In: Kates SL, Borens O, eds. Principles of Orthopedic Infection Management. Thieme; 2017: 70.[20]

high bacterial load. One should avoid starting rifampin too early in an infection, as this may lead to selection for resistant staphylococci and result in superinfection.

Certain antibiotic agents are often used in combination with rifampin for treatment of staphylococcal osteoarticular infections, including fluoroquinolones, vancomycin, and clindamycin. Fluoroquinolones have the highest level of evidence based on prior studies, with no significant difference between oral and IV administration. The oral bioavailability of quinolones exceeds 95% with peak serum concentration at 1 to 2 hours. Vancomycin can be used in conjunction with rifampin, but to avoid rifampin resistance, it is important to only start rifampin after adequate vancomycin levels have been achieved and after the staphylococcal burden has decreased. There is limited data on

Table 2.3 Bone penetration of antibiotics with high oral bioavailability

Drug	Spectrum	Dose (may vary by weight, renal function, and other patient characteristics)	Typical dosing frequency	Serum-bone ratio, %	Comments
Ciprofloxacin	Gram-negative bacteria and sensitive staphylococci (only when treated in combination with rifampin)	500–750 mg	Twice daily	3–66	Multiple important toxicities; use with caution especially in the elderly
Levofloxacin	Gram-negative bacteria and sensitive staphylococci (only when treated in combination with rifampin)	500–750 mg	Daily	50–75	Multiple important toxicities; staphylococci have lower MICs for levofloxacin than for ciprofloxacin
Moxifloxacin	Gram-negative bacteria and staphylococci (only when treated in combination with rifampin); some anaerobes	400 mg	Daily	27–49	Multiple important toxicities; as compared with ciprofloxacin, also has activity against anaerobes
Linezolid	Gram-positive bacteria, staphylococci, and enterococci	600 mg	Twice daily	37–51	Monitor for toxicities including cytopenias
Trimethoprim-sulfamethoxazole (TMP-SMX)	Gram-negative bacteria, staphylococci	1 DS (double strength) tablet	Twice daily	50/15	Some risk of allergy and multiple toxicities; monitoring recommended
Doxycycline and minocycline	Staphylococci, *Cutibacterium acnes*, some gram-negatives	100 mg	Twice daily	2–6	For suppressive therapy vs. curative therapy for staphylococcal infection
Clindamycin	Many staphylococci, many streptococci, *Cutibacterium acnes*, some anaerobes	300–600 mg	Every 6–8 hours	40–67	Confirm MIC and exclude inducible clindamycin resistance prior to treatment

Table 2.3 (*Continued*) Bone penetration of antibiotics with high oral bioavailability

Drug	Spectrum	Dose (may vary by weight, renal function, and other patient characteristics)	Typical dosing frequency	Serum-bone ratio, %	Comments
Metronidazole	Anaerobes, including *Clostridium* species	500 mg	Every 8 hours	79–100	Monitor for neurotoxic effects during long-term treatment
Rifampin	Staphylococci when treated in combination with another active antistaphylococcal antibiotic	300–450 mg	Twice daily	>100	Never use rifampin as monotherapy

Abbreviations: MIC, minimal inhibitory concentration; TMP-SMX, trimethoprim-sulfamethoxazole.
Source: Adapted with permission from Spellberg and Lipsky[8] and incorporating data from Zimmerli W and Sendi P. Systemic antibiotics. In: Kates SL, Borens O, eds. Principles of Orthopedic Infection Management. Thieme; 2017: 71.[20]

the combination of clindamycin and rifampin, and the oral bioavailability of clindamycin is >90% with peak serum concentration at 1 hour.[10,11] Other antimicrobials, including beta-lactams, tetracyclines, and trimethoprim-sulfamethoxazole, may also be administered with rifampin, but the data supporting these is less robust.

Some antibiotics, such as penicillins and cephalosporins, are less bioavailable when administered orally. This, along with reduced bone penetration, leads to concerns about achievement of adequate antibiotic levels within bone. The clinical relevance of this has not firmly been established, and in fact penicillins were among the more commonly utilized oral agents in the OVIVA trial.[5] Nonetheless some experts avoid the use of oral beta-lactams for significant bone and joint infections. In cases such as for confirmed *Propionibacterium acnes* or β-hemolytic streptococcal infections, transitioning to oral therapy after appropriate IV therapy may still be appropriate.

2.2 Antiseptics

Antiseptics are topical antimicrobial agents used to eliminate microorganisms. These can only be used locally and cannot be given systemically. In contrast, disinfectants can only be used on nonliving objects and surfaces. Antiseptics disrupt bacteria mechanically and/or chemically, and unfortunately, some resistance is now starting to be reported to some antiseptics.

2.2.1 Povidone-Iodine

Povidone-iodine works by denaturing bacterial cytosolic enzymes and cell membrane proteins, although the precise mechanism of action is still under investigation. It also

displays anti-inflammatory properties and, in some studies, shows *in vitro* efficacy against biofilms.[12] It is used for cuts, bites, traumatic wounds, and surgical site preparation, and it is also used as a lavage solution after total hip and knee arthroplasty and before wound closure. Historically, it has been shown to reduce the incidence of PJI,[13] but recent reports have challenged this previous finding.[14,15] It has a rapid onset of efficacy given that iodine easily dissociates from the povidone-iodine complex and quickly penetrates bacterial cells.[11] Adverse reactions of using povidone-iodine include potential thyroid dysregulation in patients with underlying thyroid disorders due to iodine uptake into the gland impacting thyroid hormone synthesis and impaired wound healing. It is active against gram-positive and gram-negative bacteria, fungus, protozoa, and some viruses.

2.2.2 Chlorhexidine (Gluconate/Digluconate)

Chlorhexidine works by disrupting the bacterial cell wall of a broad range of microorganisms. It rapidly penetrates the cell and remains active for up to 48 hours. It can be used on intact skin, and is useful for surgical site preparation and staphylococcal decolonization. It can be used in wounds in a dilute manner, and has shown *in vitro* efficacy in reducing the microbial burden on biomedical devices. There has been mixed data regarding the efficacy of chlorhexidine for the reduction of SSI, although there is some evidence it may be more effective than povidone-iodine. Data on the efficacy of chlorhexidine when added to surgical lavage fluid is limited. Adverse reactions of chlorhexidine include potential impaired wound healing, cytotoxicity, and the risk for allergic reactions.[15,16,17]

2.3 Carriers that may be Associated with Antibiotics

Carriers are used within orthopaedics to deliver antibiotics locally directly at the surgical site. These can either be nondegradable or degradable.

2.3.1 Nondegradable

Polymethylmethacrylate (PMMA) cement is the main nondegradable material used for antibiotic delivery in orthopaedics. PMMA can be combined with antibiotics as prophylaxis against infection in primary total joint arthroplasty, as treatment to fill a bone defect after trauma or after debridement of osteomyelitis, in spacers during the first stage of a two-stage revision for PJI, and as beads for osteomyelitis and infected nonunion. Antibiotics used in PMMA must be available in powder form rather than liquid to preserve the strength of the carrier, and must be heat-stable to avoid inactivation during curing when an exothermic polymerization reaction occurs with temperatures reaching 80 °C. The release of antibiotics from PMMA depends on the composition of the bone cement and the concentration of the antibiotic. Over time, the antibiotic diffuses out of the PMMA and is transported into the tissue. Commercially made beads tend to have even more antibiotic diffusion. Allergies to cement are uncommon, although patients may exhibit an allergy to the associated antibiotic.

PMMA is most commonly used in two forms: bone cement/spacers and bead chains. Bone cement/spacers may be custom-made or commercially made. When combined with antibiotics, these serve to eliminate remaining bacteria locally. There are two main types of joint spacers: nonarticulating and articulating. Nonarticulating spacers are also

known as block or static spacers. These take the form of a block of cement between the joint or a fusion for specific joints (e.g., knee joints) with augmentation with an implant. This spacer allows for high local antibiotic concentrations while preserving the joint space, and the implant is placed to fit the joint space. However, due to the nature of the spacer, mobility is limited. Articulating spacers can be comprised of only cement, or may contain an implant for stability purposes. These spacers allow for high local antibiotic concentrations while permitting joint motion and improving function prior to re-implantation. These spacers must be carefully molded and fitted if molded by hand, although premade molds exist that are more expensive.

Bead chains (▶ Fig. 2.1) can be handmade or purchased commercially. Prior to placing the bead chains, the infected site must be thoroughly debrided and irrigated before beads are laid over the desired area. Drains may be used, but suction should be avoided if possible to prevent loss of the diffused antibiotics. Some experts advise removal of the beads within 2 to 4 weeks when antibiotic levels become low enough that they may induce resistance and the beads could serve as a nidus of infection.[18,19] Handmade bead chains allows for a variety of antibiotics to be incorporated.

The choice of antibacterials should take into account patient allergies, renal function, and organism, if known. This is covered in Chapter 2.4 Antibiotics for Use in Carriers. Gentamicin is the most common antibiotic used, although combining vancomycin and aminoglycosides allows for improved elution kinetics. Commercially available beads that are available in Europe come loaded with gentamicin and come in different sizes and lengths.

2.3.2 Biodegradable

In general, either powdered or liquid antibiotics may be utilized in biodegradable carriers. Antibiotics used in biodegradable carriers should be water-soluble (hydrophilic), and associated antibiotics must be nontoxic to human cells and have minimal systemic side effects.

Calcium Sulfate

Calcium sulfate is often used as the hemihydrate $CaSO_4$ $0.5H_2O$ ("plaster of Paris"). It may also be combined with nanoparticulate hydroxyapatite (▶ Fig. 2.2) that improves biocompatibility. Calcium sulfate has reliable release kinetics, as most of the antibiotic is released in the first few days (burst) followed by more gradual release during resorption. Calcium sulfate can be combined with multiple antibiotics, the most common ones being gentamicin, tobramycin, and vancomycin. It is resorbable and has the poten-

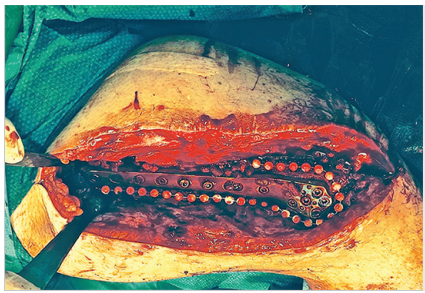

Fig. 2.1 Intraoperative use of commercially available polymethylmethacrylate (PMMA) beads. (Used with permission from Alt, V. Local delivery of antibiotics and antiseptics. In: Kates SL, Borens O, eds. Principles of Orthopedic Infection Management. Thieme; 2017: 82.)[20]

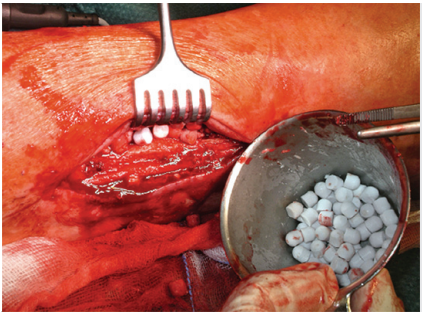

Fig. 2.2 Intraoperative use of degradable and osteoconductive pellets of calcium sulfate and nanoparticulate hydroxyapatite loaded with vancomycin for the filling of a defect in a tibial midshaft osteomyelitis. (Used with permission from Alt, V. Local delivery of antibiotics and antiseptics. In: Kates SL, Borens O, eds. Principles of Orthopedic Infection Management. Thieme; 2017: 85.)[20]

tial for new bone formation, but in practice, this capability is limited. When calcium sulfate beads are used in a bone defect, they typically dissolve within 4 to 13 weeks; when used in soft tissue, they may dissolve within 3 weeks.[21,22] Data is limited regarding the efficacy in chronic osteomyelitis.[2] Degradation products may lead to prolonged wound drainage.

Cancellous Bone Allografts

Since allografts are devitalized, they are at risk of bacterial colonization. Bacterial colonization is reduced when antibiotics are bonded to the bone graft. Antibiotics are often added when allografts are used in the setting of infection, and they must be in powder form.[2,23] Antibiotics are locally released from the allograft in an initial burst that lasts several days. Commercially available antibiotic-loaded allografts have been prepared to prolong the period of antibiotic release.[2,23] Higher antibiotic concentrations may be utilized within allografts relative to bone cement.[2,23] However, given the high local antibiotic concentrations, there is a risk of osteoblast compromise. Data is limited on the use of these preparations, however.

Chitosan Sponges

Chitosan sponges are degradable and biocompatible. These can be loaded with antibiotics by soaking them in antibiotic solutions. Commercially available sponges loaded with aminoglycosides and vancomycin are also available. Aminoglycosides and vancomycin have been assessed in combination with chitosan sponges and found to achieve antibiotic levels exceeding the MIC of target bacteria for 72 hours. This antibiotic combination also demonstrates *in vitro* and *in vivo* antibacterial activity. Sponges prepared with ciprofloxacin/rifampin have been shown to be effective against *Staphylococcus aureus* and *P. aeruginosa* in *in vitro* and *in vivo* models.[24,25] Of note, chitosan nanoparticles have shown *in vitro* activity against staphylococcal species and may be combined with PMMA cement.[26]

2.4 Antibiotics for Use in Carriers

▶ Table 2.4 summarizes the antibiotics available for use in PMMA with appropriate dosing. The benefit of using antibiotics in carriers is that they allow for high levels of local antibiotic release while minimizing serum levels and toxicity. Antibiotics loaded into carriers may be used in primary and revision arthroplasties to reduce PJI.[2] The antibiotic

used should be tailored to the organisms targeted, and it must have favorable elution kinetics when included in the carrier. Antibiotics within carriers should be dosed to ensure adequate local tissue levels that are above the MIC for targeted organisms. Caution must be taken when dosing antibiotics, however, especially in patients at increased risk of nephrotoxicity. Certain carriers have limited capacity for antibiotics without impacting the stability of the carrier, such as PMMA, which becomes weaker as more antibiotics are added. In order to preserve the mechanical strength of most cements, the antibiotic dose should be ≤5% by weight. Aminoglycosides and vancomycin are the most commonly used antibiotics within PMMA.

Table 2.4 Antibiotics available for use in PMMA

Drug	Spectrum	Dose per 40 g cement
Tobramycin	Staphylococci, gram-negative bacteria, *Pseudomonas aeruginosa*	1–4.8 g
Gentamicin	Staphylococci, gram-negative bacteria, *Pseudomonas aeruginosa*	0.25–4.8 g
Cefazolin	Staphylococci (oxacillin-susceptible), streptococci	1–2 g
Cefuroxime	Gram-negative bacteria, less gram-positive coverage	1.5–2 g
Ceftazidime	*Haemophilus influenzae*, susceptible Enterobacteriaceae, *Pseudomonas aeruginosa*	2 g
Cefotaxime	Gram-negative bacteria, no *Pseudomonas aeruginosa* coverage	2 g
Ceftaroline	Gram-negative bacteria, no *Pseudomonas aeruginosa* coverage	2–4 g
Ciprofloxacin	Gram-negative bacteria, Enterobacteriaceae	0.2–3 g
Vancomycin	Gram-positive bacteria, staphylococci, streptococci, *Propionibacterium* spp., *Enterococcus* spp.	0.5–4 g
Clindamycin	Staphylococci, streptococci, *Cutibacterium acnes*, anaerobes	1–2 g
Erythromycin	Aerobic gram-positive cocci and bacilli	0.5–1 g
Colistin	Gram-negative bacteria	0.24 g
Piperacillin-tazobactam	Streptococci, staphylococci (penicillin susceptible), *Enterobacter* spp., *Pseudomonas aeruginosa*	4–8 g
Aztreonam	Gram-negative bacteria, no gram-positive coverage	4 g
Linezolid	Gram-positive cocci, staphylococci, enterococci	1.2 g
Meropenem	Gram-positive and gram-negative bacteria, anaerobes, *Enterobacter* spp., *Pseudomonas aeruginosa*	0.5–4 g
Daptomycin	Gram-positive bacteria, staphylococci, streptococci, *Enterococcus* spp.	2 g

Abbreviation: PMMA, polymethylmethacrylate.
Source: Adapted with permission from Abdel et al.[2]

2.4.1 Gentamicin/Tobramycin

Gentamicin and tobramycin are bactericidal aminoglycosides; they prevent bacterial protein synthesis by binding to the 30s ribosomal subunit. These have activity against staphylococcal species and gram-negative bacteria, including *Pseudomonas*. Aminoglycosides are heat resistant and have good bioavailability in association with PMMA. There have been some reports of systemic absorption and nephrotoxicity associated with high concentrations of these antibiotics within PMMA.[27,28]

2.4.2 Vancomycin

Vancomycin is a glycopeptide antibiotic, and has activity against gram-positive bacteria, including MRSA. It can be used in PMMA, although it has less favorable release kinetics compared to aminoglycosides. At high concentrations, it can result in cell death. Vancomycin should be avoided if there is a history of vancomycin hypersensitivity, as there have been reports of serious hypersensitivity reactions such as drug reaction with eosinophilia and systemic symptoms (DRESS) when used in spacers.[29,30]

Antibiotics with less favorable elution kinetics from PMMA include ampicillin, cefazolin, cefotaxime, cefepime, meropenem, ertapenem, and daptomycin, although some of these antibiotics may still be employed based on the organisms targeted.

2.5 Topical Antibiotics

In addition to using antibiotics in carrier devices, topical antibiotics may be administered in irrigation solution or as a lyophilized powder. Data is limited regarding the utility of intra-articular antibiotic infusion at the time of irrigation and debridement for PJI.[2] Powdered antibiotics may be administered just prior to wound closure.

Vancomycin powder provides high tissue concentrations when given intraosseously. These achieve very high local antibiotic levels with minimal levels in the serum. The use of vancomycin powder is becoming more frequent as a preventative measure, especially in spine surgery, although high-quality data is lacking.[31] Adverse reactions are unlikely, although a case of anaphylaxis has been reported and seromas have been reported in the spine.[32] There is potential for osteoblast cell death in the setting of high local concentrations.

2.6 Treatment Failure

When a patient has osteoarticular infection that fails to resolve with antibiotic therapy, a number of possibilities must be considered. First, there may be inadequate source control. If dead or infected tissue remains after surgery, this may result in inadequate response to antibiotic therapy. Retained hardware may result in the persistence of infection due to the presence of biofilm, and the presence of an undrained abscess may also result in treatment failure. Second, there may be lack of adherence to recommended antibiotic therapy. Patients may have difficulty taking the recommended antibiotics due to a variety of social, economic, and behavioral reasons. Some patients may also use antibiotics inconsistently or discontinue them early due to adverse effects. Compliance with antibiotic instructions, such as taking with or without food, may impact efficacy. Third, there may be reduced antibiotic efficacy due to drug–drug interactions. Antibiotic concentrations may be decreased or increased through interactions

with a number of other medications. Cations such as calcium, aluminum, iron, and magnesium may decrease serum concentrations of certain antibiotics through chelation (such as ciprofloxacin, levofloxacin, and doxycycline). Antacids (such as omeprazole) may decrease the serum concentrations of certain antibiotics (such as ciprofloxacin, levofloxacin, rifampin, and doxycycline). Fourth, physiologic factors, such as decreased intestinal absorption of oral antibiotics in conditions such as inflammatory bowel disease or short gut syndrome, can affect treatment failure.

Treatment failure may also be due to special characteristics of microorganisms. Certain microorganisms such as *Staphylococcus aureus* may persist intracellularly, which can complicate elimination. Small-colony bacterial variants may persist in cells such as fibroblasts and may be more resistant to antibiotics; examples include *Staphylococcus aureus* and *Escherichia coli*. Biofilm production can be difficult to eradicate in the setting of infection, potentially leading to treatment failure. Finally, undiagnosed organisms that are not covered by the treatment regimen may lead to treatment failure, especially in the setting of polymicrobial infections.

Antibiotic resistance can contribute to treatment failure. This is less common during active therapy for infection, but it still may occur. Certain bacteria may harbor genes that permit the emergence of resistance during therapy. For example, AmpC producing bacteria such as the *Enterobacter* species may appear susceptible to cephalosporins on initial sensitivity reports, but may develop resistance during therapy.

2.7 Collaboration between Orthopaedic Surgeons and Infectious Disease Specialists

Collaboration between surgical specialties and infectious disease specialists is important for achieving an excellent outcome. With a multidisciplinary approach, the majority of patients with osteomyelitis, SSI, or PJI can achieve infection control during the first treatment course. When questions arise regarding the causative microorganism and/or susceptibilities, infectious disease specialists and microbiologists can assist with management. Involvement of infectious disease pharmacists may also be useful when determining optimal antibiotic dosing strategies. Antibiotic stewardship is of great importance when treating bone and joint infections to avoid unnecessary frequency and duration of antibiotic treatment. It is also important to recognize cases in which antibiotics alone in the absence of surgery is likely to fail, with the resulting development of resistance and biofilm persistence.

There are many situations in which the input of infectious disease physicians is strongly recommended. When managing infections in high-risk patients, such as those with immunocompromise or multiple comorbidities, infectious disease physicians' input is invaluable. This is also true for infections with resistant organisms, fungal and mycobacterial bone and joint infections, drug allergies affecting antibiotic choice, prior treatment failure, and limb-threatening infection.

2.8 Conclusion

When treating bone and joint infections, it is important to have an excellent understanding of available antimicrobial agents as well as their mechanisms of delivery. Antibiotics can be administered to patients intravenously, orally, topically, and/or as part of a nondegradable or biodegradable carrier. Important considerations when developing

an antibiotic regimen for a patient include the availability of culture data, which antibiotics achieve excellent bone penetration, and host factors such as medication allergies/intolerances, renal and hepatic function, and immunocompromise. Working together as part of multidisciplinary team to treat complex infections can be beneficial for developing a treatment plan and improving patient outcomes.

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3 Irrigation Solutions for Orthopaedic Infections

Michael Yayac, Samuel J. Clarkson, Craig Della Valle, and Javad Parvizi

Abstract
This chapter will provide an overview of antiseptic agents used to irrigate wounds for the prevention or treatment of orthopaedic infections, including their mechanism of action, spectrum of microbicidal activity, safety including potential adverse effects, efficacy in eliminating infective pathogens, and efficacy against established biofilm. Some of the common irrigation solutions include acetic acid, bacitracin and polymyxin, chlorhexidine, dilute povidone-iodine (PI), sodium hypochlorite, and hydrogen peroxide. The current guidelines for prevention of surgical site infection (SSI) from the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and International Consensus Meeting (ICM) on orthopaedic infections only recognize sterile dilute PI as the most optimal irrigation solution. PI, sodium hypochlorite, and hydrogen peroxide provide the broadest range of antimicrobial coverage. Chlorhexidine, PI, and hydrogen peroxide may be useful in eradicating biofilm. The addition of antibiotics to irrigation solutions is not recommended as it does not confer any benefit and may further contribute to emergence of antibiotic resistant pathogens. While severe adverse effects are uncommon, cases of anaphylaxis with chlorhexidine and oxygen emboli with the use of hydrogen peroxide have been reported.

Keywords: Surgical irrigation, acetic acid, antibiotic, chlorhexidine, povidone-iodine, sodium hypochlorite, hydrogen peroxide, biofilm

Practical Tips

- Dilute povidone-iodine (PI) solution, at a concentration of 0.35%, may be a preferred surgical irrigant given its broad spectrum of antimicrobial activity and efficacy.
- Addition of antibiotics to irrigation solution have not demonstrated increased efficacy in preventing infection and may contribute to antibiotic resistance.
- Broad antimicrobial coverage can be achieved with PI, sodium hypochlorite, and hydrogen peroxide.
- PI, chlorhexidine, and hydrogen peroxide have demonstrated efficacy in reducing biofilm.

3.1 Acetic Acid

3.1.1 Overview of Antiseptic Agents

Mechanism of Action

Acetic acid (AA) is a weak organic acid that has long been used in the treatment of infections and is used in bladder irrigation and otitis externa.[1] Weak acids are thought to have cytotoxic effects by disrupting the proton gradients that are required for synthesis of adenosine triphosphate (ATP) by bacteria and fungi (▶ Table 3.1).[2]

Table 3.1 Common surgical irrigants and their spectrum of activity

Irrigant	Mechanism of action	Antimicrobial activity					
		Gram +	Gram –	Actino-bacteria	Spore	Fungi	Biofilm
Acetic acid	Proton gradient disruption	Yes	Yes	Yes	No	Yes	Limited
Bacitracin and polymyxin	Inhibit cell wall synthesis; increase membrane permeability	Yes	Yes	No	No	No	No
Chlorhexidine	Increased membrane permeability	Yes	Yes	No	No	Limited	Yes
Povidone-iodine	Oxidative stress	Yes	Yes	Yes	Yes	Yes	Yes
Sodium hypochlorite	Impaired DNA synthesis	Yes	Yes	Yes	Yes	Yes	No
Hydrogen	Oxidative stress	Limited	Limited	Yes	Yes	Yes	Yes

Spectrum of Antimicrobial Activity

AA has demonstrated antimicrobial activity against gram-positive and gram-negative organisms, both in the free-floating (planktonic) and biofilm states, as well as fungal species.[3,4] Exposure to a 6% solution of AA for 30 minutes has been shown to be effective against *Actinobacteria* and *Mycobacterium tuberculosis*.[5]

Safety and Adverse Effects

AA is considered harmless to tissues at concentrations of 5% or less, but may impair wound healing at concentration as low as 0.25%.[3,6] At concentrations greater than 10%, AA can be damaging to tissues and potentially corrosive to metals, although the metals commonly used for orthopaedic implants are resistant to these corrosive effects.[3,7] Hypersensitivity to AA solutions has not been documented in the literature.

3.1.2 Efficacy as Surgical Wound Irrigant

Prophylactic Use

No studies have assessed irrigation with AA as a prophylactic measure to reduce risk of infection.

Use in Irrigation and Debridement of Infection and Efficacy against Biofilm

Due to the inability of other irrigation solutions to completely eradicate biofilms, several studies have evaluated AA irrigation during debridement when treating orthopaedic infections. Exposure of tissues to a 3% AA solution for 20 minutes has been shown to be safe and only very low concentrations (0.19%) are required to inhibit bacterial growth.[8] While three studies have assessed the efficacy of AA in eradicating biofilm, two

of these studies had clinically unfeasible exposure times of 180 minutes and 24 hours.[7,9] The third, most recent study found that concentrations of 15% AA for 10 minutes and 11% AA for 20 minutes were required to eradicate 99.9% of colony-forming units (CFUs), which defines the minimum biofilm-eradicating concentration (MBEC). These concentrations are above the safety threshold of 5%,[7] suggesting that AA is not effective in eradicating biofilm. However, at the maximal clinically acceptable concentration of 5%, AA was able to eradicate 96.1% of CFUs following 20 minutes of exposure, so AA may still have a role in treating orthopaedic infections, albeit likely not as sole therapy.[3]

3.2 Bacitracin and Polymyxin

3.2.1 Overview of Antiseptic Agent

Mechanism of Action

Bacitracin comprises a mixture of cyclic polypeptides that have both bacteriostatic and bactericidal properties. It works by inhibiting cell wall synthesis and certain bacterial enzymes.[10] Polymyxin B is also a mixture of polypeptides that increase cell membrane permeability leading to cell death.[11]

Spectrum of Antimicrobial Activity

Bacitracin is mostly effective against gram-positive organisms, predominantly staphylococcal species, but *Neisseria* species have also shown susceptibility, while polymyxin B provides gram-negative coverage.[10,11] Several common pathogenic organisms, including *Staphylococcus aureus*, *Escherichia coli*, *Streptococcus pneumonia*, and *Enterococcus faecalis*, have been reported to be resistant to these agents.[12,13]

Safety and Adverse Effects

At clinical doses, the combination of bacitracin and polymyxin has been shown to inhibit replication and function of both fibroblasts and keratinocytes, suggesting that they may impair wound healing.[6] Patients may develop hypersensitivity to bacitracin and polymyxin, which most often only presents with mild local symptoms, but cases of anaphylaxis have been described in the literature.[14] Bacitracin is known to cause nephrotoxicity when delivered through the intramuscular route, but toxicity resulting from topical use has not been reported.[10] Increasing resistance to both antibacterial agents have been described in the literature.[15]

3.2.2 Efficacy as a Surgical Wound Irrigant

Prophylactic Use

Early studies provided evidence that diluted topical antibiotics in irrigation solution reduced the risk of surgical site infections (SSIs). Commonly, the two antibiotics are added to irrigation solution to obtain a concentration of 0.05 mg polymyxin B and 50 units of bacitracin per milliliter.[16] However, recent evidence has determined that the addition of antibiotics to irrigation solutions has not demonstrated any benefit for preventing SSIs.[17,18] Additionally, unlike antiseptic agents, resistance to antibiotics is an

issue of continued growing concern, in which the misuse of antibiotics has been cited as a significant contributing factor.[19]

Use in Irrigation and Debridement of Infection and Efficacy against Biofilm

Irrigation with topical antibiotics is unlikely to be beneficial for treating orthopaedic infections. Exposure to triple topical antibiotics, namely bacitracin, polymyxin B, and gentamicin, for up to 10 minutes demonstrated no effect in eradicating biofilm.[20]

3.3 Dilute Povidone-Iodine (PI)

3.3.1 Overview of Antiseptic Agent

Mechanism of Action

PI consists of iodine conjugated to polyvinylpyrrolidone, increasing the aqueous solubility of iodine. Free iodine is released into solution at a concentration of 1%, which in turn oxidizes and deactivates nucleotides, proteins, and fatty acids found in the cell membrane and cytosol.[21,22]

Spectrum of Antimicrobial Activity

By this mechanism, PI has microbicidal effects on a broad spectrum of microorganisms including bacteria, both gram-positive and gram-negative, certain viruses, fungi, spores, and less common pathogens. Antimicrobial effects can occur within 30 seconds of exposure and have demonstrated efficacy against several drug-resistant organisms, including methicillin-resistant *Staphylococcus aureus* (MRSA). No evidence of developed resistance to PI has been documented in the literature.[21,23]

Safety and Adverse Effects

In vitro studies and case reports have raised concerns regarding safety of PI, highlighting potential cytotoxic effects on chondrocytes, osteoblasts, fibroblasts, and keratinocytes as well as the potential for metabolic disturbances.[6,24,25,26] None of these potential adverse effects have been substantiated in the several randomized-controlled trials evaluating irrigation of surgical wounds with PI.[27,28,29,30,31] True allergies to PI are uncommon, with a prevalence of 0.4%, and severe allergic reactions, such as anaphylaxis, are exceedingly rare.[32] The results of three previous studies suggest that PI in combination with chlorhexidine provides greater efficacy than either antiseptic alone. However, it is not yet known if these compounds may react to form harmful products.[33] Iodide ion is known to react with hypochlorite to form either iodine or triiodide ion,[34] and the *in vivo* effects of that combination are currently unknown. It is also unknown if other potentially harmful compounds may form from mixing NaOCl with PI. Hydrogen peroxide does not appear to react with PI in solution.[33] PI is available in both sterile and nonsterile preparations. Reports of iatrogenic infections from contaminated nonsterile PI solutions have been documented in the literature.[35] Therefore, it is recommended to only use sterile PI for surgical procedures, while nonsterile PI should be reserved for cleansing of intact skin.

3.3.2 Efficacy as a Surgical Wound Irrigant

Prophylactic Use

PI is commercially available at a concentration of 10%, which is recommended to be diluted to 0.35% by adding 35 mL of 10% sterile PI to every liter of sterile normal saline for wound irrigation (▶ Table 3.2).[22] For primary total joint arthroplasty (TJA), routine lavage with sterile dilute betadine at the end of the procedure is recommended to reduce risk of infection. Following a few minutes of lavage, the surgical wound should be irrigated with normal saline before closure.[36,37] While there may be concern that further dilution may occur during lavage, PI has been shown to reduce biofilm formation even at sub-inhibitory concentrations.[38] Additionally, the minimal inhibitory concentration (MIC) of PI is lower than the recommended concentration for many bacterial species, including MRSA, and PI eliminates bacteria upon contact.[39]

Dilute PI lavage at the conclusion of primary total joint arthroplasty and orthopaedic spine procedures has been shown to significantly reduce the postoperative infection rates and demonstrated superiority over nonantiseptic agents.[29,36,40] However, recent evidence has demonstrated higher rates of reoperation for infection in patients whose surgical wounds were irrigated with dilute PI.[41,42] Although there exists uncertainty over the optimal irrigation solution for the prevention of SSI, both the WHO and CDC recommend the use of sterile PI for all surgical procedures based on the available evidence.[43,44] The use of sterile PI as an irrigation solution in all orthopaedic procedures was also supported with strong consensus at the 2018 International Consensus Meeting on Musculoskeletal Infection.[45]

Table 3.2 Formulas for preparing common surgical irrigants (per liter)

Irrigant	Concentration used in irrigation	Volume of irrigant	Diluent	Volume of diluent
Acetic Acid	< 5%	Commercially available in dilute solution from 0.25 to 5%	No diluent required	–
Bacitracin and Polymyxin	Bacitracin: 50 µ/mL Polymyxin B: 0.05 mg/mL	One 50,000-unit vial of bacitracin powder One 50 mg vial of polymyxin B powder	Normal saline	1 L
Chlorhexidine	0.05%	Commercially available as 0.05% solution	No diluent required	–
Povidone-Iodine	0.35%	35 mL of 10% providone-iodine solution	Normal saline	1 L
Sodium Hypochlorite	0.025%	50 mL of 0.5% sodium hypochlorite (Dakin's solution)	Normal saline	1 L
Hydrogen Peroxide	3–6%	Commercially available as 3% solution	No diluent required	–
		6% solution—200 mL 30% H_2O_2	Sterile saline	800 mL

Use in Irrigation and Debridement of Infection and Efficacy against Biofilm

Dilute PI can be effectively used in the presence of biofilm and may be superior to other antiseptic agents.[46] However, it should be noted that in order to penetrate biofilm, higher concentrations or longer exposure times may be required than those used for routine lavage. According to the *in vitro* study by Schmidt et al, using a 10% PI solution for 1 minute or a 3.5% solution for 10 minutes is required to remove *Staphylococcus epidermidis* from biofilm.[20] Recent series of experiments in our laboratory have demonstrated that 0.5% sterile PI that contains a certain surfactant can destroy biofilm and is capable of destroying gram-positive and gram-negative bacteria upon contact (data not published).

3.4 Chlorhexidine

3.4.1 Overview of Antiseptic Agent

Mechanism of Action

Chlorhexidine is a positively-charged, lipophilic compound that increases the permeability of microbial cells walls, allowing intracellular contents to escape.[47]

Spectrum of Antimicrobial Activity

At low concentrations, chlorohexidine is bacteriostatic, while it is bactericidal at higher concentrations.[23] Although chlorhexidine has a broad spectrum of antimicrobial activity, including antimicrobial activity against gram-positive and gram-negative bacteria, certain fungal species, and enveloped viruses, but unlike PI, it has no activity against *Actinobacteria* or spores.[21] Bacterial strains may possess efflux pumps that confer resistance to chlorhexidine and there is evidence that the prevalence of resistance may be increasing.[23] It has a high affinity for bonding to tissues, extending its antimicrobial activity for several hours following administration.[48]

Safety and Adverse Effects

Development of allergic reactions to chlorhexidine are relatively common, with 2% of patients becoming sensitized after repeated exposure.[32] Generally, exposure only results in contact dermatitis, but severe allergic reactions can occur and may be responsible for 5 to 7% of cases of anaphylaxis in the perioperative period.[32,49] When mixed with sodium hypochlorite (NaOCl), Dakin's solution, the solution may react to form parachloroaniline, a compound known to induce methemoglobinemia in humans and shown to be carcinogenic in animal studies.[33] The combination of chlorhexidine and hydrogen peroxide may be more effective than chlorhexidine alone, but the potential byproducts of these compounds are yet to be studied. Similarly, in combination with dilute PI, increased microbicidal activity may be achieved over either individually, but potential harmful products from mixing these two compounds have not been evaluated.[33]

3.4.2 Efficacy as a Surgical Wound Irrigant

Prophylactic Use

Chlorhexidine is commonly used as a topical and oral antiseptic. Additionally, it has been used in irrigation in nonorthopaedic surgical cases,[50] but has only recently been explored as an irrigation solution in orthopaedic surgery.[51] It is commercially available as a single use 450 cc bottle of 0.05% chlorhexidine gluconate in water.[51] The manufacturer recommends irrigating wounds and allowing the tissue to bathe in the solution for 1 minute prior to rinsing with normal saline.[52] Routine irrigation of surgical wounds with chlorhexidine prior to closure results in similar rates of infection compared to other solutions, such as dilute PI or normal saline.[51] Chlorhexidine eliminates the majority of bacteria upon contact, except for MRSA, which requires exposure of greater than 3 minutes.[39] In addition to eradicating organisms from the surgical site, chlorhexidine may also prevent the formation of biofilm.[53,54] However, chlorhexidine as a surgical irrigation solution has yet to be fully investigated through clinical trials, and its routine use is not currently recommended.

Use in Irrigation and Debridement of Infection and Efficacy against Biofilm

Limited evidence suggests that chlorhexidine may be useful in the treatment of established orthopaedic infections. *In vitro* studies demonstrated that, at a minimum concentration of 2%, chlorhexidine can be effective in treating MRSA biofilm, while concentrations as low as 0.05% for 1 minute can eliminate *S. epidermidis* biofilm *in vitro*.[20,55] Scrubbing of biofilm coated implants with 4% chlorhexidine has been demonstrated to reduce bacterial load greater than irrigation alone or scrubbing with either PI or detergents.[56]

3.5 Sodium Hypochlorite (NaOCl)

3.5.1 Overview of Antiseptic Agent

Mechanism of Action

Dilute sodium hypochlorite, commonly referred to as Dakin's solution, is produced from a mixture of sodium peroxide and hydrochloric acid. Chlorine reacts with water to form hypochlorous acid, a potent antibacterial agent that it also produced by neutrophils to digest pathogenic organisms.[57] Its efficacy is thought to primarily result from inhibition of DNA synthesis and disruption of ATP synthesis.[58,59]

Spectrum of Antimicrobial Activity

NaOCl is effective against a broad spectrum of microorganisms including gram-positive bacteria, gram-negative bacteria, anaerobic bacteria, spores, fungi, and viruses. It has also shown to be effective in eliminating antibiotic-resistant organisms, such as MRSA and vancomycin resistant *Enterococcus* (VRE).[57] While acquired resistance to NaOCl has not been described, *in vitro* studies have demonstrated that exposure may induce expression of adaptive genes that confer increased tolerance.[60,61]

Safety and Adverse Effects

NaOCl can be cytotoxic to fibroblasts, especially at concentrations greater than 0.025%, which may impair wound healing. Commonly, NaOCl can result in local irritation including erythema and swelling, but allergic reactions are also possible. At diluted concentrations, the risk of systemic toxic effects is low. However, if used in conjunction with taurolidine, another antimicrobial agent, the risk of toxic effects, including metabolic acidosis, may be significantly increased.[57] Mixture with hydrogen peroxide produces singlet oxygen, which is known to be cytotoxic.[33]

3.5.2 Efficacy as a Surgical Wound Irrigant

Prophylactic Use

The use of NaOCl as an effective irrigation solution has not been evaluated in clinical studies, but it has demonstrated bactericidal efficacy *in vitro* with only 1 minute of exposure at a higher and potentially cytotoxic concentration of 0.125%.[18] Concentrations of 0.025 to 0.125% NaOCl has been reportedly used for topical antisepsis and wound debridement.[62]

Use in Irrigation and Debridement of Infection and Efficacy against Biofilm

Irrigation with NaOCl solution does not appear to be effective in treating orthopaedic infections. Even at higher concentration of 0.5%, which are considerably higher than tolerable doses, NaOCl was unable to eradicate biofilm with exposure of up to 10 minutes.[20]

3.6 Hydrogen Peroxide

3.6.1 Overview of Antiseptic Agent

Mechanism of Action

Hydrogen peroxide is extensively used as an antiseptic agent due to its potent microbicidal activity and decomposition into safe byproducts, water and oxygen.[63] However, the duration of its effect is limited by its rapid degradation.[64]

Spectrum of Antimicrobial Activity

Upon entering the cell, hydrogen peroxide reacts with catalytic metals, producing free radicals, which induce oxidative damage, leading to cell death. It has a broad spectrum of antimicrobial activity against bacteria, viruses, spores, protozoa, and even prions. Development of acquired resistance to hydrogen peroxide has not yet been discovered, but certain bacterial species can increase production of catalase when exposed to hydrogen peroxide, allowing tolerance of significantly higher concentrations.[23] Such species include *S. aureus* and *P. aueroginosa*, and concentration of less than 3% may be ineffective against these organisms.[64]

Safety and Adverse Effects

While generally considered to be a safe antiseptic, there are several reports in the literature of severe, sometimes even fatal, complications. This is due to the abundant gaseous oxygen produced, which if present in the bloodstream, can form emboli and potentially lead to stroke, myocardial infarction, or peripheral end-organ damage.[65] Only a few cases of these potentially fatal complications have been reported in the orthopaedic literature, but several reports have been described in nonorthopaedic literature.[64,65,66] *In vitro* studies have shown hydrogen peroxide to be cytotoxic and has corrosive effects on metal implants and hydroxyapatite, although the clinical implications of these effects have not yet been fully elucidated in the literature.[24,67]

3.6.2 Efficacy as a Surgical Wound Irrigant

Prophylactic Use

Despite limited evidence, use of hydrogen peroxide during wound irrigation has been described in the literature to prepare the bony interface by mechanical debridement secondary to the effervescent reaction, to achieve hemostasis, and to sterilize the surgical site.[64] Concentration of 3% is most commonly used during surgical irrigation, but 6% hydrogen peroxide concentration has been reported in the literature, as well.[68,69] Hydrogen peroxide is commercially available in a 3% solution. For higher concentrations, such as 6%, it can be prepared by diluting concentrated solutions (▶ Table 3.2).

Use in Irrigation and Debridement of Infection and Efficacy against Biofilm

Additionally, hydrogen peroxide has shown to be effective at debriding biofilms, as it is potentially superior to PI.[45] Even after only a minute of exposure, 3% hydrogen peroxide solution reduced bacterial count by 90% in *S. epidermidis* biofilm.[70]

3.7 Conclusion

Several irrigation solutions are commonly used in orthopaedic surgery with varying risks and benefits to each. While the literature has yet to declare an optimal irrigant, current evidence supports use of sterile 0.35% PI over other solutions given its broad efficacy, relative safety, and absence of the development of resistance by microorganisms. The addition of antibiotics to irrigation solution is not recommended given that recent evidence suggests it confers no additional benefit and its overuse may further contribute to antibiotic resistance.

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4 Surgical Wound Dressings after Treating Orthopaedic Infections

Patrick Moody and Bryan Springer

Abstract
The postoperative dressing functions as an important barrier to prevent orthopaedic infections and reinfections. Preoperative assessment of patient factors and intraoperative evaluation of the soft tissue and wound serve as key elements to determining the right dressing for individual patients when treating orthopaedic infections. This chapter explores characteristics of the ideal dressing and fundamental features of different dressing options available to surgeons, including standard nonocclusive dressings, occlusive dressings with or without antimicrobial impregnated materials, negative pressure wound therapy, and closed incision negative pressure wound therapy. Advantages and disadvantages of each dressing type are discussed with literature evidence. Finally, this chapter provides surgeons with an algorithmic approach to dressing selection for patients undergoing treatment for orthopaedic infections.

Keywords: Dressing, occlusive, negative pressure wound therapy, closed incision negative pressure wound therapy

Practical Tips

- When applying an occlusive dressing over a joint such as the knee or elbow with high anticipated excursion, place the dressing with the joint in flexion (20–30 degrees) to reduce tension on the dressing and thus reduce force on the surgical incision.
- Apply dressings over joints with the dressing fibers oriented in the direction of joint movement to reduce blister formation (e.g., longitudinal on the knee or elbow).
- If an incision is too long or its shape does not conform to one size of a particular prefabricated dressing, stacked dressings may be utilized by cutting the end of one or more dressings before applying a complete dressing over them to create an adequate seal.
- When removal of a dressing is appropriate, begin by methodically lifting one corner of the dressing adhesive by gently pulling up and away to release the dressing and then gently work free the adhesive edge one small area at a time until the entire adhesive portion is free. This should allow the dressing to removed more easily.
- The dressing should be carefully observed for drainage on the back side of the dressing. If just light spotting occurs, the dressing can be monitored. If there is a more saturated appearance or excessive strikethrough on the dressing, it should be removed and the incision carefully inspected.
- Be prepared in the operative room with options for negative pressure wound therapy particularly for patients at risk for wound breakdown and incisions that may prove difficult to close.

4.1 Introduction

Wound dressings are applied at the conclusion of a surgical case to cover the wound and potentially prevent reinfection when treating patients with orthopaedic infections.

Many options are available, ranging from nonocclusive gauze and tape for routine closed incisions to negative pressure wound therapy (NPWT) for large wounds that may not be closed. The challenge is to choose the right dressing for each individual patient. Much of the literature to date addressing postsurgical dressings explores the use of dressings prior to development of an infection. Nevertheless, the principles behind successful dressings remain the same when addressing the surgical wound while treating an orthopaedic infection. This chapter will examine the characteristics of optimal dressings, explore different dressing types by increasing wound complexity, and give recommendations in the form of an algorithm to help select the right postoperative dressing for patients being treated for orthopaedic infections.

4.2 Characteristics of Optimal Surgical Dressings

As postsurgical dressings have evolved over the years with the advent of technological advances, multiple factors have been identified to describe the ideal surgical dressing. Collins described the following six characteristics: (1) permeable; (2) able to remain *in situ* while the patient is bathing; (3) transparent to observe fluid accumulation; (4) low adherence; (5) barrier to bacteria, but not moisture vapor; and (6) cost-effective.[1] In addition to these qualities, the ability of the dressing to accommodate the range of motion of nearby joints must be considered.

The ability of a dressing to provide a moist environment is crucial for surgical wound healing. Dressing permeability, as well as absorptive capacity, help establish this setting.[2] Previous research has shown that, compared to dry environments, moist environments result in a faster, better quality of wound healing that minimizes wound necrosis.[3,4] Despite the negative connotation of wound exudates, these are filled with growth factors that promote growth and the migration of fibroblasts, endothelial cells, and keratinocytes. However, excessive moisture can be detrimental to wound healing, leading to blistering, maceration, and wound breakdown.[5] Therefore, an ideal dressing should be able to address excessive wound exudate while maintaining an appropriately moist environment for wound healing.

Another important quality of an ideal dressing is its ability to create an occlusive barrier to the external environment. By creating a barrier for the surgical incision, a dressing can prevent bacterial ingress and introduction of infection. Occlusive barrier dressings can create a thermally insulated, relatively hypoxic environment that actually promotes angiogenesis at the wound surface and enhances wound healing.[6]

Dressing characteristics that improve the experience of the patient and medical staff also make them ideal for use. This includes the ability of patients to retain the dressing while bathing, but also low adherence to allow for easy, atraumatic removal. Higher patient satisfaction has been seen with dressings that require less frequent changes.[7] Dressings must also demonstrate a degree of compliance to allow for movement of nearby joints to facilitate range of motion postoperatively. Transparency of dressings also allows the patient and medical staff to evaluate the saturation of the wound and determine if there is a need for replacement.

Lastly, cost-effectiveness of dressings should be considered. Standard postoperative dressings, such as gauze and tape, cost little to the patient and hospital. Alternatively, recently developed dressings with advanced technology are more expensive. However, one must weigh certain factors before choosing a dressing simply because of cost. Increased frequency of dressing changes increases cost and limits the ability to maintain the wound environment temperature more near to core body temperature, which

facilitates mitotic cell division and leukocyte activity critical for wound healing. Each time a dressing is removed, 3 to 4 hours are required to return to the same level of cellular activity.[2] Clarke et al were able to show higher skin microbial colonization in patients who had earlier dressing changes after total joint arthroplasty.[8] Despite higher costs, dressings that require less changes can potentially protect a surgical wound from pathogen exposure, can reduce patient pain, and are less of a burden to staff and family members changing the dressings at home. The price of a dressing versus further operating and hospital care costs must be weighed when selecting a dressing.

4.3 Dressing Types

Multiple dressing types exist at a surgeon's disposal. Over 3,000 types of dressings, biological materials, tissue-engineered substitutes, and mechanical devices exist to assist in surgical wound healing.[9] Each has at least some characteristics of the ideal dressing. The following paragraphs will discuss the use of nonocclusive and occlusive dressings, closed incision wound vacuum systems, and wound vacuum systems in the context of wound protection after treating orthopaedic infections. ▶ Table 4.1 highlights multiple dressings within these categories.

4.3.1 Nonocclusive and Occlusive Dressings

Nonocclusive dressings include supplies such as iodoform or regular gauze, abdominal pads (ABDs), Kerlix®, tape, or compression bandages (▶ Fig. 4.1). Following surgical debridement for infection, moist gauze dressings have traditionally been the most commonly used dressing for colonized wounds, providing a dressing option that is inexpensive and simple to use.[9] However, many surgeons are concerned about the effects of decreasing wound temperature, removal of healthy granulation tissue, vasoconstriction and subsequent wound ischemia, decrease of cellular migration and proliferation, higher costs from increased caregiver time or home nurse dressing changes, and increased frequency of dressing changes resulting in lower patient compliance associated with these dressings.[9] Despite these concerns, traditional nonocclusive dressings may represent the right option for a surgical wound under certain circumstances. Such settings may include surgical wounds requiring daily evaluation, with prolonged splint immobilization, and incisions requiring mechanical debridement of necrotic tissue that can be addressed with wet-to-dry dressings.

Early experiments by Winter demonstrated the importance of the moist environment created by occlusive dressings, which ignited a wave of research and development of multiple occlusive dressings.[3] Occlusive dressings were found to form excellent protective barriers to the external environment, which allow patients to participate in activities such as showering while improving epithelialization and granulation of wounds.[24] Further clinical studies have showed significant decreases in wound problems and lower infection rates associated with the use of occlusive dressings.[7,25,26] Occlusive dressings are either fully occlusive or semi-occlusive based on their permeability to water vapor. Both can be waterproof. There are currently multiple types of occlusive dressings available to address the surgical wound after treating orthopaedic infections, which can be generally categorized into regular occlusive dressings and those impregnated with antibacterial materials such as silver.

Table 4.1 A selection of currently available dressings for orthopaedic surgical wounds. Price as available on medicalmonks.com, accessed November 20, 2019

Dressing category	Product name	Manufacturer name	Characteristics	Antibacterial material	Duration recommended	Price (15 cm incision)	Relevant literature
Nonocclusive	4×4 inch Gauze	Multiple	• Contain absorbent cellulose fibers	None	Variable	$0.28	Ubbink et al[10]
Occlusive without Impregnated Material	Tegaderm™	3 M™ (Maplewood, MN)	• Transparent • Semi-occlusive • Waterproof	None	Variable	$3.57	Rubio[11]
	OPSITE	Smith & Nephew (London, UK)	• Waterproof • Transparent • Absorbent pad	None	Variable	$1.19	O'Brien et al[12]
	Comfeel® Plus Transparent	Coloplast (Minneapolis, MN)	• Hydrocolloid • Semipermeable • Adaptable to body contour	None	Variable	$7.38	Goodhead[13]
Occlusive With Impregnated Material	Aquacel® Ag Surgical	ConvaTecInc. (Reading, UK)	• Hydrofiber® and • hydrocolloid technology • Waterproof	Silver available in Aquacel Ag	7 days	$64.99	Jones et al[14] Springer et al[7]
	Mepilex® Border postoperative	Mölnlycke Health Care (Gothenburg, Sweden)	• Flexible for use around joints • Waterproof	Silver available in "Ag" form	7 days	$33.99	White[15] Johansson et al[16]
	Acticoat Surgical	Smith & Nephew (London, UK)	• Flexible • Fenestrated pad to assist removal	Silver	7 days	$46.99	Wright et al[17] Yin et al[18]
ciNPWT	PICO 7	Smith & Nephew (London, UK)	• Portable • Can be placed on weight-bearing surfaces • 2 AA batteries may need replacement	None	7 days	$364.99	Dowsett et al[19] Scalise et al[20]

Table 4.1 (*Continued*) A selection of currently available dressings for orthopaedic surgical wounds. Price as available on medicalmonks.com, accessed November 20, 2019

Dressing category	Product name	Manufacturer name	Characteristics	Antibacterial material	Duration recommended	Price (15 cm incision)	Relevant literature
	Prevena™ 125	KCI (San Antonio, TX)	• Portable • 3 AA batteries, may need replacement • −125 mm Hg only	Silver-impregnated sponge	7 days	$634.99	Singh et al[21]
	Avelle™	ConvaTec Inc. (Reading, UK)	• −60 to −100 mm Hg • ciNPWT or traditional NPWT • Hydrofiber® technology	None	• As long as needed • Pump has 30-day lifespan	$86.99	Limited Company Data
NPWT	V.A.C.ULTA™	KCI (San Antonio, TX)	• Foam contours to wound • Can be used for ciNPWT • Hospital use only • 6 hr battery life	• Silver-impregnated foam available	• Variable with sponge/plastic changes • Changes every 2–3 days	Variable	Halvorson et al[22] Gabriel et al[23]
	ACTIV.A.C™	KCI (San Antonio, TX)	• Similar to V.A.C. Ulta but more portable for outpatient use • 14 hr battery life	• Silver-impregnated foam • available	• Variable with sponge/plastic changes • Changes every 2–3 days	Variable	
	Invia® Liberty™	Medela (Baar, Switzerland)	• 40 to −200 mm Hg • Can be used for ciNPWT • 14 hr battery life	Silver contact dressing available	• Max: 7 days with changes every 2–3 days. Consider more often for infected wounds	Variable	• Limited CompanyProvided Case Reports
	Ally™	Cardinal Health™ (Dublin, OH)	• 24 hr battery life • Simultaneous irrigation possible	None	• Changes every 2–3 days	Variable	Limited

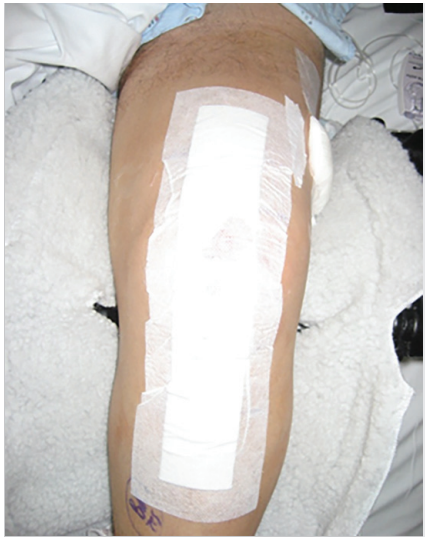

Fig. 4.1 Example of a standard, nonocclusive postoperative dressing. The dressing employs gauze and tape elements.

Regular Occlusive Dressings

Regular occlusive dressings employ a single layer of transparent film, such as Tegaderm™ (3M; Maplewood, MN) or Hydrofilm® (Hartmann; Heidenheim, Germany), to create a waterproof covering that can be used as a secondary dressing over another dressing layer, such as gauze or Xeroform® (multiple companies). Newer occlusive dressings possess an occlusive outer layer with the advent of advanced technology to address exudates and the wound surface, including Hydrofiber® (ConvaTecInc; Reading, UK) and hydrocolloid technology. Hydrofiber® technology allows for significant absorption of exudate, but does so via a process called vertical wicking. This process removes exudate directly from the wound, preventing lateral wicking that could result in maceration of wound edges.[5] Such maceration has the potential to cause wound breakdown and infection. Hydrofiber® dressings also facilitate the formation of a fibrin layer that prevents dressing ingrowth and damage to the wound during removal. It also serves as a barrier to the harmful effects of local granulocytes toward wound healing.[27]

Like Hydrofiber® dressings, hydrocolloid technologies also have high absorptive capacity. However, these dressings absorb exudate differently by forming a gel, such as acrylate, that makes the dressing more permeable to water vapor. This allows the dressing to absorb more exudate while maintaining an appropriately moist environment.[28] Beyond this unique property, hydrocolloid dressings are relatively atraumatic to the skin. Some dressings, such as Aquacel® (ConvaTecInc), employ a combination of both Hydrofiber® and hydrocolloid technologies in attempts to provide an optimal wound healing environment (▶ Fig. 4.2).

Impregnated Occlusive Dressings

Occlusive dressings impregnated with antimicrobial substances can further reduce the risk for infection. Silver ions impregnated into dressings can provide an antimicrobial effect by disrupting bacterial cell walls, nuclear membranes, and denaturing bacterial deoxyribonucleic acid (DNA) and ribonucleic acid (RNA).[9] Retrospective data

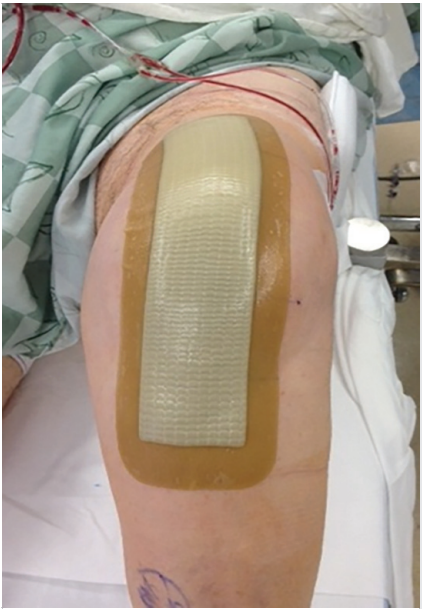

Fig. 4.2 Example of an occlusive, silver-impregnated dressing that uses a combination of both Hydrofiber® and hydrocolloid technology.

demonstrated a reduction in acute periprosthetic joint infections with the use of silver-impregnated occlusive dressings compared to standard dressings.[25,29] Silver is also featured in the sponges of some NPWT systems. However, it should be noted that silver-impregnated dressings should not remain on for an extended period of time due to their cytotoxic effects, particularly on fibroblast and keratinocyte cell lines.[30] Because different dressings contain varying amounts of silver, it is difficult to recommend a maximum duration of application for a silver-containing dressing. Manufacturer recommendations should be followed.

Other options for antimicrobial-impregnated occlusive dressings include those containing iodine (Iodoflex®, Smith & Nephew; London, UK) and bismuth tribromophenate (Xeroform®). Cadexomer iodine is a hydrophilic modified starch polymer containing 0.9% iodine by weight. Despite less widespread use within orthopaedics, cadexomer iodine has proven efficacious against the formation of biofilms in chronic wounds.[31] The use of bismuth tribromophenate-impregnated gauze (Xeroform®) has been studied extensively in burn and skin graft donor site care, as it possesses antimicrobial activity.[32,33] However, recent studies have shown minimal antimicrobial activity of bismuth tribromophenate-impregnated gauze dressings against common bacteria found in burns, many of which are common cutaneous bacteria that are culprits in orthopaedic surgical infections.[34]

4.3.2 Dressing Application Tips and Tricks

After an appropriate surgical wound dressing has been selected for the wound, the dressing should be placed in optimal position. When addressing wounds over a joint such as the knee or elbow with high anticipated excursion, the authors recommend that the dressing should be applied in flexion. This applies less tension on the dressing

which then applies less force on the surgical wound during flexion of the joint.[35] Preferably, the dressing fibers should be placed in the direction of joint movement to reduce blister formation.[2]

Some surgical wounds are too long for one particular dressing or angle in various directions. If this is the case, the authors recommend cutting the end of one dressing before applying it. Another separate, complete dressing is then applied over this cut end to complete coverage of the wound while creating a seal with the initial dressing. Stacking the dressing in this manner can help establish a complete barrier over the entire surgical wound despite the use of multiple dressings.

Dressings should be inspected by the provider and patient, then removed when recommended by the specific dressing instructions or earlier for direct evaluation of the incision if desired. However, there are times when dressings should be removed prematurely and potentially exchanged. These certainly include evidence of infection such as erythema, induration, and persistent drainage. Other indications for early dressing removal include compromise from loosening of the dressing edges, leakage, and excessive saturation. Clinical discretion should be used when deciding how much saturation is too much for a particular dressing, as some dressings are able to tolerate more exudate than others. Examples include dressings composed of Hydrofiber® or hydrocolloid material that possess higher absorptive capacity.[2] Aseptic technique should be used for dressing changes if possible.

Dressings should be removed carefully so as to not damage the wound or surrounding skin. At times, dressings can prove difficult to remove for the patient or medical personnel. Subjective evidence suggests the methodical lifting of one corner of the adhesive part of the dressing and gently working the adhesive edges one small area at a time until the entire adhesive portion is free. This should allow the dressing to lift off more easily. Sometimes the dressing can be strongly adhered to the wound bed. If this is the case, sterile water or normal saline can be dropped onto the adhered area to soften the dressing and allow for its safe removal.[36] This may require multiple rounds of partial removal based on the patient's toleration, with loosened ends trimmed between rounds. If the patients will be removing the dressing themselves, clear instructions should be provided.

4.3.3 Wound Vacuum Systems

Standard NPWT traditionally involves application of a foam pad into an unclosed surgical wound with an overlying protective adhesive layer through which suction delivers negative pressure.[37] NPWT provides surgical wound retraction, removal of tissue debris, removal of excessive exudate and edema, and protection from the external environment. By applying mechanical stress on wound edges, standard NPWT stimulates angiogenesis and granulation tissue formation.[38] NPWT systems are often changed every 2 to 3 days before delayed closure of the wound is performed or tissue transfer is required for coverage.

Standard NPWT systems have many orthopaedic indications, including treatment of contaminated acute wounds with or without fracture, chronic wounds, large tissue defects, and fasciotomies.[39] They are especially useful for addressing orthopaedic infections with their ability to remove potentially contaminated exudate and edema while reducing dead space and preventing premature walling off of cavities.[40,41,42,43] Considerable necrotic or infected tissue is often removed during surgical debridement for infections, resulting in large voids or exposure of tendon, bone, or hardware. Due to

circumstances such as impaired blood flow or risk of wound contamination, plastic surgery for coverage cannot be performed in all circumstances. In these cases, NPWT can provide a means for potential wound closure through contraction and granulation tissue formation, as the use of NPWT decreases the need for flap coverage after initial prediction for its need.[44]

The use of NPWT in the treatment of orthopaedic infections is contraindicated in certain scenarios, particularly regarding tissue coverage, bleeding, and infection. NPWT foam cannot be placed directly in contact with exposed nerves or blood vessels, which could result in nerve damage and excessive bleeding, respectively. Excessive bleeding is also a contraindication to using NPWT; thus hemostasis must be achieved prior to NPWT application. Thorough irrigation and debridement must be performed prior to placement of NPWT in the case of orthopaedic infections, as NPWT does not provide deep debridement of necrotic or infected tissue.[39] NPWT is also not recommended in patients with cerebrospinal fluid leaks, bleeding disorders, and allergic reactions to vacuum-assisted closure (VAC) materials. With regards to the latter, some NPWT systems utilize an acrylic adhesive coating to which some patients may have an allergy or hypersensitivity, thus contraindicating use of the VAC. Silver hypersensitivity is also a contraindication should an NPWT system utilize a dressing or foam with silver. Other relative contraindications for NPWT include ischemic wounds and fragile skin.[39]

Additionally, optimal settings for NPWT have not yet been established. This includes the pressure setting, continuous or intermittent suction, and duration of use, which vary across the literature. Evidence suggests that the pressure level should be set somewhere between −50 and −150 mm Hg.[45] After their instrumental study that popularized use of NPWT, Morykwas et al examined the use of the −125 mm Hg versus higher and lower subatmospheric NPWT pressures, confirming that −125 mm Hg was optimal for granulation tissue formation.[46] Importantly, this study included porcine subjects with clean surgical incisions, not infected orthopaedic wounds. Ultimately, the surgeon should consider pressure level on a case by case basis, as patients with ischemic tissue, diabetic foot ulcers, and skin transplantation may require lower pressures, or no NPWT due to the risk of further soft tissue damage.[45]

The parameters of intermittent versus continuous suction must also be considered. As its title implies, intermittent mode NPWT involves cycling between on and off periods, often 5 minutes on and 2 minutes off before repeating the cycle, which has dynamic effects on angiogenesis and oxygenation in healing wound beds.[47] Morykwas et al found improved formation of granulation tissue in acute and chronic wounds using intermittent suction compared to continuous suction.[46] Despite experimental evidence supporting the use of the intermittent mode, the continuous mode is the most commonly used in current practice.[48] This can be attributed in part to the pain experienced by patients during transitions of the intermittent mode.[49] Variable mode, where different pressures are administered without a complete off phase, may serve as a viable option to address pain while still producing favorable effects on wound healing.[47] Nevertheless, if an infected wound is expected to produce a large amount of exudate, continuous suction may be the best mode of choice.[50]

The duration of treatment must also be decided by the surgeon based on patient and device factors. Standard NPWT may require longer durations of treatment until wound edge approximation and satisfactory removal of exudate, with changes occurring every 2 to 3 days.[50] Duration of device battery life varies amongst systems used for standard NPWT, often lasting between 14 and 18 hours; however, device batteries are easily recharged in systems functional with an electrical power supply. No definite time limit

exists for NPWT use. One manufacturer's reference material suggests NPWT may be used for up to 6 weeks or more as long as satisfactory progress of the wound is being made.[51] Should a wound show little to no progress toward healing or show signs of detriment toward the skin or soft tissue, the wound VAC should be discontinued. Surgeons should adhere to the specific recommendations for each individual NPWT system.

Incisional Wound Vacuum Systems

NPWT has found alternative applications since its introduction to the management of acute and chronic wounds in the 1990s. While standard NPWT systems traditionally apply a sponge within a wound, closed incision negative pressure wound therapy (ciNPWT) was developed to apply negative pressure to the incision at the skin level to remove fluid that could prevent wound healing. Benefits include improved local blood flow, wound contraction, and wound healing by reduction of excess exudate and edema, which has made this a viable option for high-risk wounds after treating orthopaedic infections.[52] High-risk wounds include but are not limited to wounds closed over considerable dead space, with high anticipated drainage, and with poor host healing factors. This technology was first featured by Gomoll et al in 2006 for the successful prevention of infection in orthopaedic trauma patients and has gained traction amongst multiple orthopaedic subspecialties to prevent wound complications and treat patients with orthopaedic infections.[53]

ciNPWT creates a protective, airtight environment utilizing a suction pad over a transparent drape that sufficiently covers a sponge placed over the closed incision (▶ Fig. 4.3). Multiple functions are served by this device, including incision tension

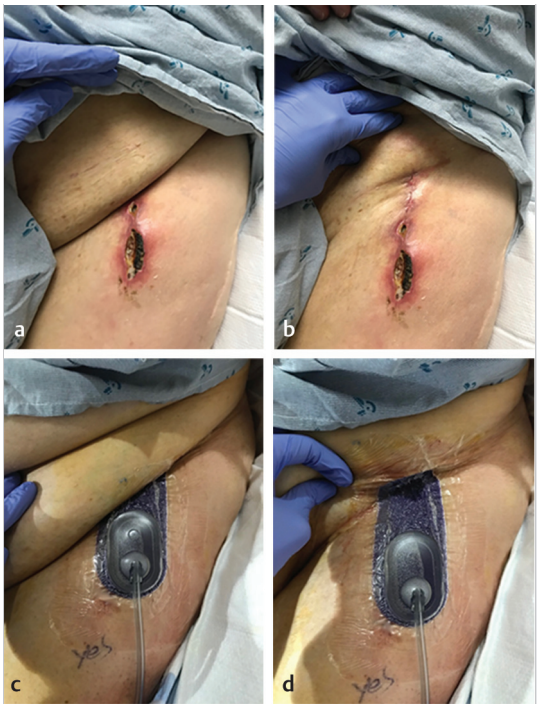

Fig. 4.3 Clinical photos of an 81-year-old male, 4 weeks postoperative from a left total hip arthroplasty via a direct anterior approach. **(a, b)** Wound prior to irrigation and debridement with and without soft tissue retraction. At the conclusion of the irrigation and debridement with primary closure of the dehisced wound, a closed incision negative pressure therapy device was applied **(c, d)**.

reduction, edema and exudate reduction, protective sealing, and dressing change reductions. Lateral wound tension is reduced, resulting in increased wound breaking strength compared to standard control dressings.[54] Hematoma and seroma formation are also reduced by ciNPWT.[50] However, most relevant to this chapter is the reduction of infection and wound dehiscence risk seen with the use of ciNPWT. This starts with the sterile environment created when the ciNPWT is applied in the operating room and continues with the elimination of frequent dressing changes. Because persistent wound drainage has been associated with surgical site infections, eliminating excessive wound drainage may decrease deep infection rates. In a randomized, prospective, multicenter study in which ciNPWT was applied to high-risk fractures of the tibial plateau, plafond, or calcaneus after surgical stabilization, Stannard et al found statistically significant reductions in infection and wound complications with the use of ciNPWT compared to standard postoperative dressings.[55] Furthermore, a meta-analysis performed by Hyldig et al, encompassing multiple surgical disciplines including orthopaedics, compared ciNPWT versus standard dressings and found that ciNPWT significantly reduced wound infection and seroma rates.[56]

Despite multiple benefits, there are drawbacks to ciNPWT that can limit its use. Adverse events such as blister formation under the wound VAC have been noted, but can be mitigated with the utilization of a nonadherent, protective layer between the foam and skin.[52] Another drawback is cost. The cost of use of ciNPWT after primary total knee arthroplasty was nine-fold higher than standard dressings.[57] Although not extensively studied, "homemade" wound VACs are another ciNPWT option, which can be more cost-effective.[58] Steps to creating a "homemade" wound VAC can be found in ▶ Table 4.2. The surgeon must weigh the risks and cost associated with ciNPWT systems with the potential benefits to the patient when addressing an infected surgical wound.

As in the case of traditional NPWT systems, optimal settings have not yet been established. With regards to pressure settings, subjects in the study by Stannard et al received ciNPWT at −125 mm Hg, continuous suction, and variable duration of application from 21 to 213 hours.[55] In contrast, Gomoll et al reported the preferred use of ciNPWT at −75 mm Hg, presumably on a continuous setting, with anticipated removal in 3 to 5 days.[53] Because no concrete evidence exists for the ideal pressure in ciNPWT, it is recommended to use a pressure between −75 and −125 mm Hg with ciNPWT.[50] Likewise, there is no consensus on continuous versus intermittent suction. In fact, many of the available single-use ciNPWT systems only offer continuous therapy, giving the surgeon less options. This is an area where further research is needed.

Multiple companies offer different ciNPWT options that are more portable and may prove easier to use than traditional NPWT systems. These include the Prevena™

Table 4.2 Guide to creating a "homemade" NPWT system

Step 1	Cut open cell sterilized foam cut geometrically to fit wound
Step 2	Pass simple suction tubing with multiple holes through foam
Step 3	Place plastic adhesive drape dressing over foam to overlap wound margins, completely surrounding drain tubing to create airtight seal
Step 4	Connect tubing to wall suction if patient at hospital or ordinary suction machine for home-based treatment
Step 5	Set suction at −125 mm Hg
Step 6	Collect fluid in a clear container for measurement

Abbreviation: NPWT, negative pressure wound therapy.

(KCI; San Antonio, TX) and PICO™ (Smith & Nephew) systems, among others. Some systems, such as the Avelle™ (ConvaTecInc), can be used for both ciNPWT and traditional NPWT, the latter with additional wound packing. Each uses either a rechargeable battery, such as Prevena™, or employs replaceable lithium batteries, such as the PICO™ system. Interestingly, because the current Prevena™ system recommends no more than a total of 7 days of therapy, the system will time out after 7 days once therapy is started.[51] Not all systems deactivate after 7 days, but others do recommend 7 days maximum use of the ciNPWT dressing. Along with the World Union of Wound Healing Societies, the authors recommend leaving the ciNPWT VAC in place for 5 to 7 days according to the manufacturer's instructions unless there is concern about the wound.[59]

4.4 Algorithm for Surgical Dressing Selection

The patient is the first thing to consider when choosing a postoperative dressing following surgical intervention to treat an orthopaedic infection. Patients at high risk for further soft tissue breakdown should be identified early. Risk factors for wound complications include tobacco use, older age, nutritional deficiencies, uncontrolled diabetes, rheumatoid arthritis, obesity, male sex, anticoagulation, and open injuries (▶ Fig. 4.3).[60,61,62,63] These risk factors do not include the fact that the patient has already sustained an infection, placing them at significantly higher risk for wound breakdown.[64] Based on the presence of one or more of these factors, arrangements should be made for a ciNPWT or an NPWT system to be available, if necessary.

After intraoperative debridement, the wound should be evaluated for its ability to be closed. If the wound is unable to be closed without significant tension, a standard NPWT system should be used until the wound can be closed or the patient can undergo soft tissue coverage in the future. A standard NPWT may also be indicated if there is a significant soft tissue defect, which could provide a location for bacterial growth or seroma formation. If the wound is able to be well approximated and closed, yet poses a

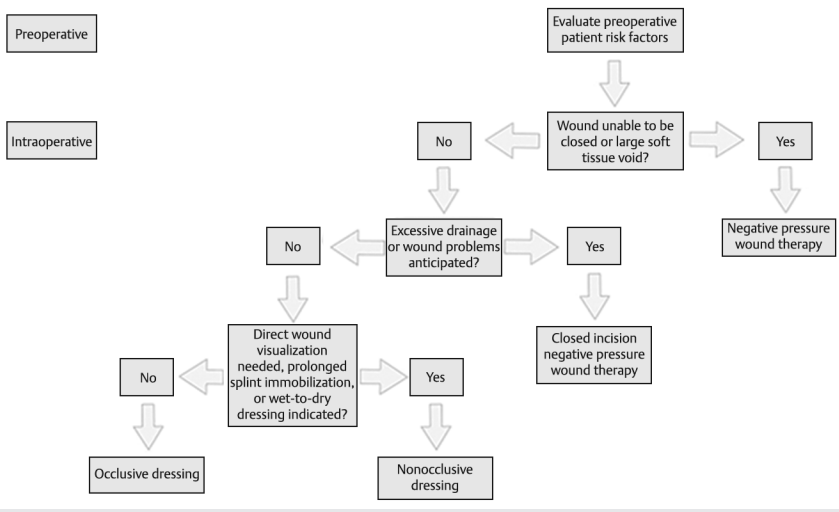

Fig. 4.4 Orthopaedic infection dressing selection algorithmic diagram.

threat of excessive exudate production, ciNPWT should be considered for wound management. If, after closure without significant tension, the wound is not anticipated to produce excessive exudate, the wound can be covered with occlusive or nonocclusive dressings. Occlusive dressings are preferable in the setting of orthopaedic infection treatment to reduce the risk of reinfection. However, nonocclusive dressings can be utilized if the wound needs to be examined on a daily basis, lies under prolonged splint immobilization, or would best be treated with wet-to-dry dressings. All of these modalities have individual strengths and will help prevent further wound contamination. Surgeons are subject to the availability of the dressing options at their facility, but should make appropriate decisions to give the individual patient the best chance to heal.

4.5 Conclusion

The type of dressing chosen by surgeons following surgical treatment of orthopaedic infections is an important decision that can affect the risk of reinfection. Preoperative assessment of patient factors coupled with intraoperative evaluation of the wound allows surgeons to select the optimal dressing type for each patient. These dressings include from standard nonocclusive dressings, occlusive dressings with and without antimicrobial impregnated materials, to closed incision and standard negative pressure wound vacuum therapy devices. Each dressing has one or more features of the ideal postoperative dressing. Surgeons can approach postoperative wound management in an algorithmic manner to select the appropriate postoperative dressing that is both effective and cost-efficient for the patient.

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5 Osteomyelitis

Martin McNally

Abstract

Osteomyelitis is a fascinating condition that can affect all parts of the human skeleton. It presents in several distinct ways, but all have varying degrees of inflammation, systemic ill health, bone death, and soft-tissue compromise. Understanding the components of the disease and the interplay between bacteria, biofilm formation, and the host response is critical to successful treatment. Recent advances in diagnostic methods, imaging, local delivery of antimicrobials, and bone reconstruction have greatly improved the outcome for many patients. Surgery remains central to the effective treatment of chronic osteomyelitis and many acute cases. Eradication of infection is largely dependent on the skill of the surgeon in identifying the areas of dead bone and removing them during surgery. Osteomyelitis is challenging and rewarding to treat, and most patients should enjoy prolonged disease-free periods or cure. Holistic care of the patient requires close collaborative working in a multidisciplinary team including physicians, surgeons, nurses, and therapists to achieve the best outcomes.

Keywords: Osteomyelitis, fracture-related infection, diagnosis, surgical treatment, local antibiotics, classification

Practical Tips

- Accurate diagnosis is the starting point for successful treatment. Preoperative investigations and tissue sampling should be completed with a standardized protocol and sterile equipment.
- In most cases, there is no urgency for treatment. Patients can be assessed, optimized, and treatment carefully planned over several weeks.
- Acute osteomyelitis can often be treated with antibiotics alone, if it is diagnosed early and the patient does not deteriorate.
- Chronic infection always requires surgery with targeted antimicrobial therapy for eradication. Single-stage surgery is possible for many patients.
- Surgical excision of dead bone needs experience and an understanding of the patterns of the disease.

5.1 Introduction

Osteomyelitis has been present on the earth since the development of bone tissue. It has been identified in dinosaur bones from the Jurassic period (▶ Fig. 5.1) and is widely reported in classical medical writings in Greek and Roman literature.[1] Native bone infection remains common worldwide, but the epidemiology is changing. In the developed world, bone infections arising from surgical intervention, injury, peripheral vascular disease, and as sequelae of diabetes mellitus are now more frequent than hematogenous osteomyelitis. Intravenous (IV) drug abuse and being immunocompromised (from human immunodeficiency virus [HIV] and cytotoxic therapy) are now major risk factors.[2,3]

Fig. 5.1 (a, b) This fibula of a 65-million-year-old tyrannosaur exhibits all of the features of established chronic osteomyelitis in the diaphysis. The dinosaur must have survived the infection for many months or years to develop the mature involucrum and extensive sinuses present on the fibula. (© Field Museum [2018], Chicago.)

In the past, bone infection was limb or life threatening without appropriate treatment. A study of acute hematogenous osteomyelitis in Glasgow, United Kingdom (UK), reported a 33% mortality between 1936 and 1940, but this fell to under 10% after 1941, with better use of early surgery and antibiotics.[4] Now, infection often presents more insidiously, with less specific symptoms and gradual bone destruction, in the absence of systemic features. The gradual evolution of the chronic disease causes irreversible changes in tissues, particularly around bone, that can result in loss of function and make successful treatment difficult.

The introduction of antimicrobial therapy 80 years ago has greatly improved the outcome for patients with severe systemic infections, but there are very few occasions when bone infection can be effectively treated by antimicrobials alone. In most cases, a good outcome depends on carefully planned and executed surgery with adjunctive antibiotics.

5.2 Terminology

There are several clinical scenarios that merit a clear definition, as they affect patients differently and require modification of treatment.

Osteomyelitis is an inflammatory condition of cortical and medullary bone caused by an infecting organism, usually limited to a single bone but can be multifocal.

Hematogenous osteomyelitis arises from the spread of bacteria in the blood (bacteremia). This is unusual, as healthy bone is very resistant to bacteria, and it is difficult to

induce osteomyelitis experimentally without causing bone death or without using a very large bacterial inoculation. The infection begins in the medulla but can rapidly spread to involve the cortex with fistulation, subperiosteal abscess formation, and soft-tissue extension. In young children, the infection may fistulate to the adjacent joint and present as septic arthritis.

Acute osteomyelitis may be defined as a bone infection presenting within the first 2 weeks of symptom onset. It occurs in approximately 5 per 100,000 children per year, with males twice as likely to be affected.[5] The most common site is the metaphysis of the lower limb bones; infection in other sites is associated with delayed diagnosis and worse outcome.[5] Initially, acute osteomyelitis affects living bone, but progression leads to bone death, which signals the onset of chronic infection.

Brodie's abscess is a medullary, hematogenous osteomyelitis with a subacute presentation, first described by Sir Benjamin Brodie in 1845.[5] The central bone abscess is often surrounded by dense new bone (medullary *involucrum*), which potentially prevents sinus formation (▶ Fig. 5.2).

Contiguous osteomyelitis occurs when bacteria invade the bone from an adjacent infective focus. It is the most common type of bone infection in adults, usually following an open fracture, an orthopaedic operation, or skin breakdown. Patients with contiguous osteomyelitis often have other medical conditions (e.g., diabetes with foot ulcers, paraplegia with pressure sores, and peripheral arterial or venous insufficiency with ulceration) that require treatment alongside the bone infection.

Fracture-related infection (FRI) describes contiguous osteomyelitis following an open fracture or internal fixation of closed fractures.[7]

Chronic osteomyelitis may begin as acute hematogenous or contiguous disease. In 1984, George Cierny and Jon Mader described the condition in the statement: "The hallmark of chronic osteomyelitis is infected, dead bone within a compromised soft-tissue envelope."[8] This important summary highlights the features that contribute to chronicity that need to be addressed in treatment. The combination of subperiosteal abscess formation, medullary ischemia with intravascular thrombosis, and activation of inflammatory cells all contribute to bone death. Dead bone fragments may separate from living bone tissue (*sequestration*) and if they are small, they can be absorbed or move to the surface along *sinus tracts*. Discharge of these *sequestra* may arrest the

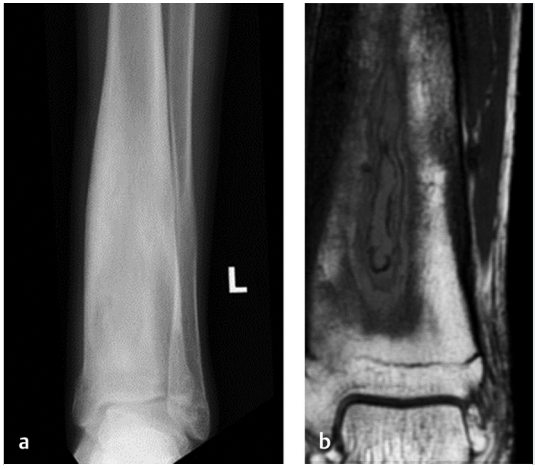

Fig. 5.2 **(a)** Radiograph and **(b)** magnetic resonance imaging (MRI) of a Brodie's abscess. This subacute form of osteomyelitis is medullary with dense new bone formation around the central nidus. Over time, the bone may become expanded, as seen in this case.

progression of the infection and allow the limb to heal. However, residual dead bone and bacterial colonization within the bone will often lead to recurrence (▶ Fig. 5.3).

Large sequestra remain trapped within a surrounding layer of new bone formation (*involucrum*) (▶ Fig. 5.4). Bacteria attach to bone through interactions between bacterial adhesins and host proteins. Adherent bacteria divide and, together with the host cells, produce an extracellular polysaccharide matrix (biofilm), leading to chronicity. Additionally, intracellular survival within osteoblasts and macrophages can occur, particularly in *Staphylococcus aureus* infections.[9]

Reactivation of infection may occur over many years, with discharge of pus from cutaneous *sinuses* and further bone death. Long-term drainage from sinuses prevents systemic ill-health, but risks the development of squamous carcinoma (*Marjolijn's ulcer*) in the wall of a chronic active sinus.

Chronic sclerosing osteomyelitis (of Garré) is a rare form of osteomyelitis mainly affecting the tibia or clavicle. It presents with pain, but does not form draining sinuses. It has a typically dense, sclerotic appearance on X-ray and is invariably culture-negative. It may affect more than one bone when it is also known as *chronic relapsing multifocal osteomyelitis (CRMO)*. It may be associated with SAPHO syndrome (Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis).[10] Many rheumatologists now believe it is an autoimmune condition and not an infective disorder. In the past, it was regarded as a benign condition that was self-limiting in adult life, but pain may persist for many years.

5.3 Classification

Osteomyelitis can be classified by the onset of symptoms (acute or chronic), the source of the infection (hematogenous or contiguous focus), or the cultured organism. These characteristics can be difficult to determine and are not often helpful in designing treatment regimens or predicting outcome.

The Cierny and Mader classification defines the features of infection in the bone (four anatomic stages) and relates this to the physiological condition of the patient.

Three "host groups" (A, no active concurrent disease; B, compromised host; C, severe comorbidity preventing surgery) are described. Group B patients, with conditions that compromise wound healing, reduce the efficacy or tolerance of drug therapy, or prevent effective surgery, have worse outcomes compared to healthy uncompromised hosts (▶ Table 5.1).

Group C hosts have either severe comorbidities that can prevent adequate treatment, or have symptoms from their infection that are minor and do not merit the risks of curative surgery.

The anatomic staging of osteomyelitis is based on the specific distribution of infected bone in the limb. There are four types, each of which tends to be related to a particular etiology of infection (▶ Fig. 5.5).

5.3.1 Type 1 (Medullary)

In Type 1, only medullary cancellous bone is involved. There are no sinuses and the surrounding soft tissues may be inflamed but are not involved in the infection. Structural stability is rarely affected. It is mostly an acute hematogenous infection in childhood. It is uncommon in adults, occurring mainly in those who are immunocompromised, are bacteremic, or have sickle cell disease. Brodie's abscess is a subacute form of type 1 osteomyelitis.

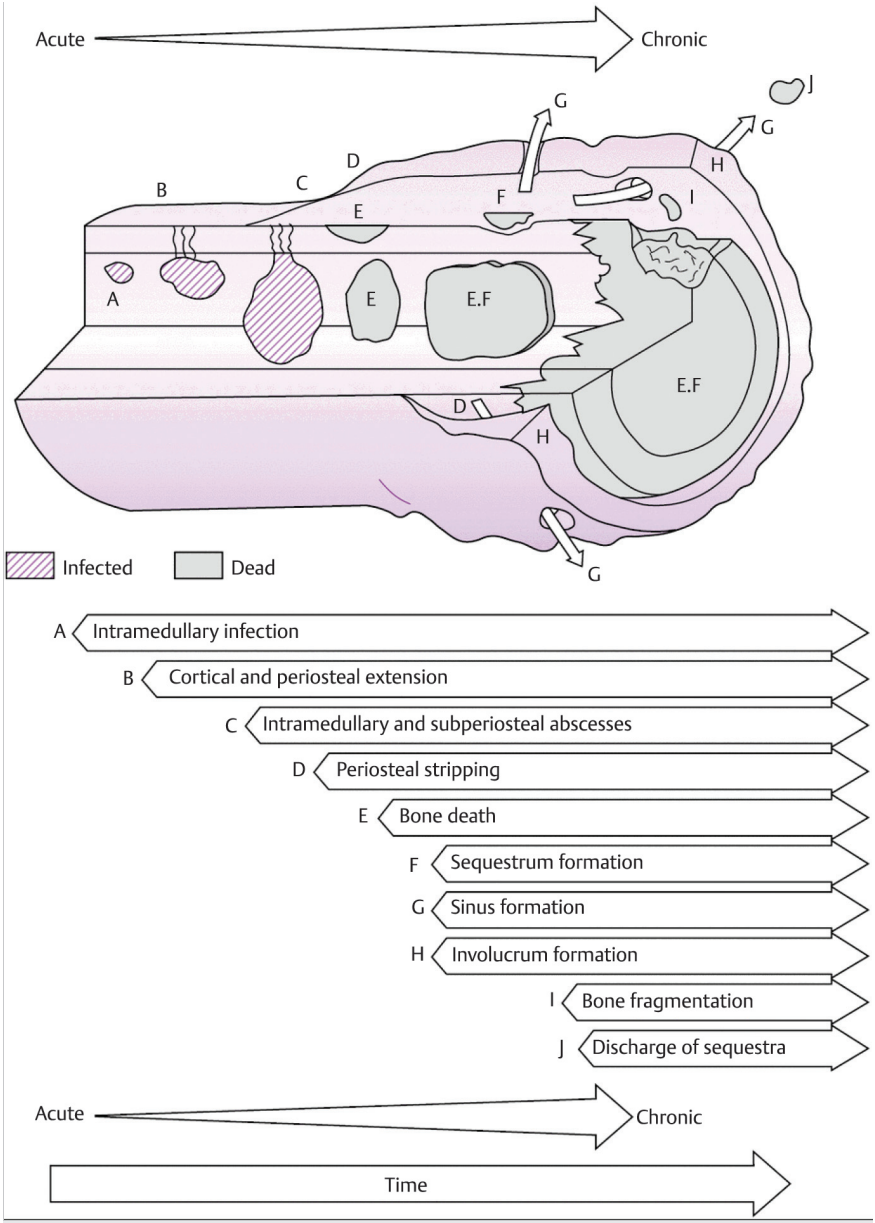

Fig. 5.3 Pathology of osteomyelitis, illustrating the progression from acute to chronic infection, with bone death, sequestration, and sinus formation. (Reproduced from McNally MA, Berendt AR. Osteomyelitis. In: Firth J, Conlon C, Cox T, eds. Oxford Textbook of Medicine. 6th edition. Oxford, United Kingdom: Oxford University Press; 2020:4688–4695 with permission from Oxford University Press.)

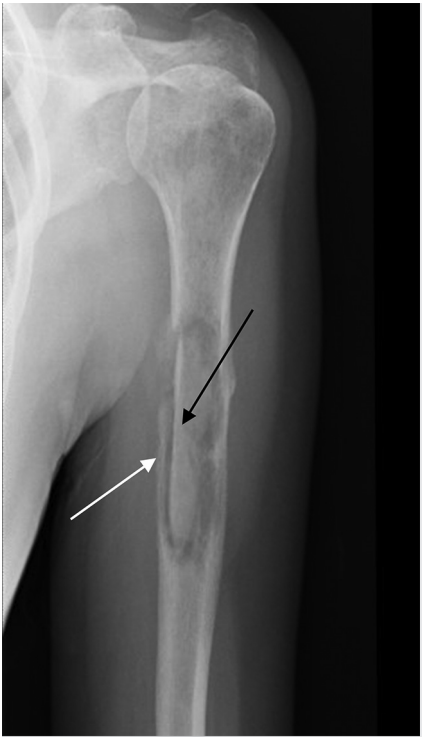

Fig. 5.4 After 6 weeks of the onset of hematogenous osteomyelitis. The peripheral new bone (involucrum) has developed and the central dead bone has separated (sequestrum, *black arrow*). The involucrum is well vascularized and will eventually reform a new humeral diaphysis (*white arrow*).

Table 5.1 The Cierny and Mader classification defines a group of patients (Group B hosts) who have conditions which will adversely affect the treatment options or outcome after surgery

Conditions which compromise the treatment of osteomyelitis	
Local factors in the limb (B_l-host)	**Systemic factors (B_s-host)**
Arterial ischemia	Malnutrition
Venous insufficiency	Diabetes mellitus
Previous surgery	Smoking
DVT	IV drug abuse
Lymphoedema	Hypoxia
Radiation fibrosis	Renal/Liver failure
Tissue scarring	Immunosuppression/Deficiency
Retained foreign material/implants	Malignancy
Osteoporosis	Sickle cell disease
Compartment syndrome	Drug therapy/Allergies
Obesity	Mental illness

5.3.2 Type 2 (Superficial)

In this stage, only the outer part of the cortical bone is affected. It is a contiguous infection arising from an overlying area of skin loss usually following injury, venous insufficiency, burns, or pressure ulceration. Common sites are over the mid-tibia, olecranon, ischial tuberosity, and malleoli.

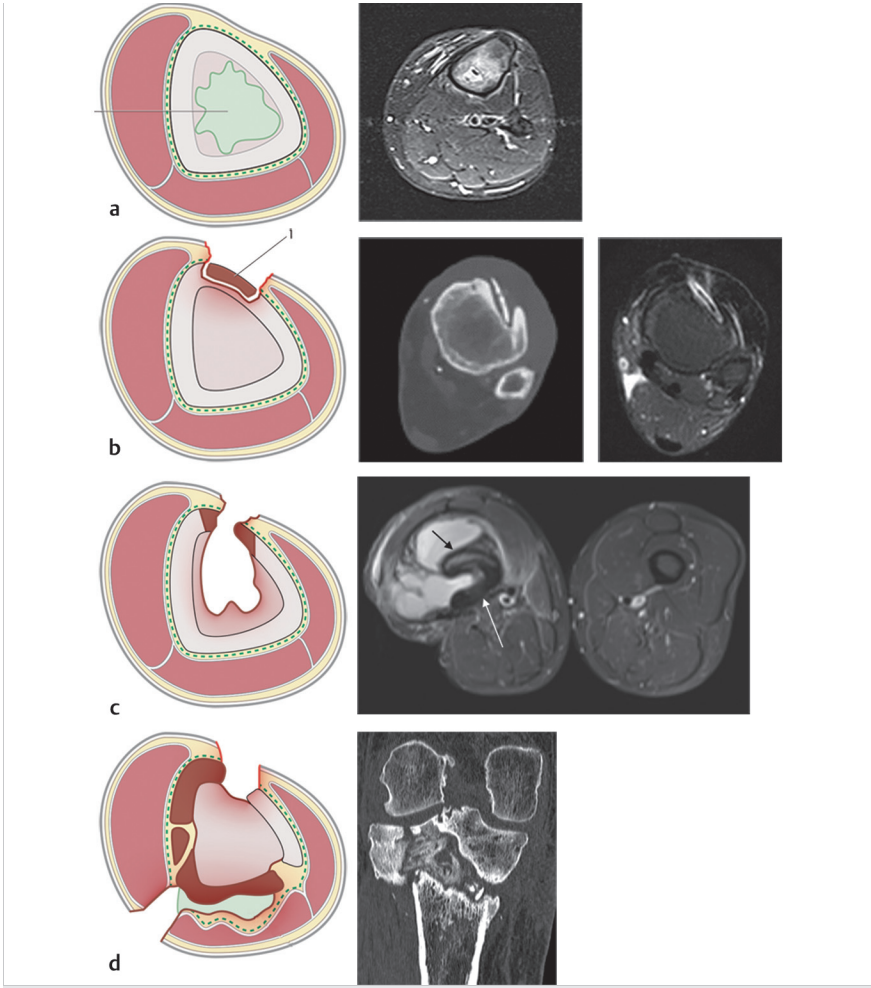

Fig. 5.5 (a–d) The anatomic types of the Cierny and Mader classification for osteomyelitis (with drawings and magnetic resonance imaging [MRI] and computed tomography [CT] pictures). **(a)** Type 1 Medullary. This tibia has a central sequestrum and surrounding edematous cancellous bone. There is no involvement of the cortex and no sinus formation. **(b)** Type 2 Superficial. There is a cortical sequestrum with surrounding new bone formation (involucrum). The magnetic resonance short-tau inversion recovery (MR STIR) image confirms that there is no medullary infection. **(c)** Type 3 Localized. This is the most common type of osteomyelitis in the long bones. There is medullary and cortical involvement, with sinus formation and subperiosteal stripping of the external cortical surface (*black arrow*). The bone remains in continuity, with a healthy bridge of bone crossing the infected zone, seen at the posteromedial aspect of the femur in this MRI scan (*white arrow*). **(d)** Type 4 Diffuse. An entire segment of the bone is infected. All the features of types 1 to 3 are present. (Reproduced with permission from: McNally MA. Infection after fracture. In: Kates SL, Borens O, eds. Principles of Orthopedic Infection Management. AO Trauma Thieme Verlag; 2016:139–165.)

5.3.3 Type 3 (Localized)

This is the most common form of osteomyelitis, usually complicating an open fracture or inadequately treated acute medullary disease. Involvement of the medullary bone and cortex is present, but affects only a part of the circumference of the bone. There is always a healthy bridge of bone crossing the infected zone, which maintains stability.

5.3.4 Type 4 (Diffuse)

This involves the entire circumference of the bone and surrounding soft tissues. All infected fracture nonunions are type 4, and many longstanding hematogenous infections will become diffuse with cortical involvement and extensive subperiosteal abscess formation.

The Cierny and Mader classification has been widely adopted, but it does not include two of the major features of infection that dictate therapy and outcome: the condition of the soft tissues and the microbiological diagnosis. To address this, the BACH classification has been developed (Bone Involvement, Antimicrobial Options, Coverage by Soft Tissue, Host Status) (▶ Fig. 5.6).[11] This has been shown to be easily applied with very high interobserver agreement, and it also correlates with final outcomes in patients after treatment of long bone osteomyelitis.[12] It divides patients into "Uncomplicated," "Complex," and "Limited options for curative treatment." This allows assessing clinicians to identify the components of treatment and to refer complex patients early to specialist infection centers.

	Bone involvement	Antimicrobial options	Coverage by soft tissue	Host status
Uncomplicated	B_1 Cavitary infection without joint involvement (including cortical, medullary and non-segmental cortico-medullary)	A_x Unknown / culture negative osteomyelitis A_1 All isolates: ▪ Sensitive to ≥80% of susceptibility tests and resistant to ≤3 susceptibility tests	C_1 Direct closure possible: Plastic surgery expertise not required	H_1 Well-controlled disease *Or* Patient is fit and well
Complex	B_2 Segmental infection without joint involvement B_3 Any bone infection with associated joint involvement	A_2 Any isolates: ▪ Sensitive to <80% of all susceptibility tests performed *Or* ▪ Resistant to ≥4 susceptibility tests *Or* ▪ Resistant to anti-biofilm antibiotics in the presence of an implant	C_2 Direct closure not possible: Plastic surgery expertise required	H_2 Patient with poorly controlled co-morbidity *Or* Severe co-morbidity (with evidence of end organ damage) *Or* Recurrent osteomyelitis after previous debridement
Limited options		A_3 Any isolates: ▪ Sensitive to 0 or 1 susceptibility test performed		H_3 Unfit for definitive surgery despite specialist intervention *Or* Patient declines surgery

Fig. 5.6 The BACH classification of osteomyelitis.

5.4 Diagnosis

5.4.1 Clinical Features

The diagnosis of any bone infection is primarily clinical. Local signs of inflammation (pain, swelling, erythema, and warmth) are common, but systemic upset is variable and may be absent, even in acute cases. Around 50% of children with hematogenous osteomyelitis present without fever after a period of up to 3 months of vague limb symptoms.[13]

Chronic infection may be even more difficult to diagnose. Pain unrelated to activity is the only common symptom, but is rather nonspecific. Acute systemic upset is less prominent but many report fevers, rigors, sweating attacks, and anorexia occurring with flare-ups of the disease.

Examination reveals bony tenderness, subtle swelling, or increased temperature. In recurrent chronic osteomyelitis, there may be signs of old healed sinuses, active discharging sinuses, soft-tissue abscesses, or scars from previous surgery or injury.

Although acute osteomyelitis can produce major systemic illness with potential mortality, chronic disease is less dramatic, but equally life-changing. Chronic osteomyelitis, with recurrent need for medical treatment, poor general health, with or without sinus drainage, and ongoing pain, can result in unemployment and social isolation. Such patients have been shown to have a high risk of depression and other mental illness.[14]

5.4.2 Laboratory Tests

There are no specific blood tests that can confirm or exclude the diagnosis of bone infection. In acute presentation, the serum white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) levels may be raised due to osteomyelitis or other comorbidities or infection, but they are often normal in chronic infection. In children, the combination of CRP and ESR gave the best sensitivity (98%) for diagnosis of osteoarticular infection.[13,14]

If the patient is pyrexial, blood cultures should always be taken before administration of antibiotics.[13] Around one-third of children with acute osteomyelitis will have positive blood cultures.[13]

Atypical infection with *Brucella*, *Bartonella*, or *Spirochetes* (syphilis and yaws) can be diagnosed with blood serology.

5.4.3 Imaging

Plain radiology remains the best screening test for bone infection (▶ Fig. 5.7a). Initially, the X-ray may be normal but within 5 to 7 days, localized osteopenia, bone destruction, cortical breeches, periosteal reaction, and involucrum become apparent. Sequestra may be seen at around 10 days. During treatment, disuse of the limb produces generalized radiographic osteopenia. Any residual dead bone will remain radiodense, as avascular bone cannot be demineralized, and will become more obvious with time.

Contrast sinography is indicated when there is any concern about extension of the infection to an implant or internal viscera. In pelvic osteomyelitis, sinography or retrograde urethrocystography can diagnose fistulas between the bone and bladder or bowel, which is often seen following radiotherapy for bladder or prostate cancer, or in patients with inflammatory bowel disease.

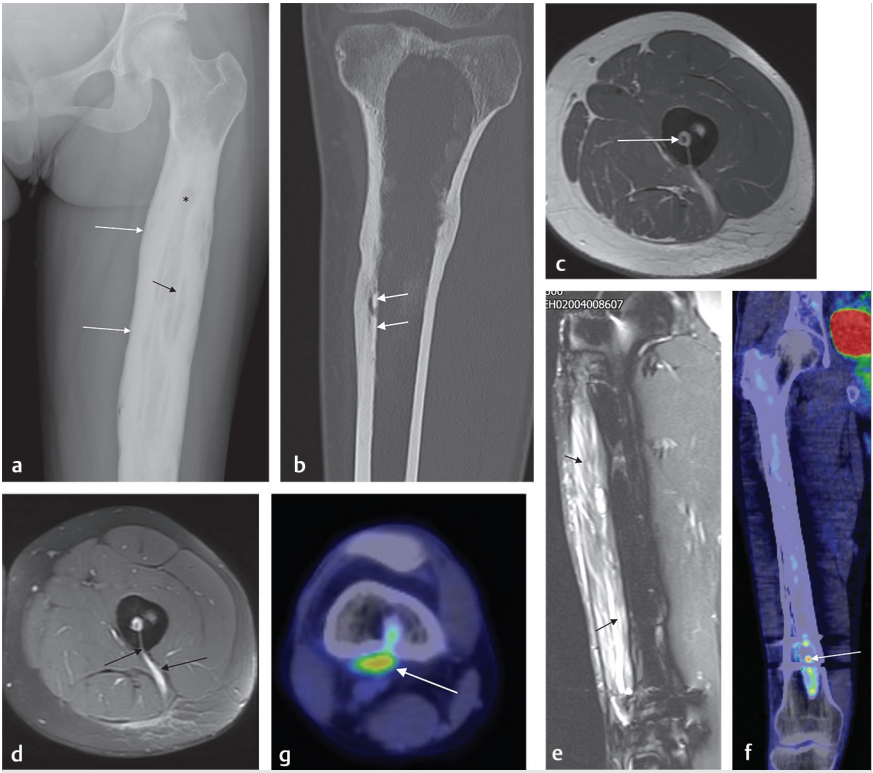

Fig. 5.7 (a–e) Imaging modalities for osteomyelitis. **(a)** This plain X-ray shows features of chronic osteomyelitis with central sequestration (*black arrow*), bone lysis (*asterisk*), and mature involucrum formation (*white arrows*), causing thickening of the cortex. **(b)** Computed tomography (CT) of a tibia with extensive medullary osteomyelitis, previously treated with reaming. The residual endosteal sequestra (*white arrows*) are seen as radiodense areas under the thickened cortex. **(c)** Short-tau inversion recovery (STIR) and **(d)** T2 magnetic resonance imaging (MRI) images show central osteomyelitis with a sequestrum (*white arrow*), posterior cloaca, and sinus track (*black arrows*) to the subcutaneous tissue and a secondary area of bone lysis in the femur. Sinuses typically take the "route of least resistance" between muscles, along the intermuscular septum. **(e–g)** In this case of infection around an intramedullary nail, the MRI scan **(e)** shows the lateral soft-tissue inflammation well (*black arrows*) but cannot identify the area of bone involvement due to metal artefact. ^{18}FDG PET-CT **(f)** coronal and **(g)** axial views show the medullary infection around the nail and demonstrate a cloaca passing posteriorly, forming a subperiosteal abscess (*white arrows*).

Ultrasound is invaluable for early identification of soft-tissue abscesses and joint effusions. It also allows for guided biopsy of infected areas and limited drainage of painful subperiosteal collections.

Computed tomography (CT) can identify bone destruction and periosteal reaction early, but is not diagnostic for osteomyelitis. Fine-cut CT can identify small sequestra and aid in the design of limited surgical approaches to excise disease (▶ Fig. 5.7b).

Magnetic resonance imaging (MRI) is the investigation of choice in osteomyelitis. It is highly sensitive for diagnosis (>99%), and a normal MRI almost excludes bone infection.[15]

It can show early medullary changes and define the extent of the infection around bone in the soft tissues. In T2-weighted images, water is bright and the MRI may show extensive areas of high signal in the medulla. This may overestimate the extent of the infection, as some of the peripheral high signal may be due to reactive edema. Short-tau inversion recovery (STIR) images are more sensitive in demonstrating fluid in osteomyelitis (▶ Fig. 5.7c, d). T1 images show good anatomical detail and can also identify cortical bone involvement. Usually, cortical bone (normal, infected, or dead) appears black on all MRIs, but subtle changes on the bone surface or in the adjacent soft tissues can suggest type 2 cortical osteomyelitis.

MRI specificity is limited by the presence of metal implants and is affected by recent surgery.[16] Artifact reduction techniques have been investigated,[17] but the images are still difficult to interpret, particularly for surgical planning. Postoperative MRI changes may persist for many months and can be difficult to distinguish from recurrent infection. It should not be used to monitor response to treatment.

Bone scintigraphy has been advocated with bone tropic isotopes (^{99m}Tc or ^{68}Gallium Citrate). Although these tests exhibit high sensitivity for infection, they are nonspecific and lack resolution. ^{111}In or ^{99m}Tc-labelled WBC scintigraphy and antigranulocyte antibody scintigraphy have been shown to be accurate for the diagnosis of FRI, but anatomical resolution remains poor.[18]

More recently, new camera systems have allowed nuclear techniques, such as single photon emission computed tomography (SPECT) or fluorodeoxyglucose positron emission tomography (^{18}FDG-PET), to be combined with localizing scans (CT or MRI) giving excellent diagnostic accuracy and good resolution, even in the presence of metal implants.[15,16] ^{18}FDG-PET with CT scanning is quicker and more convenient for patients. It allows very good visualization of dead bone and clearly defines areas of active infection. It is difficult to interpret within 1 month of injury or surgery, whereas WBC scintigraphy may be more accurate.[18] ^{18}FDG-PET with CT is very valuable in surgical planning, particularly when MRI is not available or when metal implants are present (▶ Fig. 5.7e–g). ▶ Fig. 5.8 summarizes the use of imaging in diagnosis and surgical planning.

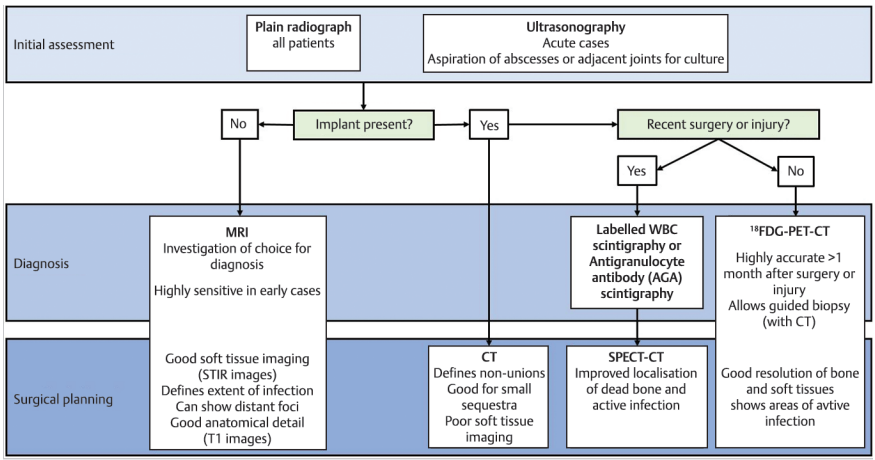

Fig. 5.8 The use of imaging modalities in the diagnosis and surgical planning of osteomyelitis.

5.4.4 Microbiological Diagnosis

The gold standard diagnostic test for osteomyelitis is microbiological culture of the infecting organism from two or more deep tissue specimens, taken with strict aseptic precautions in a patient who has not received any antimicrobial agent for at least 10 days.[19,20] There is no place for culture of superficial swabs from sinus tracts or ulcers. Culture of this tissue correlates poorly with the flora obtained from deep samples.

Aspiration of deep fluid collections, guided percutaneous bone biopsies, and blood cultures may all give an accurate microbiological diagnosis, especially in acute osteomyelitis and diabetic foot disease. They are mandatory if a patient is to be treated without surgery, in order to direct appropriate antimicrobial therapy. In chronic osteomyelitis and implant-related infection, bacteria are often sparsely distributed in the tissues in low numbers. Therefore, culture-negative biopsies are common.

Sampling technique must be performed fastidiously during surgery to avoid contamination by using new instruments for every sample. It is recommended that a sterile instrument kit be prepared to collect samples. At least five separate deep tissue samples should be taken and transferred to the laboratory without delay. The sensitivity of diagnosis is greatly affected by the number of samples taken.[19,21] It has been recommended that prolonged aerobic and anaerobic cultures (14 days) should be performed to allow for growth of low-grade organisms, such as *Cutibacterium acnes*. However, with the advent of BACTEC automated cultures in broth, over 99% of organisms should be identified within 10 days.[22] Bacterial identification is now rapidly achieved when matrix-assisted laser desorption/ionization-time of flight (MALDI-TOF) mass spectrometry is available,[23] with results within minutes of a single colony being visible in culture.

When atypical infection is suspected, due to factors such as recent foreign travel, unusual clinical features, and animal bites, special culture techniques may be needed. Very long culture (6 weeks) is required to isolate tuberculosis (TB) and low temperature cultures may be needed for some nontuberculous *Mycobacteria.* Immunocompromised patients and those with open wounds treated previously with negative-pressure wound therapy (NPWT) should have cultures for fungi and other unusual organisms, which should also be held for 6 weeks.

Sonication enhances diagnosis in prosthetic joint infection (PJI) by liberating organisms from biofilm on implants. It can also be applied in osteomyelitis and FRI. Sonication is only effective on hard materials, so sonication of samples of infected cortical bone or sequestra are ideal.[19,21]

Molecular studies have been widely investigated in PJI, but there is limited data for osteomyelitis. Detection of the bacterial 16S ribosomal RNA gene with sequencing of the DNA and multiplex polymerase chain reaction (PCR) have been applied with reasonable results.[24] However, more recently, whole genome sequencing of bacterial DNA may be a better technique.[25] All molecular techniques give little information on antimicrobial resistance and cannot be used alone in treatment planning.

5.4.5 Histological Diagnosis

Osteomyelitis due to *Mycobacterium tuberculosis*, fungi, or actinomycosis can be diagnosed on histology alone, with direct visualization of organisms. In other cases, the di-

agnosis relies on identifying an acute neutrophilic inflammatory infiltrate. In acute infections, Gram staining may reveal organisms in tissues, but this is rare in chronic disease. Histology is valuable in cases with negative cultures by the demonstration of multiple features of inflammation.[26]

Histological tissue should be examined after hematoxylin and eosin staining. At least 10 fields should be examined at high-powered (× 400) magnification. The presence of an average of more than five neutrophils per high power field has been shown to be highly accurate in diagnosing infection in fracture nonunions. The complete absence of any neutrophils almost excludes infection.[27]

5.5 Diagnostic Criteria

Many inflammatory conditions, such as rheumatoid disease or endocarditis, have established criteria for diagnosis. In osteomyelitis, this is not the case. The International Consensus Group on Fracture-related Infection has developed good criteria for FRI that are valid in osteomyelitis.[7,20] Osteomyelitis can be considered to be present if:

- Phenotypically identical organisms are grown from two or more separately harvested deep tissue samples.
- An average of five or more neutrophils are seen per high-powered field (× 400 magnification) on histology (usually 10 fields are reviewed).
- There is a draining sinus from the bone or pus is drained during surgery.

Clinical signs without sinuses, positive nuclear imaging, elevated serum biomarkers, or a single positive microbiological culture are suggestive of infection, but do not confirm the diagnosis.

5.6 Microbiology

Hematogenous osteomyelitis is most frequently caused by *Staphylococcus aureus* in both adults and children, accounting for around half of vertebral infections and one-third of appendicular infections. Many other organisms can cause bone infection, particularly in immunocompromised patients (▶ Table 5.2).

Tuberculous osteomyelitis accounts for 2% of tuberculosis cases worldwide, with half affecting the vertebral bodies. Biopsy should be taken for histology and mycobacterial culture, with surgery reserved for stabilization or compromise of adjacent structures. HIV testing must be offered.

Contiguous infections arising from injury or after surgery, or chronic infections with a sinus, are often polymicrobial. Antibiotic exposure increases the risk of multidrug-resistant infection including vancomycin-resistant *Enterococci* (VRE), extended spectrum beta-lactamases (ESBL), and carbapenemase-producing *Enterobacteriaceae* (CPE).

There is concern with increasing reports of multidrug resistant bacterial strains and some pan-resistant organisms. Methicillin resistant *S. aureus* (MRSA), methicillin resistant *S. epidermidis* (MRSE), and VRE have been detected in osteomyelitis and FRI cases. They are more common after prolonged periods of open wound treatment in hospital, the use of NPWT for more than 7 days, and inappropriate use of recurrent courses of empiric antibiotics.

Table 5.2 The common organisms which cause osteomyelitis

Organism type	Bacterium	Acute hematogenous osteomyelitis	Chronic osteomyelitis (hematogenous, contiguous focus, postoperative and metalwork-associated)	Chronic osteomyelitis (Type B hosts and diabetic foot infection—frequently polymicrobial)
Gram positive	*Staphylococcus aureus*	+++	+++	+++
	Staphylococcus epidermidis and other coagulase-negative staphylococci	+	++	+
	Streptococcus pyogenes and other beta-hemolytic streptococci (Groups A, B, C, and G)	++	+	++
	Other streptococci	++	+	+++
	Enterococcus spp.		++	++
	Corynebacterium striatum and other corynebacteria		+	++
	Cutibacterium spp.		Especially upper limb and spinal infection	
	Clostridium and other gram-positive anaerobes		+	++
Gram negative	*Haemophilus*, *Kingella*, and other respiratory gram-negative rods	Usually associated with adjacent septic arthritis		
	Brucella spp.	Should be considered in case of travel history and systemic symptoms; warn laboratory		
	E. coli and other intestinal gram-negative bacteria	Neonatal infection	++	+++
	Bacteroides spp. and other gram-negative anaerobes		+	++
	Pseudomonas spp.		+	++

Table 5.2 (*Continued*) The common organisms which cause osteomyelitis

Organism type	Bacterium	Acute hematogenous osteomyelitis	Chronic osteomyelitis (hematogenous, contiguous focus, postoperative and metalwork-associated)	Chronic osteomyelitis (Type B hosts and diabetic foot infection—frequently polymicrobial)
	Burkholderia pseudomallei	Consider in unwell returning traveller from Southeast Asia or Northern Australia; warn laboratory		
Requires special laboratory testing	*Actinomyces*, *Nocardia*, and *Streptomyces* (bacteria); environmental fungi			Madura foot; infection does not respect tissue planes
	Non-TB mycobacteria			+
	Mycobacterium tuberculosis	+	Consider even if there is no prior pulmonary disease, especially if systemic symptoms are present; warn laboratory	
Fungi	*Candida* spp.	May occur in context of candidaemia in compromised patients	Seen after prolonged use of negative-pressure wound therapy	+

5.7 Treatment of Osteomyelitis

Identification of the cause of infection, disease classification, and an understanding of the pathogenesis of the condition allows for planning of treatment for individual patients. There is no single antibiotic regime or surgical procedure that is appropriate for all patients. ▶ Fig. 5.9 summarizes the principles of treatment of osteomyelitis.

5.7.1 General Considerations

Bone infection is an ideal condition for treatment with a multidisciplinary team. This principle has been highly developed in bone sarcoma management, which shares many of the complexities of osteomyelitis.

The first management decision is where the treatment should be performed. The BACH classification has shown that simple cavitary osteomyelitis caused by sensitive

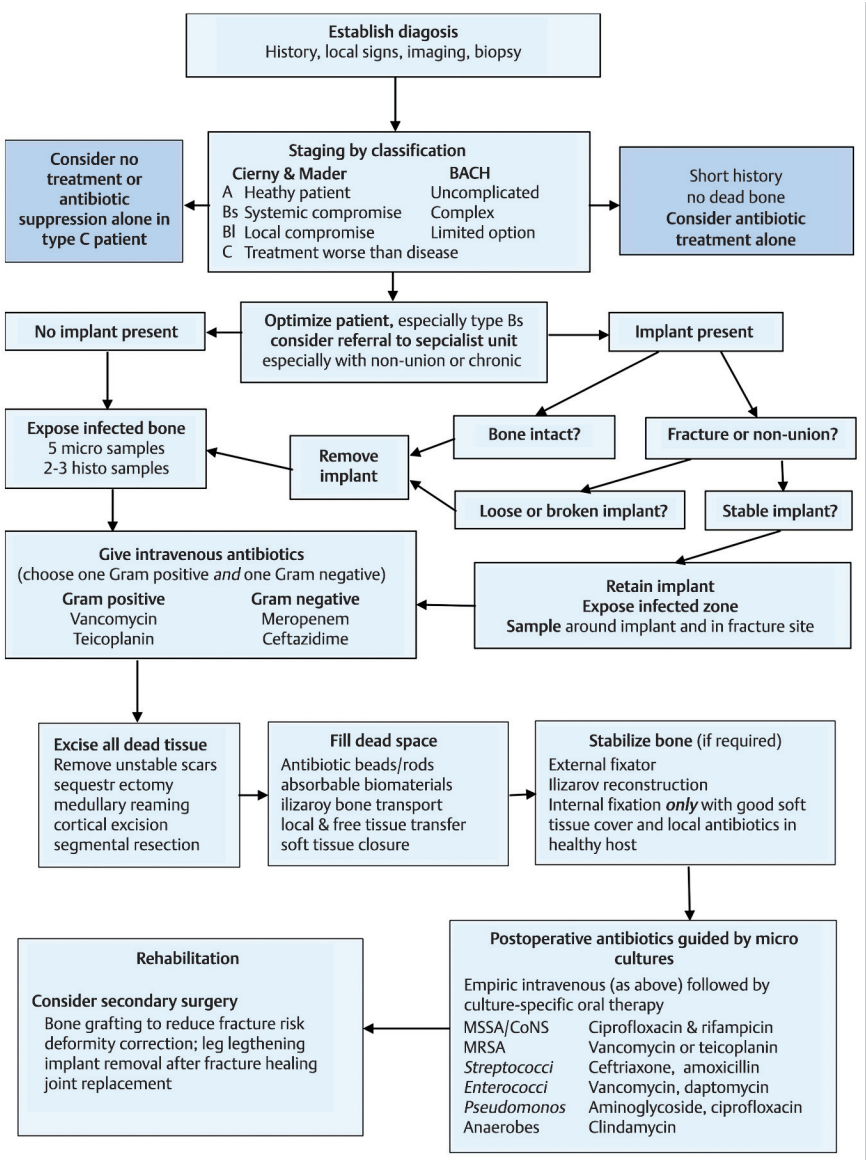

Fig. 5.9 Management of osteomyelitis.

bacteria in patients without major systemic illness can be safely and effectively managed in many centers. More complex infections, multidrug resistant infections, and all recurrent infections should be referred to a specialist center. Segmental, diffuse osteomyelitis, infected nonunions, and pelvic bone osteomyelitis should only be treated by dedicated bone infection teams.

5.7.2 Acute Osteomyelitis

It is appropriate to treat acute bone infection with antibiotics alone when the following criteria have been met:

- Diagnosis confirmed within a few days of the onset of symptoms.
- No dead bone seen on imaging.
- Rapid systemic response to drug treatment (no ongoing fever after 48 hours).
- No adjacent septic arthritis.
- Tuberculous osteomyelitis.
- Vertebral osteomyelitis without cord compression.

Treatment should begin rapidly with administration of high dose antibiotics after blood culture. Empiric antibiotics should be targeted at mainly gram-positive organisms (*S. aureus*, *Streptococci*) and gram-negative rods, such as *E coli*. Cephalosporins or flucloxacillin is recommended. Benzylpenicillin should be added for children not immunized against *H. influenzae*. Gentamicin is advocated in children under 1 year as gram-negative coverage. Vancomycin should be substituted if there is the possibility of MRSA infection and clindamycin when a penicillin allergy is present.

The limb should be rested, good analgesia given, and comorbidities addressed.

Definitive microbiology allows for early conversion to specific oral antimicrobial therapy in the majority of cases. Treatment should continue for 2 to 3 weeks in uncomplicated cases.

If the patient does not respond rapidly, the limb deteriorates, or there is imaging evidence of progression of disease, surgery is indicated to prevent bone destruction and the onset of chronic osteomyelitis.

Acute mycobacterial osteomyelitis will require targeted multidrug therapy, guided by local infectious disease protocols. Treatment should continue for many months.

Over 90% of children treated early for acute osteomyelitis recover completely.[5] Acute osteomyelitis may be complicated by concurrent septic arthritis, deep vein thrombosis, and septicemia. Older children are at greater risk of local complications, including abscess formation; fever is an adverse prognostic sign.[5,13,28] Surgical drainage is more likely to be required in children presenting with more severe illness. Elevated respiratory rate and CRP were able to predict the need for surgery in one prospective cohort.[28]

5.7.3 Chronic Osteomyelitis

In chronic osteomyelitis, there is rarely any need for rapid treatment. There is time for preoperative assessment, completion of investigations, involvement of other specialists, and planning of interventions, all within an outpatient setting. Antibiotics should be stopped at least 2 weeks before surgery to improve bacterial yield in cultures. Drugs which adversely affect wound or bone healing (steroids, nonsteroidal anti-inflammatories, cytotoxics) should be stopped, if possible. A successful outcome will only be achieved with delivery of a series of components of care that are directed at all aspects of the patient condition. Definitive treatment, aimed at curing the chronic infection, must include surgery.

Curative treatment may involve extensive surgery and prolonged time in treatment. For some patients (particularly those with limited treatment options), suppressive antibiotic therapy, which allows arrest of the current symptoms but with the potential for later recurrence, may be more acceptable. This is a common approach in FRI, when the fracture is stable and there is good potential for fracture healing and later definitive

implant removal and cure of infection. Guided biopsy of the infected bone may give added information for the selection of appropriate antimicrobial therapy.

Occasionally, patients may elect to have long-term antibiotic suppression to keep symptoms at bay, rather than have surgery aimed at disease eradication. Drugs with high bone bioavailability are needed. Clindamycin or ciprofloxacin with rifampicin has been advocated when the organism is sensitive. Rifampicin has very high bone penetration but should never be used alone and is better reserved for curative treatment after surgery.

The effectiveness of suppressive management in osteomyelitis is not well reported in the literature, and surgeons should be aware that the health status of a patient can change. There is little evidence concerning the duration of antibiotic therapy or the rate of later recurrence and the need for surgery.

Amputation is often considered as a simpler and effective method of eradicating chronic osteomyelitis. However, in a series of 482 lower limb amputations, 17% had recurrence of infection[29] and not all patients are able to tolerate prostheses.

The components of care include:

- Preoperative:
  - Clinical and diagnostic assessment and classification of disease (uncomplicated, complex, limited options).
  - Patient values-based discussion of treatment options and potential outcomes.
  - Optimization of compromised hosts and treatment of comorbidities.
- Operative:
  - Multiple, uncontaminated deep bone and tissue sampling.
  - Excision of all dead or poorly perfused tissue.
  - Empiric IV antibiotics after sampling.
  - Bone stabilization (if required).
  - Dead space management.
  - Closure of the soft tissues.
- Postoperative:
  - Continued antimicrobial therapy guided by culture results.
  - Functional rehabilitation.
  - Monitoring for early recurrence or adverse events.
  - Second-stage reconstruction (if required).

Optimization of patients with complex comorbidities can be challenging. Efforts should be focused on nutrition optimization, smoking and drug cessation, correction of anemia, blood glucose control, and psycho-social support. In patients with HIV, viral load should be reduced before surgery. Limb vascularity is paramount for successful surgery. Magnetic resonance scanning with angiography (MRA) may be helpful to identify arterial lesions amenable to angioplasty proximal to infected zones and define suitable recipient vessels for soft-tissue transfer.[30]

5.7.4 Operative Treatment

Surgery is performed under tourniquet when possible, to allow for good visualization of dead bone. It is not necessary to release the tourniquet to assess bone bleeding. Regional anesthesia with peripheral nerve blocks or spinal/epidural techniques allows for good pain relief and rapid postoperative recovery.[31] Antibiotics are withheld at the start of surgery and only given after tissue sampling. Surgical approaches should be

designed to limit damage to unaffected parts of the limb and to avoid stripping periosteum from healthy cortical bone.

5.7.5 Tissue Sampling

Microbiological samples are not taken from around a skin sinus. If a longstanding sinus is present, it should be excised and sent for histology, to exclude squamous carcinoma.

Sampling should deliver a series of representative and uncontaminated pieces of tissue to the laboratory, which can be relied upon for diagnosis. Specimens should be taken early in the operation. Surgeons should not put their hands in the wound during sampling.

At least five samples of bone and soft tissue should be taken for microbiological culture and two to three samples for histology (**Video 5.1** and **Video 5.2**).[21] Pus can be aspirated and sent for culture. Each sample is harvested with a separate instrument, which has not been used elsewhere in the operation, and has not touched the patient's skin. It is helpful to have a simple "specimen set" to aid clean sampling (▶ Fig. 5.10). Metal implants can be sent for sonication, together with pieces of cortical bone.[19] In general, small metal implants are easier to handle. Intramedullary nails or large plates will often be contaminated during extraction, rendering sonication less useful.

Bacteriology samples should be transferred promptly, and the laboratory should be given clear clinical details to help decide if any special culture techniques are required or atypical organisms are suspected.

5.7.6 Tissue Excision

After sampling, the initial exposure may be extended to allow for effective tissue excision. All adherent skin and scarred soft tissues around the wound should be removed. It is not necessary to remove all tissue that may be infected. Well-vascularized tissue containing bacteria can be treated adequately with antimicrobials. This is the basis of most infection treatment (chest infections, ear infections, etc.). Surgery is required to remove dead material that can harbor biofilm and prevent antibiotic penetration, and any poorly perfused tissue that can inhibit wound healing.

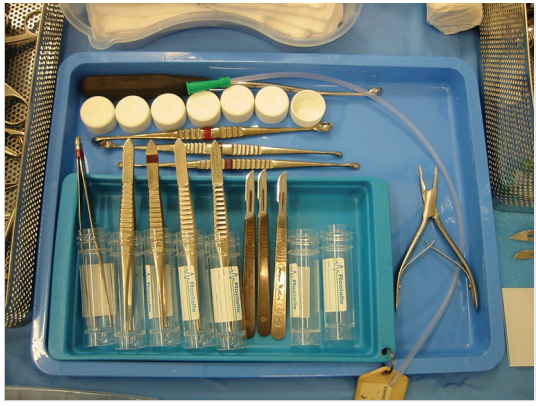

Fig. 5.10 The Oxford specimen set. This simple set allows for collection of five samples for microbiology and two for histology, all taken with separate instruments.

If sinuses are present, they are excised with an ellipse of skin and traced through the limb to the cloaca in the bone. They may have a complex, branching shape and can be difficult to fully excise.

Bone excision must be planned based on the anatomic location of dead bone and with an understanding of the patterns of osteomyelitis (▶ Fig. 5.5). Careful review of preoperative imaging will target the surgical excision. Distinguishing dead from living tissue requires experience. Living bone will exhibit the "Paprika Sign" with punctate bleeding over the surface when cut. Dead cortex is usually brittle and often yellowish in color. It splits when cut with an osteotome. Healthy bone will curl up (like a wood shaving) under a chisel.

In hematogenous medullary osteomyelitis, the dead bone can be excised through a metaphyseal cortical window, created with a slow-speed, cooled drill. The medullary contents are removed as samples. The canal is then reamed above and below the lesion. There is often a layer of dead bone on the inner surface of the cortex (*endosteal sequestrum*) (▶ Fig. 5.7b) that must be removed. Metaphyseal infection will require more extensive resection, with curettes and osteotomes. If the disease is confined to the isthmus of the bone, reaming from one end may allow full excision of the diseased bone without a cortical window. However, it is important to remove all debris in the canal after reaming and this may only be possible with a distal cortical opening.

It is a mistake to consider infection after intramedullary nailing as a purely medullary infection. Usually, there will be dead bone around the locking screw sites with areas of biofilm or dead bone at the fracture site. This will require open excision of these areas, together with medullary reaming (▶ Fig. 5.7f, g).

Cortical osteomyelitis is often a reflection of severe compromise of the overlying skin with bone exposure. Prior to surgery, an MRI can define the extent of dead bone involvement and particularly confirm the absence of any medullary infection (▶ Fig. 5.5b). Resection is performed after skin removal with sharp chisels, down to a healthy bleeding surface. It may not be necessary to remove the full thickness of the cortex.

Excision of cavitary osteomyelitis must be carefully planned to avoid removing the healthy section of bone that maintains stability (▶ Fig. 5.11). The cavity is approached by extending cloacas, or by creating windows through the thinnest part of the cortex. Cooled drills and osteotomes are used to make oval windows in the bone. Sharp corners will predispose to postoperative fractures and should be avoided.

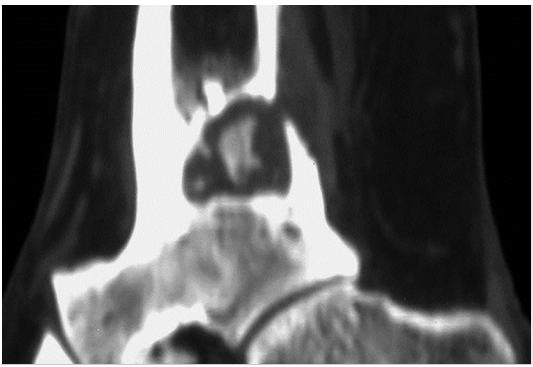

Fig. 5.11 This ankle fusion was complicated by osteomyelitis. The computed tomography (CT) shows that the sequestrum lies in the central medulla but the cortical bone loss is posterior. Approaching this infection through the previous anterior incision would have removed the viable bone maintaining stability.

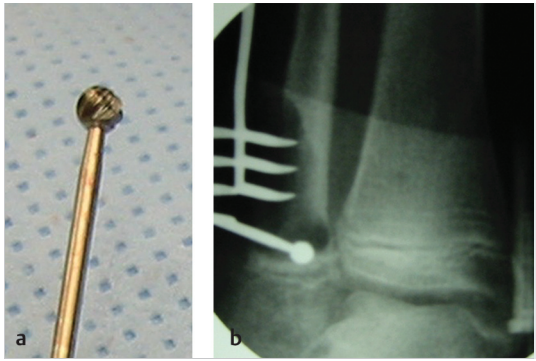

Fig. 5.12 A cooled bone burr **(a)** can facilitate removal of dead bone in this fibular metaphyseal osteomyelitis **(b)** in a child. The burr can be used with fluoroscopic imaging to allow safe resection close to the growth plate.

These infections require a systematic approach, starting at one end of the cavity and progressing patiently, ensuring removal of all dead bone. This is best achieved with sharp osteotomes, but a cooled bone burr may be helpful in small spaces, close to joint surfaces, or around physes (▶ Fig. 5.12). Excision should continue until the surface bleeds ("Paprika Sign"). The medullary canal should be opened above and below the cavity, but it is not necessary to ream into healthy medullary bone.

Diffuse osteomyelitis will require a segmental resection to eradicate the infection. This may also include excision of an adjacent joint. It is often helpful to apply an external fixator before excision to maintain length and alignment.

The most difficult decision in osteomyelitis surgery is to know when to stop resection. There are no imaging or other tests which can aid this. Experience is needed. At the end of a good excision, the macroscopic dead bone is gone, but there will be small, perhaps microscopic, areas of biofilm and dead bone remaining, with many planktonic bacteria. The management of this "imperfect surgery" requires effective delivery of high dose antimicrobials into the bone defect.

5.7.7 Antimicrobial Therapy

After sampling, high dose empiric antibiotics should be given intravenously. During surgery, the microbiology is rarely known with certainty, so a broad antibiotic regime must initially be used, such as IV vancomycin with meropenem. This regimen has been shown to cover 97.8% of the pathogens in a large series of cases over a 10-year period in a single institution.[32] However, it is only used until a culture-specific regimen can be determined, which is usually possible within 7 days. The recent Oral Versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA) trial showed that over 95% of patients can be safely changed to an oral drug combination.[32,33]

Empiric antibiotics are used to treat the inevitable bacteremia that follows operative intervention and to kill bacteria in planktonic state around the bone and soft tissues. There is good evidence that systemic administration delivers low levels of drug below the minimum inhibitory concentration (MIC) in bone cavities or areas of hematoma (dead space) after surgical excision.[34] If systemic antibiotics are used alone, this may predispose the patient to recurrence and antimicrobial resistance.

The optimal duration for antimicrobial therapy is not known. After complete segmental resection, 2 weeks of therapy may be sufficient to manage the residual soft-

tissue contamination. Longer courses are often advised, particularly when implants are retained or used to stabilize infected nonunions. In general, 6 weeks is usual for cases without implants, extending to 12 weeks with implants or with suboptimal resection.

5.7.8 Dead Space Management

Reduction of the residual bacterial load is achieved by physical washing of the cavity using an antiseptic- or detergent-based solution, such as 0.05% aqueous chlorhexidine (**Video 5.3**). Antibiotic solutions are not recommended.

Delivering adequate levels of antibiotics into the dead space requires either the placement of well perfused tissue into the defect, or direct implantation of local antibiotics into the space.

The best void filler is living tissue, and this is usually all that is required for superficial, cortical defects. However, filling a deep defect with muscle will prevent bone ingrowth and increase the risk of fracture. Secondary bone grafting may be needed.

Previously, polymethylmethacrylate (PMMA) cement was used as the main carrier of antibiotics, either as beads, rods, or as a coating on implants. It remains the carrier of choice in staged segmental reconstructions using the Masquelet technique.[35] Now, there is an increasing interest in bioabsorbable antibiotic carriers. They can deliver levels of antibiotic that are above the minimum biofilm eradication concentration (MBEC) for 2 to 3 weeks after surgery, without systemic toxicity.[36] Calcium sulfate is the main constituent, but the addition of hydroxyapatite nanocrystals has been shown to promote better bone formation in the defect, reducing fractures and avoiding secondary bone grafting.[37,38]

Generally, aminoglycosides (gentamicin or tobramycin) have been used in local delivery, but glycopeptides (vancomycin) and others can be added. Rifampicin should not be used locally in bone.

The Oxford Bone Infection Unit Protocol for dead space management uses a combination of techniques and void fillers to achieve the goals of adequate antibiotic delivery, prevention of hematoma, and promotion of bone formation in cases with loss of cortical bone (▶ Table 5.3).

This protocol has been evaluated in over 900 patients (including >150 segmental defects) and has allowed eradication of infection in 95.6% of patients at 1 year after surgery (mean follow-up 21 months; range 12–61 months).[39] In many cases, a combination of techniques can be used to fill defects; for example, after nail removal, acute shortening can be performed after resection of the infected nonunion, or calcium sulfate pellets can be placed in the medullary canal and a local flap used to cover the skin defect (▶ Fig. 5.13, **Video 5.4**).

5.7.9 Bone Stabilization

It is essential to provide bony stability to help achieve eradication of infection and effective rehabilitation. This is obvious for segmental defects, but some cavitary defects will need mechanical support to prevent postoperative fracture, which has been reported in between 5 and 14% of patients.[36]

External fixation is a safe method for bone stabilization in osteomyelitis. Fixators can bridge large defects and allow for full weight-bearing. Adjacent joints can be crossed with a fixator. However, fixators are inconvenient for patients and can predispose patients to pin site infections, particularly in immunocompromised hosts.

Table 5.3 The Oxford protocol for dead space management

Bone defect	Defect filler	Rationale
Medullary	Calcium sulfate pellets with aminoglycoside*	Bone formation is not needed and the carrier delivers high dose antimicrobials
Cortical	No local antibiotic required; good soft tissue over defect with direct closure or muscle flap is essential	Systemic antibiotic can be delivered to the healthy bone surface by soft tissues
Cortico-medullary	Calcium sulfate and hydroxyapatite with gentamicin and vancomycin§	This bioceramic fills the cavity, preventing hematoma formation, giving very high antibiotic levels, and promoting bone remodelling
Segmental		
1–2 cm defect	Acute shortening	Rapid removal of the dead space
2–5 cm defect	Acute shortening with gradual relengthening at a distant corticotomy (bifocal compression/distraction)	Rapid removal of the dead space, with simultaneous length restoration
>5 cm defect	Bone transport in femur and tibia Free fibular graft in upper limb	Reliable defect management with import of healthy vascularized tissue

* Herafill with Gentamicin or Osteoset with Tobramycin.
§ Cerament G and Cerament V.

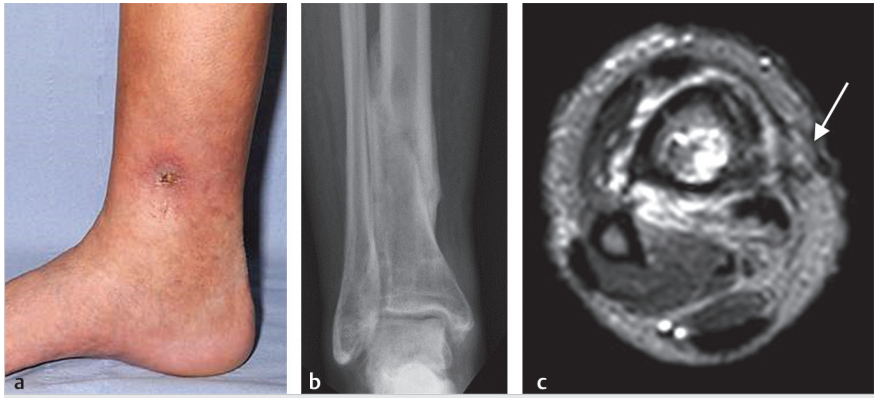

Fig. 5.13 (a–j) This 51-year-old woman suffered an open fracture of the tibia that was treated with an intramedullary nail. The fracture healed, but she remained with a draining sinus **(a)** after nail removal and reaming. The X-ray **(b)** and magnetic resonance imaging (MRI) **(c)** scan confirmed the areas of bone loss and cortico-medullary osteomyelitis, with a medial sinus (*white arrow*).

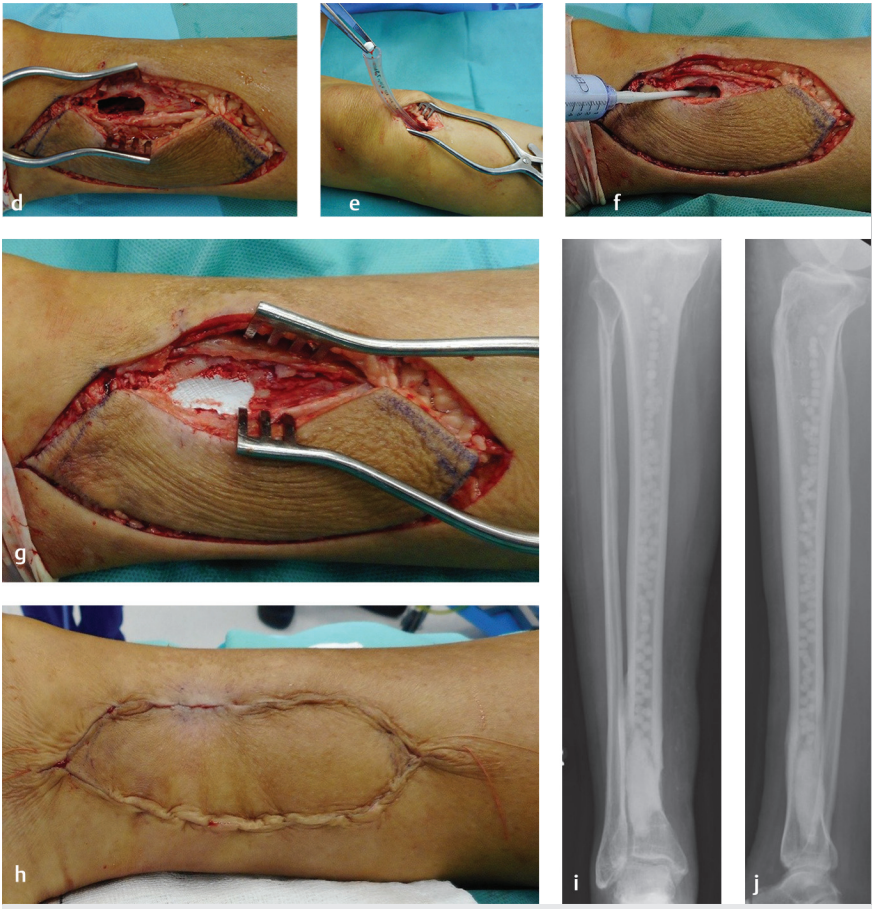

Fig. 5.13 (*Continued*) **(d)** The dead bone was excised through a direct medial approach to the distal tibia with drills and osteotomes. The canal was reamed from the proximal tibia. **(e)** The medullary dead space was filled with calcium sulfate pellets with gentamicin, using an endotracheal tube. **(f, g)** The distal cortico-medullary defect was filled with calcium sulfate with hydroxyapatite and gentamicin, to promote bone formation. **(h)** The soft-tissue defect was closed without tension using a local "keystone" flap. The postoperative anteroposterior **(i)** and lateral **(j)** X-rays show the dead space filled with antibiotic carrier and the extent of the bone resection. It is not correct to have antibiotic carrier as not all of the carrier is calcium sulphate.

Recently, there have been reports of successful management of infected segmental defects with internal fixation. Antibiotic-loaded PMMA cement covered nails have been used in infected nonunions of the femur and tibia,[40] while absorbable antibiotic-loaded ceramic can be used to coat nails and plates. Internal fixation combined with local antibiotics is safe in select patients, with the provision of healthy soft-tissue cover and when a good excision of the dead bone has been achieved.[41] It is not appropriate to leave metal exposed, even under negative-pressure dressings.

5.7.10 Soft-Tissue Coverage

After excision, the skin should be closed directly without tension, if possible. This is usual over the femur, humerus, pelvis, and spine. Tibial and many periarticular infections may require local flaps or free tissue transfer.

In general, local pedicled flaps (e.g., gastrocnemius over the proximal tibia) are reliable and easy to transfer. More extensive tissue loss can only be covered with free flaps. Muscle flaps (often gracilis or latissimus dorsi) are often preferred, and they are transferred without skin and then covered with a split skin graft. There is little difference in clinical outcomes with regards to infection recurrence or bone healing between flap types, but muscle flaps have a lower complication rate and lower reoperation rate compared to fasciocutaneous flaps in osteomyelitis.[30] They are robust and resistant to injury or later surgery.

Muscle flaps can be combined with external fixation and Ilizarov distraction techniques. Preoperative planning of these cases is critical as fixator design may need modification to allow plastic surgeons access for microvascular anastomosis or transfer of skin flaps (**Video 5.5**).

NPWT was designed for superficial wound management (ulcers and burns). It has a very limited place in osteomyelitis surgery. Occasionally, in a systemically unstable patient, a rapid drainage of the infection can be performed with a short period of NPWT. Within 7 days of application, the NPWT is always removed and definitive infection surgery is performed so that the wound can be closed.[42] It is also indicated for wound management of extensive pressure ulceration over osteomyelitis prior to surgical excision and closure. Prolonged NPWT increases polymicrobial infections with multiresistant strains and may make final wound closure more difficult.

5.7.11 Staging of Surgery

Traditionally, surgeons treated osteomyelitis in several stages, often leaving final reconstruction of the bone and soft tissues until the infection had been eradicated or at least rendered quiescent. This approach condemns patients to very prolonged treatment times and numerous secondary complications. It has not been shown to be safer than single-stage treatment, which has become the norm in many centers.[30,37,41,42] Multistage treatment is much more expensive and requires many more days in the hospital.

In patients with fulminant sepsis, it is prudent to address the acute infection and leave reconstruction until the patient is well. In most chronic infections, all components of the treatment can be managed in a single episode. This means that all members of the treating team need to be involved before surgery begins and learn to work together in the operating room and during the postoperative period.

5.8 Conclusion

Osteomyelitis is a rewarding condition to treat, for patients and surgeons alike. The pattern of disease is changing, and new treatment methods are evolving. Effective management is only possible with a clear understanding of the pathogenesis and classification of bone infection, and an appreciation of the interaction between the host and the pathogen.

Adherence to the basic principles of treatment described above can deliver high success rates. These successes are best achieved by a committed, skilled team of physicians, surgeons, nurses, and therapists.

Acknowledgments

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6 Treatment of the Septic Native Joint

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Abstract

A septic native joint can be a debilitating condition that is associated with significant morbidity and mortality. Traditionally, a septic native joint was considered one of the few surgical emergencies in orthopaedics, as a delay in diagnosis and treatment can result in joint destruction and loss of joint mobility and even mortality. While prompt diagnosis is crucial, diagnosis can be challenging, as it can be difficult to differentiate between a septic native joint from crystalline arthropathy, and rheumatological and osteoarthritis flares. Diagnosis of a septic joint relies on clinical findings, serological test, synovial aspiration, and culture results. Traditionally, a synovial fluid white blood cell cutoff of 50,000 cells/mm^3 is often used; however, it is important to note that infectious arthritis may frequently occur in patients with lower cell counts who are immunosuppressed or are infected with a less virulent organism. The mainstay of treatment for a septic joint is appropriate antibiotic therapy and surgical treatment. This chapter will focus only on native septic joint rather than periprosthetic joint infection, or a joint infection in the presence of a prostheses.

Keywords: Septic arthritis, septic joint, pyogenic arthritis, treatment, diagnosis

Practical Tips

- Clinical symptoms, such as fevers and chills, are often not present in the setting of septic arthritis.
- A C-reactive protein (CRP) cutoff of 10.5 mg/dL has demonstrated a high correlation with septic arthritis.
- Useful serum tests include erythrocyte sedimentation rate (ESR), CRP, procalcitonin, and tumor necrosis factor alpha for the diagnosis of septic arthritis. Aspiration should be performed in patients with high clinical suspicion or high serological values.
- *Staphylococcus aureus* is the most common infecting organism with increasing rates of antibiotic resistant cases being encountered.
- Arthroscopic treatment of a septic joint has demonstrated equivalent or superior outcomes to open treatment.

6.1 Introduction

Septic arthritis has an incidence of 2 to 7 cases per 100,000 people per year and has been increasing due to increased life expectancy, invasive procedures such as injections, and immunosuppressive therapies.[1] A septic joint is associated with cartilage destruction and damage, resulting in significant morbidity and high rates of mortality, as high as 42% in some studies.[2] This high rate of morbidity and mortality is mostly attributed due to sepsis and bacteremia in patients who are often fragile and have many comorbidities.[2]

6.2 Diagnosis

6.2.1 Risk Factors

Iatrogenic causes of septic arthritis range from 17 to 53% of cases, due to arthrocentesis in the majority of cases (43%) followed by open joint surgery (34%) and arthroscopy (23%).[1,3] Given that these cases frequently occur after an invasive procedure, it is important to have high suspicion for septic arthritis after any procedure that violates the joint. Several other risk factors for septic arthritis should be considered, and pre-existing joint disease is one of the most common, as 47% of patients with a septic joint have had prior joint problems.[4] A high index of suspicion should be had in patients with rheumatological conditions such as gout, pseudogout, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA). Patients with RA and SLE are at particularly high risk given that they often have pre-existing joint damage, require chronic immunosuppressive medication, and have poor skin conditions. Despite an increased risk in these patients, diagnosis is frequently difficult and can be delayed as clinical manifestations of RA flare can be similar to that of a septic joint. Particular vigilance is needed in patients with a monoarticular flare up, as immunosuppressive medications increase the risk of septic arthritis by fourfold.[4] Other comorbidities or conditions that should raise the suspicion of a septic joint include bacteremia, especially from an invasive procedure such as a colonoscopy that may result in hematogenous seeding, intravenous drug use, and other comorbidities that influence the immune system such as diabetes mellitus, renal failure, and immunosuppressive medications (Box 6.1).

Box 6.1 Septic arthritis risk factors

- Iatrogenic or postoperative
- Rheumatologic conditions
  - Systemic lupus erythematosus (SLE)
  - Gout
  - Pseudogout
  - Rheumatoid arthritis
- Immunosuppression
  - Human immunodeficiency virus (HIV)
  - Chronic immunosuppressive medications
  - Hypogammaglobulinemia
  - Tuberculosis
- Bacteremia
  - Prior invasive procedure (colonoscopy)
  - Intravenous drug abusers
  - Endocarditis
- Comorbidities
  - Diabetes
  - Renal failure
  - Liver disease

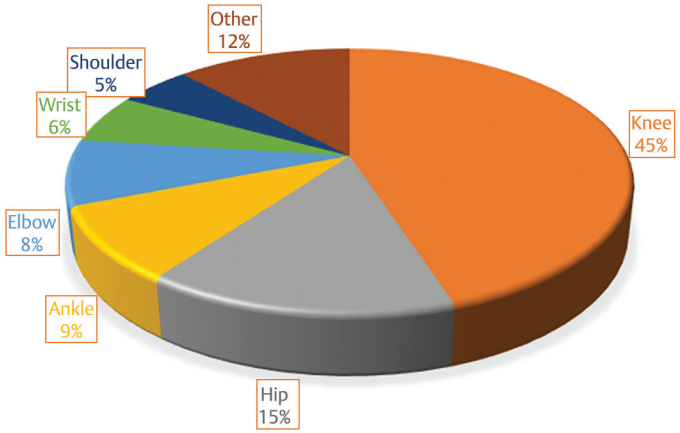

Fig. 6.1 Joint involvement in native septic arthritis.

6.2.2 Joint Involvement

The knee is the most commonly infected joint, as it makes up 45% of cases.[4] Other large joints that are infected include the hip (15%), ankle (9%), elbow (8%), wrist (6%),[4] and shoulder (5%) (▶ Fig. 6.1). Septic arthritis of cartilaginous joints of the axial skeleton are rare except in cases of bacteremia and intravenous drug users. In this population, the pubic symphysis, sternoclavicular, and sacroiliac joints may be affected.[4]

6.2.3 Clinical Manifestations

A septic joint is one of the few surgical emergencies in orthopaedics, as prompt treatment can prevent further morbidity from joint destruction and even mortality. Timely diagnosis of a septic joint is thus crucial and relies on a combination of clinical and laboratory tests. The most common clinical manifestations include acute joint pain, joint effusion or swelling, erythema or warmth, joint immobility, and other constitutional symptoms such as fevers, chills, or rigors. It is important to note that sensitivity of fevers and chills are quite poor as a fever is present in only 58% of patients and chills in 25% of patients with a septic joint.[5] Although septic arthritis is usually monoarticular, it may involve multiple joints in up to 20% of cases, especially if bacteremia is present.[4] The knee is involved in 72% of cases in which there is polyarticular involvement.

Physical examination should be used to help determine if the swelling and inflammation are intra-articular versus periarticular, such as a prepatellar bursitis. In addition, erythema and warmth of the skin may be indicative of cellulitis. However, it is important to note that septic arthritis may still be present in the setting of cellulitis. Pain with passive range of motion is one test that may help distinguish septic arthritis from cellulitis or periarticular involvement such as a bursitis, as the latter two should not have pain with joint range of motion. Furthermore, joint immobility is often present in septic arthritis as the joint is often in a position to maximize intra-articular space. For example, the knee is often in an extended position and the hip is often abducted and externally rotated when infected to accommodate the maximum amount of joint fluid.

6.2.4 Serum Evaluation

While the clinical impression remains the mainstay of septic arthritis diagnosis, the diagnosis is often supplemented with laboratory data. Serum markers are often the first tests ordered and include white blood cell (WBC) count, polymorphonuclear cell count, C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR) (Box 6.2). In addition, serum procalcitonin and tumor necrosis factor alpha (TNF-α) have been demonstrated to help discriminate between septic versus inflammatory arthritis.[6,7,8] Interleukin-6 (IL-6) has not demonstrated strong diagnostic utility for a septic joint unlike in periprosthetic joint infection.[8] Blood cultures should also be obtained, especially when hematogenous spread or sepsis is suspected. In patients with bacteremia or sepsis, a serum lactate should be obtained as a surrogate for tissue perfusion as part of the sepsis guidelines.[9] These markers increase with inflammation and are nonspecific, since a variety of conditions can cause an increase in these markers. A CRP level of 10.5 mg/dL has demonstrated a high correlation with septic arthritis in native joints despite lacking specificity.[10] When ordering CRP, it is critical that the units are converted. Recently, highly sensitive CRP has been introduced in order to better quantify values in the normal range which has increased confusion. However, little difference has been found after unit conversion between the different CRPs.[11] Furthermore, recent studies,[6,7,12] including one by Hügle et al, have also demonstrated that procalcitonin may outperform CRP in terms of specificity and sensitivity.[7] In addition, these markers may also be useful in order to monitor the therapeutic response as they may be a proxy for infection control.

Box 6.2 Diagnosis of septic arthritis

- Clinical manifestations
  - Swelling, pain, joint immobility, erythema, fever
- Serum evaluation
  - White blood cell count (elevated)
  - Erythrocyte sedimentation rate (elevated)
  - C-reactive protein (>10.5 mg/L)
- Synovial fluid evaluation
  - White cell count* (50,000 cells/mm^3 traditionally used)
  - Polymorphonuclear percentage (>90%)
  - Culture
  - Leukocyte esterase
  - Crystals (may be present)
  - Procalcitonin

* Synovial fluid cell count may be lower in patients with fastidious organisms, gonococcal disease, and prior antibiotics.

6.2.5 Synovial Analysis

Aspiration of the involved joint should be performed in patients with a suspicion for infection or who have elevated serum inflammatory markers. The aspiration should be

performed in a sterile manner using an alcohol or povidone-iodine preparation using an appropriate path that provides access to the joint while avoiding any areas of cellulitis. This may be performed under image guidance or by a radiologist. Synovial fluid should be sent for synovial WBC count with differential, crystal analysis, gram stain, and culture. While a gram stain has poor sensitivity (45%), it has high specificity in the literature.[13] Furthermore, synovial lactate and synovial IL-6 may also be ordered as they both demonstrate high accuracy in the literature.[14,15,16]

Traditionally, a cell count of greater than 50,000 cells/mm^3 and a polymorphonuclear cell count greater than 90% have been directly correlated with septic arthritis; however, there is significant overlap with crystalline arthroplasty.[10] Furthermore, the common mantra is that a cell count from 0 to 2,000 cells/mm^3 corresponds to a noninflammatory etiology and a cell count of 2,000 to 50,000 cells/mm^3 represents an inflammatory arthropathy. However, it is important to note that cell counts lower than 50,000 cells/mm^3 can occur in infectious arthritis. One investigation demonstrated this cutoff value as having a sensitivity of only 64%, as nearly one-third of patients had a cell count lower than 50,000 cells/mm^3.[4] Patients with lower synovial fluid cell counts may occur in people with atypical or fastidious organisms, disseminated gonococcal disease, and immunosuppression. Furthermore, it is important to note that septic arthritis can occur in the setting of crystalline arthropathy, as the presence of crystals does not rule out a septic joint. In some reports, up to 5% of patients with proven crystalline arthritis have concomitant septic arthritis.[17] Besides synovial WBC count, leukocyte esterase (LE) may be a useful test, as a prospective study by Gautam et al reported a 100% sensitivity of LE for acute septic arthritis with a positivity predictive value of 94%.[4,5,18] Leukocyte esterase testing is performed using synovial fluid from the joint. It is first spun down using a centrifuge in patients with a bloody aspiration and a drop is then placed on a urine analysis stick.

While the fluid is often sent for cultures, over 20% of cases may have negative cultures.[18] Several possible explanations include premature antimicrobial therapy, an insufficient volume of fluid, inadequate incubation duration, or fastidious growth requirements. A study by Hindle et al demonstrated that premature antibiotic administration decreased the yield of culture from 79 to 28%, suggesting that administration of antibiotics should be avoided when feasible until a culture is isolated.[19]

In some cases, cellulitis may be present in the setting of possible septic arthritis. In patients with surrounding cellulitis, there is concern that an aspiration through involved skin cellulitis may seed the joint. Thus, it is advisable to aspirate the joint through normal appearing skin when possible. In these patients, we are very careful to ensure that the procedure is performed in a sterile fashion with an alcohol or povidone-iodine solution. In addition, we take precautions to avoid touching the affected skin during the procedure. Furthermore, we have a lower threshold to have a musculoskeletal radiologist perform the aspiration, especially when the aspiration sites most commonly used have overlying cellulitis. However, if there is high clinical suspicion for a native septic joint, an aspiration may be performed through cellulitic skin, given that a missed or delayed diagnosis may outweigh the risk of inoculating an uninvolved joint with bacteria.

Unfortunately, there may be instances when the diagnosis is not clear, particularly when premature antibiotic therapy or an impaired immune system is present. Patients may thus have a nonconfirmatory cell count but a clinical concern for infection. In these instances, some options include repeat clinical examination, aspiration, and waiting for cultures. However, if high clinical concern remains, surgical treatment is likely warranted given the morbidly and mortality associated with delayed diagnosis and treatment.

6.2.6 Imaging

Imaging can be beneficial for diagnosis of a septic joint. Plain films may detect fractures, chondrocalcinosis, or signs of inflammatory arthritis. Furthermore, ultrasound may be used to detect effusions, particularly in deep joints such as the hip. MRI may also be useful to detect intra-articular infection with the presence of fluid and any concomitant osteomyelitis that may be present. In addition, MRI may be useful in atypical joints that are difficult to examine, such as the sacroiliac joint. Moreover, imaging may be used to aid arthrocentesis of deep joints such as the hip, sacroiliac, and costochondral joints.

6.3 Treatment

6.3.1 Common Organisms

A variety of organisms have been found to cause septic joint (▶ Fig. 6.2). Of the bacterial causes, the most common cause is *Staphylococcus aureus*, which accounts for approximately 41% of cases. Methicillin-resistant *Staphylococcus aureus* (MRSA) has been increasing, especially in the United States, and makes up approximately 21 to 50% of septic joint cases.[20,21] While staphylococci is the infecting organism in the majority of cases, other bacterial causes include streptococci (28%), gram-bacilli (19%), mycobacteria (8%), gram-negative cocci (3%), gram-positive bacilli (1%), and anaerobes (1%).[22]

Gram-positive staphylococci and streptococci make up the majority of bacterial septic joint cases and are often associated with drug abuse, cellulitis, abscesses, endocarditis, and osteomyelitis. Beta hemolytic *Streptococcus* is often polyarticular (32%) and is associated with a high mortality rate (9%).[23] In addition, *Streptococcus pneumoniae* comprises approximately 6% of cases, with 50% having an underlying focus.[24] Mortality is also very high with this infecting pathogen at 19%.[24] Gram-negative bacilli make up the next most common group and are associated with urinary tract infections, intravenous drug use, immunosuppression, and skin infections. Of the gram-negative bacilli, the two most common organisms are *Pseudomonas* and *Escherichia coli*. Functional outcomes are particularly poor in these patients (32%) with a mortality rate of 5%.[25,26]

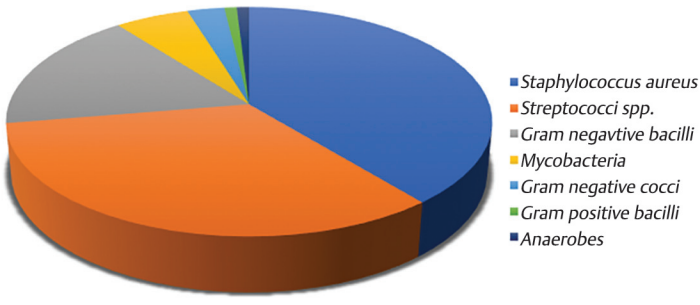

Fig. 6.2 Organism profile in native septic arthritis.

6.3.2 Gonococcal Arthritis

In usually young, healthy, and sexually active patients, disseminated gonococcal arthritis should be considered. These patients often have a migratory polyarthralgia and have blood and synovial cultures that are less frequently positive at a rate of approximately 50%.[27,28] The majority of these cases (75%) occur in women, with menses and pregnancy increasing the risk of dissemination.[29] The characteristic rash associated with gonorrhea is present in only 42% of patients.[29] When disseminated gonococcal arthritis is suspected, potentially infected sites such as the urethra, rectum, pharynx, and cervix should be tested. Molecular testing, such as polymerase chain reaction (PCR), may also be useful in culture-negative cases as it has a sensitivity of 76% and a specificity of 96%.[19] With appropriate surgical treatment and antibiotics, complete recovery is common and joint sequelae are rare with this organism.

6.3.3 Other Pathogens

Fungal arthritis is an infrequent cause of a septic joint and often has an indolent course. They often occur in endemic areas and in patients that are immunosuppressed. Mycobacterial infections, most notably *Mycobacterium tuberculosis*, is also an indolent organism and can cause considerable damage as a delay in diagnosis is frequent. Symptoms are often present for over a year before a diagnosis is made.[3] Tuberculosis frequently affects the knee or hip and causes 2% of septic arthritis. It is usually caused by reactivation of previous dissemination. Synovial biopsy and mycobacterial culture with either a liquid or solid medium reveal the highest yield. Cultures should be held for at least 10 days.

Lyme disease is also another common migratory arthralgia usually found in large joints such as the knee. In the northeastern United States, there should be high clinical suspicion for this disease as this is the endemic area of *Borrelia burgdorferi*. This organism cannot be cultured from synovial fluid and diagnosis relies on serological testing followed by a Western blot or PCR testing. Furthermore, arthritis may persist after treatment as the cell wall may be a persistent immunogen.[30]

In pediatric septic joints, staphylococci and streptococci continue to be the most dominant organisms. However, there is increasing awareness that *Kingella kingae*, one of the fastidious gram-negative rods, is often present. In these cases, synovial fluid specimens should be collected in pediatric blood culture bottles to improve culture yield and held for a minimum of 10 days.

6.3.4 Antimicrobial Therapy

Antimicrobial treatment is frequently tailored toward the infecting or most likely organism. Due to the destructive nature of septic arthritis, broad spectrum antibiotics against gram-positives and gram-negatives (e.g., vancomycin plus ceftriaxone or cefepime) are usually given despite culture results not being available. Given the increasing prevalence of MRSA, the initial antibiotic agent should include appropriate coverage for this organism, such as vancomycin.[28] In patients that are critically ill or have a high risk of gram-negative infection such as those that are immunocompromised, elderly, or who are active drug abusers, gram-negative bacilli coverage should also be included. The antimicrobial therapy should then be targeted based on culture sensitivity data and treatment should occur for at least 3 weeks. However, there is minimal literature on the ideal duration of treatment.

6.3.5 Surgical Treatment

Once a diagnosis has been made, prompt surgical treatment of a septic joint is critical as delayed treatment can result in irreversible joint destruction with subsequent joint immobility and impaired functional outcomes. In addition, there is a significant mortality rate, with an estimated rate of 11%.[2] The mainstay of surgical treatment is removal of purulent material and destructive enzymes from the joint space. This can be achieved either through closed needle aspiration, or surgical irrigation and debridement either open or arthroscopic. However, in patients with Lyme disease or gonococcal arthritis, antimicrobial treatment alone is usually sufficient to treat the arthritis. Furthermore, patients with crystalline arthropathy alone should be treated with anti-inflammatories and nonoperative treatment.

6.3.6 Needle Aspiration

Needle aspiration is often performed as an initial mode of treatment of joint sepsis. There is minimal literature on the outcomes of serial aspiration as definitive treatment with antibiotic therapy versus surgical treatment.[31] However, many studies have demonstrated that needle aspiration demonstrates favorable outcomes, particularly in pediatric patients.[23] Furthermore, only one study has directly compared serial needle aspiration with surgical treatment. Goldenberg et al found that 67% of patients treated with needle aspiration recovered without sequalae and concluded that needle aspiration is a reasonable initial option, as they could not find a significant difference in reinfection rates.[32] Given the lack of clinical studies comparing[33,34]debridement, evacuation of any loculated substances can be performed. However, needle aspiration can be considered in patients that cannot undergo the morbidity of surgery or in the very early stages of septic arthritis.[25]

6.3.7 Arthroscopic Treatment

The decision to perform arthroscopic versus open treatment remains controversial and largely depends on the surgeon's preference, the joint involved, and the surgeon's skill set. Arthroscopic management of the shoulder and knee are the most common, as it is easy to access these joints and arthroscopic surgery has several benefits over an open procedure including smaller incisions, reduced tissue damage, less morbidity, and less wound complications.[33,34] However, concerns exist regarding the thoroughness of the debridement given the limited access to certain areas of the joint.

For the most commonly involved septic joint, the knee, multiple cases have reported outcomes of arthroscopic and open arthrotomy alone. However, few have compared the results of open versus arthroscopic treatment. To our knowledge, five studies have directly compared open versus arthroscopic treatment with conflicting results.[33,34,35,36,37] Of these studies, the majority actually demonstrate reduced reinfection rates, less surgery, and improved functional outcomes with arthroscopic surgery.[33,34,36,37] In a prospective clinical trial, Peres et al revealed that arthroscopy demonstrated a lower reinfection rate than the arthrotomy cohort. Furthermore, Johns et al found that in a series of 166 septic knees, the cumulative success rate was 97% in the arthroscopic treatment group compared to 83% in the open treatment group.[34] When using multivariate analysis to control for potential confounders, arthroscopy demonstrated an over two-fold increased odds of treatment success (2.56) compared to open debridement.[34,35] In addition, the arthroscopy group had less irrigation procedures, greater postoperative motion, and decreased length of stay.[34] There may be several expla-

nations for this increased success rate: (1) the wounds are smaller with arthroscopy and there may be a reduced risk of recontamination, (2) irrigation may be more thorough with arthroscopy, as fluid may better accumulate rather than escaping through the larger arthrotomy, and (3) a selection bias may be present in these studies as there may be a tendency for surgeons to treat more severe infections with open treatment.

Septic arthritis of the shoulder, wrist, and ankle may also be more likely to be treated with arthroscopic treatment. In a systematic review of septic shoulders, Memon et al could not demonstrate the superiority of either arthroscopic or open arthrotomy.[38] Sammer et al compared arthroscopic and open treatment of 40 septic wrists and found that arthroscopy (62%, 13/21) had improved infection management in patients with isolated septic arthritis of the wrist and demonstrated a reduced length of stay compared to the open arthrotomy group with infection eradication in 8 out of 19 (42%) wrists.[39] Furthermore, while hip arthroscopy is rarely performed for septic hip, one study demonstrated that it can be safe and effective in select patients who are not immunocompromised and have no deformity.[40]

For arthroscopic treatment, there is minimal literature on the optimal irrigation solution volume, and the influence of the thoroughness of the debridement. However, we recommend that a thorough debridement of all necrotic or fibrinous tissue should be performed, and a high volumes of saline should be used to irrigate the joint or until the fluid is clear.[41] At a recent International Consensus Meeting (ICM) on Musculoskeletal Infection, it was agreed upon that a complete synovectomy is not necessarily required in all circumstances.[41] There was a strong consensus that a synovectomy should be reserved for severe and chronic infections, as the synovial membrane serves as a natural barrier to infection. Although topical antibiotics such as polymyxin and bacitracin are frequently added to irrigation solutions, the World Health Organization and the Centers for Disease Control and Prevention no longer recommend this practice due to fears of antimicrobial resistance and because multiple studies have demonstrated that the addition of topical antibiotics has no significant effects on bacterial removal. The ICM also recommends that saline alone be used.[41]

There are many joints in which arthroscopy is difficult to perform such as the sternoclavicular joint, hip joint, and sacroiliac joint. In these cases, open treatment is often relied upon.

6.3.8 Open Treatment

Open Arthrotomy and Irrigation and Debridement

While there is a trend toward arthroscopic treatment of native septic joint infections, open arthrotomy can be performed for every joint and can be indicated in almost all scenarios. Open arthrotomy and irrigation and debridement are often the preferred treatment in difficult-to-access joints and after recurrently failed arthroscopic treatment. Additionally, open treatment may be beneficial in infections that are loculated. As mentioned earlier, recent literature has suggested arthroscopic treatment may result in equivalent or even improved eradication rates compared to open treatment.[33,34,37,39] However, there may be a selection bias in many of these studies, as surgeons may be more aggressive and perform open arthrotomy rather than arthroscopic treatment in patients with more severe infections or virulent organisms, or in patients who are immunocompromised. There is minimal literature on the number of arthroscopic washouts prior to pursuing open arthrotomy. However, there is literature to suggest

that repeat arthroscopic treatments can produce good results. The ICM found that an arthroscopic irrigation and debridement can be performed up to six times.[41] Despite the invasiveness of open arthrotomies, it often remains the standard for treatment of native septic joints because of the lack of contraindications.

Spacer Insertion

In patients with pre-existing arthritis who develop septic arthritis or who develop arthritis due to cartilage destruction from a native septic joint, an antibiotic spacer may be inserted. The rationale of the antibiotic spacer is to allow for delivery of local antibiotics, similar to that of a two-stage exchange arthroplasty for periprosthetic joint infection. The antibiotic in the spacer should be targeted toward the infecting organism when possible; however, vancomycin and tobramycin are the most frequently used antibiotics because they are heat stable. In a 40-g bag of cement, 0.5 to 4 g of vancomycin and 1 to 4.8 g of tobramycin are usually placed.[42] Spacers can be either dynamic (▶ Fig. 6.3) or static (▶ Fig. 6.4).

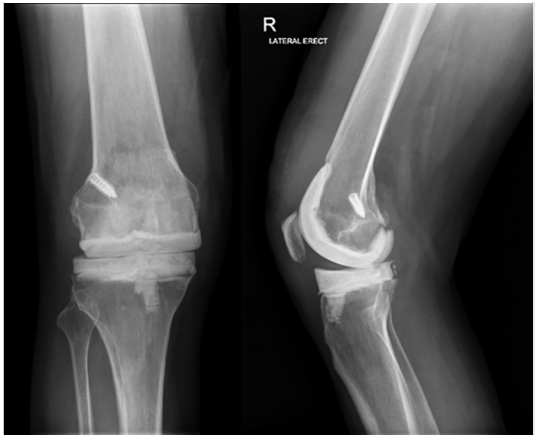

Fig. 6.3 Articulating knee spacer.

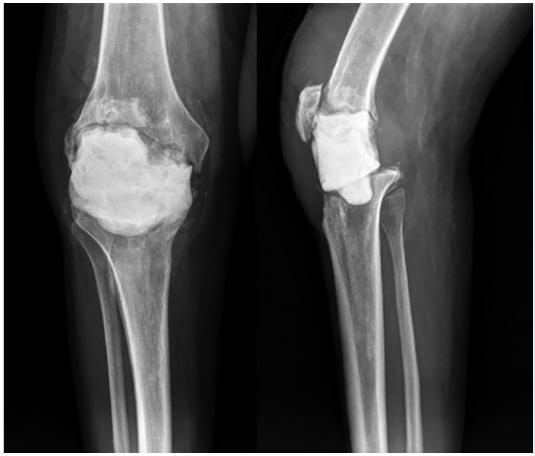

Fig. 6.4 Static knee spacer in the setting of severe bone loss.

Sequalae and Arthroplasty

It is not uncommon for a septic joint to result in severe articular cartilage destruction from enzymatic degradation, significant bone loss, and soft tissue contractures. These patients often have significant pain and develop end-stage arthritis that may benefit from total joint arthroplasty (TJA). However, patients with a prior history of septic arthritis are at an increased risk of developing subsequent complications, especially periprosthetic joint infection. In a meta-analysis of 1,300 TJAs following prior septic arthritis of the same joint, the reported PJI rate from the literature was found to be 5.96% (95% confidence interval (CI): 4.24–7.94),[43] which is much higher than the reported PJI rate of primary TJA (approximately 1%).[44,45] Despite these dramatically higher complications, several studies have demonstrated that arthroplasty for a septic arthritis etiology can improve function and provide durable pain relief.

Due to the increased risk of complications, surgeons are often faced with a dilemma on when and whether these patients can undergo arthroplasty safely. Unfortunately, there is minimal literature and unclear metrics to guide surgeons on when elective arthroplasty should be performed.[43,46] The International Consensus Meeting on Orthopaedic Infections recommends that it is crucial for active infection to be ruled out and that all diagnostic tests are normal.[46] When there is suspicion of infection or elevated laboratory tests, a two-stage approach with a spacer to deliver local antibiotics can be utilized while a one-stage approach may be considered if all diagnostic tests are negative. There is unfortunately limited literature on how long surgery should be delayed from the initial septic joint, or what laboratory tests should be utilized to determine persistent or active infection.

Arthroplasty should never be performed in the setting of active infection but may be performed after clinical infection eradication. While there are many single surgeon studies reporting the outcomes of each treatment type,[47,48,49,50,51,52,53,54,55,56,57,58,59,60] only one study has directly compared treatment outcomes between one stage for quiescent and a two-stage exchange arthroplasty approach.[61] Bauer et al found no difference in infection eradication rates after two-stage exchange (87%, 26/30) for evolutive septic arthritis and one-stage exchange (95.6%, 22/23) for quiescent septic arthritis in a series of 53 patients.[61]

6.4 Conclusion

Timely diagnosis and treatment of septic arthritis is critical to the prevention of long-term sequelae due to systemic seeding and cartilage destruction. Serological and synovial evaluation is the mainstay for diagnosis, and is often needed to differentiate septic arthritis from crystalline arthropathy and inflammatory arthritis. Surgical treatment combined with antimicrobial therapy is almost always needed, except for gonococcal and Lyme arthritis that can be often managed with antimicrobial therapy alone. Arthroscopic management has demonstrated results that are equivalent or superior to open arthrotomy.

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7 Management of Periprosthetic Joint Infection

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Abstract
Periprosthetic joint infection (PJI) continues to be a devastating problem in the field of total joint arthroplasty. There are a number of surgical options to decide from and management decisions are based upon the interplay between host, pathogen, and surgeon characteristics. The goal of management is to maximize function, prevent systemic complications, and eradicate infection. Throughout this chapter we will discuss the most relevant recent literature and guiding theories to assist the treating orthopaedic surgeon in the surgical decision-making process.

Keywords: Periprosthetic joint Infection, one-stage Exchange, two-stage exchange, DAIR

Practical Tips

- Management options of periprosthetic joint infection (PJI) are based on the chronicity of infection (acute versus chronic PJI).
- Acute PJI can be managed successfully with debridement, antibiotics, irrigation, and component retention (DAIR).
- Appropriate debridement should consist of both mechanical and chemical debridement.
- Chronic PJI requires irrigation and debridement, removal of prosthesis, and reimplantation in one or two surgeries.
- If one-stage exchange arthroplasty is chosen, patients should be immunocompetent, be infected with a known nonvirulent organism, have a healthy soft tissue envelope and adequate bone stock to accept a prosthesis, and have the medical reserve to tolerate a lengthy procedure.

7.1 Introduction

Periprosthetic joint infection (PJI) is a devastating problem affecting 0.5 to 2% of all hip and knee replacements and continues to be one of the leading causes of revision arthroplasty in the United States.[1] The surgical and nonsurgical management of PJI is complex and depends on the host, surgeon, and disease factors. In this chapter, we will discuss the most recent literature regarding surgical management of PJI with the goal of guiding the treating orthopaedic surgeon to appropriately manage this difficult problem. Traditionally, PJI management entails the use of pathogen directed antimicrobials in combination with a surgical procedure to decrease the bacterial bioburden within the affected joint. However, there are a number of procedures to choose from, including debridement, antibiotics, irrigation, and component retention (DAIR), one-stage exchange arthroplasty, two-stage exchange arthroplasty, resection arthroplasty, fusion, and amputation (▶ Table 7.1). DAIR should be considered in patients with acute onset

Table 7.1 Surgical management of periprosthetic joint infection (PJI): indications

Management options for PJI	Indications
Debridement, Antibiotics, and Implant Retention (DAIR)	• Acute or late hematogenous PJI • Well-fixed prosthesis • Healthy soft tissue envelope with absence of sinus tract
One-Stage Exchange Arthroplasty	• Chronic PJI • Immunocompetent host without signs of sepsis • Physiologic reserve to withstand a lengthy anesthetic • Healthy soft tissue envelope • Adequate bone stock to accept prosthesis • Preoperatively known, nonvirulent, nonresistant pathogen
Two-Stage Exchange Arthroplasty	• Chronic PJI • Medically comorbid, immunocompromised, or nutritionally deficient host • Polymicrobial, virulent, resistant, or unknown pathogen • Poor bone stock precluding prosthesis implantation • Soft tissue compromise precluding primary closure • Presence of sinus tract (relative) • Actively septic • Failure of DAIR or one-stage exchange arthroplasty • Able to tolerate multiple surgeries and lengthy rehabilitation
Salvage Procedure *(Resection Arthroplasty, Fusion, Amputation)*	• Medically comorbid or immunocompromised host • Persistent or recurrent chronic PJI • Boney or soft tissue compromise that preclude successful prosthetic reimplantation • Decision between resection, fusion, or amputation is individualized based on the specific patient anatomy and patient functional goals
Antibiotics Alone *(Lifelong Suppression)*	• Chronic PJI • Unable to tolerate multiple surgeries • Known pathogen with known sensitivities • Must be able to tolerate prolonged systemic antibiotics (i.e., appropriate hepatic and renal function) • Presence of well-fixed prosthesis • Aligned with functional goals of the patient

or late hematogenous PJI with a known organism, a well-fixed prosthesis, and a healthy soft tissue envelope. One-stage exchange arthroplasty should be considered in chronic infections in an immunocompetent host, with a known nonvirulent organism preoperatively, with both a healthy soft tissue envelope and adequate bone stock to accept a prosthesis, as well the medical reserve to tolerate a lengthy procedure. Two-stage exchange arthroplasty should be considered in medically comorbid or immunocompromised patients with polymicrobial, virulent, resistant, or unknown infecting pathogens, or bony or soft tissue compromise. Antibiotics suppression alone can be considered in patients with chronic PJI with well-fixed prosthesis components who are either too sick to tolerate surgery or who have exhausted their reconstructive options and do not wish to proceed with fusion, resection arthroplasty, or amputation. The goal of suppression is to prevent systemic symptoms of their local infection and maximize function. Renal and hepatic functions must be assessed in order to ensure patients can tolerate

extended antibiosis. Lastly, fusion, amputation, and resection arthroplasty are the three mainstay salvage options available for patients with persistent or recurrent PJI who are no longer candidates for successful prosthetic reimplantation. Choosing between these options is individualized for each patient and depends on the overall clinical status, the local soft tissue and bony environment in conjunction with patient's preference. Treating orthopaedic surgeons should have each of these surgical options in their armamentarium and apply them in the appropriately selected patient and clinical context. Throughout this chapter, we will discuss the most relevant literature and guiding theories so that the most appropriate management options can be chosen for each individual patient presenting with PJI.

7.2 Chronicity of Infection

In order for one to understand the varying surgical treatment options for PJI, it is vital for the managing surgeon to understand the appropriate classification of PJI for both total hip arthroplasty (THA) and total knee arthroplasty (TKA). A large majority of current guidelines for PJI diagnosis differentiate PJI based on timing of infectious symptoms relative to prosthesis implantation. The reason duration of symptoms and/or time of symptoms since implantation is the first step in determining the PJI treatment algorithm is because the development of bacterial biofilm on implanted devices is thought to be a time-dependent process.[2] Thus, the overall successful treatment of PJI is thought to be due to the appropriate reduction in biofilm. Thus, it makes sense that international guidelines on the treatment of PJI differentiate infections into two overall categories: acute (early onset) or chronic (delayed or late onset) infections (▶ Table 7.2).[3,4,5] An early or acute PJI is thought to occur within either 3 weeks or <30 days from implantation, or in the case of late acute hematogenous infection, presentation within 3 weeks of the development of infectious symptoms.[6] Any infection developing thereafter is then considered late or chronic by certain classification systems.[3] The distinction between acute and chronic infection was originally based on the assumption that biofilm develops within 3 weeks on the surface of components, and thus DAIR alone would not suffice in reducing the bioburden of infection.[7] However, this distinction, while still used clinically, may need to be revisited as studies have shown that the development of biofilm occur within hours to days after inoculation.[2,8] It is widely accepted that acute infections may be initially managed with DAIR and late or chronic infections require implant resection in either one or two stages before reimplantation of a new prosthesis.[9]

Table 7.2 Definitions of chronicity of periprosthetic joint infection (PJI)

PJI chronicity	Definitions
Acute PJI	Periprosthetic joint infection occurring within 3 weeks or <30 days from implantation
Late Hematogenous PJI	Development of a periprosthetic joint infection in a long-standing infection-free joint secondary to another known infectious source (e.g., dental work, urosepsis)
Chronic PJI	Periprosthetic joint infection occurring after >3 weeks or 30 days from prosthesis implantation

7.3 Antibiotic Management Alone

Treatment with antibiotics alone for patients with PJI is a rarely utilized treatment strategy, as suppression of the infection may only limit systemic effects. When antibiotic management is used in isolation, there is little hope for infection eradication and should only be considered after a lengthy discussion regarding the goals of care with the patient. Patients who undergo this treatment strategy are either compromised hosts that cannot tolerate surgery or hosts that have exhausted their surgical options for reimplantation and do not wish to proceed with fusion, amputation, or resection arthroplasty procedures.

Predictably, suppression is more successful in highly sensitive organisms. Antibiotic suppression alone is only indicated when the components are well-fixed without signs of instability, the antibiotic chosen is safe to administer orally for prolonged periods of time, the patient has adequate renal and liver functions, and the patient has the ability to undergo regular testing to monitor for the safety and effectiveness of prolonged antibiotic use. Contraindications to long-term antibiotic suppression are usually radiological signs of loosening or any signs of osteomyelitis.[10] If this is the case, surgical salvage options should be considered that will be discussed later in this chapter.

7.4 Irrigation and Debridement

Irrigation and debridement (I&D) continues to be a primary tool for the treatment of acute PJI. Historically, I&D consisted of three techniques: arthroscopic debridement, open I&D without modular component exchange, and open I&D with the exchange of modular components, more recently termed DAIR. However, studies have shown that I&D either arthroscopic or open without the exchange of modular components leads to an unacceptably high failure rate and leads to worse outcomes in subsequent revision surgeries for persistent infection; thus, DAIR has emerged as the recommended treatment modality for acute onset and late hematogenous PJI.[11] Overall, one can consider DAIR for PJI in the setting of early postoperative infections that occur within 30 days of the index procedure. Additional indications for DAIR include patients with late acute hematogenous PJI that occurred within 3 weeks of an inciting event with less than 3 weeks of presenting symptoms.[12] The success of these procedures is variable and ranges anywhere from 0 to 89%.[13]

7.4.1 Irrigation and Debridement without Polyethylene Exchange

Historically, there was a question of whether the removal of modular components (i.e., polyethylene) was necessary when attempting an I&D for appropriately selected PJI. Overall, there is little evidence in the literature specifically addressing the need for modular component exchange. Changing modular components during DAIR incurs added expenses of new components, increased surgical time, and potential increased morbidity. However, the overwhelming dogma in arthroplasty surgery is that removal of polyethylene and other modular components is necessary for a successful debridement to get access to all compartments.[12,14,15,16] With the information stated above, it is unsurprising that arthroscopy has strikingly worse outcomes for PJI than open I&D and should play no role in the treatment algorithm for PJI.[14,17,18] Overall, I&D without removal of polyethylene should play a minimal role in the overall management of PJI, and modular components should be exchanged whenever possible.

7.5 DAIR

The standard of care for acute onset PJI is an extensive open I&D with the removal and exchange of modular components along with directed antibiotic management. This treatment strategy can be considered in the setting of acute onset PJI (i.e., within 30 days of prosthesis implantation) with a well-fixed prosthesis without the evidence of soft tissue compromise.[3,19] Additionally, DAIR is also used in the setting of late hematogenous PJI with the prerequisites of a well-fixed prosthesis without a sinus tract or soft tissue compromise.[3,20,21,22] The removal of modular components allows access to otherwise inaccessible areas of the joint, which is especially true for access to the posterior joint capsule in TKA.[6,23,24] Additionally, polyethylene removal usually reveals a viscous fluid collection on the tibial tray underneath the polyethylene insert, and removal of the polyethylene allows debridement of this fluid layer and decreased bacterial bioburden.

DAIR with modular component exchange in conjunction with parenteral antibiotics helps to prevent infection recurrence in up to 71% of acute-onset infections.[14,25,26] Many believe that in order for DAIR with modular component exchange to successfully eradicate infection, the pathogen must be known and appropriately susceptible to oral antimicrobial agents.[3] As expected, success rates are higher in those hosts with less comorbidities, less virulent organisms, and shorter duration of symptoms.[27] Sinus tracts, soft tissue envelope compromise, and loose prostheses are all contraindications for DAIR.[27] Furthermore, even in the setting of acute onset or late hematogenous PJI, if the patient is demonstrating signs of sepsis with hemodynamic compromise, then DAIR should be abandoned and all components should be resected if the patient can medically tolerate the procedure.

DAIR may be slightly delayed in order to appropriately optimize the patient prior to the procedure. All efforts should be made to correct any immediately reversible medical conditions and organ dysfunction, including coagulopathy, anemia, and hyperglycemia. Nutritional status should be checked and nutritional supplementation should be provided, as needed.[27] Once optimized, the patient should be taken into the operating room, and DAIR with polyethylene exchange should be performed in a meticulous manner. In the operating room, the skin is prepped with solutions that combine ethyl alcohol with iodophores (DuraPrep™) or chlorhexidine gluconate (ChloroPrep™). These preparations are used as they are resistant to removal and inactivation by blood or irrigant solutions. Additionally, these agents have been shown in several studies to be more effective at reducing skin bacteria counts than traditional iodine "paint."[28,29,30,31] There have been studies showing that the chlorhexidine formulation was more effective than the iodophore formulation in reducing bacterial counts of the skin in shoulder and ankle surgery.[32,33] However, chlorhexidine formulation can erase the surgical site markings and interfere with drape adhesion.[34] After skin preparation, the surgical site should be draped with an iodine-impregnated adhesive drape to prevent bacterial recolonization.[30] Once prepped, the joint should be accessed through the same incision as the primary procedure, even in the presence of surrounding erythema. Scar excision is not routinely implemented. The fascia should be opened to clean out the deep wound space, and it is recommended to take at least 5 representative tissue and fluid samples from the periprosthetic region to help guide antibiotic treatment.[3] The areas should be sampled from the most macroscopically infected appearing region based on surgeon's decision-making. Areas should include superficial, deep, periprosthetic layers and interfaces between modular components. These sam-

ples should be submitted for aerobic and anaerobic cultures.[35] Prophylactic antibiotics do not need to be held in cases of proven preoperative acute PJI.[36] Once cultures are obtained, a thorough debridement ensues, including the removal of necrotic soft tissue, debris, hematoma, or collections of pus from around the prosthesis. At that point, all modular components are removed, and further debridement continued, especially the posterior capsule of the knee. Next, the prosthesis is assessed at both the cement–bone and implant–bone interfaces, and one can proceed with implant retention if the components are well-fixed. Once modular components are removed, then mechanical debridement of all metallic surfaces should ensue. This can be done with a sterile toothbrush,[37] or sterile betadine or chlorhexidine brush.[38] Although newer advances such as devices that perform hydrosurgery (i.e., VERSAJET, Smith and Nephew, Memphis, TN, USA) may be useful, there are no large long-term studies in the arthroplasty literature assessing their efficacy.[39] Once a successful mechanical debridement is undertaken, all modular components are removed, and if the implant is felt to be biomechanically stable, then the surgeon can proceed to copiously irrigate and chemically debride the wound with 9 L of saline solution via low-pressure pulse lavage.[14,27] At this stage, most surgeons recommend the addition of a chemical agent to enhance bacterial neutralization. However, the addition of bacitracin to irrigation is not recommended based on recent Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) guidelines, as there appears to be no added benefit based on the literature but may lead to increased antibiotic resistance.[40,41,42] Additionally, *in vitro* studies have shown that bacitracin added no increased bactericidal efficacy when added to irrigation solutions.[43,44,45] The goal is to dislodge any nonviable tissue while simultaneously diluting the bacterial bioburden.[44,46] There have been studies demonstrating that aqueous chlorhexidine gluconate acts as both an antiseptic and detergent, and has a greater ability than dilute povidone-iodine and castile soap to decrease bacterial bioburden in biofilm-forming organisms.[24,47,48,49] However, other solutions such as dilute povidone-iodine and acetic acid (vinegar) have also demonstrated benefit. When compared to five commercially available solutions, dilute povidone-iodine showed the most optimal combination of being bactericidal while maintaining host cell viability.[50] Other clinical studies have demonstrated significant decreases in infection rate with the use of dilute betadine.[51,52] The argument against betadine use is that it is not used in a manner that allows it to reach its full bactericidal potential via drying and desiccation and is deactivated by blood,[53] making chlorhexidine theoretically more advantageous. When used as adjuvant chemical debridement in PJI, 3% acetic acid has also been shown to be safe and effective, but larger comparative studies are needed before formal recommendations are made.[54,55] Nonetheless, the optimal chemical irrigation solution is still unknown and should be chosen at the surgeon's discretion.

After I&D, the surgeon should inspect the tissues again, and if the wound appears clean and free of necrotic tissue, new drapes, gloves, gowns, and instruments should be used,[56] and modular components should be trialed and reimplanted. The wound is then closed in layered fashion using nonbraided suture, such as polydiaxonone suture (PDS) and monocryl. Drains are used at the discretion of the treating surgeon. Currently, there are no recommendations for the role of either catheter infused intra-articular antibiotic infusions after DAIR, vancomycin powder, or the use of resorbable impregnated pellets.[27] All of these augmentations have been described in the literature with encouraging results,[57,58,59,60,61] but further research with large comparative studies are needed before formal recommendations can be made (**Video 7.1**).

Overall, the success rates for DAIR vary widely in the literature and range from 16 to 83%.[12,14,23,62,63,64,65,66,67,68 69] The largest series of combined THA and TKA PJI showed a success rate of 51.8%, with more recent series showing success rate of 65% at an average of 38-month follow-up.[62] Studies have tried to assess what factors can be used to predict success of DAIR with modular component exchange. Patients who have a high risk of failure of DAIR include those with significantly elevated erythrocyte sedimentation rate (ESR) preoperatively, methicillin-resistant *Staphylococcus aureus* (MRSA) or methicillin-sensitive *Staphylococcus aureus* (MSSA) PJI, vancomycin-resistant *Enterococcus* (VRE), as well as symptom duration greater than 21 days.[23,64,70]

It is recommended that 2 to 6 weeks of pathogen-specific parenteral antibiotics should be used after DAIR, with transition to oral antibiotics thereafter. Recommendations for oral antibiotics after DAIR are 3 months after THA and 6 months after TKA in conjunction with rifampin for biofilm penetration for *Staphylococcus* infections.[3] Unfortunately, two-stage exchange arthroplasty after DAIR failure leads to worse clinical outcomes.[69] A recent study evaluating 216 cases of DAIR had a failure rate of 57% after 4 years, with nearly 20% 5-year mortality. Of those that failed DAIR, 54.1% went on to two-stage exchange, 11.1% required amputation, and 6.4% underwent a fusion procedure. The other 28.4% of patients that failed initial DAIR required multiple I&Ds for successful eradication.[71] Nonetheless, DAIR remains a useful technique and should be implemented in the appropriate clinical setting.

7.6 One-Stage Exchange Arthroplasty

It is widely accepted that the standard of care for chronic and late onset PJI (i.e., greater than 30 days) often requires explantation of the infected implanted prosthesis to achieve infection eradication. This has been described in either one or two stages.[72] Two-stage exchange arthroplasty is considered by most to be the “gold standard” treatment for chronic PJI, and is the preferred procedure in the United States, with one-stage exchange arthroplasty gaining considerably more popularity in Europe as the first line of treatment for late onset and chronic PJI.[73] The concept of one-stage exchange arthroplasty involves performing two procedures in a single trip to the operating room. The first procedure in both one- and two-stage exchange arthroplasties is an extensive synovectomy and debridement that culminates in explantation of the infected prosthesis. For one-stage exchange arthroplasty, this is followed by prosthesis reimplantation with antibiotic-impregnated cement within the same anesthetic time period.[3] Overall, the appropriate candidate for one-stage exchange is controversial and often debated within the literature.[74] Despite that, there are recent published reports with inclusion and exclusion criteria that can guide treatment decision-making.[75,76]

Patients can be considered for one-stage exchange if they are immunocompetent hosts without signs of sepsis or hemodynamic compromise. There must be a healthy soft tissue envelope that can be closed postoperatively, and the extent of debridement needed should not compromise soft tissue closure. Postdebridement bone stock needs to be adequate to accept new components. The organism(s) must be known preoperatively and should have low virulence with available antibiotic sensitivities known prior to surgery for organism-directed antibiotic management. Conversely, the medically comorbid, immunocompromised host infected with virulent, resistant, or unidentified organisms, with significant soft tissue and bony compromise, or decompensated septic patients are not candidates for one-stage exchange arthroplasty.[75,76,77,78] Whether or not the presence of sinus tract or fistula communicating with the joint in question is a

contraindication to one-stage exchange is controversial.[77] Sinus tracts are considered a relative contraindication to one-stage exchange given the widely held belief that a chronically draining sinus is a poor prognostic sign of PJI eradication. Despite this belief, there are still reports of patients who presented with chronically draining sinuses and were treated with a one-stage exchange with resolution of their infection.[79,80,81] Lastly, and perhaps most importantly, the patient needs to have the physiologic reserve to undergo a prolonged revision procedure and tolerate general anesthesia,[82] as one-stage exchange arthroplasty can be lengthy and have considerable blood loss.

From a technical standpoint, the one-stage exchange technique can be divided into four distinct stages[75,77]: *Preparation, Initial Debridement, Temporary Closure, and Prosthesis Reimplantation.*

7.6.1 Preparation

In the operating room, patients are positioned appropriately with hair already clipped. The skin is then preliminary washed with a sterile 0.5% povidone-iodine or chlorhexidine surgical brush combined with water to remove any dead skin or gross necrotic tissue from the surgical site. The solution is left on the skin for at least 3 minutes for optimal effect.[83] Next, the skin is prepped twice with a preoperative skin preparation containing alcohol (i.e., 2% chlorhexidine gluconate [CHG]/70% isopropyl alcohol [IPA] formulation). Drapes are then placed in standard sterile fashion, and the incision is marked with a sterile marking pen. Every effort should be made to use the same surgical incision as the previous procedure. The prepared skin is then enclosed in antimicrobial incision drapes, with the intention to circumferentially seal the entire extremity. Prophylactic preoperative antibiotics should also be administered based on previous synovial analysis and pathogen sensitivities in conjunction with infectious disease consultation.[84] This can be done prior to obtaining samples, as the organism should already be identified.

7.6.2 Debridement

An extensile incision should be used preferably incorporating the previous incision, and the approach performed based on surgeon's preference, although augmented approaches should be used as needed to ensure appropriate visualization of the involved joint and surrounding structures. After performing a layered dissection and arthrotomy, the implant should be visualized and an extensive soft tissue debridement should be undertaken. Debridement can then be further broken down into mechanical and chemical phases. The mechanical debridement is undertaken initially with a complete synovectomy, as well as any overly infected/necrotic surrounding soft tissues and bone. Attempts should be made to save any key ligamentous structures to maximize joint stability, but any grossly infected tissue should be resected. As in oncologic procedures, it is vital that a necrotic free margin be developed to decrease the bioburden of bacteria and limit devitalized tissue that may be a future nidus for infection.

Next, the implants are removed using explant devices as needed, while paying special attention to minimizing unnecessary bone loss. Once the components are explanted, special attention should be made to debride any soft tissue behind the implants, such as the posterior knee capsule that is often overlooked.[23,24] Attention should then be turned to the intramedullary canals, with the goal to remove intramedullary biofilm and all remaining cement, if present. Sequential intramedullary reaming should be performed

as needed to remove sclerotic bone that prevents access to the terminal intramedullary canals until there is healthy bleeding cancellous bone remaining. A minimum of five tissue cultures should be obtained. In the knee, synovium, femur, tibia, femoral canal, and tibial canal samples should be obtained from mechanically debrided tissue. In the hip, debrided tissue from the synovium, femur, acetabulum, femoral canal, and behind the acetabular cup should be sent for culture.

Once a thorough mechanical debridement is complete, chemical debridement should be performed using low-pressure pulse lavage with normal saline, again with the goal of dislodging nonviable tissue while simultaneously diluting the bacterial bioburden.[44] The volume of irrigant is debatable, with many using 6 to 9 L, and up to 12 L of solution, while some surgeons electing to use antibiotic laden solutions.[46] Once large volume lavage is complete, the next step is to pour aqueous povidone-iodine (1% available iodine) in the wound bed, which is left in place for 5 minutes to allow for appropriate antimicrobial action.[85] The solution is then washed with normal saline until the wound is visibly clear of iodine-containing solution. The last step entails pouring a mixture of 100 mL of 3% hydrogen peroxide and 100 mL of sterile water to remove any remaining loose debris from the wound bed, simultaneously delivering an antimicrobial solution. Again 100 mL of sterile water solution is then used to wash the tissue free of hydrogen peroxide. Other available irrigation solutions include 4% acetic acid,[54] sodium hypochlorite,[43] and aqueous chlorhexidine.[47,86] As mentioned in earlier sections, there is no large comparative studies comparing these antimicrobial solutions, and thus these irrigants may be used in the place of aqueous povidone-iodine, or as an additional step in the chemical debridement process, making sure to thoroughly remove the lavaged fluid with either sterile saline or water prior to moving forward with the next step in the process.

7.6.3 Temporary Closure

After final inspection demonstrates a clean wound bed without any remaining necrotic debris, the surgeon can then proceed to temporary closure. This section of the procedure is essentially synonymous with the end of the first stage in a two-stage exchange, but rather than fully closing the wound for a future return to the operating room, the joint is prepared for immediate reimplantation in a new sterile environment. To begin with, povidone-iodine soaked gauze is packed into the wound bed, and the skin is then temporarily closed using either running or interrupted nylon sutures. Once the wound is closed, the previous antimicrobial drapes are removed, and a new antimicrobial drape is placed on top of the closed surgical site, essentially sealing off the sterile environment. Next, leaving the antimicrobial drape and underlying gauze undisturbed, the previous surgical drapes and any used instruments should be removed from the surgical field. The room is cleaned as much as possible. The surgical team then removes their contaminated gowns. Subsequently, as if starting the second stage of a two-stage exchange, the surgical team re-scrubs and re-gowns, and the patient's skin is re-prepped with antimicrobial solution. New drapes are placed on the patient, and new unused sterile equipment is opened as if starting a completely new case.

7.6.4 New Prosthesis Implantation

With the new surgical field in place, the sutures and povidone-iodine soaked gauze are removed and wound is then washed with 1 L normal saline to remove any residual

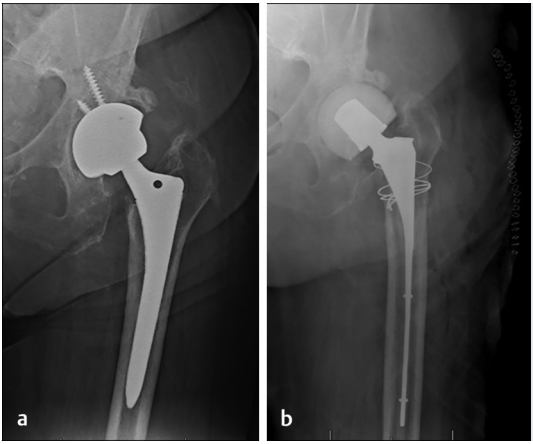

Fig. 7.1 (a, b) Preoperative and postoperative radiographs demonstrating the removal of an ingrown stem for periprosthetic joint infection utilizing an extended trochanteric osteotomy fixed with three cerclage wires.

iodine from the wound. The bone is then prepared to accommodate the appropriate prosthesis. As with all revision TKA, constrained and stemmed components may be needed, along with cones and sleeves. For revision THA, jumbo cups, cages, dual mobility, and revision stems may be needed. It may be beneficial to use titanium cerclage bands or wire cables to secure the trochanter after extended trochanteric osteotomy (▶ Fig. 7.1) during explantation of a well-fixed femoral stem.[87] After component trialing, the bone is washed and dried in standard preparation for implantation. The new prosthesis may be secured with antibiotic-laden cement, and any bone graft used should be combined with vancomycin powder.[88] After the antibiotic cement is hardened, the wound is irrigated one last time. If cement is not utilized during reimplantation, there have been reports of combining of antibiotic-eluting absorbable calcium sulfate beads at the bone–implant interface or using an intra-articular infusion of antibiotics.[46,89,90] [91] Drains are used at the discretion of the treating surgeon, and the wound is closed in a standard layered fashion with nonbraided suture.

7.6.5 Outcomes of One-Stage Exchange Arthroplasty

Recent systematic reviews of one-stage versus two-stage exchange arthroplasty for PJI have shown a reinfection rate of one-stage exchange arthroplasty to be between 4 and 8%.[92,93,94] Prior to these systematic reviews, the success rate of one-stage exchange arthroplasty varied widely in literature. When diving deeper into outcomes, it appears that one-stage exchange arthroplasty for hip PJI have lower reinfection rates compared to TKA. Raut et al demonstrated an 84% eradication rate in 183 infected THAs with 7-year follow-up,[95] with a subsequent subgroup analysis of 57 patients with draining sinuses treated with one-stage exchange having an 86% eradication rate.[79] In a study with even longer follow-up, Ure et al reported on 20 patients with THA PJI treated with one-stage exchange with no reinfection over 11 years.[96] In another study with 10-year follow-up, Callaghan et al similarly demonstrated good results in 24 THA patients with a reinfection rate of 8.3%.[97] In a 2014 systematic review of THA, results were similar between one- and two-stage exchange arthroplasties.[98]

For TKA, the results are more variable for one-stage exchange with an overall trend toward higher reinfection rates in studies with longer follow-up. For example, a study with 2-year follow-up showed 100% eradication rate[99] compared to a study with

10-year follow-up demonstrating an eradication rate of 64%.[100] Other studies by Göksan and Freeman showed a 95% success rate after 5 years, while Soudry et al reported an 80% eradication rate after 8-year follow-up.[101,102] Despite these varying results, two 2016 systematic reviews demonstrated no significant difference in reinfection rates across the published literature in one-stage versus two-stage exchange.[92,93]

7.7 Two-Stage Exchange Arthroplasty

Although there has been an increase in popularity of one-stage exchange arthroplasty in Europe and the United States, two-stage exchange arthroplasty continues to be widely accepted as the standard of care[1] for treatment of chronic PJI in the United States and around the world.[103,104,105] The technique for two-stage exchange was first described by Insall et al[106] in 1983 for the management of infected total knees. Currently, the indications for two-stage exchange are patients with chronically infected arthroplasties associated with a sinus tract, severe soft tissue and/or bony compromise, actively septic, virulent, resistant, fungal, or unknown pathogens, or failed prior DAIR or one-stage exchange.[1] Furthermore, two-stage exchange should be used as first-line management in patients who do not fit the tight inclusion criteria for one-stage exchange, specifically, hosts with comorbid conditions, who are immunocompromised or nutritionally deficient, and are medically unfit to undergo a lengthy one-exchange procedure.[3]

7.7.1 First Stage: Debridement and Antibiotic Spacer Implantation

The first stage of the two-stage exchange is analogous to the first part of a one-stage exchange, and many of the principles are the same. The process begins by removing all foreign material and hardware from the joint, followed by an extensive debridement of all nonviable soft tissues, bone, and synovium. Intramedullary canals should be debrided as well. Five cultures should be sent of deep tissue, including matter from the intramedullary canals. Chemical debridement should be performed as described above. Once the joint is considered to have necrotic-free margins, an antibiotic-laden cement spacer (either articulating or static) is inserted.[107,108,109]

Although there are many techniques to fashion a static spacer (▶ Fig. 7.2) for the knee, one technique involves using two 3 mm Steinman pins placed in the femoral and tibial canals that overlap in the articular space connected by an antibiotic-laden cement block that fills the joint space. The cement block is fashioned to fit between the femoral and tibial surfaces, making sure the soft tissues are appropriately tensioned, which will aid in reimplantation during the second stage. Once appropriately filled within the joint space, more antibiotic-laden cement can be placed in the suprapatellar pouch in order to prevent quadriceps tendon from scarring to the femoral surface. Other options for fixation include tibial/humeral nails and ex-fix bars.

There is no consensus with regard to preparing antibiotic cement for spacers; however, two to three 40 g bags are typically required, with 1 to 4 g of vancomycin per 40 g cement bag and 2.4 to 4.8 gentamicin or tobramycin per 40 g bag of cement.[110] The goal is for the cement spacer to have the right antibiotic concentration to release high enough doses to the surgical field to kill bacteria while low enough to not disrupt the mechanical properties of the cement or cause systemic complications.[111]

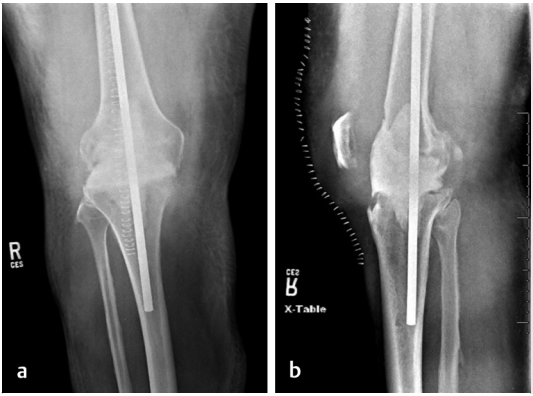

Fig. 7.2 (a, b) Radiographic examples of a knee static antibiotic spacer placed for treatment of periprosthetic joint infection during two-stage exchange arthroplasty.

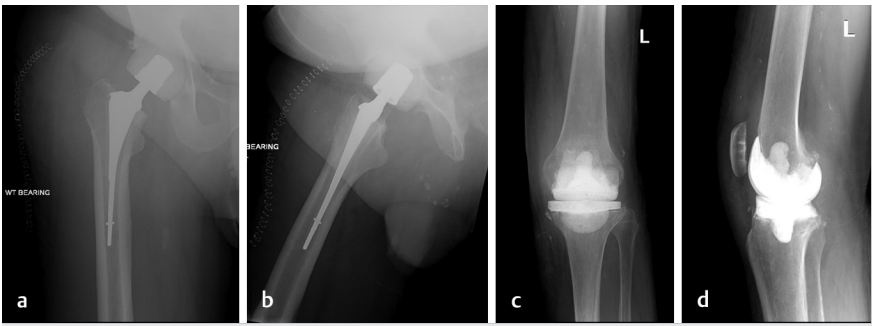

Fig. 7.3 Radiographic examples of both a hip **(a, b)** and knee **(c, d)** articulating spacer implanted after explantation for periprosthetic joint infection during two-stage exchange arthroplasty.

There are several techniques described for creating articulating spacers (▶ Fig. 7.3), including cement-on-cement and metal-on-polyethylene. Cement-on-cement articulating spacers come as preformed spacers or ones that are molded intraoperatively.[112] Varying molds are available commercially and come in various sizes and dimensions. The custom-made molds can be assembled intraoperatively using standard TKA provisional components that are the same size as the original prosthesis.[113] The cement is loaded with vancomycin or gentamicin at previously stated concentrations. Once the appropriately sized mold is selected, cement is poured into the mold in the late doughy phase and left to rest until polymerization is achieved.[114] There are also premolded antibiotic cement spacers available for use made by multiple companies.[115] For prefabricated or molded articulating spacers, the tibial component is normally inserted first and cemented in place with extra antibiotic-laden cement. Every effort should be made to maintain the joint line. The femoral component is then cemented in place. The goal should be to appropriately adhere the cement spacers to the bone surface using another bag of cement while avoiding potential bony damage with excessive cement penetration into the residual bone stock.[116] One can augment the molded articulating spacers with 3-mm K-wires covered in antibiotic-laden cement to act as intramedullary stems for added intramedullary antibiotic delivery and increased stability of the articulating spacer.[117,118]

Alternatively, a new femoral component and all polyethylene tibial component can be used as an articulating spacer, with the addition of dowels that deliver antibiotics to the intramedullary canals (**Video 7.2**).[119] The PROSTALAC® system is another option for articulating spacers, which consists of femoral and tibial components, each containing antibiotic-laden cement. The femoral side is associated with a bicondylar metal shell and a complementary polyethylene component on the tibial side which articulates in a posterior stabilized (PS) fashion. On the femoral side, there is a cross bar connecting the two halves of the articular surface, acting as the cam mechanism in a PS design. In the tibial side there is an antibiotic-cement spine that engages the cam like any other PS knee. These spacers are available in different sizes and thicknesses.[120,121]

The argument for using articulating spacers is the potential for maintaining interim joint motion, preventing extensor mechanism shortening in TKA, and facilitating reimplantation, all with the goal of improving postoperative function. Despite these theoretical advantages, postoperative functional scores have been shown to be equivalent in a systematic review, and thus is left to the discretion of the treating surgeon.[108] Once the spacer is implanted, the soft tissue and skin are then closed with nonbraided suture for a permanent closure. Postoperatively, in addition to the local antibiotics within cement, systemic antibiotics are given intravenously. As always, antibiotics should be tailored to the infecting organism through infectious disease consultation.

7.7.2 Second Stage: Reimplantation

After 6 to 8 weeks of postoperative intravenous antibiotics, the surgeon can now consider reimplantation after a 2-week antibiotic holiday.[122] The surgeon can proceed with the second stage or reimplantation stage after completing antibiotics, when the wound has healed, and the control of infection has been confirmed using serum ESR and C-reactive protein (CRP) and/or synovial fluid evaluation.[122,123,124,125] If ESR and CRP are elevated, and/or the wound appears infected, then the patient should undergo a repeat I&D and antibiotic spacer exchange. Unfortunately, the optimal timing for reimplantation remains unknown, and there is no “gold standard” criteria currently in the literature to guide treatment.[123] Multiple studies assessing serum markers such as ESR and CRP for the optimal timing of reimplantation have been undertaken and no cutoff values have been determined.[124,126,127,128,129,130] Overall, most surgeons rely on the decreasing trend of both ESR and CRP before proceeding with reimplantation. Similar issues have been shown for synovial fluid analysis,[124,125,129,130,131,132] as the results of cell count, culture, and biomarkers before reimplantation can be contradictory. Overall, since there are no definitive metrics to guide reimplantation, timing should be based on resolution of clinical signs of infection, downtrends in serological markers, and results of synovial fluid analysis.[133]

When counseling patients for potential reimplantation, the surgeon should obtain consent from patients for reimplantation of implants as well as possible I&D and repeat antibiotic cement spacer implantation. After performing the arthrotomy, if there are greater than five polymorphonuclear cells per high-power field based on histology[134,135,136] or the joint appears grossly infected intraoperatively, then the patient should undergo repeat I&D and antibiotic spacer exchange with another round of systemic antibiotics. If the joint does not appear infected, the second stage entails removal of the antibiotic cement spacer, repeat I&D and reimplantation with revision hip or knee arthroplasty components, similar to the second half of a one-stage exchange arthroplasty.[106]

7.7.3 Outcomes of Two-Stage Exchange Arthroplasty

As with the other procedures discussed in this chapter, the reported success rates of two-stage exchange arthroplasty have been variable in the literature with eradication rates ranging from 66 to 95%.[128,137,138,139,140,141] There have been many reports of equivalent eradication rates between one- and two-stage exchange arthroplasties; however, these studies are difficult to interpret clinically.[92,94,142,143] A multitude of inconsistencies are present including sample size, operative technique, length of follow-up, and definition of treatment success. Additionally, while infection control is the primary concern in the treatment of PJI, there are other outcomes that need to be considered. There have been preliminary studies of one-stage exchange suggesting superior results in terms of mortality, functional score, and healthcare costs,[81,92,144,145,146] which has triggered the new-found popularity of one-stage exchange. While these recent results may be promising in appropriately selected candidates, it is too early to make definitive treatment decisions based on the limited available data. Many of these questions will hopefully be answered in the near future, as there are two ongoing prospective randomized control trials both in Europe and North America comparing one-stage versus two-stage exchange arthroplasty.[147,148]

7.8 Salvage Procedures for PJI

Fusion, amputation, and resection arthroplasty are three mainstay treatment options available for patients with persistent or recurrent PJI who are no longer candidates for successful prosthetic reimplantation. The indications for each of the aforementioned procedures are individualized and controversial.[149]

The choice between arthrodesis and amputation is still debated in the literature, and consensus on surgical decision-making in this population has yet to be made.[150] Patients with inadequate bone stock and lack of soft tissue envelope may benefit from amputation compared to arthrodesis. However, if both procedures are possible, one meta-analysis demonstrated that knee arthrodesis provided the highest expected quality of life after failing two-stage exchange arthroplasty for treating prosthetic knee infection.[151] Another study stated that patients who underwent fusions had better function and ambulatory status compared to patients who underwent above-knee amputation, which had poor functional outcome and a high mortality rate.[152] An alternative view is that amputation provides a greater ability for reconstruction with an external prosthesis representing a functional knee joint.[153] However, as most patients undergoing lower extremity arthroplasty are elderly, actual utilization of external prosthesis needs to be considered as age can be inversely correlated with prosthesis utilization.[154]

Resection arthroplasty is another option for salvage procedures used in patients that are unable to accept a prosthesis after multiple rounds of failed management for PJI. This option attempts to avoid the need for amputation while still controlling the infection by I&D but no prosthesis implantation.[149] The goal is to control infection and maintain the operative extremity at the expense of joint function, limb shortening, and potential instability. The functional outcomes can be acceptable with 74% of patients reporting satisfaction and 90% being able to ambulate, although with some form of walking assistance.[155] However, a recent study of patients undergoing girdlestone resection arthroplasty as salvage for THA PJI showed lower patient reported outcome scores compared to patients with lower limb amputations.[156] Overall, the specific surgical management

needs to be individualized for the patient and depends upon amount of adequate bone stock left after debridement, any persistent soft tissue infection, abductor weakness in the case of THA, the patient's clinical status, and patient's preference.

7.9 Conclusion

Periprosthetic joint infections in hip and knee arthroplasties are difficult problems to treat. Surgery is almost always indicated and there are multiple options to choose from. The goal of management is to eradicate infection, maximize function, and limit patient morbidity. The surgical options discussed in this chapter have different success profiles for each of the aforementioned goals, and it is vital that the treating surgeon understand his/her options and how it affects a patient's ultimate outcome. Choosing the appropriate surgical option is based on a thorough understanding of the chronicity of infection, the characteristics of the infecting pathogen, the local environment of the extremity, and the overall clinical status and wishes of the patient.

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8 Infection after Fracture Fixation and Infected Nonunions

Arvind von Keudell and Michael J. Weaver

Abstract
Infection after fracture surgery is a challenging entity. Prompt diagnosis and treatment is of paramount importance. Successful treatment includes culture-specific antibiotic therapy in collaboration with the infectious disease team.

Keywords: Infection, fracture surgery

Practical Tips

- Prompt identification of early deep infection is of paramount importance to avoid the sequalae of chronic osteomyelitis.
- Accurate microbiology diagnosis using multiple and adequate samples is crucial for targeted antibiotic therapy.
- In the case of Grade 3B open fractures, adequate debridement in conjunction with a plastic surgeon to enable expeditious closure has been shown to reduce infection.

8.1 Antibiotic Prophylaxis for Open Fractures

Open fractures represent a marker of high-energy trauma and significant soft-tissue injury. They are associated with an increased risk of infection, as bacteria on the skin or in the environment are given access to the deep soft tissues and fracture site.[1] Often, there is macroscopic contamination of the bone ends themselves. Further, areas of muscle or bone necrosis resulting from the trauma can make infections more difficult to control once established.

The prophylactic use of antibiotics in the setting of open fractures has been commonplace for over half a century. Open fractures are typically classified according to the system of Gustilo-Anderson (▶ Table 8.1).[2] When classifying open fractures, the injury is

Table 8.1 Gustilo-Anderson classification of open fractures classifies injuries based upon their most severe characteristic

Fracture type	Wounds	Fracture	Contamination	Other
Type I	< 1 cm	Minimal comminution and periosteal stripping	None	
Type II	1–10 cm	Moderate comminution, minimal periosteal stripping	Minimal	
Type IIIa	>10 cm	Severe comminution and periosteal stripping	Significant	
Type IIIb	>10 cm	Severe comminution and periosteal stripping	Significant	Requires soft tissue/flap coverage
Type IIIc	N/A	N/A	N/A	Requires vascular repair

assigned a type based on its worst feature. For example, an injury with a 2 cm wound, extensive fracture comminution, and periosteal stripping would be assigned type IIIa. The risk of infection in open fractures is directly related to Gustilo-Anderson type. While type I injuries have an infection risk similar to closed injuries when treated with prophylactic antibiotics and timely surgery, the risk of infection in type IIIb and IIIc fracture approaches 30 to 50% in some series.[3] The risk of infection in types II and IIIa fractures falls between these extremes.

Early administration of antibiotics has been shown to reduce the risk of infection in open fractures.[4] The American College of Surgeons (ACS) recommends that antibiotics be given within 1 hour of presentation to the hospital. Many systems now try to administer antibiotics on the scene or during transport by Emergency Medical Service (EMS) personnel.

Other factors that are associated with reduced risk of infection include a timely and thorough soft-tissue debridement and early soft-tissue coverage when a flap is required.[5,6,7] The exact timing of debridement remains controversial. Historically, open fractures were treated as an emergency and every attempt was made to take the patient to the operating room within 6 hours of the injury. The ACS now recommends that all open fractures be treated in the operating room within 24 hours, if possible. There are some injuries, particularly ones with extensive soft-tissue injury and/or contamination that may benefit from a more urgent debridement.

There is little agreement on the optimal choice of antibiotic for prophylaxis for open fractures. Many surgeons advocate for a first-generation cephalosporin for prophylaxis against low-grade open fractures (type I or II). High-grade open fractures (type IIIa/b/c) likely benefit from expanded coverage with either an aminoglycoside, fluoroquinolone, monobactam, or glycopeptide.[1] For injuries with soil contamination, the addition of penicillin or metronidazole can cover clostridial infections. An example of a reasonable prophylaxis protocol is presented in ▶ Table 8.2.

Antibiotic prophylaxis should be initiated as soon as feasible. Once started, it should be continued for 24 hours for low-grade injuries and up to 72 hours for high-grade injuries. Predebridement wound cultures have not been helpful in predicting infection or the organism of an eventual infection.[8] Postdebridement cultures may have some value in targeting any remaining bacteria before an infection becomes entrenched.[9]

Table 8.2 Guidelines for antibiotics prophylaxis in open fractures. Antibiotics should be administered within 1 hour of presentation to the emergency room

Fracture type	Preferred antibiotic regimen	β-lactam allergic patients	Duration
Low grade open (Types I and II)	Cefazolin 2 g (3 g if >120 kg) IV every 8 hours	Vancomycin 15 mg/kg IV every 12 hours	To continue until 24 hours following definitive wound closure
High grade open (Type III)	Ceftriaxone 2 g (3 g if >120 kg) IV every 24 hours	Vancomycin 15 mg/kg IV every 12 hours and Ciprofloxacin 400 mg IV every 12 hours	
Soil contamination	Add metronidazole 500 mg IV every 8 hours		

Abbreviation: IV, intravenous.

8.2 Diagnosis

8.2.1 Clinical Diagnosis

Infection after fracture surgery remains difficult to diagnose and historically has not been standardized. More recently, a consensus statement related to the definition has been proposed (▶ Fig. 8.1). Fracture-related infection (FRI) has been categorized into confirmatory criteria, such as fistula, sinus, wound breakdown, or purulent drainage from the wound, and suggestive criteria such as clinical or radiological signs indicating infection, joint effusion, elevated inflammatory markers, or wound drainage. This new definition may allow for better diagnostic accuracy and communication among surgeons. However, FRI does not attempt to classify infection, help with guiding treatment, or consider anatomical variations.[10]

FRI can occur at any point after fracture surgery. Diagnosis of early infection within the first 2 weeks is difficult. Trauma to the soft tissue may confound the clinical picture, and the classic clinical signs and symptoms of wound infection (i.e., pain, warmth, erythema, swelling, and fever) may be attributed to trauma or the operation. In general, a wound, with continuous drainage, that fails to epithelize within 7 to 10 days should raise the suspicion of a deep infection and should be treated surgically without delay (▶ Fig. 8.2).

The clinical signs of infection are generally more obvious 2 weeks after the fracture surgery. Early loosening of the hardware, pain, fever, and erythema around the incision site are common signs.

Late infection (>10 weeks) can be difficult to treat due to the likely development of biofilm, dead tissue, and fracture instability. Therefore, early diagnosis of deep infection is warranted to prevent major complications and prolonged treatment, which are associated with the development of chronic infection. Clinical signs, such as a sinus tract, are pathognomonic of a deep space infection after fracture surgery (▶ Fig. 8.3).[11]

8.2.2 Laboratory Tests

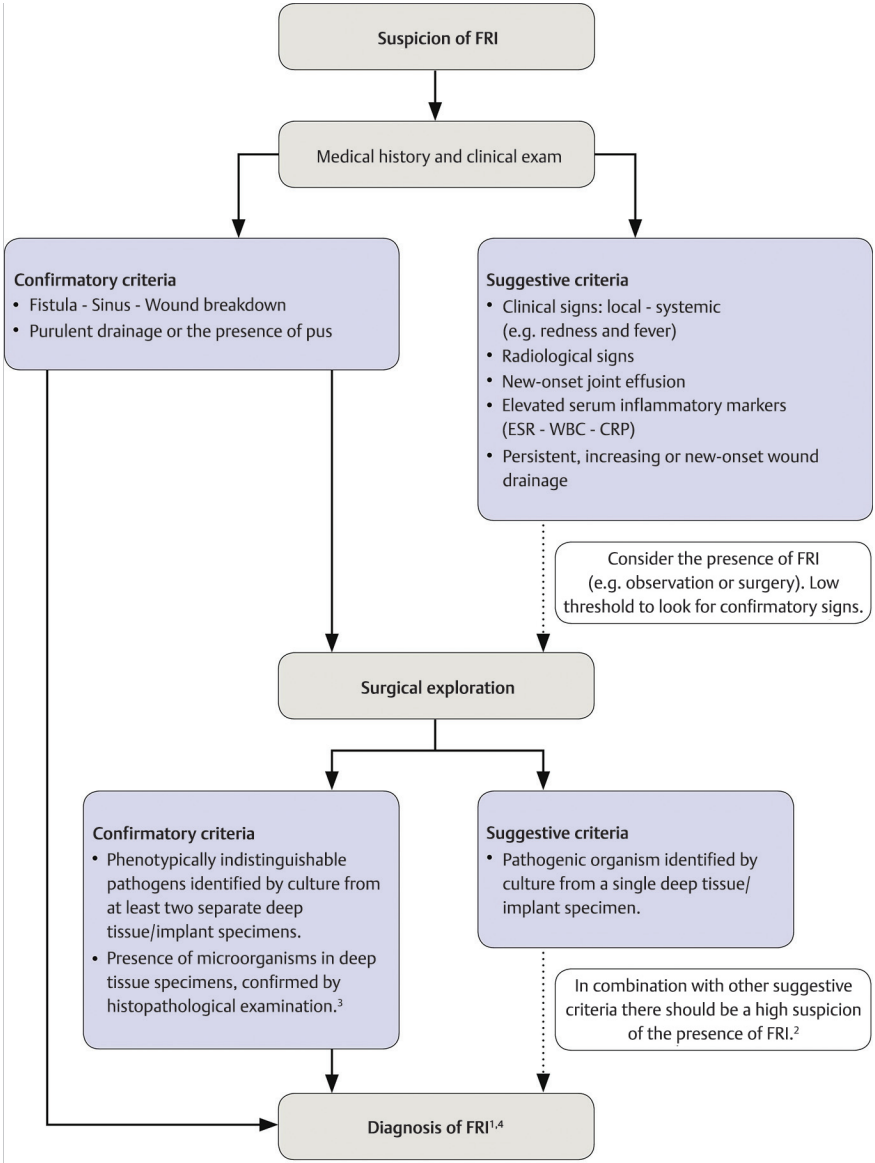
Laboratory studies looking for elevated serum inflammatory markers, such as white blood cell count (WBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), should be obtained. It is important to understand that these studies may not provide sufficient specificity but may be used as screening tools. WBC may be elevated in early infection but is often normal in chronic infections.[12] ESR is often elevated for the first 6 months after fracture surgery and therefore has a limited role in the early diagnostic workup. However, due to the high sensitivity of ESR, it may be used as a screening tool. Multiple variables such as poor nutrition, illicit drug use, age, fluid status, smoking, or infection elsewhere may influence the level of ESR.[13]

In contrast, CRP is an acute phase reactant with a half-life of 24 to 28 hours and usually normalizes within 2 to 3 weeks after the initial fracture surgery. An elevation after 2 weeks should raise the suspicion for deep infection and is generally more sensitive than ESR.[14]

8.3 Imaging

8.3.1 Radiography

Regular X-rays can be helpful in the later stages for diagnosing chronic infections but is not as useful for diagnosing acute infections. Similar to ESR, conventional radiography



[1] In cases of purulent drainage or fistula/sinus/wound breakdown, the presence of pathogens identified by CUlture is not an absolute requirement (e.g. in the case of chronic antibiotic suppression).
[2] If the positive culture is from sonicati0n fluid, it is highiy likely that FRI is present. This is especially true when virulent bacteria (i.e. *Staphylococcus aureus*) are present.
[3] The presence of microorganisms is confirmed by using specific staining techniques for bacteria and fungi.
[4] Future research iS required on the following criteria: acute inflammatory cell infiltrate on histopath0l0gĪCdl examination (e.g. PMN count), molecular diagnostics (e.g. PCR) and nuclear imaging (e.g. WBC scintigraphy).

Fig. 8.1 Diagnosis of fracture-related infection (FRI). CRP, C-reactive protein; ESR,erythrocyte sedimentation rate; PCR, polymerase chain reaction; PMN, polymorphonuclear; WBC, white blood cell count.

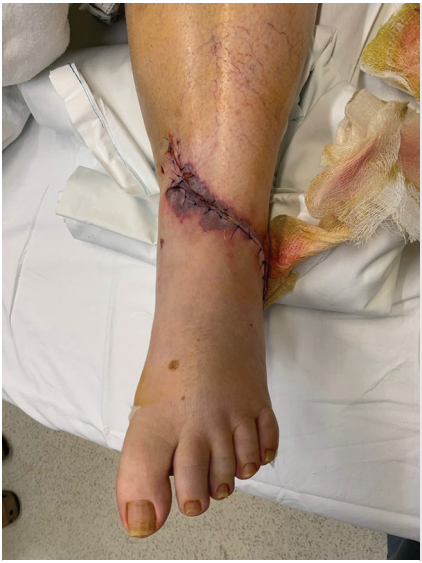


Fig. 8.2 A clinical photograph of a patient presenting with wound drainage and wound necrosis, 10 days following irrigation and debridement and surgical repair of an open type IIIa ankle fracture/dislocation.

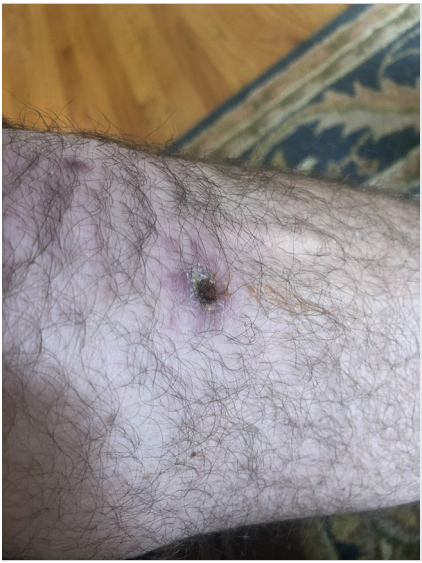


Fig. 8.3 A clinical photograph of a patient presenting with a draining sinus following intramedullary fixation of an open tibial shaft fracture. He developed a draining sinus 6 months following his injury at the site of one of the proximal interlock screws consistent with chronic osteomyelitis.

is not very specific for diagnosing FRI, but can rule out other causes of pain after surgery. Chronic infections can have multiple radiographic findings, such as hardware failure or loosening, osteolysis, periosteal elevation, or endosteal scalloping (▶ Fig. 8.4). Sequestrum, which is dead sclerotic bone, can often be visualized in the subacute or chronic stages of osteomyelitis. It is defined as an area of calcification within a lucent lesion, completely separated from the surrounding bone. In contrast, an involucrum is periosteal new bone formation around a sequestrum. An intraosseous abscess or

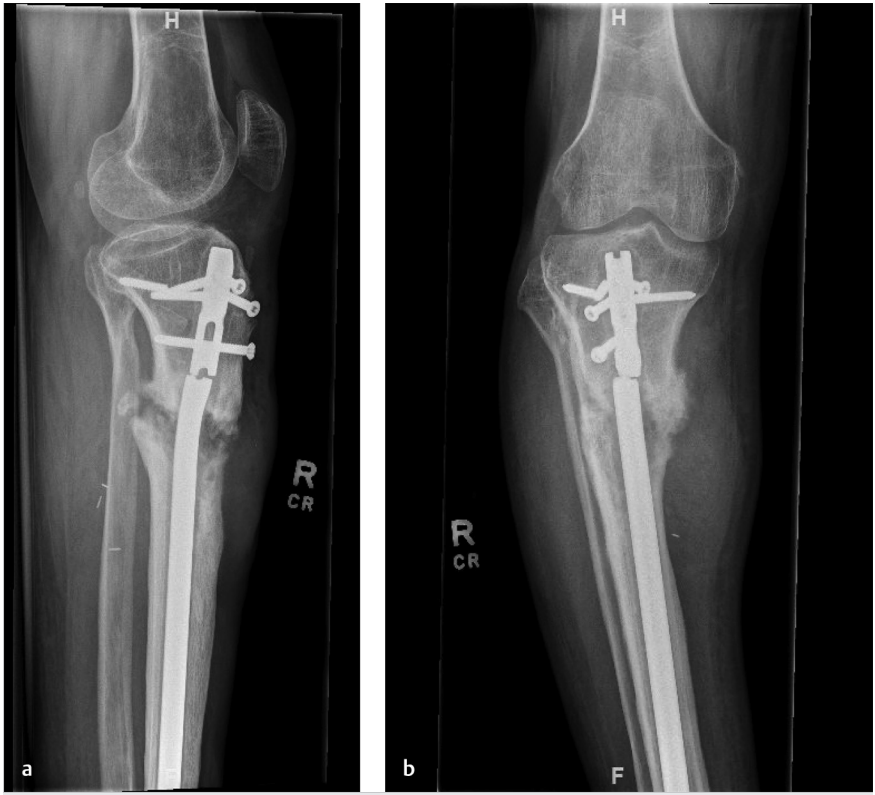


Fig. 8.4 **(a)** Anteroposterior and **(b)** lateral X-ray of a patient with an infected tibial nonunion with hardware failure.

Brodie's abscess can be present in chronic osteomyelitis and radiographically identified as an intramedullary cystic cavity.[15]

8.3.2 Computed Tomography

Computed tomography (CT) is a useful diagnostic tool to identify the spatial architecture of osseous destruction and the addition of intravenous contrast can show the extent of infection. It also is helpful to characterize the specific dimensions of a sequestrum or the presence of a sinus tract (▶ Fig. 8.5).[16] It may be easier to identify a sequestrum on cross-sectional imaging and can be useful for surgical planning.

8.3.3 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has evolved as one of the primary imaging modalities in the evaluation of the soft-tissue component of acute or chronic FRIs. It is very sensitive for the detection of osteomyelitis.[17] The three-dimensional imaging possibilities with multiple pulse sequences can highlight different soft-tissue characteristics. Fluid sensitive sequences show pathologic edema within bone and can delineate the extent of disease.

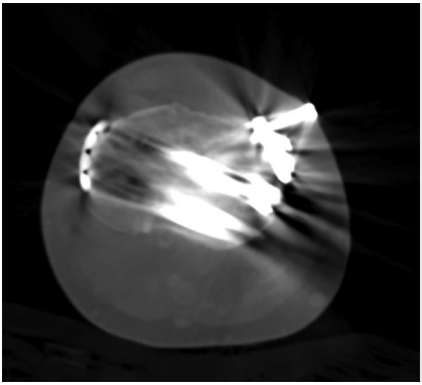


Fig. 8.5 Axial computed tomography (CT) scan demonstrating a sinus tract to the plate and screw construct of the proximal tibia.

T1-weighted images allow for the determination of anatomical details such as the medulla, cortex, periosteum, and soft tissues. T2-weighted images or other fluid sensitive sequences can display reactive bone marrow edema and other areas of infection. Abscess and sinus tracts can be better characterized with the addition of gadolinium administration with peripheral enhancement.[18]

8.3.4 Nuclear Medicine Studies

Nuclear medicine studies have been found to have a limited role in the setting of osteomyelitis after fracture surgery. The imaging modality is sensitive but not very specific with poor anatomical characterization. These studies generally involve the administration of an intravenous radionuclide that is detected by a gamma camera, such as the triple-phase bone scan, gallium, white cell scans, or 18 F-fluorodeoxyglucose positron emission tomography (FDG-PET).[19] Out of all these radionuclide studies, FDG-PET has been suggested to have the highest sensitivity in the diagnosis of chronic osteomyelitis.[20] Nuclear medicine studies may still have a role in the workup of chronic periprosthetic joint infection.

8.4 Microbiology

8.4.1 Cultures

When possible, it is ideal to hold antibiotics for approximately 2 weeks prior to obtaining cultures to improve yield. It is advisable to obtain at least three intraoperative cultures to send for aerobic and anaerobic, fungal, and acid-fast bacilli (AFB) testing, and to maintain cultures for a minimum of 14 days to detect slow growing bacteria such as *Cutibacterium acnes*. If fungus or *Mycobacterium tuberculosis* is suspected, cultures should be held for 4 to 6 weeks. In general, a greater number of cultures from multiple sites in patients with lower grade infections can be useful to improve the capability of detecting an organism. Swabs from superficial wounds or sinus tracts are commonly polymicrobial and are not useful for targeted antibiosis. More recently, sonication has been suggested as a way to definitely diagnose late FRIs. Sonication, or application of low intensity ultrasound, can dislodge the biofilm from the implant and the sonication fluid can subsequently be cultured on a bacterial media.[21,22] This process has been found to be highly sensitive for deep infection, but evidence remains weak in FRIs and therefore can be used as an adjunct to tissue cultures. Similarly, molecular techniques

Table 8.3 Most common microorganisms from fracture-related fixation devices causing infections and possible antimicrobial treatment options

Microorganism	Frequency (%)	Possible antimicrobial agent
Staphylococcus aureus	30	MSSA—Rifampin/Ciprofloxacin MRSA—Rifampin/Vancomycin
Coagulase-negative Staphylococci	22	MSSA—Rifampin/Ciprofloxacin MRSA—Rifampin/Vancomycin
Gram-negative bacilli	10	Cefepime
Anaerobes	5	Clindamycin
Enterococci	3	Penicillin G or ampicillin
Streptococci	1	Penicillin G or ceftriaxone
Polymicrobial	27	Amoxicillin/Clavulanic acid or Meropenem
Unknown	2	

Abbreviations: MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-susceptible *Staphylococcus aureus*.
Source: Adapted from Trampuz et al and Zimmerli et al[24,25]

such as polymerase chain reaction (PCR) or other sequencing techniques have been found to have low utility in FRI.[23]

8.4.2 Common Organisms

Staphylococcus aureus is the most common organisms responsible for FRI, followed by *Staphylococcus epidermidis* and gram-negative organisms (▶ Table 8.3). The targeted antibiotic regimen should be based on culture data and administered by the infectious disease team.

8.5 Surgical Treatment

The goal of surgical management is to debride all devitalized tissue, debulk the infection, provide skeletal stability, and achieve adequate soft-tissue coverage. A thorough exploration in the operating room is imperative. All dead tissue must be removed, and infectious and all purulent material should be copiously irrigated. Skeletal stability is important to protect the soft tissues and promote fracture healing. Skeletal stability dictates whether the hardware should be retained, should be removed and a temporary antibiotic spacer placed, or should be removed entirely. Once the fracture is addressed, soft-tissue coverage can be particularly challenging and may require soft-tissue rearrangement or transfer to provide dead space management. Postoperatively, it is critical to address and optimize each patient's nutritional status to optimize healing.

8.5.1 Irrigation Solutions

Various different irrigation solutions with additives have been used in the past to help with removal of cellular debris and surface pathogens. To date, the largest study to assess the most efficacious fluid solution and application to reduce reoperations has been performed for open fractures, but can likely be extrapolated to FRI.[26] The study found that low pressure, normal sterile saline irrigation has the lowest rate of reoperations. There is

currently no consensus whether antibiotic additives such as bacitracin, or antiseptics such as diluted betadine solutions, have a clinically meaningful benefit.[27]

8.5.2 Pin Tract Infections

Pin tract infections are common. Most pin site infections are due to poor surgical technique causing soft-tissue impingement and tethering due to small skin incisions, which can be alleviated by making larger skin incisions. It has also been suggested that excessive heat generation during insertion can be avoided by predrilling. Thermal necrosis can lead to early loosening, and this loosening can lead to pin tract infections. There is currently no consensus on optimal postoperative pin site care to reduce pin site infections. Many studies evaluate different variables, such as cleansing solution or frequency of cleaning, in a nonstandardized fashion that prevents drawing conclusions.[28]

Pin tract infections have been categorized into five different clinical scenarios by Dahl et al with grade 0 being normal and 5 defined by purulent drainage and osteolysis, as well as sequestrum or a Brodie's abscess within the medullary canal (▶ Table 8.4).[29] Oral antibiotics and daily pin site care can be useful to suppress local infection in the early stages to avoid pin loosening. Although there is no standard of care for pin site, one recommended regimen includes twice daily pin site care with a solution of 1:1 hydrogen peroxide and normal saline, limiting the weight bearing, elevation of the extremity, and oral antibiotics, such as cefadroxil. Once osteolysis is visible on X-ray, the pin needs to be removed or replaced.

The authors' preferred method for pin care entails daily cleaning with a sterile cotton-tipped applicator that has been soaked in a solution of 1:1 hydrogen peroxide and normal saline. Sterile gauze is then wrapped around each pin site and daily showering is allowed, starting from postoperative day 3.

8.5.3 Irrigation and Debridement with Hardware Retention

Irrigation and debridement, hardware removal, and intravenous antibiotics are considered the most definitive treatment for FRIs. However, for early infections after fracture fixation surgery, mechanical stability is paramount for facilitating bony union. It has been suggested that mechanical instability promotes infection. Early infection is usually associated with rapid soft-tissue and bony destruction with loss of fixation. All infected or dead-appearing tissue has to be radically debrided at the time of surgical intervention, but the hardware may remain in place if it is stable and adequate soft tissue can cover the area. Once bony union has been achieved as suggested on CT or X-ray, the hardware should ideally be removed due to the development of the biofilm on the hardware and potential persistence of chronic infection even after debridement.[30]

Table 8.4 Pin site infections as categorized by Dahl et al and treatment options

Grade 0	Normal, treat with daily pin care
Grade 1	Inflamed, treat with daily pin care
Grade 2	Serous drainage, treat twice with daily pin care and start oral antibiotics
Grade 3	Purulent discharge, treat twice with daily pin care and start oral antibiotics
Grade 4	Osteolysis, pin removal
Grade 5	Ring sequestrum, debridement

8.5.4 Irrigation and Debridement with Hardware Removal

The development of a biofilm on metal is usually resistant to antimicrobial therapy due the presence of the extracellular matrix protective covering on the hardware. Similarly, the presence of devascularized bone fragments may limit the penetrance of antimicrobial therapy. In these situations, hardware removal and excision of dead bone fragments with its associated dense fibrous tissue is part of successful treatment of chronic infections. Bony debridement should be performed until punctuate bleeding from the bone is visible (Paprika sign).[31] If the bone demonstrates sufficient stability, no further revision fixation is necessary. If the fracture is not united, then either a one- or two-stage approach may be appropriate, depending on the clinical scenario.

8.5.5 Irrigation and Debridement and Revision Fracture Surgery—One-Stage

If there is significant instability or motion at the fracture site after hardware removal, the application of an external fixation device could be considered. Revision fixation with new hardware can be contemplated in areas where external fixation is not applicable, such as the proximal femur, proximal humerus, or pelvis. Revision fixation, however, has been associated with a higher rate of infection recurrence and often requires future hardware removal once bony union has been achieved.[32]

Sometimes debridement leaves a large bony gap that the body is unable to overcome, but revision surgery can be performed. In these situations, multiple reconstructive options are available, including limb shortening, autogenous or allogeneic bone grafting, or the usage of distraction osteogenesis. These are complex surgical procedures that should be referred to a tertiary care center.

8.5.6 Irrigation and Debridement with Hardware Removal and Antibiotic Spacer Placement—Two-Stage

For severe infection without bony union, a “hardware holiday” may be required. The wound is debrided and all fracture implants are removed. Temporary stabilization is provided with an antibiotic spacer, an external fixator, or a splint. Dead space management after radical debridement is critical and can be achieved using antibiotic impregnated polymethyl methacrylate (PMMA) in the form of beads, rods, or blocks. These spacers elute antibiotic locally up to 90 days.[33]

One may consider using Palacos bone cement impregnated with gentamicin (Heraeus, Hanau, Germany), which has been shown to elute antibiotics better than other cement forms mixed with 1 vial (1.2 g) of tobramycin and 1 g of vancomycin powder.[33]

In cases of chronic infections of an intramedullary device, the hollow part of the nail may act as a dead space and host dead bone can harbor infection with retention of the implant. In general, the infected nail should be removed and the canal overreamed by 1 to 2 mm while ensuring adequate irrigation and a distal venting hole to prevent endosteal thermal necrosis. If instability exists after nail removal, reinsertion of an antibiotic covered nail can be considered.[34] The antibiotic PMMA mixture described above can also be used to custom mold an intramedullary antibiotic covered nail using a chest tube with a 2- or 3-mm guidewire and a cement gun. Mineral oil can be applied to the chest tube to prevent adherence of the cement to the tube.

Once the infection is controlled, as determined by decreasing serum inflammatory laboratory values and complete wound healing, definitive fixation and wound coverage can then be attempted. Usually after 6 to 8 weeks, the PMMA construct can be removed and bony reconstruction can be performed with revision plating or intramedullary nail fixation.

8.6 Soft-Tissue Coverage

Dead space management and soft-tissue coverage are critically important to reduce the risk of infection. In general, it is advisable to involve a plastic surgery consultant early on to help with soft-tissue coverage. Timely *soft-tissue coverage* has been suggested to prevent desiccation of bone and associated *tissues*, expedite healing, clear bacteria, and thereby possibly reduce the risk of *infection*. Depending on the location of the infection, local flaps such as the gastrocnemius flap for proximal tibia defects can be utilized. Distal tibia soft-tissue defects are more commonly addressed with a free flap.[35]

8.7 Antibiotics

After the initial debridement for FRI, empiric and broad-spectrum antibiotics should be initiated until sensitivities from the deep culture data are available. Often, the best antibiotic regimen can be determined through consultation with the infectious disease service. Musculoskeletal infections are commonly treated with 6 weeks of organism-specific intravenous antibiotics via a peripherally inserted central catheter. There are some who advocate for primary treatment with an oral regimen, although this has not become common practice at this time.[36]

If there are clinical signs of infection, but cultures remain negative, empiric treatment with 6 weeks of intravenous antibiotics should be considered. Patients with "culture-negative" infections treated by surgical intervention and antibiotics have similar outcomes as those with identified organisms.[12]

There may be a role in an oral tail of suppressive antibiotics following the initial course of antibiotic therapy to give soft tissues and bone time to fully heal and allow for implant removal if the infection recurs.[10]

8.8 Conclusion

Infections following fracture surgery are challenging to treat. They require a multidisciplinary approach involving orthopaedic surgeons, infectious disease specialists, and often plastic surgeons. The principles of treatment are aggressive surgical debridement with removal of all devitalized tissues, skeletal stabilization, adequate soft-tissue coverage, and culture-specific antibiotic therapy.

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9 Spine Infections

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Abstract
Spine infections can have significant morbidity and mortality if not identified and treated appropriately. This category of orthopaedic infections can include infections involving the epidural space (spinal epidural abscesses), vertebral column (vertebral osteomyelitis), or the intervertebral disks (diskitis). These conditions can predispose patients to significant consequences including neurologic compromise, deformity, and pain. Accurate diagnosis of spine infections is based on clinical history and examination, along with appropriate imaging and laboratory tests. Treatment of these infections entails medical management with antibiotic therapy, or, in cases with progressive neurologic deficit or deformity, surgical methods that include open decompression with correction of deformity as indicated.

Keywords: Epidural abscess, vertebral osteomyelitis, diskitis, spinal fusion, spinal cord compression, kyphosis

Practical Tips

- Spinal infections can affect several locations in the spine, including the epidural space, vertebrae, or intervertebral disks, and can arise from several different mechanisms.
- Clinical manifestations of spinal infection often include fever, back pain, and occasionally, neurologic deficits.
- Detailed, serial neurologic examination should be performed in any patient with suspected spinal infection. MRI with gadolinium contrast is the mainstay of imaging studies that aid diagnosis, while laboratory studies often demonstrate elevated white blood cell count and inflammatory markers.
- Medical management should typically be considered first for spinal infection, although the presence or progression of neurologic deficit or spinal cord compression, worsening of disease, or spinal mechanical instability frequently warrants surgical intervention.
- In both medical and surgical cases, infectious disease consultation is invaluable in the treatment of spinal infection and typically requires at least 6 weeks of antibiotic therapy.
- When required, surgical intervention often involves irrigation and debridement of affected bone/soft tissue and decompression of neural elements as necessary. Despite active infection, instrumentation and fusion may be indicated to provide mechanical stability or address spinal deformity caused by the disease.

9.1 Spinal Epidural Abscesses

9.1.1 Introduction and Epidemiology

A spinal epidural abscess (SEA) is a collection of pus in the epidural space of the spinal canal. While these can present atypically and have a relatively benign course, they can

also lead to neurologic compromise or death. The incidence of SEAs has risen in recent years, from 0.2 to 1 cases per 10,000 hospital admissions to 5.1 cases per 10,000 hospital admissions, which is thought to be due to the increasing aging population in the United States, improved diagnostic modalities, and increasing prevalence of risk factors such as intravenous drug use (IVDU), alcoholism, renal insufficiency, immunosuppression, and diabetes mellitus.[1,2,3,4] Other risk factors for SEA previously identified include human immunodeficiency virus (HIV) infection, dental abscesses, hemodialysis, tattoos, and acupuncture.[5,6] More broadly, SEA can result from any condition that causes bacteremia.[3] Diabetes mellitus remains the strongest risk factor for SEA, although SEAs resulting from IVDU and epidural catheterization or pain pump placement are becoming increasingly prevalent.[7] SEAs have a median age of onset of 50 years of age, although the highest prevalence occurs in the sixth and seventh decades of life.[3] SEAs tend to occur more commonly in males, with a ratio of men to women of 1 to 0.56 in one meta-analysis.[8]

9.1.2 Anatomy and Pathogenesis

SEA is thought to arise through several different means, including: (1) direct inoculation from trauma, spinal surgery, or procedures such as pain catheter placement or epidural anesthesia, (2) hematogenous seeding, or (3) contiguous spread from adjacent soft tissues or bone (e.g., psoas abscess or vertebral osteomyelitis). Despite this, approximately one-third of cases have no identifiable source of the infection.[9,10,11]

Approximately 86% of cases arise in the thoracic or lumbar spine, while 14% arise in the cervical spine.[12] This is in part due to the larger epidural space in the thoracolumbar spine, as well as the presence of more fatty tissue that may create a favorable environment for infection persistence.[9,13,14] SEAs are also found to occur more frequently in the posterior spinal column, with anterior SEAs comprising only 20% of all cases; this is thought to be due to the contiguous spread of infection from adjacent vertebral bodies in the setting of vertebral osteomyelitis or from the intervertebral disk in the setting of pyogenic infectious diskitis.[9,15] As the epidural space is a vertical sheath, epidural abscesses typically involve multiple levels of the spinal cord, averaging three to five levels in one study.[13]

Noncontiguous SEAs (skip abscesses) may also occur, although these are much more uncommon (9% of all SEA cases), with one prior study noting delay in presentation by >7 days, serum erythrocyte sedimentation rate (ESR) >95 mm/hour at presentation, and a concomitant area of infection outside of the spine as three significant risk factors of noncontiguous SEA.[16] In this study, the probability of a skip lesion was 73% in patients with all three predictors, 13% in patients with two, 2% in patients with one predictor, and 0% in patients with none of the above predictors.[16] Damage to the spinal cord from SEA is thought to result from multiple mechanisms, including direct compression of the spinal cord, compression of local venous or arterial blood supply, and indirectly via the presence of bacterial toxins or production of inflammatory mediators during the immune response.[7]

9.1.3 Presentation and Diagnosis

Although classically described as presenting with the triad of fever, spinal pain, and neurological deficit, SEAs often present with nonspecific initial manifestations at onset leading to delayed or missed diagnosis.[17] Prior literature has suggested that only a small

proportion of patients have all three components of the classically described triad at presentation (13% in one study), highlighting the importance of accurate history and physical examination and proper diagnostic and laboratory testing.[6] Indeed, one recent retrospective study of 250 cases of SEA demonstrated that up to 55% of SEA cases had a missed or incorrect diagnosis during the course of initial workup with up to a 12-day delay in diagnosis of these cases.[18] Fever was also only found to be present in 48% of patients in another case series from a single tertiary care center, and another study demonstrated that the median number of visits to the emergency department was two before admission and treatment.[19,20] Additionally, 98% of patients in this case had one or more of the features missing from the classic triad of SEA.[20] As such, although the diagnosis of SEA is overall uncommon, it is important to consider SEA and rule out the diagnosis before attributing presenting complaints to other etiologic sources.

Since few patients display the classic triad of symptomatology, SEAs may follow the sequence of focal and severe back pain, followed by radicular pain, motor weakness, and finally bowel or bladder incontinence and paralysis as late-stage symptoms that rapidly become permanent.[13] With regard to the prevalence of symptoms, back or neck pain is most common (88%), followed by fever (61%), paresis (54%), bladder/bowel dysfunction (37%), sepsis (17%), and radiculopathy (12%).[21] It is imperative that the diagnosis of SEA be considered in any febrile patient with spinal pain, particularly in those who have recent or known bacteremia, risk factors for SEA, or neurologic symptoms such as radicular pain or motor weakness.

Laboratory studies that may be helpful in the diagnosis of SEA include ESR (normal ranges 0–20 mm/hour in females and 0–15 mm/hour in males) and C-reactive protein (CRP) (normal range typically <10 mg/L). ESR has been shown to be of more important utility over CRP, with ESR elevated in 94% of patients in one study, while CRP was elevated in 87%.[8] Davis et al demonstrated ESR elevation in 100% of patients with SEA, while only 33% of patients without SEA had elevated ESR; the average elevated ESR in this study was 76.5 mm/hour.[20] Serum white blood cell (WBC) count is typically less useful, with this study showing that only 60% of patients who had SEA presented with leukocytosis to the emergency department.[20]

Imaging is crucial for diagnosing SEA. MRI with gadolinium contrast is the imaging modality of choice, as it is highly sensitive for SEA early in the course of infection, and allows for the highest imaging resolution for localization and extent of SEA involvement (▶ Fig. 9.1). Imaging of the entire spinal cord should be considered in patients with risk factors of noncontiguous SEA as noted previously, or in those with symptoms that do not localize well to only one region of the spine. In patients in whom gadolinium contrast is contraindicated, MRI without contrast is often still sufficient for diagnosis, with the most sensitive feature being paraspinal edema.[22] In patients who cannot undergo MRI, computerized tomography (CT) scanning with intravenous (IV) contrast is the

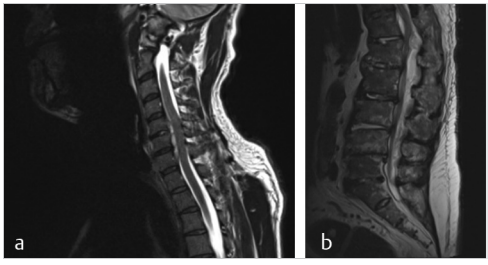


Fig. 9.1 Examples of anterior spinal epidural abscess (SEA) (**a**), posterior contiguous SEA (**b**).

Table 9.1 Initial presentation and workup of spinal epidural abscesses (SEA)	
Clinical manifestations	• Fever, spinal pain, neurological deficit (triad)
Initial laboratory tests	• Complete blood count with differential, ESR, CRP, two sets of blood cultures
Imaging studies	• MRI with gadolinium contrast • If unable to undergo MRI, CT scan with contrast • X-ray images typically only useful in diagnosis of long-term sequelae of concomitant osteomyelitis or diskitis
Other workup	• Consider IR-guided aspiration of abscess (difficult to do in anterior SEA) • Lumbar puncture recommended against given low diagnostic yield and potential to inoculate subarachnoid space

Abbreviations: CRP, C-reactive protein; CT, computed tomography; ESR, erythrocyte sedimentation rate; IR, interventional radiology; MRI, magnetic resonance imaging.

next option of choice. X-rays of the spine are typically insufficient for diagnosing SEA and may only demonstrate the longer term sequelae of changes from concomitant or causative osteomyelitis or diskitis, and myelography is typically not recommended due to its invasiveness and potential for iatrogenic contamination of the subarachnoid space.[2,3,13,23]

Once SEA has been identified by imaging, two sets of blood cultures should be obtained to try to isolate the responsible organism. Aspiration of the SEA itself can also be considered, as this is more likely to be positive than blood cultures, although the location of the SEA may make interventional radiologic aspiration difficult, especially in anterior SEA.[5] A lumbar puncture is typically not recommended due to the low diagnostic yield and the risk of iatrogenic inoculation of the subarachnoid space if the diagnostic needle traverses the SEA. One study demonstrated the rate of positive cultures from the SEA itself to be 90%, while blood cultures were only positive in 62% of SEA cases, with cerebrospinal fluid (CSF) being the least diagnostic at 19%.[5,13] A summary of initial presentation and workup are stated in ▶ Table 9.1.

Staphylococcus aureus is the most common organism identified as causing SEA, accounting for approximately two-thirds of all cases.[5,9,24,25] This is followed by gram-negative bacilli (16%), streptococci (9%), and coagulase-negative staphylococci (3%), which are often observed in patients with spinal instrumentation.[5,25] Within *S. aureus* infections, the presence of methicillin resistance ranges from 25 to 68% and varies based on institution.[4,5,17] An important cause of SEA in the developing world is also *Mycobacterium tuberculosis*, which may be in the setting of tuberculous spondylitis (Pott's disease).[26,27] *Pseudomonas aeruginosa* is also an important organism to consider in SEA, particularly in patients with history of prior or current IVDU.[28]

Differential diagnoses for SEA include vertebral diskitis and osteomyelitis, meningitis, herpes zoster (prior to presence of vesicular lesions), degenerative disk disease or disk herniations, and metastatic tumors of the spine.

9.1.4 Management and Surgical Decision-Making

Antibiotics should be started rapidly for empiric coverage of SEA after the collection of blood cultures once the diagnosis of SEA is suspected. The duration of antibiotic therapy is typically 4 to 8 weeks of IV antibiotics dictated by culture data. This is often dictated by infectious disease consultation, and longer courses may be selected in patients in whom hardware or bone graft (in particular, allograft) must be retained in order to

preserve the mechanical stability of the spine.[29,30] Frequently, empiric regimens are vancomycin (15 to 20 mg/kg every 8 to 12 hours with a goal serum trough concentration of 15 to 20 mcg/mL) and either a third- or fourth-generation cephalosporin, such as ceftriaxone (2 g IV every 12 hours) or cefepime (2 g IV every 8 hours). This allows for *Staphylococcus* (including methicillin-resistant *S. aureus* [MRSA]) coverage as well as *Streptococcus*, and aerobic gram-negative pathogens.

Medical management alone may be considered in patients who have no neurologic deficit and in those who have significant medical comorbidities in whom surgery may not be tolerated.[3,31] In addition, the location of the epidural abscess may influence the decision for medical management, as lumbar epidural abscesses may be better tolerated than thoracic epidural abscesses given the presence of the spinal cord at the thoracic levels as opposed to only the cauda equina in the lumbar spine below the level of the conus, which may be more tolerant of space occupying lesions such as SEA.[32] One retrospective study of 52 patients demonstrated that 83% of patients with SEA that were medically treated had good or excellent early neurologic outcomes at a median follow-up of 2 months, with excellent outcome defined as complete recovery, and good outcome defined as ability to walk without aids but with residual pain.[33] If medical management is selected, serial neurologic examination is of paramount importance, as any deterioration in neurologic status is an indication for surgical treatment.

Based on the location of the SEA, percutaneous drainage via interventional radiologic approaches may also be considered in select cases, particularly in patients who have adjoining abscesses such as psoas or paravertebral abscesses, with one recent study demonstrating effective treatment in 69% of cases of SEA.[34]

With regards to surgical management, this is typically determined on a case-by-case basis, with indications for surgery being symptomatic spinal cord compression, progressive neurologic deficit, spinal instability, or persistence or progression of disease despite appropriate antibiotic therapy. In these patient groups, surgical intervention within 24 hours after the onset of neurologic symptoms leads to improved outcomes.[35] Prior studies have demonstrated predictive factors for failure of medical management, including age greater than 65, impaired neurological status, diabetes, and MRSA infection.[1] When surgical intervention is indicated, the standard of care is typically laminectomy and debridement in the case of posterior SEAs, while anterior SEAs may require anterior decompression in order to adequately decompress the lesion and subsequent stabilization via anterior and/or posterior approaches.[32,36] Cultures should be taken prior to initial irrigation. There is variability amongst surgeons with regard to preferences for volume and type of irrigation, but in our experience, this is typically 9 L of saline via gentle gravity. After initial irrigation, any hardware or graft that can be removed without compromising mechanical stability should also be removed, although typically instrumentation in nonfused spines is initially retained. At this point, any compromised bone should also be removed after appropriate preoperative planning that accounts for any mechanical instability that may be introduced. Indeed, cages, allograft, or autograft may also be beneficial or mechanically necessary in the case of larger defects in the anterior spine, with fibular allograft and humeral allograft historically used successfully for cervical and thoracolumbar spine reconstruction.[32] In these cases, surgical judgment must be used to adequately debride infected tissue while balancing the consideration of maintaining spinal stability and the introduction of hardware or graft into an infected site. In these patients, infectious disease consultation becomes particularly useful postoperatively in determination of postoperative antibiosis, which may require long-term suppression or eventual need for planned hardware removal,

such as in the case of spinal fusion pending bony fusion.[21,29] Prior studies have also shown that surgical debridement alone versus debridement with instrumentation had similar rates of failure and recurrence, suggesting instrumented therapy can be safely performed in conjunction with appropriate parenteral antibiotic therapy when indicated.[37]

Then, irrigation with another 9 to 12 L of saline should be repeated, with cultures obtained post irrigation. Closure should typically be with nonbraided monofilament suture and vancomycin powder may be considered, although its effect is still a topic of debate and has not been specifically studied in the context of SEA.[38] Negative pressure wound therapy may also be considered for its effect in improving local wound environment.[39] Postoperative care should involve empiric IV antibiosis pending infectious disease consultation, with postoperative activity dictated based on the specific type of surgery performed and the relative stability of the spine pending surgical intervention, typically 6 to 8 weeks after surgery.

Follow-up MRIs may be obtained in cases of persistent infection or deterioration of symptoms. In general, shorter treatment courses using IV antibiotics are implemented in patients in whom either surgical drainage has occurred or who do not have retained hardware or concomitant osteomyelitis, while longer courses may be provided to medically managed patients, those responding poorly to antibiotic therapy, or those with retained hardware or graft as a necessity to preserve mechanical spinal column stability.[37]

9.1.5 Prognosis

SEA has a 5% rate of mortality typically as a result of sepsis, while paralysis occurs in approximately 4 to 22% of patients[5,7,9,13] with SEA. Residual weakness is associated with diagnostic delay of more than 24 hours (45% vs. 13% in one study), and duration of neurologic deficits predicts the degree of neurologic recovery after treatment.[20] One prior case-control study assessing 5-year outcomes of 29 patients with SEA matched with patients with traumatic spinal cord injury (TSCI) demonstrated a much higher rate of conversion of patients from American Spinal Injury Association (ASIA) Impairment Scale (AIS) grade A deficits to incomplete status (grade B or higher) compared to the TSCI group (73% vs. 9%), and a higher rate of conversion from motor complete (ASIA A or B) status to motor incomplete status when compared with TSCI-matched controls (76% vs. 32%).[40] This suggests that although recovery may still be significantly delayed, some improvement in neurologic status related to SEA may be possible, while the course of recovery from SEA is not easily predicted for the TSCI patient population.[40] With early recognition and vigilant diagnosis of SEA, however, overall good outcomes can be achieved with medical and/or surgical management as indicated.

9.2 Vertebral Osteomyelitis and Diskitis

9.2.1 Introduction and Epidemiology

Infectious spondylitis, or inflammation of the bones of the spinal vertebrae or intervertebral disks in the setting of infection, encompasses a broad spectrum of pathology that can be broadly broken down into vertebral osteomyelitis (VO) and diskitis. VO is an infection of the vertebral bodies and diskitis is an infection of the inter-vertebral disk space. These often occur concurrently and have similar pathophysiology, presentation, and management. VO has been rising in incidence and is an increasing burden to the healthcare system. The incidence of VO has increased from 2.9 cases per 100,000 to

5.4 cases per 100,000 between 1998 and 2013.[41] The incidence of VO increased at a rate of about 0.3 cases per 100,000 with increasing age.[42] This has been associated with a rise in healthcare dollars for the treatment of VO from $188 million to $1.3 billion.[41] Diskitis occurs at a rate of 0.4 to 2.4 cases per 100,000.[43,44] Some estimates have noted a higher incidence among males with a ratio as high as 5:1 compared to females,[42,45] although other studies indicate that VO affects males and females equally.[41] A similar male predominance is seen in diskitis with males having 1.5 to 3 times more cases of diskitis.[46]

9.2.2 Anatomy and Pathogenesis

Sources of infection in VO and diskitis include hematogenous spread, direct procedural inoculation, or contiguous spread; similar to SEA. Hematogenous spread is the most common cause and typically affects the lumbar spine.[47] As the nucleus pulposus is avascular, it is hypothesized that bacteria depositing in the end-arterial zones of the vertebral body metaphysis leads to ischemic bone that then become super-infected and cause spread of infection to the adjacent disk space.[44] With regard to hematogenous spread, the most common source is typically from IV catheters and urinary tract infections.[48] In several case series, the urinary tract was found to be the most common source of infection.[45,49] Endocarditis may also be associated with the development of VO, with one case series of 91 cases of pyogenic VO noting that up to 30% of patients had concurrent endocarditis.[50]

Interestingly, VO has been associated with bacteremia for up to a year prior to the onset of its diagnosis, and as such, the index of suspicion for VO should be high in patients presenting with back pain and a history of bacteremia within the preceding year.[51] Medical comorbidities that also increase the risk of VO or diskitis include diabetes mellitus, cirrhosis, coronary heart disease, malignancy, autoimmune diseases requiring immunosuppression, and chronic kidney disease, especially patients on hemodialysis.[52,53,54] The lumbar spine is the most common location of infection for both VO and diskitis (about 60% of cases), followed by the thoracic spine and the cervical spine, with rare cases involving multiple spinal segments (5% of cases).[51,52,55]

Staphylococcus aureus is by far the most common pathogen causing VO and diskitis with rates ranging from 30 to well over 50% of cases.[42,43,56,57] *S. aureus* is particularly virulent in spondylitis owing to its ability to adhere to tissue and implants, form biofilms, and enzymatically invade tissue.[47] Risk factors for *S. aureus* infectious spondylitis include invasive procedures, insulin use, hemodialysis, catheter infection, and recent bacteremia.[53] Gram-negative rods including *Enterobacter* and *Escherichia coli* are the next most common pathogens[58] and are more prevalent among older, medically complicated patients.[52] *Staphylococcus epidermidis* and coagulase-negative staphylococci may also be identified in the case of postoperative or postprocedural cases of infectious spondylitis[49]; *Propionibacterium acnes* and other biofilm forming organisms are more likely to be observed in late-onset infections following instrumentation or implants.[59] Rarely, other pathogens implicated in spondylitis include *Brucella* and fungal infections.[60,61,62]

In areas of the world where tuberculosis (TB) is endemic, mycobacterial infection of the spine, or Pott's disease, is a common cause of VO, with rates as high as 30% of all cases.[62,63] In contrast to pyogenic VO, mycobacterial infections may only affect the vertebral body and leave the intervertebral disks unaffected, leading to phenomena such as concertina collapse or gibbus spine (focal kyphotic deformity in the thoracolumbar spine, ▶ Fig. 9.2).[64,65] Other unique microbial associations include *Salmonella* in sickle

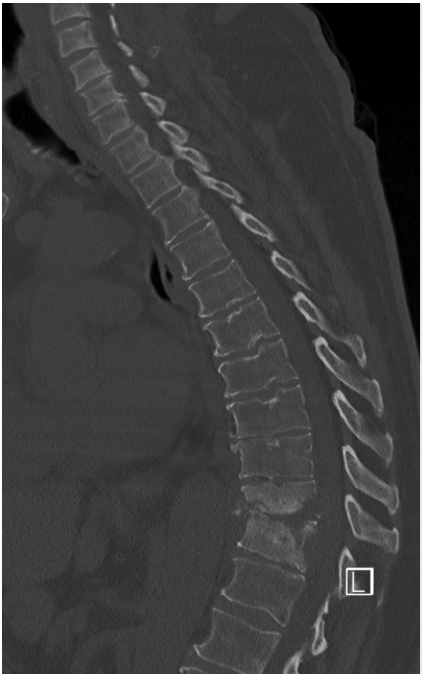


Fig. 9.2 Example of gibbus deformity of a spine with vertebral body collapse on CT imaging of the thoracolumbar spine.

cell patients, *Bartonella henselae* in HIV patients, and *Candida albicans* and *Aspergillus* in immunocompromised patients.[47]

9.2.3 Presentation and Diagnosis

Similar to SEA, symptoms of VO and diskitis may be nonspecific. Back pain is the most common presenting symptom of VO and diskitis, occurring in up to 86% of cases.[45] Radicular pain and other neurological findings such as motor weakness, bowel or bladder incontinence, or sensory loss may be also present depending on the extent of the infection and the concurrent presence of an abscess.[62] Similar to SEA, fever is much less consistent than back pain, with rates of fever in cases of infectious spondylitis ranging from 30 to 70% in various case series.[45,62,66] Some symptomatologic differences occur based on age of presentation; however, elderly patients (age 65 and older) do not commonly present with fever (38% vs. 63%) and rigors (24% vs. 42%), and are more likely to present with hypotension (18% vs. 5%) and delirium (24% vs. 11%) compared to younger (<65 years old) patients.[67]

With regards to laboratory markers, WBC, ESR, and CRP are all used as markers of infection. ESR and CRP are elevated in over 80% of cases.[68] Some studies have pointed to CRP as the most accurate indicator of infection with earliest rise in spondylitis and fastest downtrend in response to treatment.[69,70] ESR has also been shown to correlate with good clinical outcomes if it falls by more than 50% within the first month of treatment, although it may remain elevated despite other evidence of clinical resolution of infection.[49,70] Similar to SEA, the presence of leukocytosis with a neutrophilic predominance is less specific for identifying VO, as one series of 133 cases of *S. aureus* osteomyelitis found only 64% of cases had a leukocytosis and only 39% had a neutrophilic

predominance.[71] A similar low rate of leukocytosis was found in cases of spontaneous diskitis, with only 34% of patients having a leukocytosis.[55]

MRI is the most sensitive imaging modality for identifying infectious spondylitis and should be urgently performed in patients with neurological signs or symptoms.[72] In the case of diskitis, diffusion weighted imaging (DWI) sequences of MRI can differentiate between infection and degenerative disk disease.[73] Nevertheless, plain radiography may be the quickest early imaging modality available and can show periosteal reaction, disk space narrowing, and bony destruction or quickly rule out other causes of back pain.[71,74,75]

Bone biopsy is likely to yield the most accurate culture with a specificity as high as 93%.[76] Indeed, biopsy is more likely to identify a causative pathogen than blood cultures alone, with 77% of positive bone biopsies compared to only 58% of blood cultures.[45] In cases of VO, open biopsy is more likely to identify a pathogen compared to needle biopsy, with a 93% versus 48% yield, respectively.[54] Similarly, open biopsy had a yield of 76% compared to 48% with needle biopsy for identifying a pathogen in infectious diskitis.[77] Ideally, depending on the clinical stability of the patient, antibiotics should be deferred until after a culture and/or biopsy has been obtained to increase the likelihood of identifying a pathogen and avoiding a false negative diagnosis.[78] Histopathology can also be used to identify granulomas in the case of mycobacterial infection.[78]

9.2.4 Management and Surgical Decision-Making

As with SEA, the main principle in choosing antimicrobial therapy for infectious spondylitis treatment is targeted therapy based on culture and sensitivity data. In clinically unstable patients where urgent antibiosis is needed, or when culture data is not available, empiric antibiotics should cover the most commonly isolated pathogens including staphylococcal, streptococcal, and gram-negative species. An appropriate empiric regimen typically includes vancomycin and a third- or fourth-generation cephalosporin.[79] Some studies have shown that aminoglycosides have the highest penetration followed by cephalosporins and then penicllins.[80,81,82] Rifampin may be added in the case of *S. aureus* infections, especially in the case of spinal instrumentation or implants, but this must be used in combination with other drugs and not as monotherapy.[83] The consideration of oral or IV antibiotics should be decided in conjunction with an infectious disease consultant, although similar to the case of SEA, IV antibiotics and duration of the course of treatment are typically associated with factors such as poor response to therapy or the presence of hardware or allograft.[21,29]

The duration of antibiotic therapy is typically at least 6 weeks. A randomized controlled trial of 359 patients with pyogenic VO randomized to 6 versus 12 weeks of antibacterial therapy (IV or oral) found that 6 weeks of therapy was noninferior to 12 weeks in terms of no infection recurrence at 1 year.[84] However, a retrospective review of 300 cases assessing the risk of VO relapse noted a 34.8% risk of relapse in high-risk patients who received antibiotics for 4 to 6 weeks (defined as patients with the presence of MRSA infection, an associated abscess, or end-stage renal disease) compared to a 9.6% rate of relapse in patients receiving at least 8 weeks of antibiotic therapy.[85] This suggests that in high-risk patients, at least 8 weeks of parenteral antibiotics should be considered in order to achieve lasting eradication of infection.[86] In the case of diskitis, the ability of antibiotics to penetrate disk tissue differs from that of bone due to the relatively low vascularity of the intervertebral disk. In this high-risk patient group (defined in this study to have either diabetes, cirrhosis, malignancy, immunosuppression, end-stage renal disease, rheumatic disease), it was suggested that antibiotic

courses be undertaken for even longer periods of time than in VO, potentially up to 12 weeks or longer.[86]

As opposed to SEA, infectious spondylitis may allow for greater possibility of medical management alone. Indications for surgical intervention include neurological compromise, the presence of an associated spinal epidural abscess, and spinal instability. Surgery may be performed classically from an anterior and/or posterior approach, allowing for exposure of the disk and vertebral body. Disk and vertebral body decompression may be done in the same stage as posterior instrumentation and fusion or can occur in a staged manner.[46,87,88,89]

As before, concerns with regard to hardware implantation in the setting of infection has been previously studied. Indeed, in a retrospective study, patients who underwent debridement alone versus debridement with spinal instrumentation had similar outcomes, including rates of failure and recurrence, suggesting instrumented therapy can be safely performed in conjunction with appropriate parenteral antibiotic therapy when indicated.[37] As with SEA, allograft and autograft are frequently used, although studies involving cases in light of infection have suggested viability of this implant without increased rates of chronic infection. This may be attributed to the lack of porosity of titanium that can serve as a nidus for bacterial biofilm.[90,91]

With regard to decision-making regarding anterior, posterior, or combined approaches in surgical cases, it depends largely upon the extent to which debridement of the vertebral body or facets must occur. From a posterior approach, debridement of the facet joints necessitates a posterior instrumented fusion in order to restore stability, while preservation of 50% or more of the facet joints typically does not require instrumented fusion. Similarly, should an anterior approach be warranted due to location of the infection in the vertebral body or ventral to the spinal cord, consideration of an interbody cage or graft may be considered in order to restore the continuity of the vertebral column. Combined approaches may be considered in cases that are particularly disruptive to the integrity of the spine, such as in cases with significant deformity or involvement. In these settings, a corpectomy with interbody cage or strut may be considered as a first stage followed by posterior stabilization with instrumentation.

For example, consider the case of a 40-year-old female with a history of IVDA who presented with complaints of several months of back and radicular right-sided chest wall pain, progressive kyphotic deformity, and increased difficulty with balance and ambulation. At presentation, she was afebrile with elevated WBC count and inflammatory markers. She had a kyphotic appearance with a focal kyphotic deformity in her thoracic spine, and exquisite tenderness to palpation overlying her thoracic spine centered in her mid-thoracic spine. She had mild proximal lower extremity weakness as well as bilateral lower extremity hyperreflexia, but was otherwise neurovascularly intact. Imaging demonstrated VO and diskitis at her T6–T8 levels with a focal collapse of the T7 and T8 vertebral bodies resulting in a focal kyphotic deformity with moderate retropulsion into the spinal canal with associated tenting of the spinal cord over the deformity (▶ Fig. 9.3). She was diagnosed with VO and diskitis, and was empirically started on vancomycin and cefepime. MRI of the rest of her spine was unremarkable for noncontiguous lesions. Standing X-ray and CT imaging were performed to better assess the extent of bony destruction (▶ Fig. 9.4 and ▶ Fig. 9.5).

Given her kyphotic deformity, spinal cord compression, severe pain, and neurologic compromise, the patient was offered and elected to undergo anterior and posterior decompression and fusion with T7–T8 corpectomies. She underwent an anterior approach to the thoracic spine via right posterolateral thoracotomy and corpectomy of

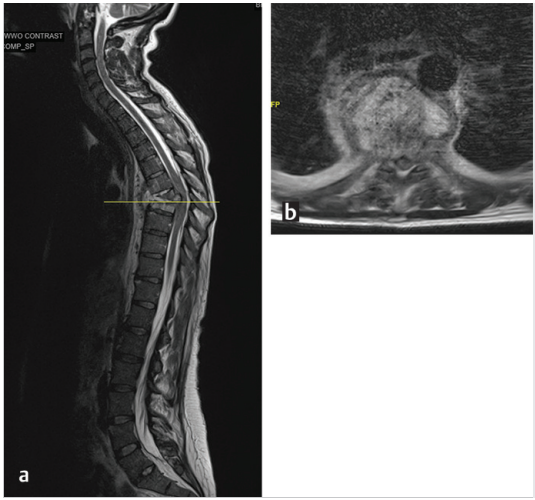


Fig. 9.3 Sagittal (**a**) and axial (**b**) T2-weighted images of the entire spine demonstrating focal kyphotic deformity in the setting of T7 and T8 vertebral bodies collapse.

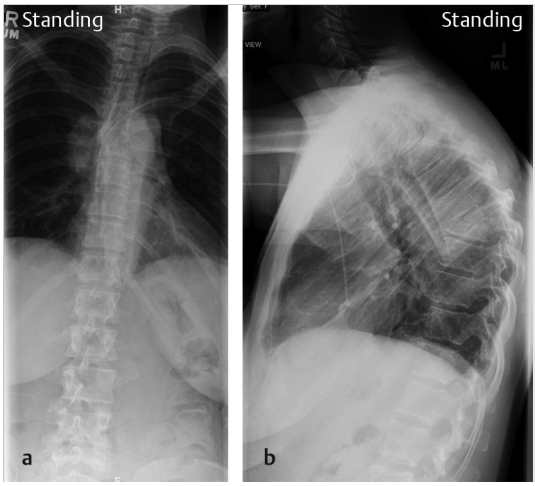
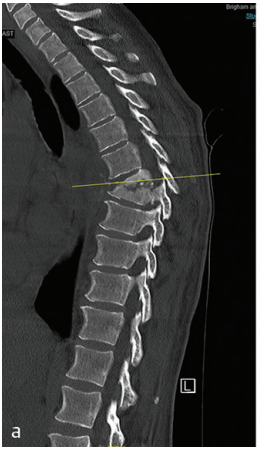


Fig. 9.4 Anteroposterior (**a**) and lateral (**b**) X-rays of the thoracic spine with kyphotic deformity centered about T7 and T8.

T7 and T8 with placement of a titanium expandable cage. She was continued on IV antibiotics and 2 days later, she went back to the operating room for a posterior stabilization of her thoracic spine with posterior spinal instrumented fusion from T4 to T11 (▶ Fig. 9.6). She did well postoperatively. Her thoracic radicular pain resolved as did her lower extremity weakness and gait disturbance. Her intraoperative cultures grew MRSA and her antibiotic regimen was narrowed to vancomycin alone and was placed on a 6-week course of antibiotic therapy. At her most recent 3-month follow-up, she reported resolution of her pain and deformity, with no recurrent infection.

9.2.5 Prognosis

VO carries a mortality rate of less than 5% with modern antibiotic therapies, and less than 7% for residual neurologic deficits in patients with VO.[92] In contrast, however,



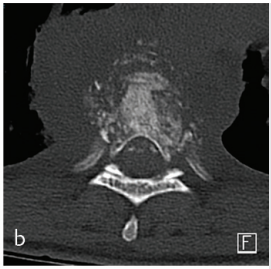
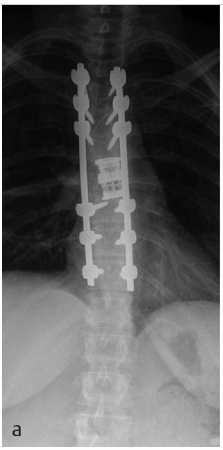


Fig. 9.5 Sagittal (**a**) and axial (**b**) CT images of the thoracic spine demonstrating almost complete destruction of the T7 and significant collapse of the T8 vertebral bodies.



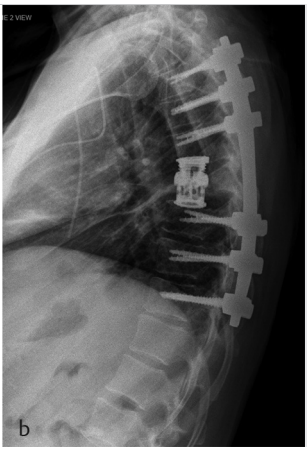


Fig. 9.6 Postoperative anteroposterior (**a**) and lateral (**b**) radiographs of posterior spinal fusion instrumentation from T4 to T11. Expandable cage was placed during first-stage procedure after corpectomy of T7 and T8 vertebral bodies; posterior instrumentation was placed during second-stage procedure 2 days later. Regional kyphosis improved from 57 degrees of thoracic kyphosis preoperatively to 32 degrees postoperatively.

long-term back pain and relapse are noted to be much more prevalent in patients with VO, with approximately 32% of patients with persistent back pain in one study and relapse occurring in 14% in another study.[93,94] In cases of relapse, prior studies have demonstrated that the majority of failures will occur within 5 months of initial diagnosis, with *S. aureus* infections associated with an increased risk of relapse.[94]

9.3 Conclusion

In summary, orthopaedic surgeons and general practitioners alike must be aware of the significant morbidity of infections involving the spine. Treatment of these infections can be complex and often involve a multidisciplinary team including emergency department or primary care physicians, orthopaedic surgeons, and infectious disease physicians. One must be attentive to the clinical history and examination and, in certain cases involving spinal cord compression, act quickly in order to curtail serious complications such as neurologic compromise, deformity, or death.

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10 Graft Infections

Robert Tisherman, Itamar Neto, Orr Limpisvasti, and Carola F. van Eck

Abstract

Ligament reconstructions are one of the most frequently performed orthopaedic procedures. Postoperative graft infection, although a rare complication, is one of the most serious complications of ligament reconstructions. Graft infections represent a uniquely challenging situation with the goal of maintaining joint stability while eradicating the infectious process. Intra-articular infections occur following 0.05 to 1.9% of anterior cruciate ligament (ACL) reconstructions and 0.5% of posterior cruciate ligament (PCL) reconstructions, and gram-positive bacteria are typically responsible for infection. Patients typically present with signs and symptoms of septic arthritis during the acute (<2 weeks) period postoperatively, but graft infections have been reported for up to 15 months after ACL reconstructions. Risks for infection following ACL reconstruction include hamstring autograft usage, prior knee surgery, and hemarthrosis. Graft infections typically require multiple surgical debridements and prolonged antibiotic management, adding to the overall healthcare cost. Non-operative and operative measures that preserve the graft tissue have been successful, but removal of the graft and subsequent reimplantation are sometimes necessary. Additionally, the situation of intraoperative graft contamination during ACL reconstruction is discussed and whether a contaminated graft can be safely implanted. This chapter reviews multiple aspects of graft infections including demographics, risk factors, diagnosis, management, complications, and prevention.

Keywords: Graft infection, ligament reconstruction, surgical complications, sports medicine, joint infection, ACL reconstruction

Practical Tips

- Knee aspiration can help to differentiate between superficial postoperative infection and septic arthritis in the early postoperative period.
- Surgical debridement for septic arthritis should include all prior arthroscopic, meniscal repair, and graft harvest sites, as these can represent niduses for ongoing infection.
- Arthroscopic debridement for septic arthritis after knee ligament reconstruction has a high rate of successful graft retention.
- Intraoperative graft contamination can be managed with soaking the graft in 4% chlorhexidine gluconate or polymyxin B–bacitracin solution for 3 minutes without discarding the harvested graft in many cases.

10.1 Introduction

Graft infections represent an uncommon, but potentially devastating, complication of ligament reconstruction surgery. Due to its low incidence, the quality of literature relating to graft infections varies widely. The majority of studies looking at graft infections focus on anterior cruciate ligament (ACL) reconstructions. As the incidence of

anterior cruciate ligament (ACL) reconstruction continues to rise,[1] and other ligamentous reconstruction procedures becomes more common, it is becoming more important for surgeons and other clinicians involved in the care of surgical patients to understand the etiology, diagnosis, management, and outcomes of graft infections.

Septic arthritis represents one of the most serious, but well known, complications of ligament reconstruction. Studies looking at patient risk factors, optimal management strategies, and outcomes often focus on the preferred method of the authors and are therefore should be scrutinized for their widespread applicability. Many studies on this subject are also inconclusive due to the low number of patients presenting with postoperative septic arthritis and graft infection.

Septic arthritis in the postoperative period can lead to numerous complications, including permanent cartilage damage, increased risk for graft failure, need for hardware removal, and even death.[2,3,4] Patients who present with graft infections will typically undergo multiple debridement procedures and require lengthy antibiotic therapy. Overall, this constitutes a large burden on healthcare providers, the healthcare system, and most importantly, the patient.

The objective of this chapter is to review the epidemiology, diagnosis, management, and complications of orthopaedic graft infection.

10.2 Risk Factors for Graft Infection

Various studies looking at the rate of graft infection following ACL surgery have found a rate of postoperative intra-articular infection between 0.23 and 1.9% (▶ Table 10.1).[2,5,6,7,8,9,10,11,12,13,14,15,16,17,18,19,20,21,22,23,24,25,26] The risk factors for generalized orthopaedic infections including age, diabetes, renal disease, immune disorders, and rheumatologic conditions are not routinely seen in the ligament reconstruction patient. The prototypical patient undergoing ligament reconstruction are often younger, more active, and present with fewer medical comorbidities, but several patient and operative factors have been associated in increased risk for graft failure. Patients with morbid obesity, diabetes, and other generalized risk factors for orthopaedic infection do present with low-energy dislocations requiring multi-ligament reconstruction and should be considered high risk for graft infection postoperatively.[27]

10.2.1 The Effect of Graft Type on Rates of Postoperative Infection

For any ligament reconstruction, the choice of graft is dependent upon donor site morbidity, suitability of the graft for the desired reconstruction, number of ligaments in need of reconstruction, intra- versus extra-articular nature of the ligament and prior surgical history. Donor site morbidity associated with hamstring autograft includes quadriceps weakness, donor site pain, and ecchymosis. Bone-patellar tendon-bone (BPTB) autograft is associated with increased anterior knee pain but provides the benefit of bony incorporation at both ends of the graft. Allograft is available in a wider range of sizes and does not have donor site morbidity. Allograft is widely available in the United States but increases the cost of the operation significantly and has limited availability outside of the United States.

Therefore, autograft is routinely chosen for ACL reconstruction because it is native tissue and does not have the potential disease transmission or rejection associated with

Table 10.1 Summary of published articles relating to the incidence and patient characteristics of patients presenting with septic arthritis after knee ligament reconstruction. Values presented as median (range)

Study	Number of patients	Septic arthritis – n (incidence)	Graft type (*n*)	Average age (yrs)	Average time to presentation (days)	Number of surgical procedures (range)	Follow–up (months)
Anterior cruciate ligament reconstruction							
Williams et al (1997)[37]	2500	7 (0.28%)	Hamstring (3), BPTP (4)	31.3 (17–50)	21.8 (3–79)	1.6 (1–2)	29 (7–71)
McAllister et al (1999)[16]	831	4 (0.48%)	Hamstring (1), BPTB (3)	26 (20–34)	11 (8–18)	1.5 (1–2)	36 (28–42)
Viola et al (2000)[20]	1794	14 (0.78%)	BPTB (14)	21 (17–29)	7.7 (2–20)	0.4 (0–1)	14.4 (5–43)
Indelli et al (2002)[21]	3500	6 (0.14%)	BPTB (4), Achilles allograft (2)	32.5 (20–51)	20 (9–34)	1.3 (1–3)	36 (24–96)
Schollin–Borg et al (2003)[22]	575	10 (1.7%)	Hamstring (4), BPTB (6)	28.3 (19–39)	15 (4–40)	1.3 (1–3)	35.8 (19–56)
Fong and Tan (2004)[23]	472	7 (1.5%)	Hamstring (7)	23 (19–30)	24 (7–56)	1.4 (1–3)	11.7 (5–26)
Judd et al (2006)[24]	1615	11 (0.68%)	Hamstring (11)	28 (22–35)	14 (6–45)	2.4 (2–4)	22 (10–48)
Van Tongel et al (2007)[25]	1736	9 (0.52%)	Hamstring (9)	33 (17–50)	10.9 (3–455)	1.9 (1–4)	58 (9–99)
Binnet and Basarir (2007)26	1231	6 (0.49%)	Hamstring (2), BPTB (4)	24.5(20–32)	22 (14–35)	2.7 (1–5)	102 (30–196)
Wang et al (2009)[6]	4068	21 (0.52%)	Hamstring (20), Allograft (1)	28.6 (16–58)	16 (5–32)	n/a	n/a
Sajovic et al (2009)[7]	1283	3 (0.23%)	Hamstring (3)	33 (23–48)	8 (2–14)	1	33 (4–61)
Monaco et al (2010)[8]	1232	12 (1.0%)	Hamstring (12)	24 (16–43)	16 (10–20)	0.3 (0–1)	38 (6–54)
Barker et al (2010)[9]	3126	18 (0.58%)	Hamstring (5), BPTB (7), Allograft (6)	34.1 (16–48)	28 (5–122)	1.6 (1–3)	n/a
Sonnery–Cottet et al (2011)[2]	1957	12(0.61%)	Hamstring (4), BPTB (7), QT (1)	29.2 (18–49)	16 (2–37)	1.3 (1–2)	n/a
Torres–Claramunt et al (2013)[10]	810	15 (1.9%)	Hamstring (13), BPTB (2)	33.5	24(7–35)	1.3	39 (n/a)

Table 10.1 (*Continued*) Summary of published articles relating to the incidence and patient characteristics of patients presenting with septic arthritis after knee ligament reconstruction. Values presented as median (range)

Study	Number of patients	Septic arthritis – n (incidence)	Graft type (*n*)	Average age (yrs)	Average time to presentation (days)	Number of surgical procedures (range)	Follow–up (months)
Maletis et al (2013)[11]	10626	34 (0.32%)	Hamstring (24), Allograft (17), BPTB (10)	29.5	20 (12–30)	N/A	88% >12 mo
Calvo et al (2014)[12]	1564	7(0.45%)	Hamstring (7)	27.8 (14–51)	n/a(4–30)	n/a (1–4)	n/a(12–101)
Abdel–Aziz et al (2014)[13]	2560	24 (0.93%)	Hamstring (24)	26 (19–35)	12 (5–45)	3 (1–6)	59 (18–96)
Bostrom Windhamre et al (2014)[14]	4386	43 (0.98%)	Hamstring (27/27)	27 (16–43)	8 (1–22)	3.7 (1–11)	60 (13–108)
Schuster et al (2015)[15]	7096	36 (0.51%)	Hamstring (36)	33 (15–55)	17 (4–37)	2.25 (1–6)	56 (8–134)
Murphy et al (2016)[17]	11772	55 (0.46%)	Hamstring (36), BPTB (7), Allograft (12)	32	n/a	n/a	n/a
Bohu et al (2019)[18]	1632	5 (0.31%)	Hamstring (5)	36 (20–62)	18 (12–21)	1.6 (1–2)	34 (18–58)
Posterior cruciate ligament reconstruction							
Schuster et al (2018)[19]	866	4 (0.46%)	Hamstring (3), Allograft (1)	34.5 (18–47)	18 (7–35)	1.3 (1–2)	16.5 (12–24)

Abbreviation: BPTB, bone patellar-tendon bone.

allograft, and offers a cost-effective alternative to allograft.[28] Autograft has also been shown to incorporate in ACL reconstruction in less time than allograft.[29] Currently, the most widely used autografts are hamstring, BPTB, and quadriceps tendon.[27]

The choice of donor graft is important when considering the risk of potential infection and is one of the strongest factors found across all studies. Hamstring autografts have consistently exhibited increased risk for postoperative infection compared to BPTB autograft and allograft,[7,9,17,30] as the relative risk of infection when using hamstring autograft for ACL reconstruction is 3.3 to 4.3 compared to BPTB.[9,30] Hamstring autograft has been shown to have a high risk for infection prior to transplantation, as 16 to 22% of hamstring autografts are culture-positive at the time of harvest, indicating that graft harvest and preparation are the likely source for introduction of inoculating bacterium.[31] It has been proposed that hamstring autograft has a higher rate of postoperative infection due to the tissue dissection proximity to the tibial tunnel and the possibility of hematoma formation that can extend intra-articularly. Multiple studies have shown no difference in deep infection rate when comparing BPTB to allograft (BPTB or Achilles).[9,30]

Allograft processing and contamination are discussed later in this chapter, but there is no increased risk of graft infection with allograft despite its nonsterile harvest, avascular nature, and longer ligamentization time when compared with autograft. A combined prospective and retrospective multicenter cohort study of 1,298 ACL reconstruction patients with 74.3% allografts demonstrated no cases of septic arthritis, a superficial infection rate of 2.3%, and no increased risk of clinical infection with the use of allografts.[32] Several widely publicized cases of bacterial contamination and death following ligament reconstruction have occurred due to graft infections from allograft tissue in Minnesota,[33] Florida, and Louisiana[3] due to ineffective terminal sterilization. Allografts were culture positive 7.9% of the time for bacterial contamination, with no association seen between culture-positive allografts and clinical infections.[34] With regard to bacterial infections in allografts, *Clostridium* spp. (37.5% *Clostridium sordelli*[7]) were liable for roughly 50% of cases.[35] Unlike autograft infections, gram-negative bacilli such as *Pseudomonas aeruginosa*, *Serratia liquefaciens*, and *Escherichia coli* as well as fungal infections (*Candida* sp.) have been seen at higher rates with allograft transplants.[35]

Additional risk factors include previous knee surgery,[18] hospital admission following surgery,[36] and development of hemarthrosis in the immediate postoperative period.[18] In a review of the Multicenter Orthopaedic Outcomes Network (MOON) study database, which contained 17 patients (0.8% of the entire cohort) who presented with septic arthritis following ACL reconstruction, it was found that diabetes was a significant risk factor for graft infection.[27]

There is conflicting evidence that ACL reconstruction in professional athletes has a higher rate for septic arthritis. One study found that rates of postoperative infection in professional athletes may be as high as 5.7%,[2] while other studies have shown no difference between nonprofessional athletes and professional athletes.[18]

10.3 Clinical Presentation and Management

10.3.1 Clinical Presentation

In the early postoperative period, patients present with signs and symptoms of septic arthritis at an average of 18 days postoperatively (▶ Table 10.1). The most common

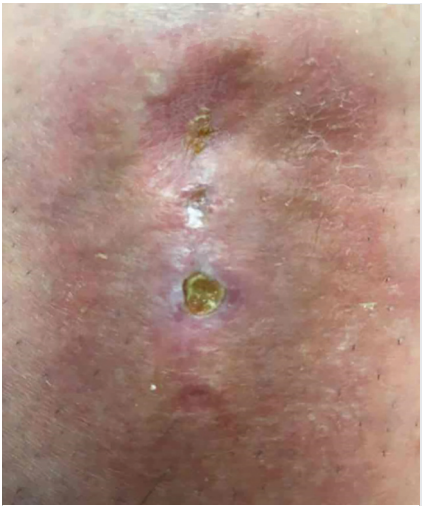

Fig. 10.1 A 43-year-old female patient 6 months postoperatively from anterior cruciate ligament, posterolateral corner, and medial collateral ligament reconstruction using allograft who presents with new drainage from the tibial incision and surrounding erythema.

presenting symptoms are fevers, pain, and effusion.[9,22,37] Other common symptoms include erythema, local knee joint drainage at the site of surgical incisions, and progressive knee pain (▶ Fig. 10.1).[18,23] While most patients present within the acute (<2 week) or subacute phase, there have been reports of graft infection occurring more than 1 year postoperatively, and the development of symptoms long time after the surgery should not be used to rule out septic arthritis.[25]

10.3.2 Laboratory Evaluation

Clinical examination of postoperative knee pain, swelling, and low-grade fevers can have a wide differential diagnosis, including hemarthrosis, tissue response to surgery, and superficial infection. Septic arthritis is often missed at the initial visit where signs and symptoms may be present, due to the overlap between postoperative healing response and acute intra-articular infection.[22] Confirming the presence of graft infection in the postoperative period is crucial for expedient management and prevention of long-term complications. Laboratory evaluation of joints with suspected graft infection should include serum inflammatory marker levels, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP), as well as serum white blood cell counts. Blood cultures are negative in the majority of cases of confirmed septic arthritis.[20]

ESR and CRP are acute inflammatory markers that can help to differentiate postoperative septic arthritis from normal postoperative healing response. CRP is elevated within 12 to 24 hours of the onset of infection and ESR shows elevation 24 to 48 hours after the onset of infection.[38] A retrospective review of ESR and CRP in noninfected and septic knees following ACL reconstruction found that the optimal ESR and CRP cutoffs for septic arthritis were 32 mm/hour and 41 mg/L, respectively.[39] These ESR and CRP cutoffs provided a sensitivity of 91.2 and 94.1% and specificity of 80.5 and 97.6%, respectively.[39]

Knee aspiration should be performed as part of the standard septic arthritis workup through superolateral aspiration under aseptic technique to avoid contamination at the portal holes. Knee aspiration revealed average leukocyte count in excess of 50,000 cells/mL in most cases,[9,21,25] but a high index of suspicion should exist for septic arthritis with aspirate cells counts over 20,000 cells/mL and a polymorphonuclear cell percentage >75%.[40]

Some experts have recommended a lower threshold of >10,000 cells/mL from postoperative knee aspirations in patients presenting with signs and symptoms consistent with septic arthritis.[24]

Laboratory evaluation can help to confirm when graft infections do occur and prevent unnecessary antibiotics and exploratory surgery.

10.3.3 Surgical Site Infection versus Intra-articular Graft Infection

Surgical site infections that do not involve the joint are a known complication of ACL reconstruction and may be seen in 0.2% of cases.[11] Clinical presentation can be similar to that of septic arthritis, and it is important to differentiate these two etiologies. Superficial infections more commonly not only present with pain at the wound, local erythema, but also often present with drainage and an effusion as seen in septic arthritis.[24] Aspiration and laboratory serum analysis can assist in differentiating these two etiologies, as surgical site infections are shown to have lower ESR, CRP, and knee aspiration cell count (<3,000 cells/mL).[24] Surgical site infections, while not shown to lead to the high morbidity associated with septic arthritis, are surgical complications that often require superficial irrigation and debridement along with a course of oral or intravenous (IV) antibiotics. Surgical site infections within close proximity to a joint may progress toward intra-articular involvement (▶ Fig. 10.2), and the threshold for arthroscopic or surgical debridement should remain low to maximize the chances for successful graft retention and prevention of cartilage injury.

10.3.4 Organisms Responsible for Graft Infection

Graft infections likely occur due to direct contamination from the skin via the tibial incision or through hematogenous spread, and almost all graft infections are caused by gram-positive skin flora. Coagulase-negative staphylococci (including *Staphylococcus epidermis*, *Staphylococcus capitis*, and over 45 other species) are the most common organism associated with graft infections and are responsible for approximately 44% of all graft infections (▶ Table 10.2).[41] Complication rates after septic arthritis differ based on the virulence of the causative organism. *Staphylococcus aureus* infections have a higher rate of graft removal (33.3%), longer antibiotic management time and worse range of motion compared to patients with coagulase-negative *Staphylococcus*.[41] However, between 22 and 31% of graft infections are culture negative,[41] likely due to difference in diagnostic criteria, culture techniques, or organism virulence.

Even in the absence of clinical symptoms, bacterial deoxyribonucleic acid (DNA) and confirmed bacteria on histologic sampling can be detected in up to 87% of revision ACL cases, indicating that subclinical graft infections may be a cause of graft failure,[42] but the rates of biofilm formation on ACL reconstructions that do not undergo revision surgery is unknown.

10.4 Management of Graft Infection

10.4.1 Nonsurgical Management

Although the majority of authors advocate for early surgical debridement in the setting of graft infection, the use of nonoperative management may represent an option in

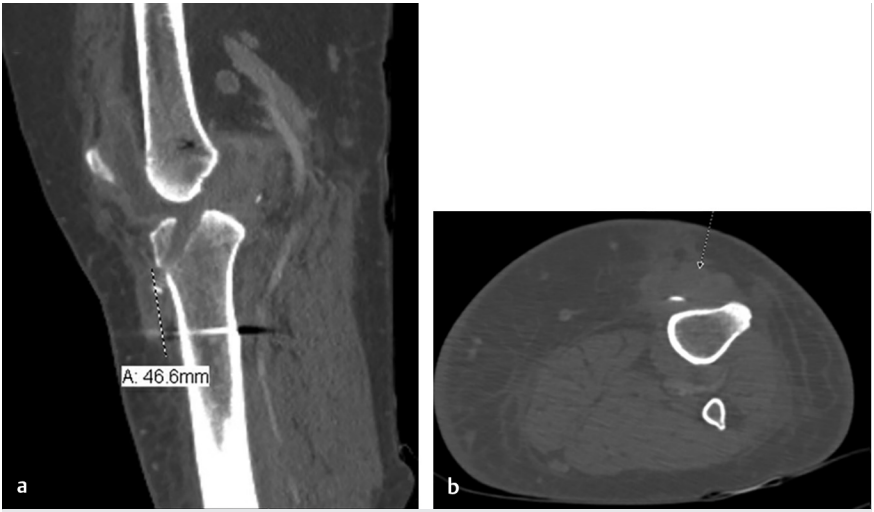

Fig. 10.2 (a, b) CT scan of a 43-year-old female 6 months postoperatively with incisional drainage and erythema which show a large joint effusion and fluid collection anterior to the tibial interference screw.

patients unable to undergo surgery or who refuse surgical intervention. Viola et al placed a small case series of 13 patients who presented with clinical symptoms and increased inflammatory markers consistent with septic arthritis following ACL reconstruction on a trial of oral antibiotics (ciprofloxacin 750 mg twice daily and amoxicillin plus clavulanate 1 g four times per day) for 15 to 90 days depending on the resolution of inflammatory markers.[20] Only 6 of 13 patients went on to require surgical debridement based on persistent elevation of inflammatory markers (ESR and CRP), with most patient symptoms resolving in 14 days with antibiotics alone. In another study of 12 patients presenting with postoperative septic arthritis, Monaco et al implemented 2 or 3 days of 4 hours/day of ambulatory irrigation of the knee through two 18 gauge spinal needles along with antibiotic therapy using an intramuscular glycopeptide (teicoplanin 200 mg twice daily) and an oral fluoroquinolone (ciprofloxacin 500 mg twice daily). Of these patients, 33% required arthroscopic debridement due to persistent fever or swelling of the knee.[8] The long-term cartilage degeneration, functional outcomes, and objective laxity following nonoperative management of graft infections remains unclear.

10.4.2 Surgical Management of Graft Infection

In 1985, Gächter proposed a classification of intra-articular arthroscopic findings in the setting of septic arthritis that is still widely used today.[43] The stages are as follows:

- Stage 1: Cloudy synovial fluid, redness of the synovial membrane with possible petechial bleeding.
- Stage 2: Severe inflammation with fibrin deposits and opacity of the effusion (▶ Fig. 10.3).
- Stage 3: Thickening of the synovial membrane, sponge-like synovial membrane transformation, and compartmentalization of the joint space with fibrous tissue.

Table 10.2 Summary of causative organisms in graft infection

Study	Septic arthritis - n (incidence)	Negative culture	Bacterial species			
			CNS	S. aureus	P. acnes	Other organism
Anterior cruciate ligament reconstruction						
Williams et al (1997)[37]	7 (0.28%)		2	6		1 - Pseudomonas
McAllister et al (1999)[16]	4 (0.48%)			4		
Viola et al (2000)[20]	14 (0.78%)	12	2			
Indelli et al (2002)[21]	6 (0.14%)		2	3		1 - Non-hemolytic streptococcus
Schollin-Borg et al (2003)[22]	10 (1.7%)	2	6	1	1	
Fong and Tan (2004)[23]	7 (1.5%)		2	4		1 - Peptostreptococcus
Judd et al (2006)[24]	11 (0.68%)		8	1	1	1 - Enterobacter
Van Tongel et al (2007)[25]	9 (0.52%)		7	2		1 - Streptococcus, 1 - Enterococcus
Binnet and Basarir (2007)[26]	6 (0.49%)	2		3		1 - Pseudomonas
Wang et al (2009)[6]	21 (0.52%)	5	11	3		1 - *Enterococcus faecalis*, 1 - Corynebacterium
Sajovic et al (2009)[7]	3 (0.23%)	1	1	1		
Monaco et al (2010)[8]	12 (1.0%)		11			1 - *Enterococcus coli*
Barker et al (2010)[9]	18 (0.58%)	6	4	6	2	
Sonnery-Cottet et al (2011)[2]	12 (0.61%)		11		1	
Torres-Claramunt et al (2013)[10]	15 (1.9%)		10	5		
Maletis et al (2013)[11]	34 (0.32%)	9	11	8	1	2 - Serratia, 2 - Other
Calvo et al (2014)[12]	7 (0.45%)		4			2 - *Enterococcus faecalis*, 1 - *Enterococcus cloacae*
Abdel-Aziz et al (2014)[13]	24 (0.93%)	3	7	7	3	2 - Peptostreptococcus, 2 - Enterococcus
Bostrom Windhamre et al (2014)[14]	43 (0.98%)	15	20	5	1	1 - P. *acnes, 1 - Klebsiella*,
Schuster et al (2015)[15]	36 (0.51%)	6	20	7	3	1 - *Enterococcus faecalis*, 1 - *Enterococcus cloacae*
Murphy et al (2016)[17]	55 (0.46%)	19	15	12	3	4 - Other, 4 - Polymicrobial

Table 10.2 (*Continued*) Summary of causative organisms in graft infection

Study	Septic arthritis - n (incidence)	Negative culture	Bacterial species			
			CNS	S. aureus	P. acnes	Other organism
Bohu et al (2019)[18]	5 (0.31%)		4	1		
Posterior cruciate ligament reconstruction						
Schuster et al (2018)[19]	4 (0.46%)	1	2			1 - Enterococcus
Total (%)	363	81 (22.3)	160 (44.1)	79 (21.8)	16 (4.4)	33 (9.1)

Abbreviations: CNS, coagulase negative Staphylococcus; *P. acnes*, *Propionibacterium acnes; S. aureus*, *Staphylococcus aureus.*

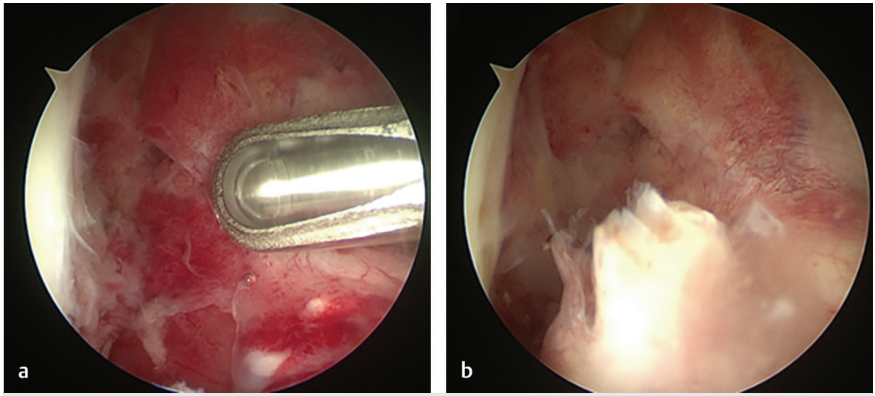

Fig. 10.3 (a, b) Arthroscopic images during debridement of a 43-year-old female who presents with a graft infection 6 months postoperatively showing extensive synovitis and areas of fibrinous exudates corresponding to Gächter stage 2 septic arthritis.

- Stage 4: Aggressive pannus formation with infiltration and possible undermining of the cartilage, radiologic subchondral osteolysis, and bony erosion or cyst formation.[43]

Stages 1–3 do not involve radiologic changes. Most patient presenting with septic arthritis after ACL reconstruction present with Stage 2 findings. Stage 3 or 4 findings are concerning for more progressive disease that may require arthrotomy, extensive debridement, subtotal synovectomy, and possible graft and hardware removal.[44] Stages 1 and 2 diseases have been successfully treated with arthroscopic debridement. Arthroscopic debridement should be performed at the earliest possible time point to avoid permanent cartilage damage.

After the diagnosis of acute graft infection has been made, surgical intervention is strongly recommended. Using the prior arthroscopic portals, immediate arthroscopic irrigation and debridement of the knee joint should first be performed including debridement of any fibrinous tissue on the graft, subtotal synovectomy, and removal of necrotic tissue. Open irrigation and debridement should be considered if there is any necrotic tissue that needs to be debrided, specifically skin, subcutaneous tissue, fat, or fascia, which is not accessible with the arthroscope. Additionally, open debridement must be considered in cases of necrotizing bacteria that would require one to leave the wound open with application of a vacuum assisted closure (VAC) device. In cases where an open arthrotomy is necessary, the prior arthroscopy portals shoulder not be used and a medial parapatellar approach should be used for debridement to allow for adequate visualization, as this may facilitate future debridements. Lavage with 10 to 15 L of normal saline should be performed. If the graft appears stable and superficial debridement of purulent or fibrinous material can be performed without damaging the graft, graft retention is the preferred mode of treatment,[23,44] especially if autograft was used for the index procedure. Prior sites of arthroscopy, meniscal repair, or multiligament reconstruction should be incised and drained at the time of arthroscopic debridement,

as these can serve as niduses for infection if there are retained fluid collections.[25] Although multiple debridement techniques and postoperative drainage systems have been suggested, the practice of the authors is to close the knee over a drain that can be removed without returning to the operating room. In cases where soft tissue debridement is extensive, the knee can be left open or managed with a wound VAC device.

Infectious diseases should be consulted after debridement for recommendations on organism-specific antibiotics based on culture and local antibiograms. Cultures from preoperative knee aspirations can be used to determine bacterial sensitivities. Until sensitivities are known, a broad-spectrum antibiotic such as cefazolin can be started using weight- and renal-based dosing per infection disease recommendations. If methicillin-resistant *Staphylococcus aureus* (MRSA) is suspected, patient should be started on vancomycin ± piperacillin/tazobactam using weight-based dosing postoperatively. When cultures become known, antibiotics can be adjusted. This can be IV or oral depending on the pathogen that is isolated from the cultures as well as patient characteristics (i.e., allergies, IV access, health status, compliance, tolerance). The length of treatment is generally 6 weeks, but may be longer if there is no resolution of inflammatory markers (ESR and CRP) to within normal levels. If there is concern for ongoing infection or confirmation of clearance is desired, a repeat knee aspiration can be performed after a 2-week "antibiotic holiday" where antibiotics are not administered for a minimum of 2 weeks prior to aspiration.

Patient should be re-examined 2 to 3 days following debridement to evaluate for continued symptoms, as this can determine if subsequent procedures are needed for complete resolution of the infection. If symptoms of knee swelling and pain persist and there is no improvement in CRP, which generally shows improvement within 24 to 36 hours of successful management, repeat debridement should be considered. If inflammatory marker levels and clinical presentation improve after the initial debridement, there may not be a need for repeat debridements.

Overall, there is 85.5% success with arthroscopic debridement of septic arthritis following ACL reconstruction.[45] After initial debridement, patients should be closely monitored for improvement in symptoms as well as laboratory trends. Wang et al demonstrated that within 48 hours of successful debridement, serum CRP decreased by 50%, while patients with persistent CRP elevation are likely to require subsequent debridement.[39]

10.4.3 Graft Retention

A meta-analysis in 2018 showed that 86% of grafts were retained at the time of initial debridement.[46] Graft retention may improve long-term outcomes compared with patients who had initial graft removal, even with delayed ACL reimplantation.[47] Excellent outcomes have also been achieved in a graft-retention protocol in 32 cases of graft infection following ACL reconstruction.[15] Recurrent instability without ACL reconstruction and the increased severity of cartilage damage seen in septic arthritis requiring graft removal may explain the inferior outcomes in patients with graft removal.[48] However, grafts that were retained resulted in an increased risk for early reoperation, including a secondary debridement, while patients who underwent graft removal were more likely to undergo reoperation at a later time.[46]

While the majority of modern operative recommendations for septic arthritis following ligament reconstruction advocate for protection of the graft if at all possible,[10] there

are a subset of patients who do not respond to initial irrigation and debridement. In these cases, a more radical open debridement is necessary. Successful management of these complex cases has been seen with arthrotomy, complete synovectomy, removal of implants and graft, and curettage of the tibial and femoral tunnels followed by 6 weeks of antibiotic therapy.[49] Graft reimplantation indications and timing are discussed further in the section Graft Replantation.

10.4.4 Hardware Retention

In the early postoperative period, ACL reconstruction relies upon mechanical fixation of the graft within the tunnel using hardware. However, bacteria can form biofilm on hardware, potentially making it harder to eradicate the infection. Thus, there is concern over retaining hardware required for graft fixation when performing surgical intervention for septic knee arthritis after ligament reconstruction. There have been reports of successful graft infection treatment with complete retention of all hardware, including femoral interference screws[20] and tibial hardware.[50] Once the graft has incorporated, some experts have advocated for removal of the hardware to reduce the risk of reinfection and biofilm formation. In a set of three patients with septic arthritis following ACL reconstruction, McAllister et al performed a late operation for removal of hardware at an average of 11 months after the initial procedure once the graft had incorporated and did not have any cases of recurrent instability at an average of 36 months follow-up.[16]

10.4.5 Graft Replantation

In studies looking at revision ligament reconstruction following graft infection, many patients decide to not undergo further surgery and accept the risk for potential instability without a graft as to not risk subsequent infection.[50,51] Often, the joint becomes stiff and painful after an infection; therefore, conservative treatment without reconstruction should be considered first. In cases where patients desire reimplantation, it is important to ensure complete resolution of the infection before revision surgery following graft infection and graft removal. Proposed criteria for revision ACL reconstruction following graft infection include normalization of inflammatory markers, completion of antibiotics, return to normal knee motion, and resolution of knee swelling.[51] Inflammatory markers must be normal at least 2 weeks after cessation of antibiotics, and a repeat aspiration and culture must be normal to ensure complete infection resolution. Most authors recommend earliest revision at 6 to 12 months after a graft infection has occurred, to allow for complete resolution of symptoms and rule out indolent infection.[10,41,44] Several authors have looked at reimplantation of ACL grafts following septic arthritis. Early reimplantation, occurring 1 to 6 weeks after finishing 6 weeks of antibiotics therapy, was performed in a small case series of four patients without signs of recurrent infection and resulted in high patient reported outcomes (average Lysholm score 92.5).[50] Early reimplantation offered 3 months after graft infection was attempted in four patients with excellent patient reported outcomes (average Lysholm 92, International Knee Documentation Committee [IKDC] 86) at 6-year follow-up with no evidence of reinfection in any patient.[51] Graft choice for reconstruction remains controversial, but autograft may be considered if additional autograft options exist for the patient, including the contralateral side. Depending on the geographic availability, allograft may be considered for recon-

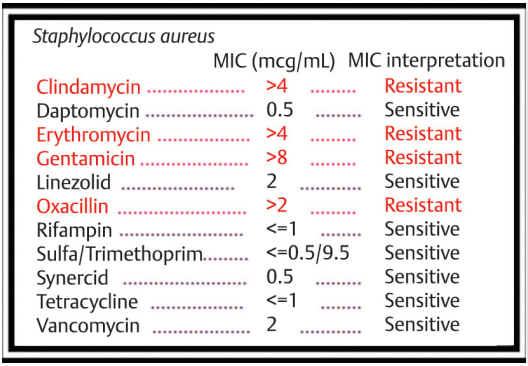

Fig. 10.4 Antibiogram after culture of debrided tissue from a 43-year-old female who presented with a graft infection 6 months after anterior cruciate ligament (ACL) reconstruction showing methicillin-resistant *Staphylococcus aureus*. Patient was successfully managed post debridement with 6 weeks of intravenous vancomycin with no return of symptoms.

struction following infection and debridement. Vancomycin soaking of the new graft may be considered to reduce the risk for subsequent infection.[52]

10.4.6 Antibiotic Management

In addition to surgical debridement, antibiotic therapy remains the mainstay of septic joint management. Multiple studies have shown successful management of intra-articular infections using IV and oral antibiotics regimens, although treatment duration varies widely in literature. Antibiotics should be targeted toward the local antibiogram,[18] as susceptibilities of typical causative organisms show a high amount of geographic variability (▶ Fig. 10.4). Pérez-Prieto et al showed successful resolution of staphylococcal knee infections (*S. aureus* and coagulase-negative *Staphylococcus*) following ACL reconstruction using a 6-week course of combination levofloxacin and rifampin and noted complete resolution of symptoms in 12 of 13 patients within 3 weeks; the one patient who did not improve ended up with graft removal due to continued symptoms.[53]

Examples of successful protocols include:

- Intravenous cloxacillin 2 g three times a day or clindamycin 600 mg three times a day by mouth until CRP <50 mg/L and then oral antibiotics for 6 weeks or until CRP is less than 10 mg/L with re-examination 1 week after discontinuation of antibiotics.[14]
- Ciprofloxacin 750 mg twice a day by mouth and 1 g amoxicillin-clavulanic acid four times a day by mouth for 15 to 90 days until complete resolution of symptoms, with discontinuation of antibiotics 2 days after normalization of serum ESR and CRP.[20]
- Intravenous penicillin and gentamicin for 3 days, followed by 6 weeks of organism-specific oral antibiotics.[2]

With widespread use of inflammatory marker monitoring, the duration of antibiotic therapy can be tailored to the patient needs. Many experts now recommend the use of antibiotics for only 2 weeks after the ESR and CRP fall within normal ranges.[54,55] When studying the effect of treatment on inflammatory markers, CRP normalized faster than ESR, on average falling below the 41 mg/L threshold at day 5 of treatment with antibiotics whereas ESR took on average 14 days to normalize below a 31 mm/hour threshold.[39] In all cases where there is uncertainty, infectious disease specialists can and should be utilized to help guide antibiotic choice and duration of therapy based upon local antibiograms.

10.5 Outcomes and Complications

10.5.1 Recurrent Instability and Reoperation

Graft infection following ACL reconstruction is often managed with graft retention. In long-term follow-up studies, up to 80% of knees have no residual pivot shift,[55] a similar rate to primary ACL reconstruction without infection.[56] Despite intraoperative testing of the stability of the graft at the time of arthroscopic debridement for septic knees, damage to the graft may destabilize the fibers and lead to graft rupture at a higher rate than primary ACL reconstruction without infection.[13,14]

Septic arthritis results in a robust inflammatory response, leading to infiltration of the joint space with inflammatory markers and cells. Infection results in a fivefold increased risk for developing clinically significant arthrofibrosis requiring manipulation under anesthesia or arthroscopic lysis of adhesions.[57]

10.5.2 Patient Reported Outcomes Following Graft Infection

There is controversy about the long-term effects of graft infection on patient outcomes and satisfaction. A systematic review of the literature on ACL reconstruction infections found no differences in IKDC scores and other outcome measures including Lysholm scores, return to activity, and residual instability between patients who did and did not have a graft infection.[58] Additionally, a review of 27 Swedish patients who presented with septic arthritis following ACL reconstruction compared with age-matched controls showed no significant difference in Lysholm score, pain, and knee injury and osteoarthritis outcome score (KOOS).[14]

There are many studies that demonstrated inferior outcomes in patients who underwent ligament reconstruction complicated by infection. Bohu et al. reported that subjective IKDC, KOOS-symptoms, KOOS-sport, and KOOS-quality of life were all significantly lower in patients who experienced graft infections after ACL reconstruction at 1-year follow-up.[18] Average Lysholm scores were 75 to 83 after septic arthritis[18,22,25,26,55] compared with 85 to 91 in patients without septic arthritis.[18,55] Despite this, measures of overall patient satisfaction may be the same between those who have a postoperative infection and those who do not.[18]

10.5.3 Graft Infection Cost

Management of postoperative graft infections involve surgical debridements, extended hospital stays, lengthy antibiotic courses, and multiple specialists. With the growing concern for healthcare costs and the looming penalization of hospital systems in the United States for surgical site infections within the global postoperative period, there is increasing scrutiny over the cost of individual complications. McAllister et al reviewed the cost of postoperative graft infection at their local institution and found that the total cost ranged from $18,000 to $41,000.[16] In a set of seven cases of primary and revision ACL complicated by infection, Bohu et al estimated that the cost of hospital care, surgical management, antibiotics, and additional testing added between $2,611 and $5,874 to the cost of the index procedure.[18]

10.6 Graft Infection Prevention

The use of perioperative antibiotics has been the standard of care for decades, showing clear benefits for reducing orthopaedic infection rates through the use of preoperative antibiotics at the time of surgery,[59] but there are infection prevention issues specific to the use of grafts in orthopaedic procedures.

10.6.1 Intraoperative Graft Antibiotics

Various studies have measured the rate of graft contamination at the time of graft harvest, and found that up to 16.5% of grafts at the time of harvest grow bacterial colonies when cultured.[5] Grafts represent an initially avascular construct that can be a nidus for infection in the early postoperative period. To combat intraoperative bacterial contamination, local antibiotics have been used to decrease postoperative infection risk in hamstring allograft by presoaking the graft in a sterile gauze swab soaked in dilute vancomycin (5 mg/mL) solution.[60] In 1,300 consecutive patients who underwent ACL reconstruction with autograft, vancomycin soaking of the autograft resulted in no infections, significantly reducing the risk of septic arthritis compared with standard perioperative IV antibiotics.[61]

10.7 Intraoperative Autograft Contamination

Intraoperative contamination of a harvested graft, by either touching a nonsterilized portion of the field or being dropped on the floor, has been encountered by 25% of board-certified sport-medicine orthopaedic surgeons. Factors that have been suggested to increase the risk for intraoperative contamination include early career surgeons, changes in staff, and changes in venue, with most cases of graft infection occurring early after a change has occurred.[62] Although infrequent, when this occurs, the surgeon is presented with a choice to use the contaminated autograft after disinfection, harvest an additional autograft, or convert to allograft. Additional autograft harvest increases donor site morbidity, while the use of allograft significantly increases the cost of the operation. All of these possibilities should be discussed with the patient preoperatively during the consent process to avoid surgical delays in the case of graft contamination. In a survey, 75% of surgeons who experienced graft contamination advocated proceeding to implant the previously contaminated graft following proper processing.

Multiple studies have investigated the optimal method for disinfection of autograft that has been contaminated.[63,64,65,66] Povidone-iodine is inferior to both 2 to 4% chlorhexidine gluconate solution and bacitracin solution. A review of this subject shows that soaking the autograft in a 4% chlorhexidine gluconate solution for 3 minutes produces the most effective disinfection compared to povidone-iodine, and that a polymyxin B–bacitracin solution is almost equally effective (▶ Fig. 10.5).[67] There are concerns over the effect of graft processing on the final mechanical properties of the graft. Graft treatment with 4% chlorhexidine gluconate does not negatively affect the mechanical properties of hamstring allograft when compared with fresh-frozen samples.[65] A contaminated graft treated with either bacitracin or chlorhexidine solution has a lower rate of colonization compared to native hamstring graft in laboratory testing.

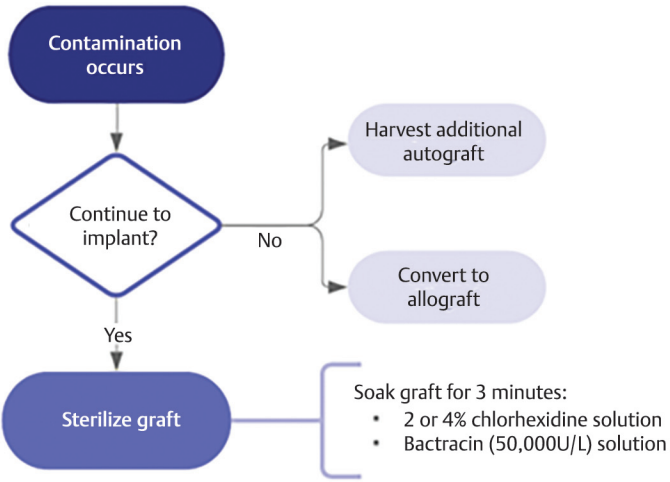

Fig. 10.5 Management strategy for intraoperative graft contamination.

10.8 Conclusion

Infection following knee ligament reconstruction is a rare complication, involving 0.05 to 1.9% of all cases. Management options for infection following knee ligament reconstruction include arthroscopic or open debridement and antibiotics, as determined by the severity of the infection and causative bacteria. Repeat ACL reconstruction following infection has worse outcomes than primary ACL reconstruction, but is a viable option in few cases of reinfection reported in the literature. New literature suggests that intraoperative soaking of grafts with antibiotics may reduce the risk of infection following knee ligament reconstruction.

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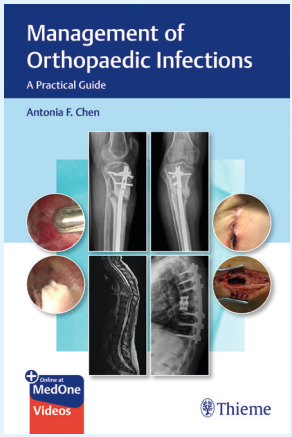

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