Musculoskeletal Infections

edited by

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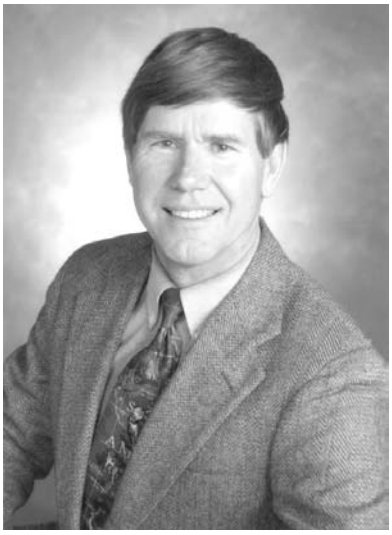
In memory of Jon T. Mader
March 21, 1944–October 25, 2002



Dr. Jon T. Mader died while this book was in its final stages of production. What was to be simply a compilation of what we've learned about musculoskeletal infections over the last several decades has taken on a much greater importance. This book now serves as a tribute to a remarkable man. Jon was a pioneer in the field of musculoskeletal infections; his work over the years helped to increase our understanding of the treatment of these difficult problems. He worked with many of the authors in this book on numerous projects, was a founding member of the Musculoskeletal Infections Society, and had many other colleagues in the areas of infectious diseases and hyperbaric medicine. I had the pleasure of working closely with Jon for almost 20 years. His energy and compassion were contagious. He loved his work and cared deeply for his patients. It is with great joy and sadness that I dedicate this to Jon's memory and his remarkable contribution to the field of musculoskeletal infections.

For my wife, Karen, and children, Zoey, Ken, and Sadie.

JHC

To my wife, Donna, and my children, Sam and Jon Henry, who have provided me a loving sanctuary that gave me the energy and courage to complete this project.

JTM

Preface

The treatment of musculoskeletal infections continues to evolve. We have gleaned our knowledge from past and current masters and our patients. Our knowledge will be expanded and passed on to future generations. We are but a bridge between the past and future.

Jon T. Mader

The United Nations has declared the years 2000–2010 the Bone and Joint Decade. One of the major components of bone and joint disorders are musculoskeletal infections. We have spent the past 20 years treating patients with musculoskeletal infections and conducting research on these difficult infections.

When we first started this endeavor there was not much that could be done for such patients, especially those with long bone osteomyelitis and severe diabetic foot infections. In addition, there was not much interest in musculoskeletal infections. These infections were considered more of a nuisance than a topic for serious clinical and basic science research. At that time, the gold standard was debridement or amputation and six weeks of parenteral antibiotics. Over the past two decades, treatment of these infections has changed. We now have better staging systems, surgeries, antibiotics, and adjunctive therapies. The interest in this topic has also grown. We have a Musculoskeletal Infections Society, and more clinical and basic research is being done in the field. The purpose of this book is to outline the current concepts for the treatment of musculoskeletal infections and to explore emerging techniques for treatment.

The first chapter, on the basic science of these infections, explores the statement, "The environment is everything and the bacteria are nothing." Physicians must understand the location of the infection (environment), the infecting organism(s), and the defenses of the host in order to treat and eradicate the infection. The triad of infection is described in detail including the infecting pathogen, the properties of the host, and the source and location of the infection.

In order to understand and treat musculoskeletal infections we must have treatment templates. Classification of musculoskeletal infections helps provide this template. Chapter 2 describes a staging system for osteomyelitis that helps stratify the infection and guide therapy.

Musculoskeletal infections are more difficult to treat in compromised hosts. The reasons for the difficulty are carefully explored in the chapter on systemically and locally immunocompromised hosts. Physicians must develop a systematic approach for patients with compromised immune systems who present with soft tissue, joint, and bone infections.

It is better to prevent musculoskeletal infections rather than treat them. Chapter 4 explores the history and current rationale for the use of prophylactic antibiotics in musculoskeletal infections. The timing of antibiotic administration, role of interoperative dosing, duration of use, and choice of antibiotic(s) are also discussed.

Specific musculoskeletal infections and the state-of-the-art treatment are described in the chapters on open fractures, long bone osteomyelitis, septic arthritis, hand infections, total hip infections, total knee infections, diabetic foot infections, and vertebral osteomyelitis. Vertebral osteomyelitis is further stratified into hematogenous pyogenic infection of the spine, postoperative infections of the spine, and granulomatous infections of the spine.

The treatment of osteomyelitis in neonates, infants, and children is different from that in adults. Neonates and infants are compromised hosts, while children are superhosts and are easier to treat than adults. Because of these differences, we have included a chapter on pediatric osteomyelitis.

The mainstays of musculoskeletal infections are surgery and culture-directed antibiotic therapy. Specific antibiotics that are useful in musculoskeletal infections and their potential toxicities are described in detail in Chapter 16. Included in that chapter is a section on resistant organisms and their treatment.

Surgery is usually mandatory for the treatment of musculoskeletal infections. The standard surgeries have been described in the sections on specific infections. Muscle flaps are useful in almost all the infections, especially when there is soft-tissue compromise. While the rationale for the use of muscle flaps is described in the specific chapters, the technical aspects and details are presented in Chapter 17.

The management of musculoskeletal infections includes antibiotics, surgery, and adjunctive therapy. The chapter on adjunctive therapy discusses

the roles and effectiveness of such therapies in the management of musculoskeletal infection, including bioimplants, electrical stimulation, and hyperbaric oxygen therapy. The use of bioimplants includes PMMA, collagen hydroxyapatite, synthetic polymers, and fibrin sealant. Bioimplants are being used for the delivery of antibiotics and bone morphogenic protein, as scaffolding, and as a vehicle for osteogenic cell delivery. The use of bioimplants is undergoing an expansion and has the potential to change how we treat musculoskeletal infections.

The final chapter discusses the state of the art in gene therapy in musculoskeletal repair. Management of nonhealing wounds and bone defects has been aided by the development of new agents, including growth factors, cytokines, and bone morphogenic proteins. A way to get these agents to the right location is through gene therapy. The most attractive feature of gene therapy is that therapeutic proteins can be delivered locally to the appropriate site in relatively high concentrations and in a sustained fashion. Current goals include the improvement of transfection efficacy and specificity, optimizing inducible or cell-type specific promoters, and improving local application techniques. Gene therapy will change how we treat musculoskeletal infections and their complications in the future.

Musculoskeletal infections are common problems that involve a variety of specialties, including orthopaedics, infectious diseases, plastic surgery, vascular surgery, internal medicine, pediatrics, family medicine, podiatry, and others. We felt it was important to write a comprehensive book where all of these specialties could find common ground. There are numerous articles and book chapters spread across different specialties but it is difficult to find the important and pertinent information in one place. We hope that this book will fill that void.

We would like to thank our patients who have provided guidance. We are indebted to Kristi Overgaard, who was the driving force behind this book. Ms. Overgaard organized, edited, and shepherded our book to the publishers. Acknowledgment must also be made to others who directly and heavily contributed to this publication; for this we gratefully thank Drs. Joe Wang, Luca Lazzarini, Mark Shirtliff, Jack LeFrock, and Shazia Amina. We would also like to thank the many contributors whose dedication to their patients and to the treatment of musculoskeletal infections contributed not only to this book, but also to the entire field of musculoskeletal infections.

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Jon T. Mader

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1
The Basic Science of Musculoskeletal Infections

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I. INTRODUCTION

The occurrence, type, severity, and clinical prognosis of bone and joint infections depend upon the interplay within a factor triad that includes the characteristics of the infecting pathogen, the properties of the host, and the source of infection. In order to describe accurately why certain types of microbes cause certain types of musculoskeletal infections (MSIs), the relative contribution of each one of these factors must be taken into account (Fig. 1). Therefore, we first discuss the various species of microbes responsible for MSIs. The virulence factors of the pathogens responsible for the majority of musculoskeletal infection cases are also addressed within this introductory chapter, with specific emphasis on *Staphylococcus aureus*, the most commonly isolated bacterial species in these infections. We also discuss host factors, including normal properties such as blood supply and its relation to infection, as well as host defects such as local trauma, age, vascular insufficiency, immunocompromise, phagocyte defects, and implanted medical devices. The final part of the infection triad to be discussed is the source of infection, whether it be via hematogenous introduction, extension of a contiguous focus of infection, or direct inoculation from penetrating trauma, compound fracture, bites, or surgical contamination.

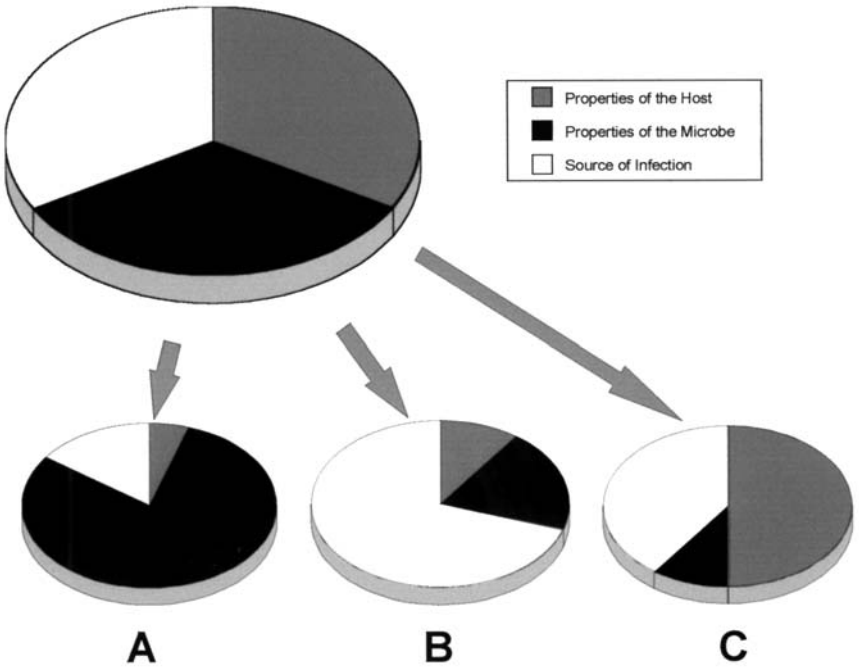


Figure 1 The triad of causal factors in musculoskeletal infections in which the relative contributions of the properties of the host, properties of the microbe, and source of infection are diagrammatically displayed for three types of musculoskeletal infections: (A) properties of the infecting microbial species dominate (e.g., *S. aureus* osteomyelitis), (B) the source of the infection is the dominating factor in the development of this infection (e.g., hand osteomyelitis by *Pasteurella multocida*), or (C) the host defect is the major determinant in the infectious process (e.g., *Bacteroides* spp. osteomyelitis of the foot in a diabetic patient).

II. MICROBIAL SPECIES RESPONSIBLE FOR MUSCULOSKELETAL INFECTIONS

Virtually every bacterial species has been reported to cause MSIs. In a 1999 prospective review of patients ($N = 164$) suffering from long bone osteomyelitis between 1994 and 1996, *Staphylococcus* spp. represented 53% of all isolated bacteria (1). Specifically, *S. aureus* constituted nearly 80% of all *Staphylococcus* spp. isolated from patients with osteomyelitis. *Staphylococcus* spp. are capable of causing osteomyelitis in immunocompetent hosts as well as in immature and immunocompromised individuals. Some other pathogenic microorganisms asso-

ciated with osteomyelitis are *Enterococcus* spp., *Streptococcus* spp., *Pseudomonas aeruginosa*, *Enterobacter* spp., *Mycobacterium* spp., as well as anaerobic and fungal species (specifically *Candida* spp.). Each of these pathogenic species individually represents a very small minority of infections. The immature or compromised immune status of the host is the primary cause of initial infection and development into a persistent and chronic osteomyelitis infection by these other species.

Vertebral osteomyelitis is usually hematogenous in origin but may also be secondary to trauma. Most hematogenous infections are monomicrobic. In the normal host, *S. aureus* remains the most commonly isolated organism. However, aerobic gram-negative rods are found in 30% of cases. Usual sources of infection include the genitourinary tract, skin and soft tissue, respiratory tract, infected intravenous catheter sites, postoperative wound infections, endocarditis, dental infection, and unknown sources. However, the primary infection focus is usually unknown. Intravenous drug abuse causes a high incidence of infection by *P. aeruginosa* and *Serratia marcescens* (2).

Most instances of long bone hematogenous osteomyelitis occur in children after a bacteremic event. A single pathogenic organism is almost always recovered from the bone (3–5). The most common bone isolates are *Staphylococcus* spp., the most common gram-negative organism is *P. aeruginosa*, and the most common anaerobes are *Peptostreptococcus* spp. (Table 1). However, in the immunocompromised patient, other organisms must also be considered including fungi and mycobacteria. In contrast to hematogenous osteomyelitis, in contiguous focus osteomyelitis multiple organisms are usually isolated from the bone. *S. aureus* and coagulase-negative *Staphylococcus* spp. account for 75% of the bacterial isolates (3–5). However, gram-negative bacilli and anaerobic organisms are frequently isolated. A higher rate of nasal and skin colonization with *S. aureus*, defects in host immunity, and impaired wound healing all play roles in foot infection, especially in an inmmunocompromised host such as a diabetic patient. Superficial fungal skin infections, which are common in diabetic patients, may also allow bacterial entry through macerated or broken skin.

Multiple organisms are found in patients with osteomyelitis involving the small bones of the feet, including *S. aureus*, coagulase-negative *Staphylococcus* spp., *Streptococcus* spp., *Enterococcus* spp., gram-negative bacilli, and anaerobes. Aerobic gram-negative bacilli are usually a part of mixed infection (6).

The virulence and tropism of the microorganisms combined with the resistance or susceptibility of the synovia to microbial invasion are major determinants of joint infection. *S. aureus*, *Streptococcus* spp., and *Neisseria gonorrhoeae* are examples of bacteria that have a tropism for the synovia, probably related to adherence characteristics and toxin production. Aerobic gram-negative bacilli such as *Escherichia coli* rarely infect the synovia except in the presence of an underlying and compromising condition. Once the organism

Table 1 Osteomyelitis: Commonly Isolated Organisms

Long bone hematogenous osteomyelitis (monomicrobic infection)		
Infant	Childhood	Adults
<1 Year	1–16 Years	>16 Years
Group B *Streptococcus*	*Staphylococcus aureus*	*Staphylococcus aureus*
Staphylococcus aureus	*Streptococcus pyogenes*	*Staphylococcus epidermidis*
Escherichia coli	*Haemophilus influenzae*	Gram-negative bacilli
		Pseudomonas aeruginosa
		Serratia marcescens
		Escherichia coli

Contiguous focus osteomyelitis without vascular disease (polymicrobic infection)
Staphylococcus aureus
Staphylococcus epidermidis
Streptococcus pyogenes
Enterococcus species
Gram-negative bacilli
Anaerobes

Diabetic foot osteomyelitis (polymicrobic infection)
Staphylococcus aureus
Streptococcus species
Enterococcus species
Proteus mirabilis
Staphylococcus epidermidis
Peptostreptococcus species
Diphtheroids
Pseudomonas aeruginosa
Anaerobes
(e.g., *Bacteroides* spp.)

Vertebral osteomyelitis (monomicrobic infection)
Staphylococcus aureus
Staphylococcus epidermidis
Pseudomonas aeruginosa

is inside the joint, the virulence of the organism varies. In rabbits, intra-articular injection of 10^5 *S. aureus* into the knee joint resulted in major joint destruction, but identical injections of *N. gonorrhoeae* or *S. epidermidis* caused no joint inflammation (7).

The most common etiological agent of all septic arthritis cases in Europe and all nongonococcal cases in the United States is *S. aureus* (8–12). The representation of *S. aureus* is more pronounced in patients with either rheumatoid arthritis or diabetes. After *S. aureus*, *Streptococcus* spp. are the next most commonly isolated bacteria from adult patients suffering from septic arthritis (11–16). Whereas one study showed a high representation of *Streptococcus pneumoniae* (13), *Streptococcus pyogenes* is usually the most common streptococcal isolate, often associated with autoimmune diseases, chronic skin infections, and trauma (11–14). Groups B, G, C, and F, in order of decreasing preponderance, are also isolated, especially in patients suffering from immunodeficiency, diabetes mellitus, malignancy, and severe genitourinary or gastrointestinal infections (11–14). Gram-negative bacilli account for approximately 10%–20% of cases (10–14,16). Patients with a history of intravenous drug abuse, extremes of age, or immunocompromise display a higher prevalence of gram-negative infection. The most common gram-negative organisms are *Pseudomonas aeruginosa* and *E. coli*. Anaerobes are also isolated in a small percentage of cases, usually those of diabetic patients and patients with prosthetic joints. Approximately 10% of patients with nongonococcal septic arthritis have polymicrobic infections.

Historically, *Haemophilus influenzae*, *S. aureus*, and group A streptococci were the most common causes of infectious arthritis in children below 2 years of age. However, the overall incidence of *H. influenzae* as a cause of septic arthritis is decreasing because of the *H. influenzae* type b (Hib) vaccine now given to children (17). A 1999 study of 165 cases of acute hematogenous osteomyelitis or septic arthritis treated in the years before and after the advent of the Hib vaccine demonstrated that musculoskeletal infection due to this bacterial species was reduced to nearly nonexistent levels (18). Therefore, the coverage of *H. influenzae* as part of the empirical antibiotic coverage may no longer be needed in the management of acute septic arthritis in Hib vaccinated children. While *H. influenzae* has lost its predominance as the most commonly identified gram-negative pathogen in pediatric populations, the normal oropharyngeal resident of young children, *Kingella kingae*, may have taken its place, specifically in patients less than 24 months of age (19–22). In fact, a 1995 study found that the nearly half of the clinical isolates from acute septic arthritis patients less than 2 years old were *K. kingae* (21). However, these results have yet to be repeated in other centers. Clinical data suggest that the organism may gain access to the bloodstream in the course of an upper respiratory infection or stomatitis (23). In children above the age of 2, *S. aureus*, streptococci, *H. influenzae*, and *N. gonorrhoeae* have usually been isolated (24–26), although *H. influenzae* may have also lost its predominance in this patient age group (19).

Microbiological associations exist with concomitant disease states. Septic arthritis that follows cases of infectious diarrhea may be caused by *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., or *Yersinia* spp. (27,28). However, these cases may reflect a form of reactive arthritis. A rare form of migrating polyarthritis may be caused by *Streptobacillus moniliformis*. In human immunodeficiency virus–(HIV)-infected patients, *S. aureus* continues to be the most common isolate (approximately 30%) (29). However, there is an increased number of opportunistic pathogens isolated from this patient subset, including *S. pneumoniae*, mycobacterial species, and fungal species (29,30).

Relatively rare in Western Europe, the diplococcus gram-negative bacterial species *N. gonorrhoeae* is the most common cause of septic arthritis in the United States (11,12,31). The number of cases of gonorrhea decreased by 72% between 1975 and 1997 and this decrease was correlated with a reduction in disseminated gonococcal infection and arthritis (32). However, the reported rate increased by 9.2% between 1997 and 1999 and in 2000 stood at 133.2 cases per 100,000 per year (32). Specifically, the rate of gonococcal infection among homosexual men has demonstrated an alarming increase. These increased incidence rates may also cause higher numbers of observed gonococcal arthritis cases.

A. Properties of the Microbes in the Development of Musculoskeletal Infections

Since *S. aureus* has been extensively studied with regard to its role in MSIs and causes the majority of the infectious cases, we use this bacterial species as the "typical" pathogen in our discussion of bone and joint infections. Other representative species, including *N. gonorrhoeae* and *P. aeruginosa*, are also described in their relation to MSIs.

1. *Staphylococcus aureus*

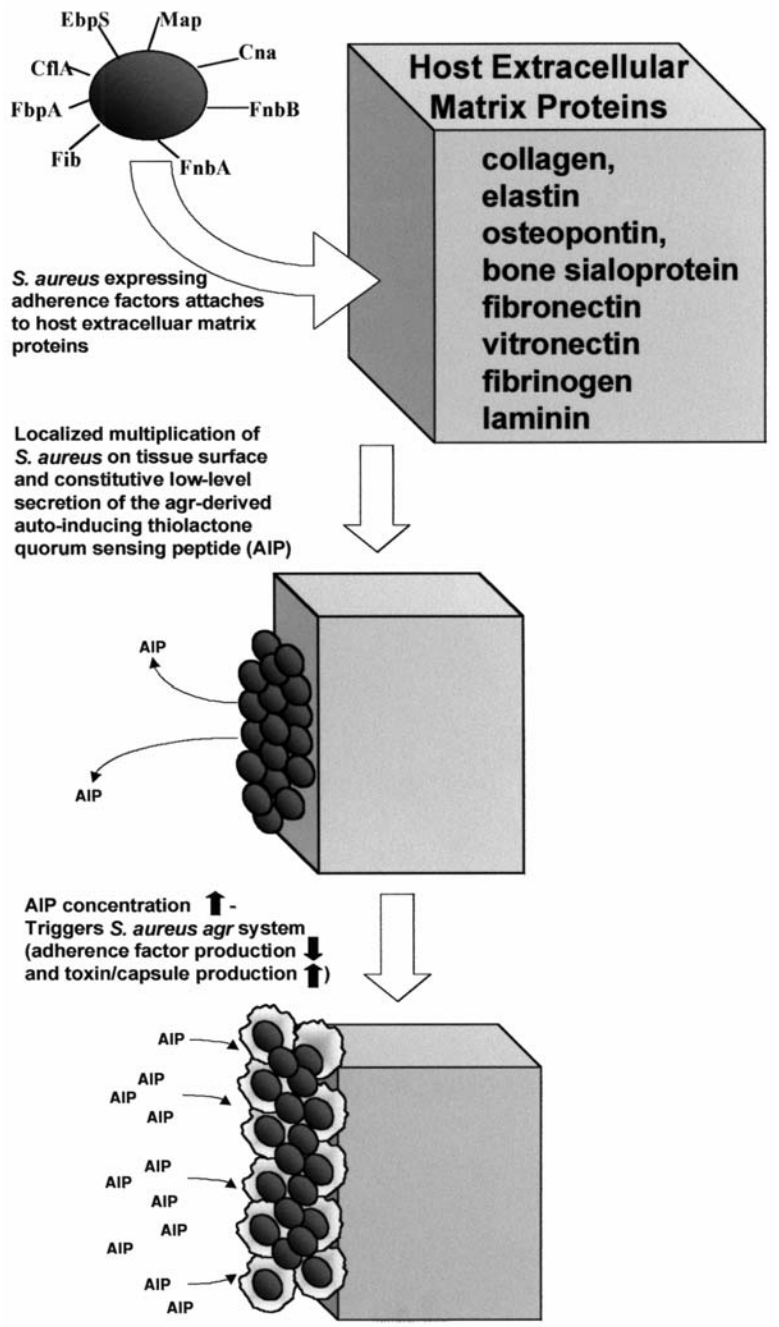
Since *Staphylococcus aureus* spp. demonstrate a wide diversity of infections (tropical pyomyositis, lower respiratory tract infections [pneumonia], superficial skin infections [boils, sties, carbuncles], localized abscesses, endocarditis, osteomyelitis, toxic shock syndrome, serious skin infections [pyodermatitis], food poisoning, bacteremia, empyema, pyopneumothorax, and exfoliative diseases), it is not surprising that *S. aureus* has evolved a wide variety of virulence products to cause disease. The pathogenesis of staphylococcal infections is multifactorial, and it is difficult to determine the precise role of any given factor in infection. Most of the virulence factors seem to be specifically adapted to survival and infection within the host. Staphylococcal products that have a role in infection may be classified as virulence factors responsible for adherence, direct host damage, or immunoavoidance. There are also a number of enzymes and extracellular proteins

that may have a role in virulence. These factors have a specific role in the colonization and infection process in bone and joint infections, and their expression is coordinated throughout the various stages of infection (Figs. 2 and 3). Therefore, the differential regulation of these virulence factors due to staphylococci population levels and environmental factors is extremely important in the development of infection.

a.) *Regulation*. *Staphylococcus aureus* produces a large number of extracellular and cell-associated products that may contribute to virulence and development of persistent infections. Most of these virulence factors seem to be specifically adapted to survival and infection within the host.

During early exponential growth when cell density is low, proteins that promote adherence and colonization (such as fibronectin binding protein, protein A, staphylokinase, and coagulase) are expressed. When cell growth reaches high densities, the production of the adherence and colonization factors is suppressed, while secreted toxins and enzymes are expressed (such as enterotoxins B, C and D, epidermolytic [exfoliative] toxin A, α-, β-, and δ-hemolysin, serine protease, nuclease, type 5 capsular polysaccharide, clumping factor, leukocidin, phosphatidyl-specific phospholipase C, fatty acid modifying enzyme, lipase, hyaluronate lyase [hyaluronidase], and toxic shock syndrome toxin 1). Many of these post-exponential phase proteins are involved in damaging the host, obtaining nutrients from the host for pathogen growth, and disseminating after the organism has adequately colonized and increased in number to promote an active infection.

The expression of most of these staphylococcal products is under partial or complete control of the staphylococcal accessory regulator (*sar*) and the accessory gene regulator (*agr*) system. During early logarithmic growth, a protein encoded by repressor of toxins (*rot*) inhibits the expression of *agr*-activated virulence factors (33). Once activation of the *agr* and *sar* regulatory loci occurs during the late exponential phase, there is an increased transcription of an *agr* regulatory RNA molecule known as RNAIII (34). RNAIII immediately blocks transcription of surface protein genes and, with a hypothesized timing signal, upregulates transcription of extracellular pathogenicity factors (such as exotoxins). The primary regulatory function of RNAIII is at the level of transcription by an undetermined mechanism that may involve one or more regulatory proteins (35). This regulatory RNA molecule is also capable of controlling production of at least two virulence factors, α-hemolysin (*hla*) and protein A (*spa*), at the level of translation. At the beginning of exponential phase growth, the expression of α-hemolysin is normally inhibited through intramolecular base pairing that blocks the ribosomal binding site (35,36). Later in exponential phase growth, RNAIII is expressed and folds into a stable but inactive regulatory molecule. After a significant lag, the secondary structure of RNAIII changes through an unknown agent, and the 5′ region of RNAIII is then able to hybridize with a complementary


EbpS
Map
Cna
ClfA
FbpA
FnbB
Fib
FnbA
Host Extracellular Matrix Proteins
collagen,
elastin
osteopontin,
bone sialoprotein
fibronectin
vitronectin
fibrinogen
laminin
S. aureus expressing adherence factors attaches to host extracelluar matrix proteins
Localized multiplication of S. aureus on tissue surface and constitutive low-level secretion of the agr-derived auto-inducing thiolactone quorum sensing peptide (AIP)
AIP
AIP
AIP concentration ⬆ - Triggers S. aureus agr system (adherence factor production ⬇ and toxin/capsule production ⬆)
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5′ untranslated region of α-hemolysin mesenger RNA (mRNA), thereby making the transcripts accessible for translation initiation (36). Conversely, the 3′ region of RNAIII contains sequences complementary to the leader sequence of *spa* and hybridization is believed to inhibit translation of protein A. In addition, SarA (the primary product of *sar*) has been shown to have an inhibitory effect on the expression of a number of genes, including *cna*, *sea*, *sar*, and the *agr* operon (37). Therefore, *sarA* expression may be autoregulated, but the interactions with this complex system are still being elucidated.

It has been hypothesized that the activity of RNAIII is regulated through a population-sensing autocrine system (quorum sensing) that involves the products of the *agr* locus (38–41). This locus consists of two divergent transcription units, driven by promoters P2 and P3. The P2 operon contains four genes, *agrB*, *agrD*, *agrC*, and *agrA*, and the P3 operon codes for RNAIII (see previous discussion) (42). An octapeptide with a unique thioester ring structure (referred to as the *agr* autoinducing peptide [AIP]) is generated from its precursor, AgrD, and secreted out of the cell through the action of the AgrB membrane protein (Fig. 4) (43). As the concentration of AIP increases in the extracellular microenvironment, the interaction between AIP and the histidine kinase receptor protein, AgrC, also increases. This interaction possibly acylates AgrC and enables it to phosphorylate and thereby activate an intracellular *agr*-encoded protein (AgrA) (35,44). AgrA ~ P then increases transcription at the P2 promoter. With SarA (the major transcript of the *sar* operon), AgrA ~ P also increases the transcription at the P3 promoter, resulting in elevated intracellular levels of RNAIII (45). Therefore, as AIP concentrates in the extracellular environment, the level of RNAIII increases, allowing the growth phase–dependent reduction in adherence factor production and increase in extracellular pathogenicity factor production. AIP not only is capable of activating the *agr* regulon in self strains, but can also inhibit the *agr* activation of other *S. aureus* strains. SarA (the primary product of *sar*) has been found to be autoregulatory, and it mediates virulence factor expression through *agr* transcription by binding to the promoter region as a

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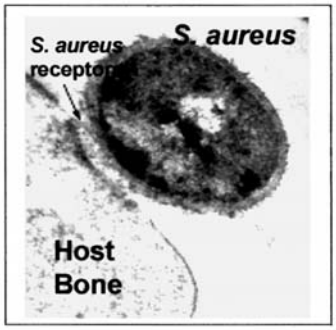
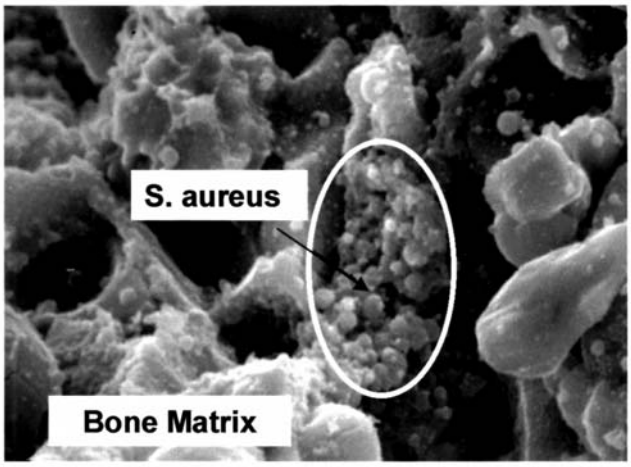
Figure 2 Diagrammatic representation of *S. aureus* attachment to tissues due to high-level expression of adherence factors to host extracellular matrix proteins. After attachment and localized multiplication, the constitutive secretion of the quorum sensing autoinducing peptide (AIP) allows the concentration of this quorum sensing signal. As the microbial population increases, individual cells within the population begin to compete with one another for nutrients. At this time the AIP is at high enough levels to activate the production of a wide variety of staphylococcal virulence factors that enable the microbe to damage the host and obtain more nutrients or explore new niches. At the same time, capsule production increases while adherence factor production is reduced, thereby enabling the *S. aureus* to become able to resist phagocytosis.



Initial Attachment to Host Extracellular Matrix Proteins

Localized Replication and Population Density Increase – Triggering of the *S. aureus* Quorum Sensing System



Toxin and capsule production increase and *S. aureus* embeds within a biofilm

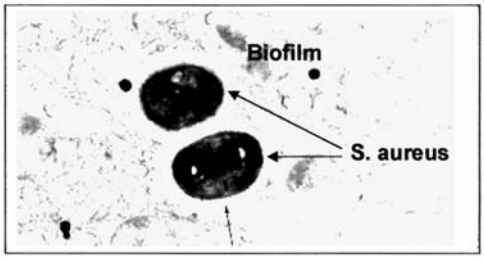


Figure 3 Scanning electron microscope (SEM) and transmission electron microscope (TEM) images of the progression of *S. aureus* osteomyelitis from colonization, to localized multiplication, to embedding within a dense glycocalyx to form a biofilm that is resistant to removal by the host immune system and antimicrobial therapy. (Photographs courtesy of Mary Elizabeth Powers, Dissertation, 1990. University of Calgary.)

dimer (46). SarA has also been shown to interact directly with the promoter regions of a number of genes, including the coding regions for the P2 and P3 promoter of *agr*, protein A, fibronectin binding protein, and α-hemolysin (37,47). However, the interactions with this complex system are still being elucidated. Since *sar* and RNAIII homologs have been identified in a number of coagulase-negative *Staphylococcus* spp., including *S. lugdunensis* (48), *S. epidermidis* (49,50), *S. simulans*, and *S. warneri* (50), this regulation system is also used by the other members of the staphylococcal genus.

Another regulatory locus, termed *S. aureus* exoprotein expression (*sae*), was discovered in 1997 (51). This system is composed of two genes, *saeR* and *saeS*, encoding a response regulator and a histidine protein kinase, respectively,

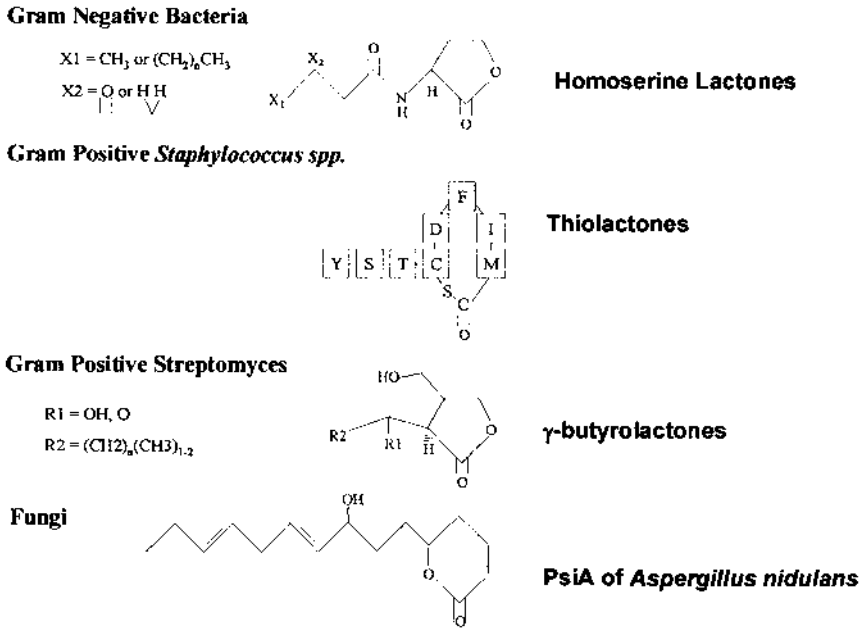


Figure 4 Structures of some common microbial signaling molecules.

with significant homology to other bacterial two-component regulatory systems (52). Its control is mediated at the transcription level, and mutation of the *sae* locus lowered in vivo virulence by drastically diminishing levels of α- and β-hemolysins and coagulase and slightly reducing levels of protein A (53,54). Several environmental signals have also been implicated in the *sar*/*agr*-dependent or -independent regulation of virulence factors. These signals include nonmaintained pH (55), osmolarity (56,57), glucose (58), deoxyribonucleic acid (DNA) topology (56), NaCl, sucrose (59), temperature (60), amino acid availability (61), and presence of O_2 and CO_2. Also, a homolog to the ferric uptake regulator (Fur) of gram negatives was isolated in 2000 and found to regulate the staphylococcal iron regulated (*sir*) operon, which has been proposed to constitute a siderophore-transport system in *S. aureus* (62). Many of the reactions of *S. aureus* to these environmental cues are classified as stress responses, and they are believed to be regulated by sigma factors that control gene expression. In this species, there are two varieties of sigma factors, the housekeeping sigma factor (σ^A) and the alternative sigma factor (σ^B), that are expressed and activate response genes upon entry into stationary phase and in response to environmental stress. σ^B Is believed to be regulated by the product of the gene directly upstream of σ^B coding region, *rsbW* (63). This protein is able to bind to the alternative sigma factor, thereby posttranslationally inhibiting its activity until a stress response is needed.

b.) *Adherence Factors.* As stated earlier, the pathogen must colonize the target tissue through adherence in order to initiate infection. *Staphylococcus* spp. have a variety of receptors for host proteins, termed *microbial surface components*, that mediate adherence to the extracellular matrix in bones and joints or implanted medical devices by recognizing adhesive matrix molecules (64–66). Some of the host matrix proteins are fibronectin and laminin (adherence proteins), elastin (which imparts elastic properties), collagen (which provides structural support), and hyaluronic acid (a glycosaminoglycan that is abundant in the joints and the matrix and provides cushioning through hydration of its polysaccharides). There are also a number of bone- or joint-specific matrix proteins. These include osteopontin (a soluble phosphoprotein that acts as a cytokine and osteoclast attachment protein and is needed for bone injury repair and remodeling), bone sialoprotein (which interacts with osteoblasts and acts as a nucleator for calcium hydroxyapatite formation), and vitronectin (an adhesive glycoprotein that regulates adhesion and the coagulation, fibrinolytic, and complement cascades and also allows bone resorption when bound to osteoclasts). Eight adhesin genes have been determined: genes encoding fibrinogen binding proteins (*fib*, *cflA*, and *fbpA*) (67–69), fibronectin binding protein (*fnbA* and *fnbB*) (70), a collagen receptor (*cna*) (71), an elastin binding protein (*ebpS*) (72), and a broad specificity adhesin (*map*) that mediates low-level binding of several proteins including osteopontin,

collagen, bone sialoprotein, vitronectin, fibronectin, and fibrinogen (73). Also, this microorganism has been shown to possess a number of other host protein–binding receptors in which the genes have not yet been determined. These include a laminin- (52 kd) (74), a lactoferrin- (450 kd) (75), and a transferrin- (42 kd) (76) binding protein. The staphylococcal receptor that binds laminin may be used in extravasation (77). These receptors were found in *S. aureus* but were absent from the noninvasive pathogen *S. epidermidis* (77). The lactoferrin and transferrin receptors bind to these host iron binding proteins and may be used as adhesins and/or as iron acquisition mechanisms. In addition, *S. aureus* expresses a 42-kd protein, protein A, which is bound covalently to the outer peptidoglycan layer of their cell walls. This adherence protein is able to bind to the host platelet gC1qR (a multifunctional, ubiquitously distributed cellular protein, initially described as a binding site for the globular heads of the complement complex C1q) (78). Therefore, protein A may be able to promote adhesion to sites of vascular injury and thrombosis and has been implicated as an important colonization factor. Protein A production is repressed by the *sar* locus via both RNAIII-dependent and -independent mechanisms during post–exponential phase growth (45). This protein is also associated with *S. aureus* immunoavoidance (discussed later). Many of these and other staphylococcal cell wall proteins must be exported out of the bacterial cell in order to interact with the extracellular environment. This export can be either a targeting process (the protein is exported and has binding domains for cell wall secondary polymers such as teichoic acids) or a sorting process (a C-terminal conserved amino acid sequence, LPXTG, that directs the export and covalent attachment to the peptidoglycan) (79).

Increasing evidence supports the importance of staphylococcal surface components as virulence determinants by allowing initial colonization. In a number of studies, mutants in these receptors strongly reduced the ability of staphylococci to produce infection. In addition, there was significant binding of *S. aureus* to bone sialoprotein, fibronectin, and collagen type 1 in a mouse model, indicating that adherence remains a key phase in the early stages of infection (80). Expression of adhesins permits the attachment of the pathogen to cartilage. In a murine septic arthritis model, inoculation of mice with mutants of the collagen adhesin gene showed that septic arthritis occurred 43% less often than in the corresponding wild type (81). Collagen adhesin positive strains were also associated with the production of high levels of immunoglobulin G (IgG) and interleukin-6 (IL-6) (81). Also, vaccination with a recombinant fragment of the *S. aureus* collagen adhesin was able to reduce the sepsis-induced mortality rate to 13%, compared with 87% in the control group (82). However, the role of collagen adhesion of *S. aureus* as a major virulence factor was questioned in 1999 since approximately 30%–60% of clinical isolates do not display collagen binding in vitro or the *cna*-encoded collagen adhesin (83). Staphylococcal fibronectin-binding proteins (FbpA and FbpB) may have a major role in the colonization

and virulence of MSIs. In a 2000 study, all of the tested clinical isolates ($N = 163$) contained one or both of the coding regions for these binding proteins and 95% of these strains had a comparable fibronectin binding capacity to that seen in a staphylococcal reference strain known to bind fibronectin efficiently (84). In addition, an in vivo study of endocarditis in a rat model showed that mutants deficient for fibronectin-binding protein were 250-fold less adherent to traumatized heart valves (85). Also, *S. aureus* adherence to miniplates from iliac bones of guinea pigs was three times higher than that of the fibronectin-binding protein–defective mutant strain (86). It is likely fibronectin-binding proteins play an important role in bone and joint infections, especially those associated with initial trauma or implanted medical devices (87). These receptors play an additional role in an intracellular immunoavoidance strategy (discussed later).

c.) *Factors Causing Damage to the Host.* During acute infection, the innate immune system responds to the peptidoglycan wall (via *N*-formyl methionine proteins and teichoic acids) of *S. aureus* to produce proinflammatory cytokines (such as interleukin-1β [IL-1β], IL-6, and tumor necrosis factor-α [TNF-α]) and C-reactive protein. Bacterial DNA (specifically unmethylated CpG motifs) has also been shown to elicit an intense inflammatory response (88,89). When bacterial DNA from *S. aureus*, *E. coli*, or synthetic, unmethylated oligonucleotides containing CpG motifs was injected into the knee joint of mice, the development of arthritis occurred quickly and lasted up to 14 days, whereas methylated DNA had no significant effect. Also, the affected tissue was characterized by monocyte and macrophage influx with the release of their associated cytokines and chemokines and the absence of T cells.

S. aureus also secretes a number of enterotoxins (A, B, C1–3, D, E, G, H, I, and J) and toxic shock syndrome toxin (TSST-1). The enterotoxins and TSST-1 have been shown to activate the immune system profoundly when evaluated in animal models, increasing mortality rates and exacerbating host inflammatory cell invasion, cytokine release, and tissue degradation in the acute phase of the infection (80,90). They act as superantigens by binding to the conserved lateral regions of the host major histocompatibility complex class II molecule and T cell receptor. Although only approximately 1 in 10,000 T cells is activated during normal presentation of a nonself antigen, 2%–20% of all T cells may be activated by a superantigen (90). These activated T cells are then able to increase the release of a number of cytokines, such as the interleukins (90), interferon-γ (IFN-γ), and TNF-α (91). This upregulated production of cytokines causes a significant systemic toxicity, suppresses the adaptive immune responses, and inhibits plasma cell differentiation. Also, the stimulated T cells proliferate and then rapidly disappear, apparently because of apoptosis (92). Therefore, immune suppression may be due to generalized immunosuppression and T cell deletion. Since

superantigen toxins are usually produced during the postexponential phase of an established infection, they may also aid in local immune deficiency and host damage seen in bone and joint infections.

The importance of these superantigen toxins in septic arthritis has been demonstrated in animal models of septic arthritis. Most animals infected with strains of *S. aureus* isogenic for TSST-1 or entertoxins (A–D) had frequent and severe joint infection (80). However, 80% of animals infected with strains devoid of these toxins had no symptoms, and those remaining animals demonstrating symptoms had only mild or transient arthritis infections (80). Vaccination with a recombinant form of staphylococcal enterotoxin A devoid of superantigenicity was able to demonstrate significant protection from *S. aureus* sepsis in mice (93). These enterotoxins and TSST-1 also subvert the cellular and humoral immune system and may thereby promote a sustained and more fulminant acute infection or enable a localized osteomyelitis to develop into a chronic infection. However, since a study in 2000 demonstrated that expression of TSST is negligible at low oxygen partial pressures (94), the importance of this toxin in the relatively O_2-deprived environment of an infected bone, when compared to that in superficial abscesses or cases of septic arthritis, is still a source of debate.

Staphylococcal hemolysin expression is increased during post–exponential phase growth. Among other stimulatory signals, the *sar/agr* regulon plays a role in this postexponential expression. α-Hemolysin is secreted as a monomer that attaches to host membranes and polymerizes into a hexameric ring channel (95) and has been found to be a significant mediator of virulence (96). Although this hemolysin only binds to human erythrocytes in a nonspecific manner, it can still mediate significant host cell lysis when produced in high concentrations in the infection environment (97). Also, α-hemolysin promotes significant blood coagulation by mediating neutrophil adhesion (98), platelet aggregation (via a fibrinogen-dependent mechanism) (99), and its nonlytic attack on human platelets (100). In addition, this hemolysin can form channels in nucleated cells (e.g., endothelial cells) through which calcium ions freely pass (101,102). The calcium influx is responsible for the vasoregulatory process and inflammatory response disturbances seen in severe infection (103). Finally, α-hemolysin has been shown to interfere with lymphocyte DNA replication (98). These multiple effects of α-hemolysin on the host contribute to the vascular disturbances and immunodeficiency seen in staphylococcal infections, thereby contributing to acute infections and the development of chronic MSIs. The pathogenic properties of α-hemolysin were found in 1999 to occur only when another staphylococcal toxin, the leukocyte-specific γ-toxin (discussed later), was also present in the infecting strain (104).

Another type of hemolysin, sphingomyelinase (β-hemolysin), has only weak cytocidal effects on human granulocytes, fibroblasts, lymphocytes, and erythrocytes (105). Instead, this hemolysin specifically attacks and kills those

cells with membranes rich in sphingomyelin, such as monocytes. The death of monocytes reduces the effectiveness of the immune response and sponsors the release of cytokines (IL-1β, IL-6, and soluble CD14). These cytokine-related events may be important in the infectious process.

δ-Hemolysin, the translation product of RNAIII of the *agr* regulon, specifically binds to monocytes and neutrophils (106). δ-Hemolysin promotes the production and release of tumor necrosis factor-α in monocytes (106). Also, this toxin upregulates the expression of neutrophil complement receptor 3. Although this toxin was unable to prime neutrophils directly for an enhanced response, it enhanced neutrophil priming by lipopolysaccharide or tumor necrosis factor. Therefore, the simultaneous presence of monocytes, neutrophils, and δ-hemolysin-producing staphylococci may overactivate host inflammatory response, resulting in host tissue damage in the microenvironment of bone infection. However, the exact role of this toxin in infection remains to be elucidated adequately.

Leukocidin (LukSF-PV) and γ-hemolysin (HlgAB and HlgCB) specifically lyse leukocytes. Each of these toxins is composed of an interchangeable two-component system. The active toxin is formed by taking one protein from the S component family (LukS-PV, HlgA, and HlgC) and one from the F component family (LukF-PV and HlgB) (107,108). The S component is most likely responsible for the specific cytopathic effect of each of the toxins; the F component is responsible for the common leukocyte binding activity. Although LukF and HlgA proteins show very strong similarity, they are encoded on different gene loci (109). Since these cytotoxins specifically interact and lyse leukocytes, they contribute to the inhibition of infection clearance by the host immune system, thereby enabling staphylococcal species to persist.

The role of exfoliative (epidermolytic) toxins A and B is well demonstrated in cases of exfoliative dermatitis (i.e., staphylococcal scalded skin syndrome) in which the epidermis separates from the stratum granulosum. However, these toxins have not been studied in relation to their effect on *S. aureus* virulence in MSIs. Also, they have been shown not to be bacterial superantigens (110). They may still contribute to virulence since they were classified in 2000 as possible serine proteases (110). In addition to this large array of toxins, a 2000 study has identified a novel gene locus that encodes five exotoxin-like proteins. The in vivo relevance of these proposed toxins must still be demonstrated (111).

d.) *Immunoavoidance Factors.* The ability of the bacteria to evade clearance by the host immune response and to promote a sustained acute infection (e.g., septic arthritis) or a persistent, chronic infection (e.g., osteomyelitis) resides in a number of staphylococcal defense mechanisms, including, but not limited to, IgG inactivation (via protein A attachment), antiphagocytic capsule production, biofilm formation, and invasion and survival in mammalian cells.

Protein A is bound covalently to the outer peptidoglycan layer of their cell walls. This receptor binds to the Fc portion of IgG and presents the Fab fragment of the antibody to the external environment. Therefore, the Fc portion is unable either to bind complement or to signal polymorphonuclear leukocytes, thereby interfering with staphylococcal opsonization and phagocytosis. This interference has been demonstrated in vitro and in animal models with subcutaneous abscesses and peritonitis. Protein A also coats the staphylococcal cell wall with host Fab fragments, and the ability of the immune system to recognize the pathogen as nonself is hindered. The importance of protein A in *S. aureus* septic arthritis was demonstrated in a 1997 study in which strains that obtained this virulence factor caused greater inflammation and cartilage destruction (96).

Capsular polysaccharide may interfere with opsonization and phagocytosis. Among the 11 reported serotypes, capsule types 5 and 8 (microcapsule producers) constitute the vast majority (75%–94%) of clinical isolates (112–114). The capsule of these two serotypes was found to be much smaller than the capsule of other serotypes of *S. aureus* (such as capsule type 1) or pathogenic species such as *Streptococcus pneumoniae*. Unencapsulated and microencapsulated strains demonstrated a high rate of serum clearance when compared to fully encapsulated strains. Therefore, the role of capsular polysaccharide in opsonization and phagocytosis was questioned (112). However, the thin capsule may be necessary in early infection stages in order to allow the interaction of staphylococcal adhesion factors with host proteins (such as fibrin and fibronectin). In one study, it was shown that a small capsule was necessary for fibroblast attachment by protein A of *S. aureus*, and a fully encapsulated strain reduced binding efficiency (115). In another study, the thin capsule was shown to be necessary for binding to bone collagen type 1, since high capsular expression actually inhibited binding (116). Once these microorganisms adhere to solid surfaces (such as bone, implants, or joint tissue), both in vitro and in vivo, staphylococci produce larger quantities of cell-associated capsule than those grown in liquid cultures (117). Specifically, type 5 and type 8 capsule production was shown to be strongly upregulated during postexponential growth (i.e., after adhesion and colonization) by *agr* regulation and perhaps other regulatory systems (118). This upregulated capsule production makes them more resistant to antimicrobial treatment and host immune clearance. Therefore, once staphylococcal adherence proteins establish the infection, the pathogen enters postexponential growth phase and begins producing a thicker capsule that covers and hides the highly immunogenic adherence proteins. This thicker type 5 and type 8 capsule has been found to be serum resistant through inhibition of phagocytosis and opsonization (112,119). The effect of this staphylococcal polysaccharide microcapsule in murine arthritis was explored in a 1997 study in which strains expressing type 5 capsule were shown to produce a higher rate of mortality, higher frequency of arthritis, and more severe form of the disease when compared

to capsule mutants (119). In a clinical trial, a vaccine (StaphVax) that consists of isolated type 5 and type 8 capsular polysaccharides was able to reduce infection rates significantly, by 57% in a high-risk population for as long as 10 months (120).

Staphylococcus spp. can also produce a multilayered biofilm. A biofilm is a modular community of microbes embedded within a host- and/or microbe-derived hydrated matrix (usually exopolysaccharide) that exists at a phase or density interface. This interface may be between a solid support (e.g., soft tissue or bone) and a liquid medium (e.g., extracellular fluid, blood, mucin) (121). Biofilm thickness can vary from a single layer to a thick community of cells embedded within a thick polymeric matrix. Structural analyses in 1995 demonstrated that biofilms possess a sophisticated architecture in which microcolonies exist in discrete pillar or mushroom-shaped structures (122). Between these structures, an intricate channel network provides access to environmental nutrients. It has been hypothesized that the development and maintenance of this phenotype may be mediated through the action of quorum sensing systems in biofilm-producing microbes (123–126).

The multilayered *S. aureus* biofilm is embedded into a glycocalyx (127). The glycocalyx develops on devitalized bone (such as the involucrum) or medically implanted devices (128). The presence of implants is a predisposing factor in the development of infection since they are coated with host proteins soon after implantation, and this provides an excellent source of attachment for any bacteria remaining after débridement surgery (64,69,129,130). Once attached, the bacteria can form the glycocalyx, or slime layer, which protects the bacteria from normal host defenses and systemic antibiotics (131–134). This pathogen usually grows in coherent microcolonies in the adherent biofilm, which is often so extensive that the underlying infected bone or implant surface is obscured. This layer prevents the inward diffusion of a number of antimicrobials, allowing bacterial escape from the bactericidal and bacteriostatic effects of antimicrobial therapy (131–134). Furthermore, those bacteria that survive antibiotic clearance often develop resistance to the impregnated antibiotic and regrow. This resistance has been clinically demonstrated by the isolation of small colony variants of *S. aureus* resistant to gentamicin from the wounds of patients treated with gentamicin-impregnated polymethylmethacrylate (PMMA) beads (135). Also, the glycocalyx displays antiphagocytic properties, thereby allowing the bacteria to evade clearance by the host's immune system (136–138). The glycocalyx is mainly composed of teichoic acids (80%) and staphylococcal and host proteins (139). Host proteins such as fibrin are derived from the conversion of fibrinogen by the staphylococcal coagulase–prothrombin complex (discussed later) (140). It was found that the biofilm produced by *S. epidermidis* also contains the capsular polysaccharide/adhesin (PS/A) that mediates cell adherence to biomaterials and a polysaccharide intercellular adhesin (PIA) that

may mediate bacterial accumulation into cellular aggregates (141,142). PS/A is a high-molecular-mass (>250-kd) molecule that is composed of acid-stable polymers of β_1,6-linked glucosamine. PIA is a polymer of β_1,6-linked *N*-acetyl glucosamine residues with a molecular mass of less than 30 kd that is synthesized through genes present on the intercellular adhesion locus (*ica*) (63,141). *S. aureus* and other *Staphylococcus* spp. also contain an *ica* locus, and its deletion results in the loss of biofilm-forming ability (63). The presence of glycocalyx was noted in 76% of *S. aureus*, 57% of *Staphylococcus epidermidis*, 75% of *Escherichia coli*, and 50% of *Pseudomonas aeruginosa* clinical osteomyelitis isolates (143).

Clinical strains of *Staphylococcus* spp. are able to persist by a number of glycocalyx properties. First, this layer has been shown to protect the embedded pathogens from the action of antimicrobial agents and the host immune system by forming a mechanical barrier (144). Second, local immune deficiency often occurs through frustrated phagocytosis since the normal phagocytic processes are devoted to the removal of the glycocalyx and the implant, if present. Therefore, the energy and resources of the immune system that would normally be used to fight infection are subverted. Third, the glycocalyx may activate monocyte production of prostaglandin E2 to inhibit T cell proliferation indirectly (145). Finally, this glycocalyx has been shown to inhibit polymorphonuclear leukocytes directly (136).

S. aureus has also been shown to survive intracellularly after internalization by cultured osteoblasts (146). Type 5 capsule production of in vivo–grown *S. aureus* (i.e. internalized in cultured osteoblasts) was shown in 1998 to be upregulated when compared to *S. aureus* grown in vitro (147). Therefore, the capsule not only may resist phagocytosis and opsonization, but may also contribute to intracellular survival. In addition to osteoblasts, staphylococci have demonstrated internalization into other cultured mammalian cells, such as bovine mammary gland epithelial cells, human umbilical vein endothelial cells, and pulmonary epithelial cells isolated from a cystic fibrosis patient (148–150). Specifically, initial adherence to glandular epithelial cells has been shown to be mediated by fibronectin receptors on this pathogen (148), possibly using fibronectin as a bridge between the host cell and bacterial receptors for this host factor. After adherence, bacteria may be internalized by host mechanisms involving membrane pseudopod formation (seen in established bovine mammary epithelial cell lines) or through receptor-mediated endocytosis via clathrin-coated pits (seen in mouse osteoblasts and epithelial cells) (148,151). In either case, the dependence upon the action of host cytoskeletal rearrangements through microfilaments is evident.

After internalization, staphylococci may induce apoptosis (via a host caspase–dependent mechanism) or survive intracellularly (148,149,152,153). Induced apoptosis may further the host cell damage seen in MSIs without causing futher inflammation. Also, staphylococci may escape clearance by the

immune system and antimicrobial therapy by persisting within these host cells. This survival was demonstrated in vivo in 2000 when *S. aureus* cells were found in the cytoplasm of embryonic chick osteoblasts and osteocytes in mineralized bone matrix (154). In another study, *S. aureus* was found within polymorphonuclear neutrophils in an in vivo infection model (155). These infected host cells were able to establish infection in naïve animals. Therefore, this pathogen may utilize invasion as an immunoavoidance technique during the host inflammatory response. After the downregulation of the adaptive immune response through T cell apoptosis (mediated by superantigens, other toxins, and invasion), fulminant and/or persistent infection may result.

e.) *Other Staphylococcal Enzymes.* Staphylokinase binds to plasminogen, and this complex activates plasminlike proteolytic activity that causes dissolution of fibrin clots. Although the activity of this enzyme has not been directly related to virulence, the importance of escaping fibrin clots to invade surrounding tissue is apparent. Another enzyme, fatty acid modifying enzyme (FAME), allows the modification of host derived antibacterial lipids in abscesses (156). Therefore, in the intramedullary abscesses associated with osteomyelitis (Brodie's abscess), this enzyme may be responsible for prolonged bacterial survival and the development of osteomyelitis. Coagulase (*cna*), although not an enzyme, is an extracellular protein that forms a complex called *staphylothrombin* by binding host prothrombin (157). This complex is able to convert host fibrinogen to fibrin in order to promote localized clotting. This protein is mainly expressed during the exponential growth phase but is thought to be downregulated during late exponential phase by direct binding and inhibition by SarA (158). Coagulase also has fibrinogen-binding capacity in the absence of thrombin (159). Although no differences in virulence were observed between wild-type strains and coagulase mutants in several infection models, the collagen binding adhesin was found to be important in the pathogenesis of corneal infection in the rabbit (160–162). Also, one can speculate as to the benefits derived from locally impeding blood flow and promoting a fibrin-rich area for augmented colonization by *Staphylococcus* spp. This genus also possesses a number of other enzymes (lipase, nucleases, serine protease, and metalloprotease) that are used to acquire host nutrients such as lipids, nucleotides, and amino acids, respectively. Staphylococcal iron acquisition is mediated through siderophores, such as the 42-kd transferrin binding protein and the 450-kd lactoferrin binding protein (composed of multimers of 62- and 67-kd subunits). Although the pathogenic effects of urease have not been evaluated in MSIs, it is a critical virulence determinant for colonization, urolithiasis, and severe acute pyelonephritis. It is an enzyme that converts urea to ammonia and carbon dioxide, thereby surrounding the bacterium in a protective layer of ammonia. The ammonia is also toxic to host cells, and urease has a direct inflammatory activity on epithelial tissue. Therefore, urease aids in penetration of

the bacterium into tissues and blood. The regulation mechanism is still being determined.

In summary, *S. aureus* infects and elicits a strong native immune response, cytokine release, and high T cell activation. This pathogen is able to use a number of immunoavoidance strategies while the host immune system causes damage to "self" tissues and blood vessels in the area of infection. Damage may cause local circulatory and immune compromise. The high T cell activation eventually results in apoptosis and a weakened immune system, enabling this pathogen to produce a sustained and destructive infection effectively. Although the bacterial products discussed have been shown to increase bone and joint damage in acute septic arthritis, many more *S. aureus* virulence factors have not yet been tested. Therefore, future studies will undoubtedly identify other factors that play a role in MSIs.

2. *Niesseria gonorrhoeae*

As mentioned previously, *N. gonorrhoeae* is the most common cause of septic arthritis in the United States (11,12,31). This diplococcus possesses a number of cell surface structures that have been implicated in virulence. Initial attachment to host epithelium is mediated by long, hairlike protein projections called *pili*. Whether this membrane structure is assembled (Pil+) or not (Pil−), also known as *phase variation*, is determined by posttranslational proteolytic cleavage, variations in homologous recombination, and slipped strand DNA replication resulting in frameshift mutations (163). In addition, the antigenic character of the pili is altered by homologous recombination between coding regions for the various pilin subunits.

Protein I is the main protein on the outer membrane. It is a porin that is expressed in two different forms, a protein IA variant that is almost always associated with disseminated infection and protein IB that is associated with strain causing localized infections. Those strains that are able to cause a disseminated infection in hosts with a normal immune system display serum resistance (164). Protein IA allows stable serum resistance by binding to host factor H. This bacterially bound host factor efficiently inactivates C3b (a central factor in both the classical and alternative complement cascade) into iC3b (165), thereby reducing the efficacy of the host complement system. This porin may also be responsible for the prevention of phagolysosomal fusion in polymorphonuclear leukocytes and a reduced oxidative burst, thereby allowing survival within these cells. Another extracellular gonococcal protein is protein II, which is also called *Opa* since colonies expressing protein II on their surface have a more opaque appearance. This protein is believed to cooperate in the more intimate attachment after initial pili interaction. In addition, protein II is able to attach to the lipooligosaccharide (LOS) of other *N. gonorrhoeae*, thereby enabling the cells

to bind to one other and form microcolonies. These microcolonies may also aid in the initiation of mucosal surface attachment. Protein II is capable of avoiding clearance by the host immune system by phase and antigenic variation (166). Phase variation occurs through slipped strand synthesis that produces a frameshift mutation and produces a prematurely terminated form of the protein. In addition, multiple variants of the protein II gene exist, and, therefore, the antigenic character of protein II can be changed by homologous recombination of these variants. Although this protein is important for mucosal infections, most isolates from DGI patients are missing protein II from their outer membrane and grow to form transparent colonies. Protein III is another porin that is prevalent on the bacterial surface. The antibodies directed against protein III are not bactericidal, and they sterically inhibit antibody binding to protein I and unsialylated LOS that would likely result in bactericidal action (167). Therefore, the generation of these blocking antibodies may prevent serum bactericidal action.

LOS is like the lipopolysaccharide of other gram-negative bacteria except that its carbohydrate portion does not have the complex structure of the repeating O side chain. LOS has endotoxin activity and is largely responsible for the synovial damage in gonococcal arthritis (168,169). Although stable serum resistance is due to protein I.A., unstable resistance is mediated by the ability of some gonococcal strains to attach covalently activated forms of host sialic acid to the galactose residues on LOS (170). This covalent attachment coats the bacterial cell in host proteins and avoids complement activation. In addition, opsonization by complement components and formation of the membrane attack complex of the complement system are inhibited. *N. gonorrhoeae* also produces an IgA protease that may aid in colonization. However, the relevance of this potential virulence factor in gonococcal pathogenesis will need further study.

3. *Pseudomonas aeruginosa*

P. aeruginosa is a gram-negative, ubiquitous, free-living bacterial species that is able to survive in a wide variety of environmental extremes. It has a predilection for moist environments and can infect plants, insects, lower animals, and humans (171). It has been described as the quintessential opportunist in human infections and is capable of causing fatal systemic disease in certain conditions. Some of these conditions arise when normal cutaneous or mucosal barriers have been breached or bypassed (e.g., penetrating trauma, surgery, or intravenous drug abuse); when immunological defense mechanisms have been compromised (e.g., by chemotherapy-induced neutropenia, hypogammaglobulinemia, extremes of age, diabetes mellitus, cystic fibrosis, cancer, or acquired immunodeficiency syndrome [AIDS]); when the protective function of the normal bacterial flora has been disrupted by broad-spectrum antibiotic therapy; and/or when the patient has

been exposed to reservoirs associated with a hospital environment (172). Therefore, this pathogenic bacterial species is able to gain access to the musculoskeletal system by a number of different routes.

a.) *Virulence Factors.* Once introduced into a susceptible location within a host, a *P. aeruginosa* biofilm may develop on devitalized tissue or medically implanted devices to produce an infection. Whereas pseudomonal adherence is mediated by type IV pili, initial colonization is augmented by the activity of flagella, which allows motility and places the bacterium close enough to solid structures for the pili to adhere (173–176). Also, this organism produces neuraminidase that enhances pili binding by removing sialic acid residues from host glycoprotein G_{M1}, making it a better receptor for the pili (177,178). Once attached, this organism can form a fully mature biofilm structure composed of a complex channel system that provides even deeply embedded bacteria access to nutrients in this modular community. It is believed that the channel system is maintained by cell-to-cell signaling (179,180).

High-molecular-weight alginate polymers are used to retain *P. aeruginosa* cells efficiently within the biofilm matrix. However, large conglomerates of cells often detach, diffuse away from the parental biofilm, and reattach to the surface, thereby allowing biofilm spread in the mature biofilm form. This detachment may be mediated by stress due to hydrodynamic flow and/or by the pseudomonal enzyme alginate lyase encoded by *algL*. This enzyme is capable of alginate degradation and therefore can induce biofilm sloughing and dispersion (181).

The bacterial biofilm phenotype has been shown to protect the embedded bacteria from normal host defenses and systemic antibiotics. Specifically, the biofilm protects the organism from direct antibody- and complement-mediated bactericidal mechanisms and from opsonophagocytosis (172). Also, the major constituent of pseudomonal biofilms, the bacterially derived extracellular polysaccharide matrix, displays antiphagocytic properties, thereby allowing the bacteria to evade clearance by the host's immune system (182). The biofilm also acts as a mechanical barrier and prevents the inward diffusion of a number of antimicrobials, thereby increasing minimal bactericidal concentrations by greater than 100 times and allowing bacterial escape from the bactericidal and bacteriostatic effects of antimicrobial therapy (183–185). Furthermore, those bacteria that survive antibiotic clearance often develop or increase their resistance to the antibiotic and regrow upon treatment cessation. Meanwhile, the organism produces a number of extracellular enzymes, including alkaline protease (*apr*), elastase (*lasB*), serine protease (*lasA*), and hemolytic phospholipase C (*plcS*). In addition, the PA-IL and PA-IIL lectins (*lecA* and *lecB*) are produced and appear to function as adhesins as well as cytotoxins for respiratory epithelial cells. *P. aeruginosa* also produces the virulence factors exotoxin A and exoenzyme S (*toxA* and *exoS*). Exotoxin A adenosine diphosphate–(ADP)-ribosylates host

elongation factor-2, causing host translation inhibition (186,187). This toxin is similar to diphtheria toxin and contributes to tissue damage and diminishes the activity of phagocytes. Exotoxin S has ADP-ribosylating activity similar to that seen in many exotoxins and has been found to ribosylate and inactivate G proteins like the pertussis and cholera toxins (188). In order to achieve full enzymatic activity, exoenzyme S must be activated by a host cell protein, termed *factor-activating ExoS* (FAS) (189). Exoenzyme S is extremely important for the ability of *P. aeruginosa* to cause disease since disrupting the gene increased the LD_{50} by a factor of 10^4 in burned mouse models (188). The breakdown of host tissues by these extracellular bacterial products creates conditions that enhance bacterial proliferation, invasion, and tissue injury. These activities may culminate in bloodstream invasion and dissemination.

b.) *Regulation.* *P. aeruginosa* regulates these virulence factors in a complex, but coordinated, way in a microbial cell density–dependent manner through quorum sensing and response to environmental cues. The quorum sensing ability in *P. aeruginosa* is very different from that in the *S. aureus* system and is dependent upon two distinct but interrelated systems, *las* and *rhl*. There is a definite hierarchy of these systems, with the *las* system taking precedence. These two systems work in concert to upregulate a number of pseudomonal factors that enable this pathogen to survive in highly diverse environments. In the *las* quorum sensing system, the *lasI* gene product directs the formation of the extracellular autoinducing signal *N*-(3-oxododecanoyl) homoserine lactone (3-oxo-C_{12}-HSL) (Fig. 4), whose secretion to the extracellular environment is aided by *P. aeruginosa* efflux pumps encoded by the *mexA-mexB-ompR* operon (190). As 3-oxo-C_{12}-HSL concentrates in the extracellular environment, it is taken up by *P. aeruginosa* cells and interacts with the LasR transcriptional activator. This LasR-3-oxo-C_{12}-HSL complex is then able to activate the expression of a number of genes, including *lasB* (elastase), *lasA* (a serine protease that nicks elastin and works synergistically with elastase), *apr* (alkaline protease), *toxA* (exotoxin A), both *xcp* operons (*xcpPQ* and *xcpR-Z*, encoding the type II secretion apparatus), *rhlR*, and *lasI* itself (191). The formation of the LasR-3-oxo-C_{12}-HSL complex may be aided by GroESL chaperonins as seen in the *lux* system of *V. fischeri* (192). These chaperonins are upregulated in response to heat shock and the resultant protein misfolding via the RpoH and AlgU alternative sigma factors. Also, the transcription of *lasR* is induced in response to glucose limitation, and this induction is mediated through the virulence factor regulator–cyclic adenosine monophosphate (vfr-cAMP) complex (discussed later) (193).

The second *P. aeruginosa* quorum sensing system consists of the regulatory protein RhlR and the diffusible autoinducer *N*-butyryl homoserine lactone (C_4-HSL) (Figs. 4 and 5) synthesized by the product of *rhlI*. In contrast to 3-oxo-C_{12}-

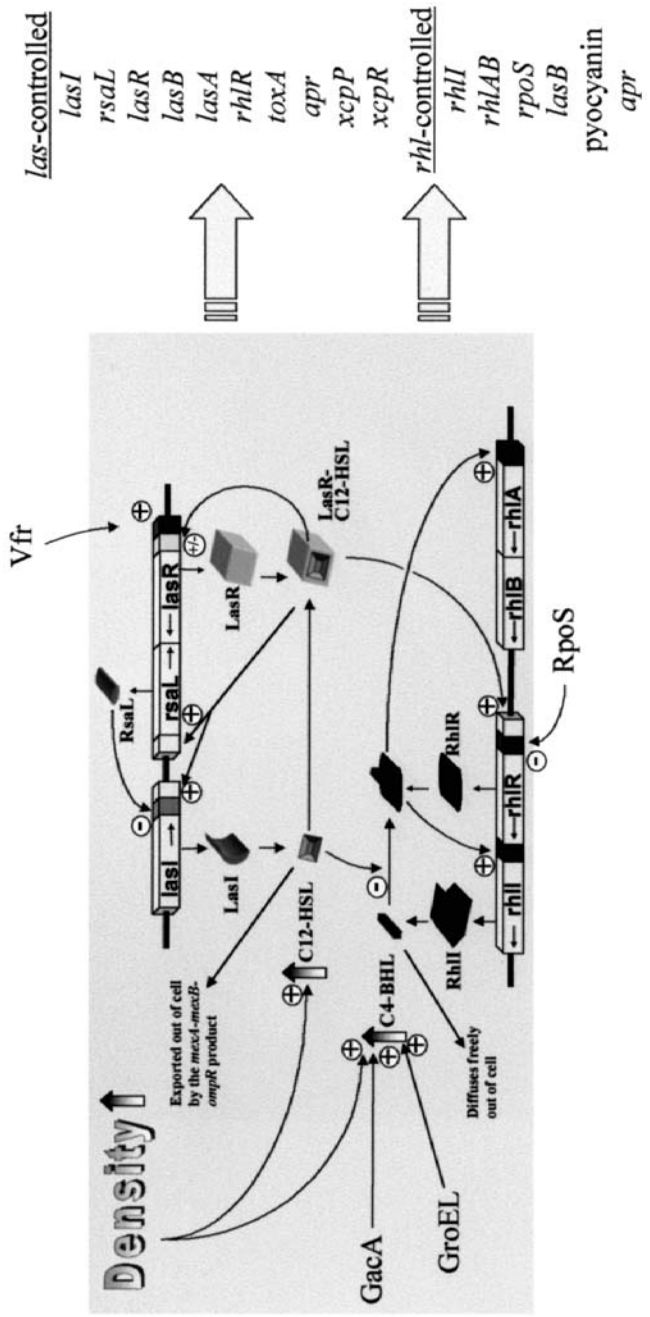


Figure 5 Model of the *las*/*rhl* quorum sensing system in *P. aeruginosa*. See text for gene descriptions. (Adapted from Ref. 179.)

HSL, C_4-HSL is freely permeable. Apparently the length and/or degree of substitution of the *N*-acyl side chain determines whether an autoinducer is freely diffusible or is subject to active efflux by *P. aeruginosa*. As in the homologous *las* system, once the diffusible autoinducer C_4-HSL attains adequate levels, it binds and activates the RhlR transcriptional regulator. RhlR-C_4-HSL has been shown to regulate the rhamnolipid biosynthesis operon *rhlAB*, alkaline protease, pyocyanin, PA-IL and PA-IIL lectins, *lasB*-encoded elastase, and *rhlI* itself (191). The hierarchy of the *las*/*rhl* system is aided by the inhibitory action of the unbound *las* autoinducer, 3-oxo-C_{12}-HSL, on the binding of C_4-HSL to the RhlR transcriptional activator. The upregulation of *lasR* transcription and the resulting elevated concentrations of the LasR-3-oxo-C_{12}-HSL complex allow the *rhl* system to be subsequently activated. The *rhl* quorum sensing system was also shown in 2000 to be inhibited by the alternative sigma factor, RpoS (194), and activated by the *gac* two-component regulatory system that responds to growth phase (Figs. 4 and 5) (187). In addition, the formation of the RhlI-C_4-HSL complex has been shown to be aided by GroESL chaperonins as seen in the *lux* system of *V. fischeri* and possibly in the formation of the LasR-3-oxo-C_{12}-HSL complex (192).

Another factor in this quorum sensing system is the negative regulator, RsaL (195). In *P. aeruginosa*, LasR and 3-oxo-C_{12}-HSL globally regulate many products associated with virulence, as well as the second *P. aeruginosa* quorum sensing system. It has been theorized that at low cell density, RsaL inhibits transcription of *lasI* by binding to the *lasI* operator region, thereby blocking activation by LasR-3-oxo-C_{12}-HSL (195). As the cell density increases, so does the intracellular concentration of 3-oxo-C_{12}-HSL, which allows sufficient LasR-3-oxo-C_{12}-HSL formation to inhibit RsaL competitively for binding to the *lasI* operator. Thus, it appears that during the early stages of growth, RsaL blocks the quorum sensing cascade by inhibiting the transcription of *lasI*. Finally, it was found that this organism produces another intercellular signal, the *Pseudomonas* sp. quinolone signal (PQS), that was identified as a 2-heptyl-3-hydroxy-4-quinolone (196,197). PQS is produced maximally at late stationary phase and works by activating transcription of the *rhlI* gene (and to a lesser degree *lasR* and *rhlR*). It is not known what activates the production of PQS, but this molecule is probably not involved in sensing cell density.

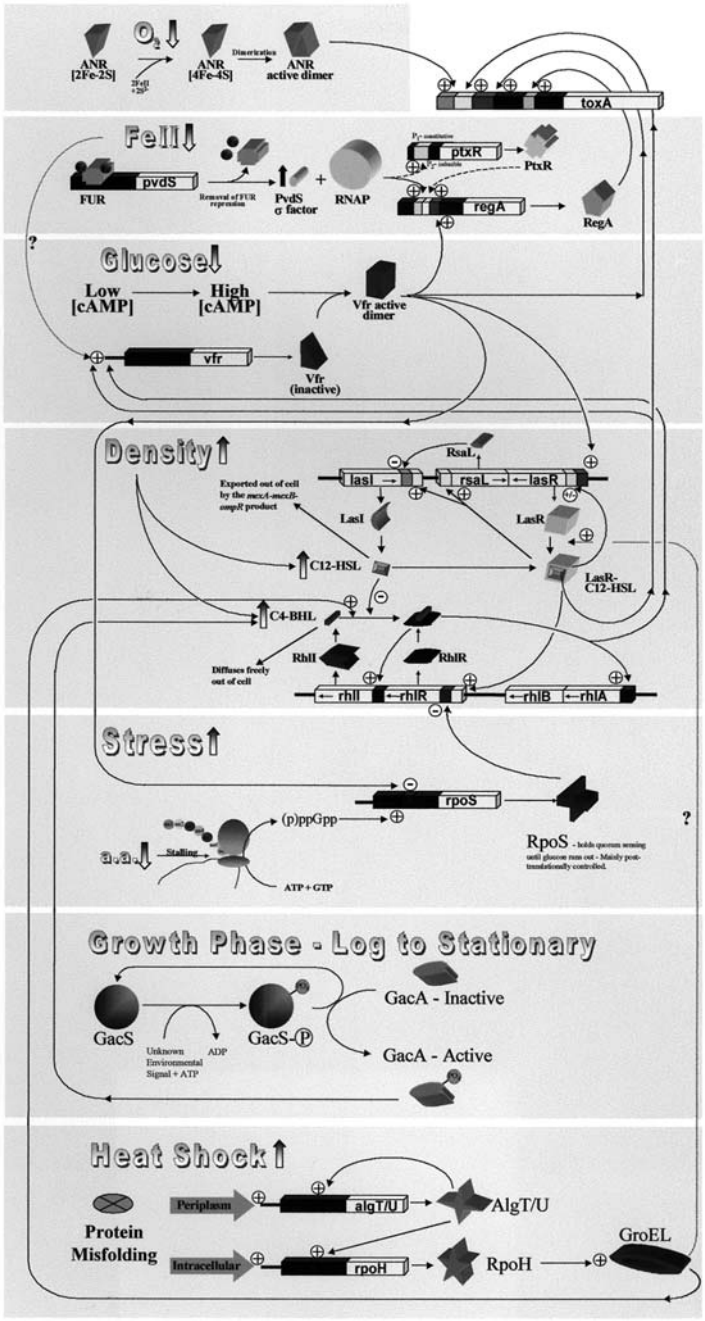
The 3-oxo-C_{12}-HSL and the C_4-HSL of the *las* and *rhl* systems, respectively, have been well studied; other homoserine lactones may have been identified in *P. aeruginosa* by using a combination of reporters, thin layer chromatography, and comparison to HSL standards (198). In *P. aeruginosa* isolates derived from cystic fibrosis–related chronic lung infections, investigators were able to detect up to five additional HSLs: *N*-hexanoyl-L-homoserine lactone (C_6-HSL), *N*-(3-oxohexanoyl)-L-homoserine lactone (3-oxo-C_6-HSL), *N*-(3-oxooctanoyl)-L-homoserine lactone (3-oxo-C_8-HSL), *N*-(3-oxodecanoyl)-L-

homoserine lactone (3-oxo-C_{10}-HSL), and *N*-(3-oxotetradecanoyl)-L-homoserine lactone (3-oxo-C_{14}-HSL). This study also noted that the production of HSLs showed pronounced reduction when the patient was subsequently cocolonized with *Burkholderia cepacia*. Although only one cocolonized patient was evaluated, the properties of multispecies infections and potential interspecies communication may be important in cystic fibrosis and in biofilms.

Although the quorum sensing system is an extremely important determinant of virulence factor expression in *P. aeruginosa*, the system must be able to respond adaptively to environmental stimuli. Stimuli that have been shown to affect this system (either directly or indirectly) include heat shock, iron and glucose availability, RpoS-mediated inhibition (possibly due to specific amino acid starvation), and entry into stationary growth phase mediated by unknown stimulators of the *gac* two-component system.

The regulation of biofilm formation and virulence factor expression is a complex interaction among a number of regulatory cascades in *P. aeruginosa*. For example, exotoxin A, the diphtherialike toxin responsible for protein synthesis disruption in eukaryotic cells, is regulated by a number of environmental and quorum sensing signals (Fig. 6). Some of the environmental signals that *P. aeruginosa* responds to are the presence of glucose, iron and nitrogen availability, oxygen levels, temperature variations, pH, osmolarity, amino acid starvation, and ultraviolet damage.

The *P. aeruginosa* response to glucose limitation is mediated through the virulence factor regulator (Vfr) that demonstrates significant homology to the cAMP receptor protein (CRP) of *E. coli* (193). When glucose is in short supply, the intracellular concentration of cAMP is upregulated in most microbes. In *P. aeruginosa*, two cAMP molecules bind the inactive Vfr dimer. This cAMP-Vfr complex is then able to bind a consensus dyad symmetrical sequence in the promoter region of a number of operons, including the quorum sensing regulator (*lasR*) and genes required for the utilization of various carbon sources, through a helix-turn-helix binding motif (193). Upon binding, the complex promotes the localization of the RNA polymerase holoenzyme (RNAP) to the promoter region through interaction between the β-subunit of the RNAP and the cAMP-Vfr complex. As previously mentioned, the cAMP-Vfr complex is able to activate the transcription of *lasR*, thereby activating the quorum sensing cascade when the autoinducer, 3-oxo-C_{12}-HSL, is present at significant levels. It is interesting to note that the transcription of the *vfr* gene itself has recently been shown to be activated by both the *las* and *rhl* autoinducer–transcriptional regulator complexes. Another carbon metabolite regulator, termed the *catabolite repression control* (*Crc*) *protein*, has been recently found. This protein is able to sense carbon source availability and affects expression of the type IV pili structural subunit PilA to promote microcolony formation on biofilms. As demonstrated in mutation studies, *P. aeruginosa* Crc mutants are only capable of forming thin biofilm


ANR [2Fe-2S]
O2
ANR [4Fe-4S]
Dimerization
ANR active dimer
toxA
FeII
pvdS
FUR
Removal of FUR repression
PvdS σ factor
RNAP
ptxR
PtxR
regA
RegA
Glucose
Low [cAMP]
High [cAMP]
Vfr active dimer
vfr
Vfr (inactive)
Density
RsaL
lasI
rsaL
lasR
Exported out of cell by the mexA-mexB-oprK product
LasI
LasR
C12-HSL
LasR-C12-HSL
C4-BHL
RhlI
RhlR
Diffuses freely out of cell
rhlI
rhlR
rhlB
rhlA
Stress
rpoS
(p)ppGpp
Stalling
ATP + GTP
RpoS - holds quorum sensing until glucose runs out - Mainly post-translationally controlled.
Growth Phase - Log to Stationary
GacS
GacS-P
Unknown Environmental Signal + ATP
ADP
GacA - Inactive
GacA - Active
Heat Shock
Protein Misfolding
Periplasm
algT/U
AlgT/U
Intracellular
rpoH
RpoH
GroEL

monolayers instead of conglomerating into a number of microcolonies through type-IV–dependent twitching motility (199). Therefore, Crc may represent a link between carbon availability and the decision on whether or not to enter into a biofilm mode of growth.

Since *P. aeruginosa* prefers aerobic metabolism that utilizes a number of iron-containing enzymes, this microbial species has evolved a number of strategies to obtain iron from its environment (200). In order to conserve energy and resources, *P. aeruginosa* tightly regulates the expression of its iron acquisition systems to limit their activity in iron-rich environments. This iron-dependent regulation centers on the activity of a recently isolated homologue of the ferric uptake regulator (Fur) in *Escherichia coli* (200,201). When iron is in ample supply, Fur binds Fe^{2+} and is able to attach to a palindromic consensus sequence (termed the "Fur box") in the promoter regions of iron-regulated genes, thereby repressing their expression. When *P. aeruginosa* is grown in iron-limiting conditions, Fe^{2+} dissociates from the complex, causing Fur release and repression removal. Genes controlled either directly or indirectly by the Fur system include those that code for other regulatory proteins (e.g., the sigma factor PvdS), iron-scavenging proteins (e.g., pyochelin and pyoverdin siderophores), proteases that degrade the iron-binding host proteins, the cytotoxin exotoxin A that enables iron release from susceptible host cells to occur, proteins involved in basic metabolic processes (e.g., Krebs cycle), and proteins responsible for oxidative stress survival (e.g., superoxide dismutase) (202–204). Alterations in iron concentrations have been shown to affect the quorum sensing system; such interactions may be mediated indirectly through the *vfr* regulation system, as seen in *V. fischeri* (205).

In reference to respiration, *P. aeruginosa* can utilize inorganic electron acceptors (other than oxygen) for growth. However, this species is incapable of fermentative metabolism and generally grows more fastidiously in oxygenated environments since it prefers aerobic metabolism. Therefore, it is not surprising that this organism alters its gene expression in response to oxygen levels. This control is mediated through the oxygen-sensing transcriptional regulator protein, anaerobic nitrate respiration (ANR) protein, which is homologous to the FNR in *E. coli* (206). This protein forms a $[4Fe\text{-}4S]^{2+}$ cluster under conditions of low O_2. This cluster formation has been shown to promote dimerization and binding to promoter regions of genes whose functions facilitate adaptation to growth under anaerobic conditions (e.g., denitrification enzymes and/or their regulators) (207). There are no data to support the direct role of ANR in the regulation of the

Figure 6 The complex interaction of the *P. aeruginosa* quorum sensing system and environmental stimuli in the regulation of *toxA* (exotoxin A) transcription. See text for gene descriptions.

quorum sensing system. However, O_2 levels must be taken into account when evaluating cell-to-cell signaling experimental data since ANR has been shown to activate the transcription of a large number of enzymes associated with anaerobic metabolism while repressing the expression of those enzymes responsible for aerobic metabolism. By taking into account the effect of oxygen-dependent regulation, one may prevent the incorrect assumption of causal relationships between gene expression and quorum sensing system activity.

This organism has been shown to adapt to amino acid starvation through a complex series of regulatory events termed the *stringent response* that has been described as a global regulation mechanism. Briefly, this response (well elucidated in *E. coli*) is mediated through the accumulation of uncharged cognate transcriptional RNA (tRNA). When the ratio of aminoacyl-charged to -uncharged tRNA falls below a critical threshold, occupation of the vacant mRNA codon at the ribosomal A site by uncharged cognate tRNA leads to stalling of peptide chain elongation. Also, the synthesis of the pseudomonal nucleotide (p)ppGpp from guanosine triphosphate and adenosine triphosphate (GTP) (ATP) is induced in a ribosomal-dependent idling reaction (208,209). It has been demonstrated in *E. coli* that the (p)ppGpp inhibits RNA polymerase, causing the downregulation of a wide range of energetically demanding cellular processes (e.g., the synthesis of stable RNA), stimulation of certain amino acid synthesis pathways (e.g., isoleucine), and induction of stationary phase-specific genes through the effects of the stationary-phase/stress-specific sigma factor (a.k.a. σ^s or RpoS) (208,210). Whereas the σ^{70} (a.k.a. σ^D) factor is responsible for the transcription of constitutive-expressed and housekeeping genes, σ^s has been implicated in the transcription regulation of over 50 genes in *E. coli* in response to not only amino acid starvation, but also osmotic stress, acid shock, heat shock, oxidative DNA damage, and transition to stationary phase. Transcriptional regulation of *rpoS* expression has been demonstrated to be under positive control by (p)ppGpp and negative control by the cAMP receptor protein. Also, translational control has been ascribed to a number of other factors including an RNA-binding protein (Hfq), a nucleoid histonelike protein (H-NS), and a small regulatory RNA (*dsrA* RNA) that destabilizes the secondary structure in *rpoS* mRNA to allow translational initiation. However, proteolysis of RpoS by the ClpPX protease (due to the removal of protection of RpoS by the chaperone protein, DnaK) seems to be the main regulation mechanism (211). This sigma factor was shown in 2000 to inhibit *rhlI* transcription, thereby reducing the level of C_4-HSL- and RhlR-RhlI-regulated gene transcription (194).

P. aeruginosa also mediates changes in gene expression through a complex array of other alternative RNA polymerase sigma factors in response to a number of environmental stressors. Heat shock is one example of an environmental stress, and the pseudomonal response is mediated through the combined effect of the extracytoplasmic stress factor, σ^E (a.k.a. AlgU), and σ^H (a.k.a. RpoH or σ^{32}) (212). AlgU and RpoH respond to the accumulation of misfolded proteins in the

periplasmic and cytosolic bacterial compartments, respectively. Specifically, AlgU is able to upregulate its own expression as well as the expression of genes coding for RpoH and the enzymes of the alginate biosynthetic pathway (212). The antisigma factor products of *mucA* and *mucB* normally inhibit the activity of AlgU (213,214). However, in patients suffering from cystic fibrosis, these anti–sigma factor coding regions are often mutated, resulting in the conversion of nonmucoid strains into the mucoid variety by allowing for the constitutive overproduction of alginate (214,215). This excess of alginate production in *P. aeruginosa* results in the formation of biofilm microcolonies consisting of exopolysaccharide-embedded cells. These biofilm microcolonies demonstrate high-level resistance to host or antimicrobial clearance strategies. In reference to RpoH, many of its regulatory effects can be linked to its activation of GroESL proteins (192). These proteins act as chaperonins that sequentially promote correct folding of a number of proteins and aid in the formation of protein complexes, possibly including the LasR quorum sensing regulator with the LasI product, 3-oxo-C_{12}-HSL, and the formation of the RhlR-C_4-HSL complex (191,192). Two other environmental stressors that regulate gene expression through alternative sigma factors are the need for flagella (mediated by σ^F, a.k.a. σ^{28} or RpoF coded by *fliA*) and nitrogen depletion (σ^N a.k.a. σ^{54} or RpoN) (216,217). All of the sigma factors discussed have been well studied in *E. coli*, but their role in pseudomonal stress response and biofilm formation is still unclear.

GacA and GacS are highly conserved among *Pseudomonas* spp. and demonstrate upregulation of expression upon entry into stationary phase as a result of an unknown signal (187). *gacS* Encodes the cognate sensor kinase that activates the response regulator coded for by *gacA* by phosphorylation (218). This GacS/GacA system strictly controls the expression of extracellular products (antibiotics, exoenzymes, and hydrogen cyanide) when cells are in the transition from exponential to stationary phase. This system has also been found to increase the production of the C_4-HSL autoinducer of the pseudomonal *rhl* quorum sensing system (187). It was hypothesized that activated GacA, by virtue of its typical C-terminal helix-turn-helix DNA binding motif, regulated the transcription of target genes. However, 1999 evidence points to posttranscriptional control by interacting with the mRNA ribosomal binding site of GacA-controlled genes (219). The importance of this regulatory system can be demonstrated by a study in which a *gacA* mutant of *P. aeruginosa* has attenuated virulence in animal models (218).

III. PROPERTIES OF THE HOST

A number of virulence factors of pathogenic microorganisms allow persistent infections, and many host factors assume a significant role. The localization of many MSIs within specific sites of the host is due to the vascular architecture of

Table 2 Systemic or Local Factors That Affect Immune Surveillance, Metabolism, and Local Vascularity

Systemic (Bs)	Local (BI)
Diabetis mellitus	Major vessel compromise
Renal, hepatic failure	Small and medium vessel disease
Malnutrition	Extensive scarring
Chronic hypoxia	Arteritis
Immunosuppression or immune deficiency	Radiation fibrosis
	Chronic lymphedema
Malignancy	Venous stasis
Immune disease	Neuropathy
Extremes of age	Tobacco abuse [≥2 packs per day]
Chronic granulomatous disease	Presence of implants
	Localized trauma

these sites. In addition, any systemic or local factor of the host that affects immune surveillance, metabolism, and local vascularity reduces the ability of the host to resolve the infection and may result in the development of MSIs (Table 2). A number of these factors are discussed in the sections that follow.

A. The Normal Host Vasculature

In cases of long bone osteomyelitis, the metaphyses of the long bones (tibia, femur) are most frequently involved (1). The anatomical characteristics of the metaphyseal region seem to explain this clinical localization (220). The afferent artery ends in the metaphyses as narrow capillaries that make sharp loops near the growth plate and enter a system of large venous sinusoids where the blood flow becomes slow and turbulent. These capillary loops are essentially the "end-artery" branches of the nutrient artery. This structure leads to a slowing of blood flow in the area and presumably allows bacteria to settle and initiate an inflammatory response. The histological features of the region may also be a contributing factor. The metaphyseal capillaries lack phagocytic lining cells and the sinusoidal veins contain functionally inactive phagocytic cells (221); this structure further allows growth of microorganisms. Any end-capillary obstruction could lead to an area of avascular necrosis. Minor trauma probably predisposes the infant or child to infection by producing a small hematoma, vascular obstruction, and subsequent bone necrosis that are susceptible to inoculation from a transient bacteremia (222). Vertebral hematogenous osteomyelitis loca-

lizes within the cancellous bones, particularly the lumbar and thoracic areas of the spine because of their rich blood supply and reduced shear, thereby allowing for colonization and infection.

In cases of septic arthritis, the architecture of the normal joint space allows for the easy hematogenous entry of bacteria since the well-vascularized synovial membrane has no limiting basement membrane. Bacteria may also gain entry into the joint by direct introduction or extension from a contiguous site of infection. Once bacteria are seeded within the closed joint space, the low fluid shear conditions allow bacterial adherence and infection. The virulence and tropism of the microorganisms combined with the resistance or susceptibility of the synovia to microbial invasion are major determinants of joint infection.

B. Generalized Vascular Insufficiency

Most patients who have MSIs and generalized vascular insufficiency suffer from diabetes (6). The diminished arterial blood supply has traditionally been considered to be the major predisposing factor in the initiation of infection and its progression to a chronic state (6). Observations in 1999 suggest that neuropathy may be an equally important factor (223). Identifiable neuropathy as a complication of diabetes mellitus is present in approximately 80% of patients with foot disease (223). Neuropathy may cause foot infection through three mechanisms. First, patients with decreased sensation suffer mechanical or thermal injuries without awareness, leading to skin ulcerations. Second, motor neuropathy affecting the intrinsic muscles of the foot predisposes the patient to gait disturbances and foot deformities, such as hammer and claw toes and Charcot foot. These anatomical alterations may lead to a maldistribution of weight, which elevates focal pressure over the bony prominences. The increase in focal pressure where the foot contacts the ground or footwear may lead to subsequent skin ulceration. Third, autonomic neuropathy contributes by interfering with sweating and causing dry, cracked skin, thereby breaching the integrity of the skin envelope, allowing entry of microorganisms into the soft tissue. All three mechanisms may cause skin ulceration with subsequent skin infection, which may lead to contiguous focus osteomyelitis. A higher rate of nasal and skin colonization with *S. aureus*, defects in host immunity, and impaired wound healing all play a role in diabetic foot infection (224). Superficial fungal skin infections, which are common in diabetic patients, may also allow bacteria entry through macerated or broken skin. Inadequate tissue perfusion in the area of trauma allows the infection to persist to a chronic state.

Decreased sensitivity, ischemia, and a decrease in the cellular response to bacteria are all characteristics of diabetic foot infection. The extent of infection depends on the type of bacteria and number of different organisms present as well as the local tissue response. The location of infection is most often the

toes/phalanges or the midfoot/metatarsals. Although osteomyelitis can develop in the diabetic foot with sensate, well-vascularized soft tissue, it is uncommon. Footwear that does not evenly distribute weight or restricts circulation in an area that is under weight bearing pressure may contribute to cellulitis and ulceration. Cellulitis is an inflammatory response that produces gross signs of redness and edema. At the cellular level there are decreased levels of blood flow, oxygen, phagocytosis, complement factors, and antibodies and increased levels of acid, microscopic debris, and bacteria. The cause of diabetic foot ulcers and/or osteomyelitis is typically a contiguous spread of bacteria and necrosis from an ulcer site. The neuropathic patient may be unaware of the problem until there is a large ulcer formation. An abscess is produced when bacterial colonization creates a local pocket of cell death that is due to acid and pressure. A soft tissue abscess, left untreated, has the potential to progress to infect the bone. Infection in the diabetic foot is caused by the combination of decreased sensitivity, ischemia, and decreased tissue response to bacteria. The extent of infection depends on the amount and type of bacteria and the way the tissue responds to it.

C. Localized Vascular Insufficiency

As with generalized vascular insufficiency, local circulation that is compromised by one or more factors (Table 2) can lead to a reduction in the ability of bone and joint tissues to prevent or eradicate infections effectively as a result of the abrogated metabolic supply to tissues, reduced immune surveillance, and the accompanying inhibition of the local inflammatory response (225). Colonization may also be aided in cases in which the bone or joint has undergone recent injury. In this environment, the production of host-derived extracellular matrix proteins that aid in healing (e.g., fibronectin) may promote bacterial attachment and progression to infection. Clotted blood, dead space, and compromised soft tissues make a medium perfect for bacterial proliferation. Within the damaged bone, necrosis of the outer tangential lamella partly is promoted by partial periosteal retrogression. Necrosis of the fracture ends caused by a disturbance of the medullary blood circulation may follow (226). Compromise of soft tissue adjacent to bone is a major reason for continued drainage (226,227). Within the bone, necrosis of the outer tangential lamella is partly promoted by partial periosteal retrogression.

D. The Involucrum and Osteomyelitis

In normal tissues, necrosis is an important feature of infection. Dead bone is absorbed by the action of granulation tissue developing at its surface. Absorption takes place earliest and most rapidly at the junction of living and necrotic bone. If the area of the dead bone is small, it is entirely destroyed by granulation tissue,

leaving a cavity behind. The necrotic cancellous bone in localized osteomyelitis, even though extensive, is usually absorbed. Some of the dead cortex (cortical bone) is gradually detached from living bone to form a sequestrum. The organic elements in the dead bone are largely broken down by the action of proteolytic enzymes elaborated by host defense and mesenchymal cells (polymorphonuclear leukocytes, macrophages, or the osteoclasts). Because of lost blood supply, dead bone appears whiter than living bone. Cancellous bone is absorbed rapidly and may be completely sequestrated or destroyed in 2 to 3 weeks, but necrotic cortex may require 2 weeks to 6 months for separation from living bone. After complete separation, termed *sequestration*, the dead bone is slowly eroded by granulation tissue and absorbed.

When the area of dead bone is too large, or the host response is systemically or locally compromised (Table 2), the process of bone resorption may be inadequate and may result in the development of the involucrum. Involucrum may be defined as live, encasing bone that surrounds infected dead bone within a compromised soft tissue envelope (228). The involucrum is irregular and is often perforated by openings through which pus may track into the surrounding soft tissues and eventually drain to the skin surfaces, forming a draining sinus tract (229). This host response is the hallmark sign of chronic osteomyelitis and is an attempt by the host to isolate the infection process. The development of the involucrum occurs once the infection is established and fibrous tissue and chronic inflammatory cells surround granulations and dead bone (228). New bone forms from the surviving fragments of periosteum, endosteum, and cortex in the region of the infection and is produced by a vascular reaction to the infection. New bone may be formed along the intact periosteal and endosteal surfaces. New bone may also form from the periosteum. The involucrum may gradually increase in density and thickness to form part or all of a new shaft. New bone increases in amount and density for weeks or months, according to the size of the bone and extent and duration of infection. Endosteal new bone may proliferate and obstruct the medullary canal. After the infection is contained, there is a decrease in the vascularization and the metabolic demands of an effective inflammatory response cannot be satisfied. The revascularization and resorption of the dead bone and scar tissue are similarly affected. The process of resorption eventually subsides and the Haversian canals are sealed by scar tissue. The decrease in vascularization produces a low oxygen tension in infected tissue that interferes with the normal oxygen-dependent intracellular killing mechanisms of the polymorphonuclear leukocyte and the angiogenesis and wound healing activity of fibroblasts (230).

The coexistence of infected, nonviable tissues and an ineffective host response leads to the chronicity of this disease. The nidus of the persistent contamination must be removed before the infection can begin to regress (229,231). Therefore, a thorough débridement is mandatory for resolution of

chronic osteomyelitis in situations in which the host defense removal of the sequestrum is inadequate. Once the sequestrum has been surgically removed, the remaining cavity may be filled with new bone, especially in children. However, in adults the cavity may persist, or the space may be filled with fibrous tissue that connects with the skin surface through a sinus tract.

E. Age and Musculoskeletal Infections

There are basic differences in the pathological features of MSIs in infants, children, and adults. In infants, small capillaries cross the epiphyseal growth plate and permit extension of infection into the epiphysis and joint space (232). The cortical bone of the neonate and infant is thin and loose, consisting predominantly of woven bone, which permits escape of the pressure caused by infection but promotes the rapid spread of the infection directly into the subperiosteal region. A large sequestrum is not produced because extensive infarction of the cortex does not occur, but large subperiosteal abscess may form. In children older than 1 year of age, infection presumably starts in the metaphyseal sinusoidal veins and is contained by the growth plate; the joint is spared unless the metaphysis is intracapsular. The infection spreads laterally, breaking through the cortex and lifting the loose periosteum to form a subperiosteal abscess. In adults, the growth plate has resorbed and the infection may again extend to the joint spaces. Also, in adults, the periosteum is firmly attached to the underlying bone, so subperiosteal abscess formation and intense periosteal proliferation are less frequently seen. The infection may erode through the periosteum, forming a draining sinus tract(s).

The elderly are more susceptible to a number of infections than younger adults, and, therefore, the aged may be considered immunocompromised. The decline in natural and induced immunity seen in the elderly results in a generalized reduction in the immune response to foreign antigens. The greater susceptibility to infections is due to the effects of age on the immune system and immune suppression caused by age-related illnesses. Specifically, the deficient immune response to foreign antigens results from the loss of thymic and T-lymphocyte function (mainly related to the production and response to interleukin-2 [IL-2]) and associated decrease in antibody production by B cells (233).

F. Implanted Medical Devices

The increased use of implanted medical devices such as intramedullary rods, screws, plates, and artificial joints has provided a physiological niche for pathogenic organisms to cause MSIs. Some bacterial species may initially colonize these implants during surgical implantation or subsequently by hematogenous spread. If the infection is of recent onset (<3 months), it is likely the

result of surgical contamination. In this setting, *Staphylococcus epidermidis* predominates as the major isolate. However, late-onset infection is usually caused by hematogenous seeding and *S. aureus* is the most common isolate, followed by *Streptococcus* spp., gram-negative bacilli, and anaerobes. An inherent problem associated with implants is their propensity to be coated in host proteins such as fibrinogen and fibronectin shortly after implantation (129). In the short term, fibrinogen/fibrin seems to be the dominant coating host protein, whereas fibronectin becomes dominant in the long term since fibrinogen/fibrin is degraded. Implants can then act as a colonization surface to which bacteria readily adhere through the binding activity of fibrinogen and fibrin binding receptors of *S. aureus*. Also, implants are often responsible for reduced blood flow and local immunocompromise by impairing natural killer, lymphocytic, and phagocytic cell activities. These implanted devices have also been linked to decreasing the amount of superoxide, a mediator of bacterial killing within professional phagocytic blood cells (234). Another mechanism by which implanted medical devices produce local immune compromise is through frustrated phagocytosis (234). In this case, professional phagocytes may undergo apoptosis when encountering a substrate of a size that is beyond their phagocytic capability. The resulting release of reactive products of oxygen and lysosomal enzymes may cause accidental host tissue damage and local vascular insufficiency, thereby increasing the predisposition to chronic osteomyelitis development. Also, a portion of the normal phagocytic processes are devoted to the removal of the implant foreign material (particularly with metals, methyl methacrylate, and polyglycolic acid), thereby using the energy and resources of the immune system that would normally be used to fight infection (235–237). Therefore, prosthetic implants not only provide a substrate for bacterial adherence, but also limit the ability of the host to deal adequately with the infection. Once colonized, bacteria (such as staphylococcal species) are able to synthesize a "slime" layer, termed the *glycocalyx* or *biofilm*. This layer prevents the inward diffusion of a number of antimicrobials and host phagocytic cells, thereby allowing the bacteria to escape the effects of antimicrobial therapy and the host immune system (238). Once an implant is colonized and chronic osteomyelitis ensues, the only treatment option is implant removal.

The risk of implant infection may be increased by a number of factors. First, certain joint replacements (e.g., total elbow arthroplasties) are more susceptible to infection because they remain close to the surface and have poor soft tissue coverage (239). Second, certain patient populations are at increased risk because of underlying conditions or systemic diseases, including those patients suffering from diabetes mellitus and rheumatoid arthritis (240). Also, of patients who are elderly, obese, or malnourished or who have undergone prior surgery at the implantation site are also at risk. Third, polymethylmethacrylate (PMMA) bone cement may be inhibitory to the activity of white cells and

complement function. Also, the heat released during PMMA polymerization may kill the juxtaposed cortical bone, thereby creating a nonvascularized area. This provides the bacteria a lush growth environment in which they are sealed off from the circulating host defenses. Finally, it has been shown that patient nasal carriage was the most important risk factor associated with surgical site infection (241). Therefore, it may be a worthwhile goal to eliminate *S. aureus* carriage prior to invasive procedures.

G. A Special Case: Inherited Forms of Phagocyte Defects

Defects of phagocyte function are due to alterations in which the normal oxidative burst of the phagocytes or phagocytic adherence ability (required for exit from the vasculature to infected tissues and opsonization of complement-coated bacteria) is reduced. These inherited defects occur in a small proportion of the population. However, the faulty phagocyte function can result in inhibition of infection clearance and progression to deep infection such as osteomyelitis. Three phagocyte defect syndromes that have been associated with the development of chronic osteomyelitis are chronic granulomatous disease (CGD), myeloperoxidase (MPO) deficiency, and hyperimmunoglobulin-E-recurrent infection (Job's) syndrome (HIE).

CGD patients have a defective cytochrome (b245) in the electron transport chain used in the production of reactive oxygen molecules (242,243). These reactive molecules are normally responsible for the oxidative burst in phagocytes that kill ingested microorganisms (243). Since catalase-positive pathogenic species (such as *Staphylococcus* spp., *E. coli*, *Pseudomonas* spp., *Aspergillus* spp., and *Candida* spp.) are able to degrade the low levels of hydrogen peroxide present in the phagocytes of these patients, they are usually associated with the deep infections encountered in CGD sufferers (244). MPO-deficient patients often are undetected since they rarely have recurrent infections unless they have a concomitant disease such as diabetes mellitus (244). However, they may be predisposed to recurrent *Candida* spp. infection (245). HIE patients have defective interferon-γ production by $CD4^+$ T helper cells that results in abnormal chemotaxis and elevated IgE levels (246). These patients are susceptible to skin infections with *S. aureus* (244). The absence of specific granules is rare, but these patients also have recurrent infections thought to be secondary to a chemotactic defect and a minor abnormality of neutrophilic killing of microbes. Other disorders that affect phagocyte function include diabetes mellitus, liver failure, glycogen storage disease, antibody deficiency (IgG, IgM), complement deficiency (complement proteins C3, C3b), leukocyte adhesion deficiency types 1 and 2 (LAD 1 and 2), glucose-6-phosphate dehydrogenase deficiency (G6PD deficiency), and Chediak-Higashi syndrome (CHS).

H. Case Example of Normal Immune Responses in *Staphylococcus aureus* Osteomyelitis

During acute osteomyelitis, the innate immune system responds to the peptidoglycan wall (via *N*-formyl methionine proteins and teichoic acids) of *S. aureus* to produce proinflammatory cytokines (such as IL-1β, IL-6, and TNF-α) and C-reactive protein. These factors enable the host to mount a protective inflammatory response that contains this pathogen and often resolves the infection. However, when the infection is not cleared by the host's innate immune system, *S. aureus* is well equipped to persist by a number of virulence factors and strategies, including, but not limited to, invading and surviving in mammalian cells, hiding within a biofilm, or producing a thick, antiphagocytic capsule. Also, the cell-mediated T helper (TH_1) and humoral (TH_2) adaptive immune responses are often inadequate. In a 1999 study using a murine model of acute hematogenous osteomyelitis, the increase in the central cytokines of cell-mediated immunity (IL-2 and IFN-γ) seemed to be only transient, whereas the inflammatory cytokines remained at elevated levels in osteomyelitic bone (247). This cytokine profile resulted in an initial expansion and activation of T-cell subsets followed by apoptosis. Therefore, *S. aureus* seemed to interfere with the antibacterial immune response by downregulating both T-cell immunity and adaptive immune cytokine production. Whereas a staphylococcal infection usually directs the immune system to a TH_1 response (i.e., T cell mediated immunity), this type of immune response has questionable efficacy in the low oxygen partial pressures of infected bone where immune cell function is inhibited. Also, it was found in a 2000 study in mice that a high level of interferon-γ (a TH_1 cytokine) plays a detrimental role in staphylococcal infection, and IL-4 and IL-10 (TH_2 cytokines) are involved in host resistance to infection through regulation of interferon-γ (248). However, the necessity of the TH_2 response to clear *S. aureus* infection was questioned in a 1999 study utilizing IL-4-deficient mice (249). It seems that a TH_2 response is only required for *S. aureus* infection clearance in certain mice, depending upon their genetic background. In addition, it was shown in 2000 that when interferon-γ was given to mice infected with *S. epidermidis* well after the initial inflammatory response, the animal was able to reduce the level of biomaterial-associated infection (250). Also, whereas intraphagocytic persistence occurred in untreated mice, those animals that received interferon-γ did not demonstrate any gram-positive intracellular invasion. Therefore, although an early increase in TH_1 cytokines during the initial inflammatory response may often result in host tissue damage, pathogen clearance may occur when these cytokines are provided to the infected host after this initial phase (i.e., during the temporal stage when the immune system has become compromised as a result of overstimulation by superantigens). This may be a valuable method to activate a correct and properly timed TH_1 immune response.

In summary, *S. aureus* infects and elicits a strong native immune response, cytokine release, and high T cell activation. This pathogen is able to use a number of immunoavoidance strategies during this time (discussed previously), while the host immune system causes damage to "self" tissues and blood vessels in the area of infection. This damage may cause local circulatory and immune compromise. The high T cell activation eventually results in apoptosis and an impotent immune system, enabling this pathogen to persist. By artificially activating the host immune system to an effective TH_1 response (via administration of interferon-γ) after the initial inflammatory response, this persistent pathogen may be cleared more easily by the host.

I. Case Example of Normal Immune Responses in *Staphylococcus aureus* Septic Arthritis

Once colonized, bacteria are able to proliferate rapidly and activate an acute inflammatory response. Initially, host inflammatory cytokines, including IL-1β and IL-6, are released into the joint fluid by synovial cells (251). These cytokines activate the release of acute phase proteins (e.g., C-reactive protein) from the liver that bind to the bacterial cells and thereby promote opsonization and activation of the complement system. In addition, there is an accompanying influx of host inflammatory cells into the synovial membrane early in the infection. Phagocytosis of the bacteria by macrophages, synoviocytes, and polymorphonuclear cells occurs and is associated with the release of other inflammatory cytokines, which include TNF-α, IL-8, and granulocyte-macrophage colony-stimulating factor, in addition to increasing the levels of already present IL-1β and IL-6. It was demonstrated in a 1998 clinical study that IL-6 and TNF-α concentrations were persistently high even 7 days after treatment was initiated, whereas IL-1β concentration decreased significantly after 7 days (252). Many of these cytokines and the associated immune response have been shown in animal models to be required for bacterial clearance and the prevention of mortality due to bacteremia and septic shock (253). Nitric oxide, a common mediator of inflammatory cytokines, is also required (254).

The T cell mediated (TH_1) and humoral (TH_2) adaptive immune responses may also play a role in the clearance and/or pathogenesis of acute septic arthritis. T cells enter the joint within a few days after infection (255). The role of $CD4^+$ T cells in joint destruction has been demonstrated since their in vivo depletion resulted in a considerably milder course of staphylococcal arthritis (255). These lymphocytes are specifically activated by bacterial antigens in association with host antigen presenting cells or nonspecifically in the case of bacterial superantigens (e.g., TSST-1). The cytokine produced by these activated T cells, IFN-γ, has been shown to reduce the level of mortality and joint destruction in a mouse model of group B *Streptococcus* spp. when delivered 18 hours after bacterial

inoculation (256). However, when *S. aureus* was used as the infecting organism in this model, IFN-γ was shown to increase the frequency and severity of septic arthritis while protecting mice from septicemia (257). Also, it was found in a 2000 study in mice that a high level of IFN-γ (a TH_1 cytokine) plays a detrimental role in staphylococcal infection, and IL-4 and IL-10, both TH_2 cytokines, are involved in host resistance to infection through regulation of IFN-γ (248). However, the necessity of the TH_2 response to clear *S. aureus* infection was questioned in a 1999 study utilizing IL-4-deficient mice (249). It seems that a TH_2 response is only required for *S. aureus* infection clearance in certain mice, depending upon their genetic background. Therefore, the exact role of T cells in host tissue damage and infection clearance is still being elucidated.

Under most circumstances, the host is able to mount a protective inflammatory response that contains the invading pathogen and resolves the infection. However, when the infection is not quickly cleared by the host, the potent activation of the immune response with the associated high levels of cytokines and reactive oxygen species leads to joint destruction. High cytokine concentrations increase the release of host matrix metalloproteinases (including stromelysin and gelatinase A/B) and other collagen degrading enzymes. When monoclonal antibodies or steroids attenuate these cytokines, cartilage degradation is minimized. The joint is further damaged by the release of lysosomal enzymes and bacterial toxins (258). Host proteoglycan degradation is initiated, followed by collagen degradation. In fact, the polymorphonuclear response with subsequent release of these proteolytic enzymes can lead to permanent destruction of intra-articular cartilage and subchondral bone loss in as little as 3 days. Metalloproteinases and the antigen-induced inflammatory response may persist and continue to damage the joint architecture even after the infection has been cleared (259,260). The infectious process induces a joint effusion that increases intra-articular pressure, mechanically impeding blood and nutrient supply to the joint. Thus, increased pressure destroys the synovia and cartilage. Because of the proximity of the epiphyseal growth plate to the joint, direct extension of a joint infection to any of the articulating bones may lead to decreased bone growth in infants and children (261,262). While bone mineralization is preserved, cartilage destruction causes joint space narrowing and erosive damage to the cartilage and bone if left untreated (263). In addition, the infection can spread to surrounding soft tissue, form sinus tracts, and disrupt ligaments and tendons in the untreated patient (264).

The interaction of the bacteria and host is of the utmost importance in the initiation and prolongation of infection and cartilage damage. There is a subtle balance between an effective immune response to eliminate the infecting organism from the host and the overactivation of this response that causes the majority of infection-related joint destruction. Therefore, care must be exercised and further studies must be performed in regard to using agents that suppress the inflammatory response in the treatment of septic arthritis.

J. Case Example of Normal Immune Responses in *Neisseria gonorrhoeae* Septic Arthritis

Gonococcal arthritis occurs in approximately 42%–85% of patients suffering from disseminated gonococcal infection (DGI) and begins with a localized mucosal infection (31,265). DGI-producing strains are unusually sensitive to the in vitro killing of penicillin G and possess unique nutritional requirements for arginine, hypoxanthine, and uracil. *N. gonorrhoeae* possesses a number of virulence factors. It is the combined effects of these factors, their phase and antigenic variation, and properties of the host immune response that enable this pathogen to persist and localized infection to become DGI.

The host may contain a gonococcal infection through the action of the innate immune response with particular dependence upon the complement system. This system is largely responsible for attracting polymorphonuclear leukocytes and the resulting cascade of inflammatory cytokines and chemokines. However, during periods surrounding early pregnancy, puerperium, and menstruation, the accompanying alterations in vaginal pH, cervical mucus, and genital flora and the endometrium exposure of submucosal vessels may predispose the female patient to *N. gonorrhoeae* invasion and DGI (31,164). Defects in the complement and/or reticuloendothelial systems may also inhibit the host's ability to prevent gonococcal MSI.

IV. SOURCE OF THE INFECTING ORGANISM AND THE DEVELOPMENT OF MUSCULOSKELETAL INFECTIONS

The source of infection is extremely important in the development of MSIs since it determines the type of infecting microbial species, the compartment to which the organism is delivered, and the size of the microbial inocula. As previously mentioned, *S. aureus* is able to cause MSIs derived from multiple sources, often independently of host factors or point of entry considerations, because of this species's vast array of virulence factors. However, many other seemingly "nonpathogenic" microbial species are only able to produce MSIs when delivered in high concentrations to specific musculoskeletal sites. These opportunistic pathogens depend upon high inoculation numbers and/or host defects to cause disease.

MSIs can result from hematogenous seeding or direct seeding. When infecting microbes are derived from transient bacteremia, this infection is usually monomicrobic with *S. aureus* predominating. However, host defects and the large inoculum size delivered directly into the bloodstream enable *P. aeruginosa* and *Serratia marcescens* to cause many MSIs in the intravenous drug user (2,266). Also, exotic isolates including fungi, mycoplasmas, and anaerobes can be found

in compromised patients. The pathogenic microbes can also cause infection by gaining entry to the circulatory system from a distal focus of infection. These types of infections are heavily dependent upon the ability of the microbe to cause an initial infection, enter the blood, avoid immune clearance, and colonize and infect another area. One example of this type of infection is the development of gonococcal septic arthritis after *N. gonorrhoeae* urogenital infection and DGI. In 0.5% to 3% of gonorrhea infections, the pathogen is able to gain access to the bloodstream from the primary mucosal site of infections and produce disseminated gonococcal infection (31,267,268). A number of risk factors have been epidemiologically associated with the development of DGI (Table 3). Females are four times more likely to have DGI than males (265). This prevalence in women may be due to the asymptomatic nature of gonorrhea infections in women and the associated delay in diagnosis, thereby providing time for the bacteria to gain access to the bloodstream. In addition, a high percentage of affected females are either pregnant or menstruating at the time of the infection (31). Also, since the clearance of gonococcal infection depends upon an effective complement mediated immunity and a functional reticuloendothelial system, complement deficiencies and systemic lupus erythematosus are risk factors in this patient subset. In addition, some cases of secondary hematogenous MSIs may arise after the dissemination of *S. aureus* from an endocarditis source or after cases of infectious diarrhea by *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., or *Yersinia* spp. (27). A rare form of migrating polyarthritis may be caused by *Streptobacillus moniliformis*. In addition, the dissemination of *Borrelia burgdorferi* (the causal microbial agent in Lyme disease) from the initial tick bite and infection may cause MSIs.

MSIs can also be caused by direct microbial seeding of the bone or joint. For example, a direct extension of a contiguous focus of infection enables microbes to be seeded into the bone or joint from adjacent soft tissue infections (e.g., diabetic foot infections). In these cases, the multiple species of seeded

Table 3 Risk Factors for Disseminated Gonococcal Infection

Infection with transparent, piliated *N. gonorrhoeae* strains capable of phase variation
Diagnosis delay (especially in females, because of asymptomatic nature on the infection)
Complement system deficiency
Systemic lupus erythematosus
Menstruation, pregnancy, and puerperium
Male homosexuality
Urban residence
Promiscuity
Low socioeconomic and educational status

microbes exist in a compromised host environment that allows their persistence, growth, and dissemination. Therefore, these types of infections are usually polymicrobic, and although staphylococcal species predominate, *Enterococcus* spp., *Proteus mirabilis*, *Peptostreptococcus* spp., diphtheroids, *P. aeruginosa*, and *Bacteroides* spp. are also found in sizable proportions of infected patients.

Direct seeding of organisms may also occur during invasive surgical procedures, such as total hip or total knee arthroplasties. If introduced during surgery, the most common contaminating bacterial species is *S. epidermidis* since it is a part of the resident skin flora and may find its way from the skin of the patient or health care provider to the surgical wound. In addition, the clotted blood, dead space, and compromised soft tissues of a surgical site make a medium perfect for bacterial proliferation once the wound has been colonized.

Trauma is the last source of direct microbial seeding. Trauma can take the form of a penetrating wound such as a stab wound or an animal or human bite. In these cases, the penetrating foreign object both generates a pocket of clotted blood and compromised soft tissue and carries microbes into these deep areas. Osteomyelitis or infectious arthritis may develop, depending upon the inoculum size, health of the host, and introduced microbe. Trauma can also take the form of seeding during open fracture. Under these infection conditions, rare species (e.g., *Pasteurella multocida*) may be isolated.

V. CONCLUSIONS

The reason why certain bacteria cause MSIs is dependent upon a clinical triad that includes the properties of the infecting microbial species, properties of the host, and source of the infection. Although *S. aureus* is the most commonly isolated bacterial species in cases of musculoskeletal infection, virtually every microbial species has been reported as the causal pathogen. The dominance of *S. aureus* in these types of infections may be explained by its wide variety of virulence products. Staphylococcal products that have a role in infection may be classified as virulence factors responsible for adherence, direct host damage, or immunoavoidance. There are also a number of enzymes and extracellular proteins that may or may not have a role in virulence. The expression of these factors is regulated throughout the various stages of infection through quorum sensing and environmental cues. However, defects in the host or a large organism inoculum is required for most other microbial species, such as the quintessential opportunistic pathogen *P. aeruginosa*, to cause a musculoskeletal infection. The localization of many MSIs within specific sites of the host is due to the vascular architecture of these sites. In addition, any systemic or local factor of the host that affects immune surveillance, metabolism, and local vascularity reduces the ability of the host to resolve the infection and may result in the development of MSIs. Finally,

the source of infection is extremely important in the development of MSIs since it determines the type of infecting microbial species, the compartment to which the organism is delivered, and the size of the microbial inocula. When these three facets of the clinical triad are taken into consideration, clues to the occurrence, type, severity, and clinical prognosis of bone and joint infections may be ascertained.

REFERENCES

1. ME Shirtliff, MW Cripps, JT Mader. Retrospective review of 728 patients with long bone osteomyelitis. American Society for Microbiology, 99th Annual Meeting. Chicago, 1999.
2. RS Holzman, F Bishko. Osteomyelitis in heroin addicts. Ann Intern Med 75:693–696, 1971.
3. FA Waldvogel, G Medoff, MN Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. 3. Osteomyelitis associated with vascular insufficiency. N Engl J Med 282:316–322, 1970.
4. FA Waldvogel, G Medoff, MN Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects (second of three parts). N Engl J Med 282:260–266, 1970.
5. FA Waldvogel, G Medoff, MN Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med 282:198–206, 1970.
6. JH Calhoun, J Cantrell, J Cobos, J Lacy, RR Valdez, J Hokanson, JT Mader. Treatment of diabetic foot infections: Wagner classification, therapy, and outcome. Foot Ankle 9:101–106, 1988.
7. DL Goldenberg, PL Chisholm, PA Rice. Experimental models of bacterial arthritis: a microbiologic and histopathologic characterization of the arthritis after the intraarticular injections of *Neisseria gonorrhoeae*, *Staphylococcus aureus*, group A streptococci, and *Escherichia coli*. J Rheumatol 10:5–11, 1983.
8. LL Barton, LM Dunkle, FH Habib. Septic arthritis in childhood: a 13-year review. Am J Dis Child 141:898–900, 1987.
9. AS Dickie. Current concepts in the management of infections in bones and joints. Drugs 32:458–475, 1986.
10. U Deesomchok, T Tumrasvin. Clinical study of culture-proven cases of non-gonococcal arthritis. J Med Assoc Thai 73:615–623, 1990.
11. L Le Dantec, F Maury, RM Flipo, S Laskri, B Cortet, B Duquesnoy, B Delcambre. Peripheral pyogenic arthritis. A study of one hundred seventy-nine cases. Rev Rheum Engl Ed 63:103–110, 1996.
12. MJ Ryan, R Kavanagh, PG Wall, BL Hazleman. Bacterial joint infections in England and Wales: analysis of bacterial isolates over a four year period. Br J Rheumatol 36:370–373, 1997.
13. DS Morgan, D Fisher, A Merianos, BJ Currie. An 18 year clinical review of septic arthritis from tropical Australia. Epidemiol Infect 117:423–428, 1996.

14. A Schattner, KL Vosti. Bacterial arthritis due to beta-hemolytic streptococci of serogroups A, B, C, F, and G. Analysis of 23 cases and a review of the literature. Medicine (Baltimore) 77:122–139, 1998.
15. DL Goldenberg, AS Cohen. Acute infectious arthritis: a review of patients with nongonococcal joint infections (with emphasis on therapy and prognosis). Am J Med 60:369–377, 1976.
16. JJ Vyskocil, MA McIlroy, TA Brennan, FM Wilson. Pyogenic infection of the sacroiliac joint: case reports and review of the literature. Medicine (Baltimore) 70:188–197, 1991.
17. M De Jonghe, G Glaesener. Type B *Haemophilus influenzae* infections: experience at the Pediatric Hospital of Luxembourg (in French). Bull Soc Sci Med Grand Duche Luxemb 132:17–20, 1995.
18. SG Bowerman, NE Green, GA Mencio. Decline of bone and joint infections attributable to *Haemophilus influenzae* type b. Clin Orthop 341:128–133, 1997.
19. JD Luhmann, SJ Luhmann. Etiology of septic arthritis in children: an update for the 1990s. Pediatr Emerg Care 15:40–42, 1999.
20. DW Lundy, DK Kehl. Increasing prevalence of *Kingella kingae* in osteoarticular infections in young children. J Pediatr Orthop 18:262–267, 1998.
21. P Yagupsky, Y Bar-Ziv, CB Howard, R Dagan. Epidemiology, etiology, and clinical features of septic arthritis in children younger than 24 months. Arch Pediatr Adolesc Med 149:537–540, 1995.
22. P Yagupsky, R Dagan, CW Howard, M Einhorn, I Kassis, A Simu. High prevalence of *Kingella kingae* in joint fluid from children with septic arthritis revealed by the BACTEC blood culture system. J Clin Microbiol 30:1278–1281, 1992.
23. P Yagupsky, R Dagan, CB Howard, M Einhorn, I Kassis, A Simu. Clinical features and epidemiology of invasive *Kingella kingae* infections in southern Israel. Pediatrics 92:800–804, 1993.
24. R Dagan. Management of acute hematogenous osteomyelitis and septic arthritis in the pediatric patient. Pediatr Infect Dis J 12:88–92, 1993.
25. CW Fink, JD Nelson. Septic arthritis and osteomyelitis in children. Clin Rheum Dis 12:423–435, 1986.
26. CJ Welkon, SS Long, MC Fisher, PD Alburger. Pyogenic arthritis in infants and children: a review of 95 cases. Pediatr Infect Dis 5:669–676, 1986.
27. A Fryden, A Bengtsson, U Foberg, B Svenungsson, B Castor, A Karnell, R Schvarcz, B Lindblom, E Kihlstrom. Early antibiotic treatment of reactive arthritis associated with enteric infections: clinical and serological study. Br Med J 301:1299–1302, 1990.
28. A Keat. Sexually transmitted arthritis syndromes. Med Clin North Am 74:1617–1631, 1990.
29. D Vassilopoulos, P Chalasani, RL Jurado, K Workowski, CA Agudelo. Musculoskeletal infections in patients with human immunodeficiency virus infection. Medicine (Baltimore) 76:284–294, 1997.
30. A Saraux, H Taelman, P Blanche, J Batungwanayo, J Clerinx, A Kagame, L Kabagabo, J Ladner, P Van de Perre, P Le Goff, J Bogaerts. HIV infection as a risk factor for septic arthritis. Br J Rheumatol 36:333–337, 1997.

31. JP OBrien, DL Goldenberg, PA Rice. Disseminated gonococcal infection: a prospective analysis of 49 patients and a review of pathophysiology and immune mechanisms. Medicine (Baltimore) 62:395–406, 1983.
32. Centers for Disease Control. Sexually Transmitted Disease Surveillance 1999. US Department of Health and Human Services, Public Health Service 15–24, 2000.
33. PJ McNamara, KC Milligan-Monroe, S Khalili, RA Proctor. Identification, cloning, and initial characterization of rot, a locus encoding a regulator of virulence factor expression in *Staphylococcus aureus*. J Bacteriol 182:3197–3203, 2000.
34. N Balaban, RP Novick. Autocrine regulation of toxin synthesis by *Staphylococcus aureus*. Proc Natl Acad Sci USA 92:1619–1623, 1995.
35. E Morfeldt, K Tegmark, S Arvidson. Transcriptional control of the agr-dependent virulence gene regulator, RNAIII, in *Staphylococcus aureus*. Mol Microbiol 21:1227–1237, 1996.
36. E Morfeldt, D Taylor, A von Gabain, S Arvidson. Activation of alpha-toxin translation in *Staphylococcus aureus* by the trans-encoded antisense RNA, RNAIII. EMBO J 14:4569–4577, 1995.
37. C Wolz, P Pohlmann-Dietze, A Steinhuber, YT Chien, A Manna, W van Wamel, A Cheung. Agr-independent regulation of fibronectin-binding protein(s) by the regulatory locus *sar* in *Staphylococcus aureus*. Mol Microbiol 36:230–243, 2000.
38. AL Cheung, YT Chien, AS Bayer. Hyperproduction of alpha-hemolysin in a sigB mutant is associated with elevated SarA expression in *Staphylococcus aureus*. Infect Immun 67:1331–1337, 1999.
39. AF Gillaspy, CY Lee, S Sau, AL Cheung, MS Smeltzer. Factors affecting the collagen binding capacity of *Staphylococcus aureus*. Infect Immun 66:3170–3178, 1998.
40. L Rao, RK Karls, MJ Betley. *In vitro* transcription of pathogenesis-related genes by purified RNA polymerase from *Staphylococcus aureus*. J Bacteriol 177:2609–2614, 1995.
41. N Balaban, T Goldkorn, RT Nhan, LB Dang, S Scott, RM Ridgley, SC Wright, JW Larrick, R Rasooly, JR Carlson. Autoinducer of virulence as a target for vaccine and therapy against *Staphylococcus aureus*. Science 280:438–440, 1998.
42. RP Novick, SJ Projan, J Kornblum, HF Ross, G Ji, B Kreiswirth, F Vandenesch, S Moghazeh. The agr P2 operon: an autocatalytic sensory transduction system in *Staphylococcus aureus*. Mol Gen Genet 248:446–458, 1995.
43. G Ji, R Beavis, RP Novick. Bacterial interference caused by autoinducing peptide variants. Science 276:2027–2030, 1997.
44. P Mayville, G Ji, R Beavis, H Yang, M Goger, RP Novick, TW Muir. Structure-activity analysis of synthetic autoinducing thiolactone peptides from *Staphylococcus aureus* responsible for virulence. Proc Natl Acad Sci USA 9:1218–1223, 1999.
45. AL Cheung, MG Bayer, JH Heinrichs. sar Genetic determinants necessary for transcription of RNAII and RNAIII in the agr locus of *Staphylococcus aureus*. J Bacteriol 179:3963–3971, 1997.
46. Y Chien, AC Manna, SJ Projan, AL Cheung. SarA, a global regulator of virulence determinants in *Staphylococcus aureus*, binds to a conserved motif essential for *sar*-dependent gene regulation. J Biol Chem 274:37169–37176, 1999.

47. SK Chakrabarti, TK Misra. SarA represses *agr* operon expression in a purified *in vitro Staphylococcus aureus* transcription system. J Bacteriol 182:5893–5897, 2000.
48. PF Chan, SJ Foster. Role of SarA in virulence determinant production and environmental signal transduction in *Staphylococcus aureus*. J Bacteriol 180:6232–6241, 1998.
49. G Lina, S Jarraud, G Ji, T Greenland, A Pedraza, J Etienne, RP Novick, F Vandenesch. Transmembrane topology and histidine protein kinase activity of AgrC, the agr signal receptor in *Staphylococcus aureus*. Mol Microbiol 28:655–662, 1998.
50. WJ Van Wamel, G van Rossum, J Verhoef, CM Vandenbroucke-Grauls, AC Fluit. Cloning and characterization of an accessory gene regulator (agr)-like locus from *Staphylococcus epidermidis*. FEMS Microbiol Lett 163:1–9, 1998.
51. S Li, S Arvidson, R Mollby. Variation in the agr-dependent expression of alpha-toxin and protein A among clinical isolates of *Staphylococcus aureus* from patients with septicaemia. FEMS Microbiol Lett 152:155–161, 1997.
52. AT Giraudo, A Calzolari, AA Cataldi, C Bogni, R Nagel. The *sae* locus of *Staphylococcus aureus* encodes a two-component regulatory system. FEMS Microbiol Lett 177:15–22, 1999.
53. AT Giraudo, AL Cheung, R Nagel. The *sae* locus of *Staphylococcus aureus* controls exoprotein synthesis at the transcriptional level. Arch Microbiol 168:53–58, 1997.
54. H Rampone, GL Martinez, AT Giraudo, A Calzolari, R Nagel. *In vivo* expression of exoprotein synthesis with a Sae mutant of *Staphylococcus aureus*. Can J Vet Res 60:237–240, 1996.
55. LB Regassa, RP Novick, MJ Betley. Glucose and nonmaintained pH decrease expression of the accessory gene regulator (agr) in *Staphylococcus aureus*. Infect Immun 60:3381–3388, 1992.
56. AH Patel, J Kornblum, B Kreiswirth, R Novick, TJ Foster. Regulation of the protein A-encoding gene in *Staphylococcus aureus*. Gene 114:25–34, 1992.
57. B Dassy, T Hogan, TJ Foster, JM Fournier. Involvement of the accessory gene regulator (agr) in expression of type 5 capsular polysaccharide by *Staphylococcus aureus*. J Genet Microbiol 139:1301–1306, 1993.
58. MT Tremaine, DK Brockman, MJ Betley. Staphylococcal enterotoxin A gene (*sea*) expression is not affected by the accessory gene regulator (agr). Infect Immun 61:356–359, 1993.
59. PF Chan, SJ Foster. The role of environmental factors in the regulation of virulence-determinant expression in *Staphylococcus aureus* 8325-4. Microbiology 144:2469–2479, 1998.
60. PK Martin, T Li, D Sun, DP Biek, MB Schmid. Role in cell permeability of an essential two-component system in *Staphylococcus aureus*. J Bacteriol 181:3666–3673, 1999.
61. AF Chalker, JM Ward, AP Fosberry, JE Hodgson. Analysis and toxic overexpression in *Escherichia coli* of a staphylococcal gene encoding isoleucyl-tRNA synthetase. Gene 141:103–108, 1994.

62. A Xiong, VK Singh, G Cabrera, RK Jayaswal. Molecular characterization of the ferric-uptake regulator, *fur*, from *Staphylococcus aureus*. Microbiology 146:659–668, 2000.
63. E Miyazaki, JM Chen, C Ko, WR Bishai. The *Staphylococcus aureus rsbW* (orf159) gene encodes an anti-sigma factor of SigB. J Bacteriol 181:2846–2851, 1999.
64. M Herrmann, PE Vaudaux, D Pittet, R Auckenthaler, PD Lew, F Schumacher-Perdreau, G Peters, FA Waldvogel. Fibronectin, fibrinogen, and laminin act as mediators of adherence of clinical staphylococcal isolates to foreign material. J Infect Dis 158:693–701, 1988.
65. C Ryden, HS Tung, V Nikolaev, A Engstrom, A Oldberg. *Staphylococcus aureus* causing osteomyelitis binds to a nonapeptide sequence in bone sialoprotein. Biochemical J 327:825–829, 1997.
66. A Yacoub, P Lindahl, K Rubin, M Wendel, D Heinegard, C Ryden. Purification of a bone sialoprotein-binding protein from *Staphylococcus aureus*. Eur J Biochem 222:919–925, 1994.
67. AI Cheung, SJ Projan, RE Edelstein, VA Fischetti. Cloning, expression, and nucleotide sequence of a *Staphylococcus aureus* gene (fbpA) encoding a fibrinogen-binding protein. Infect Immun 63:1914–1920, 1995.
68. MK Boden, JI Flock. Cloning and characterization of a gene for a 19 kDa fibrinogen-binding protein from *Staphylococcus aureus*. Mol Microbiol 12:599–606, 1994.
69. D McDevitt, P Francois, P Vaudaux, TJ Foster. Molecular characterization of the clumping factor (fibrinogen receptor) of *Staphylococcus aureus*. Mol Microbiol 11:237–248, 1994.
70. K Jonsson, C Signas, HP Muller, M Lindberg. Two different genes encode fibronectin binding proteins in *Staphylococcus aureus*: the complete nucleotide sequence and characterization of the second gene. Eur J Biochem 202:1041–1048, 1991.
71. JM Patti, H Jonsson, B Guss, LM Switalski, K Wiberg, M Lindberg, M Hook. Molecular characterization and expression of a gene encoding a *Staphylococcus aureus* collagen adhesin. J Biol Chem 267:4766–4772, 1992.
72. PW Park, J Rosenbloom, WR Abrams, RP Mecham. Molecular cloning and expression of the gene for elastin-binding protein (ebpS) in *Staphylococcus aureus*. J Biol Chem 271:15803–15809, 1996.
73. MH McGavin, D Krajewska-Pietrasik, C Ryden, M Hook. Identification of a *Staphylococcus aureus* extracellular matrix-binding protein with broad specificity. Infect Immun 61:2479–2485, 1993.
74. JD Lopes, GF Da-Mota, CR Carneiro, L Gomes, F Costa-e-Silva-Filho, RR Brentani. Evolutionary conservation of laminin-binding proteins. Braz J Med Biol Res 21:1269–1273, 1988.
75. AS Naidu, M Andersson, A Forsgren. Identification of a human lactoferrin- binding protein in *Staphylococcus aureus*. J Med Microbiol 36:177–183, 1992.
76. B Modun, D Kendall, P Williams. Staphylococci express a receptor for human transferrin: identification of a 42-kilodalton cell wall transferrin-binding protein. Infect Immun 62:3850–3858, 1994.

77. JD Lopes, M dos Reis, RR Brentani. Presence of laminin receptors in *Staphylococcus aureus*. Science 229:275–277, 1985.
78. T Nguyen, B Ghebrehiwet, EI Peerschke. *Staphylococcus aureus* protein A recognizes platelet gC1qR/p33: a novel mechanism for staphylococcal interactions with platelets. Infect Immun 68:2061–2068, 2000.
79. WW Navarre, S Daefler, O Schneewind. Cell wall sorting of lipoproteins in *Staphylococcus aureus*. J Bacteriol 178:441–446, 1996.
80. T Bremell, A Tarkowski. Preferential induction of septic arthritis and mortality by superantigen-producing staphylococci. Infect Immun 63:4185–4187, 1995.
81. LM Switalski, JM Patti, W Butcher, AG Gristina, P Speziale, M Hook. A collagen receptor on *Staphylococcus aureus* strains isolated from patients with septic arthritis mediates adhesion to cartilage. Mol Microbiol 7:99–107, 1993.
82. IM Nilsson, JM Patti, T Bremell, M Hook, A Tarkowski. Vaccination with a recombinant fragment of collagen adhesin provides protection against *Staphylococcus aureus*-mediated septic death. J Clin Invest 101:2640–2649, 1998.
83. MG Thomas, S Peacock, S Daenke, AR Berendt. Adhesion of *Staphylococcus aureus* to collagen is not a major virulence determinant for septic arthritis, osteomyclitis, or endocarditis. J Infect Dis 179:291–293, 1999.
84. SJ Peacock, NP Day, MG Thomas, AR Berendt, TJ Foster. Clinical isolates of *Staphylococcus aureus* exhibit diversity in *fnb* genes and adhesion to human fibronectin. J Infect 41:23–31, 2000.
85. JM Kuypers, RA Proctor. Reduced adherence to traumatized rat heart valves by a low-fibronectin-binding mutant of *Staphylococcus aureus*. Infect Immun 57:2306–2312, 1989.
86. B Fischer, P Vaudaux, M Magnin, Y el Mestikawy, RA Proctor, DP Lew, H Vasey. Novel animal model for studying the molecular mechanisms of bacterial adhesion to bone-implanted metallic devices: role of fibronectin in *Staphylococcus aureus* adhesion. J Orthop Res 14:914–920, 1996.
87. AH Patel, P Nowlan, ED Weavers, I Foster. Virulence of protein A-deficient and alpha-toxin-deficient mutants of *Staphylococcus aureus* isolated by allele replacement. Infect Immun 55:3103–3110, 1987.
88. GM Deng, A Tarkowski. The features of arthritis induced by CpG motifs in bacterial DNA. Arthritis Rheum 43:356–364, 2000.
89. GM Deng, IM Nilsson, M Verdrengh, LV Collins, A Tarkowski. Intra-articularly localized bacterial DNA containing CpG motifs induces arthritis. Nat Med 5:702–705, 1999.
90. PM Schlievert. Role of superantigens in human disease. J Infect Dis 167:997–1002, 1993.
91. AJ Littlewood-Evans, MR Hattenberger, C Luscher, A Pataki, O Zak, T O'Reilly. Local expression of tumor necrosis factor alpha in an experimental model of acute osteomyelitis in rats. Infect Immun 65:3438–3443, 1997.
92. T Renno, M Hahne, HR MacDonald. Proliferation is a prerequisite for bacterial superantigen-induced T cell apoptosis *in vivo*. J Exp Med 181:2283–2287, 1995.
93. IM Nilsson, M Verdrengh, RG Ulrich, S Bavari, A Tarkowski. Protection against *Staphylococcus aureus* sepsis by vaccination with recombinant staphylococcal enterotoxin A devoid of superantigenicity. J Infect Dis 180:1370–1373, 1999.

94. JM Yarwood, PM Schlievert. Oxygen and carbon dioxide regulation of toxic shock syndrome toxin 1 production by *Staphylococcus aureus* MN8. J Clin Microbiol 38:1797–1803, 2000.
95. H Tokunaga, T Nakae. Calcium ion-mediated regulation of the alpha-toxin pore of *Staphylococcus aureus*. Biochim Biophys Acta 1105:125–130, 1992.
96. CG Gemmell, SC Goutcher, R Reid, RD Sturrock. Role of certain virulence factors in a murine model of *Staphylococcus aureus* arthritis. J Med Microbiol 46:208–213, 1997.
97. A Hildebrand, M Pohl, S Bhakdi. *Staphylococcus aureus* alpha-toxin: dual mechanism of binding to target cells. J Biol Chem 266:17195–17200, 1991.
98. GG Khachapuridze, SG Nergadze, NN Lapiashvili, IN Panieva, LS Barenfel'd, NM Pleskach, MS Imedadze. The effect of staphylococcal alpha-toxin on DNA replication in human cells (in Russian). Tsitologiia 33:82–89, 1991.
99. AS Bayer, PM Sullam, M Ramos, C Li, AL Cheng, MR Yeaman. *Staphylococcus aureus* induces platelet aggregation via a fibrinogen-dependent mechanism which is independent of principal platelet glycoprotein IIb/IIIa fibrinogen-binding domains. Infect Immun 63:3634–3641, 1995.
100. M Arvand, S Bhakdi, B Dahlback, KT Preissner. *Staphylococcus aureus* alpha-toxin attack on human platelets promotes assembly of the prothrombinase complex. J Biol Chem 265:14377–14381, 1990.
101. E Gouaux, M Hobaugh, L Song. α-Hemolysin, γ-hemolysin, and leukocidin from *Staphylococcus aureus*: distant in sequence but similar in structure. Protein Sci 6:2631–2635, 1997.
102. T Tomita, Y Kamio. Molecular biology of the pore-forming cytolysins from *Staphylococcus aureus*, alpha- and gamma-hemolysins and leukocidin. Biosci Biotechnol Biochem 61:565–572, 1997.
103. F Grimminger, F Rose, U Sibelius, M Meinhardt, B Potzsch, R Spriestersbach, S Bhakdi, N Suttorp, W Seeger. Human endothelial cell activation and mediator release in response to the bacterial exotoxins *Escherichia coli* hemolysin and staphylococcal alpha-toxin. J Immunol 159:1909–1916, 1997.
104. IM Nilsson, O Hartford, T Foster, A Tarkowski. Alpha-toxin and gamma-toxin jointly promote *Staphylococcus aureus* virulence in murine septic arthritis. Infect Immun 67:1045–1049, 1999.
105. I Walev, U Weller, S Strauch, T Foster, S Bhakdi. Selective killing of human monocytes and cytokine release provoked by sphingomyelinase (beta-toxin) of *Staphylococcus aureus*. Infect Immun 64:2974–2979, 1996.
106. FJ Schmitz, KE Veldkamp, KP Van Kessel, J Verhoef, JA Van Strijp. Delta-toxin from *Staphylococcus aureus* as a costimulator of human neutrophil oxidative burst. J Infect Dis 176:1531–1537, 1997.
107. M Ferreras, F Hoper, SM Dalia, DA Cohn, G Prevost, G Menestrina. The interaction of *Staphylococcus aureus* bi-component gamma-hemolysins and leucocidins with cells and lipid membranes. Biochim Biophys Acta 1414:108–126, 1998.
108. B Konig, G Prevost, W Konig. Composition of staphylococcal bi-component toxins determines pathophysiological reactions. J Med Microbiol 46:479–485, 1997.
109. G Prevost, B Cribier, P Couppie, P Petiau, G Supersac, V Finck-Barbancon, H Monteil, Y Piemont. Panton-Valentine leucocidin and gamma-hemolysin from

Staphylococcus aureus ATCC 49775 are encoded by distinct genetic loci and have different biological activities. Infect Immun 63:4121–4129, 1995.

110. LR Plano, DM Gutman, M Woischnik, CM Collins. Recombinant *Staphylococcus aureus* exfoliative toxins are not bacterial superantigens. Infect Immun 68:3048–3052, 2000.
111. RJ Williams, JM Ward, B Henderson, S Poole, BP O'Hara, M Wilson, SP Nair. Identification of a novel gene cluster encoding staphylococcal exotoxin-like proteins: characterization of the prototypic gene and its protein product, SET1. Infect Immun 68:4407–4415, 2000.
112. A Albus, RD Arbeit, JC Lee. Virulence of *Staphylococcus aureus* mutants altered in type 5 capsule production. Infect Immun 59:1008–1014, 1991.
113. T Essawi, T Na'was, A Hawwari, S Wadi, A Doudin, AI Fattom. Molecular, antibiogram and serological typing of *Staphylococcus aureus* isolates recovered from Al-Makased Hospital in East Jerusalem. Trop Med Int Health 3:576–583, 1998.
114. T Na'was, A Hawwari, E Hendrix, J Hebden, R Edelman, M Martin, W Campbell, R Naso, R Schwalbe, AI Fattom. Phenotypic and genotypic characterization of nosocomial *Staphylococcus aureus* isolates from trauma patients. J Clin Microbiol 36:414–420, 1998.
115. D Martin, LG Mathieu, J Lecomte, J deRepentigny. Adherence of gram-positive and gram-negative bacterial strains to human lung fibroblasts *in vitro*. Exp Biol 45:323–334, 1986.
116. TB Buxton, JP Rissing, JA Homer, KM Plowman, DF Scott, TJ Sprinkle, GK Best. Binding of a *Staphylococcus aureus* bone pathogen to type I collagen. Microb Pathog 8:441–448, 1990.
117. JC Lee, S Takeda, PJ Livolsi, LC Paoletti. Effects of *in vitro* and *in vivo* growth conditions on expression of type 8 capsular polysaccharide by *Staphylococcus aureus*. Infect Immun 61:1853–1858, 1993.
118. F Vandenesch, SJ Projan, B Kreiswirth, J Etienne, RP Novick. Agr-related sequences in *Staphylococcus lugdunensis*. FEMS Microbiol Lett 111:115–122, 1993.
119. TM Nilsson, JC Lee, T Bremell, C Ryden, A Tarkowski. The role of staphylococcal polysaccharide microcapsule expression in septicemia and septic arthritis. Infect Immun 65:4216–4221, 1997.
120. B Vastag. New vaccine decreases rate of nosocomial infections. JAMA 285:1565–1566, 2001.
121. J Wimpenny. An overview of biofilms as functional communities, in: DG Allison, P Gilbert, HM Lappin-Scott, M Wilson, eds. Community Structure and Co-operation in Biofilms. Cambridge: Cambridge University Press, 2000:1–24.
122. JW Costerton, Z Lewandowski, DE Caldwell, DR Korber, HM Lappin-Scott. Microbial biofilms. Annu Rev Microbiol 49:711–745, 1995.
123. MD Parkins, H Ceri, DG Storey. Differential virulence factor expression in *Pseudomonas aeruginosa* biofilms. Big Sky, MT: American Society for Microbiology Biofilms 2000 (B2K), Abstract #27, 24. 7-16-2000.

124. PK Singh, AL Schaefer, MR Parsek, TO Moninger, MJ Welsh, EP Greenberg. Quorum-sensing signals indicate that cystic fibrosis lungs are infected with bacterial biofilms. Nature 407:762–764, 2000.
125. RJ McLean, M Whiteley, DJ Stickler, WC Fuqua. Evidence of autoinducer activity in naturally occurring biofilms. FEMS Microbiol Lett 154:259–263, 1997.
126. DJ Stickler, NS Morris, RJ McLean, C Fuqua. Biofilms on indwelling urethral catheters produce quorum-sensing signal molecules in situ and in vitro. Appl Environ Microbiol 64:3486–3490, 1998.
127. AG Gristina, M Oga, LX Webb, CD Hobgood. Adherent bacterial colonization in the pathogenesis of osteomyelitis. Science 228:990–993, 1985.
128. H Akiyama, R Torigoe, J Arata. Interaction of *Staphylococcus aureus* cells and silk threads *in vitro* and in mouse skin. J Dermatol Sci 6:247–257, 1993.
129. P Francois, P Vaudaux, PD Lew. Role of plasma and extracellular matrix proteins in the physiopathology of foreign body infections. Ann Vasc Surg 12:34–40, 1998.
130. E Gracia, A Fernandez, P Conchello, A Lacleriga, L Paniagua, F Seral, B Amorena. Adherence of *Staphylococcus aureus* slime-producing strain variants to biomaterials used in orthopaedic surgery. Int Orthop 21:46–51, 1997.
131. S Oie, Y Huang, A Kamiya, H Konishi, T Nakazawa. Efficacy of disinfectants against biofilm cells of methicillin-resistant *Staphylococcus aureus*. Microbios 85:223–230, 1996.
132. RO Darouiche, A Dhir, AJ Miller, GC Landon, II Raad, DM Musher. Vancomycin penetration into biofilm covering infected prostheses and effect on bacteria. J Infect Dis 170:720–723, 1994.
133. IG Duguid, E Evans, MR Brown, P Gilbert. Effect of biofilm culture upon the susceptibility of *Staphylococcus epidermidis* to tobramycin. J Antimicrob Chemother 30:803–810, 1992.
134. AG Gristina, CD Hobgood, LX Webb, QN Myrvik. Adhesive colonization of biomaterials and antibiotic resistance. Biomaterials 8:423–426, 1987.
135. C von Eiff, D Bettin, RA Proctor, B Rolauffs, N Lindner, W Winkelmann, G Peters. Recovery of small colony variants of *Staphylococcus aureus* following gentamicin bead placement for osteomyelitis. Clin Infect Dis 25:1250–1251, 1997.
136. DAJ Ferguson, EM Veringa, WR Mayberry, BP Overbeek, DW Lambe Jr, J Verhoef. Bacteroides and Staphylococcus glycocalyx: chemical analysis, and the effects on chemiluminescence and chemotaxis of human polymorphonuclear leucocytes. Microbios 69:53–65, 1992.
137. AL Shiau, CL Wu. The inhibitory effect of *Staphylococcus epidermidis* slime on the phagocytosis of murine peritoneal macrophages is interferon-independent. Microbiol Immunol 42:33–40, 1998.
138. MK Dasgupta. Biofilm causes decreased production of interferon-gamma. J Am Soc Nephrol 7:877–882, 1996.
139. M Hussain, MH Wilcox, PJ White. The slime of coagulase-negative staphylococci: biochemistry and relation to adherence. FEMS Microbiol Rev 10:191–207, 1993.
140. H Akiyama, M Ueda, H Kanzaki, J Tada, J Arata. Biofilm formation of *Staphylococcus aureus* strains isolated from impetigo and furuncle: role of fibrinogen and fibrin. J Environ Pathol Toxicol Oncol 16:2–10, 1997.

141. D McKenney, J Hubner, E Muller, Y Wang, DA Goldmann, GB Pier. The ica locus of *Staphylococcus epidermidis* encodes production of the capsular polysaccharide/adhesin. Infect Immun 66:4711–4720, 1998.
142. C Heilmann, O Schweitzer, C Gerke, N Vanittanakom, D Mack, F Gotz. Molecular basis of intercellular adhesion in the biofilm-foming *Staphylococcus epidermidis*. Mol Microbiol 20:1083–1091, 1996.
143. SI Alam, KA Khan, A Ahmad. Glycocalyx positive bacteria isolated from chronic osteomyelitis and septic arthritis. Ceylon Med J 35:21–23, 1990.
144. RP Evans, CL Nelson, WR Bowen, MG Kleve, SG Hickmon. Visualization of bacterial glycocalyx with a scanning electron microscope. Clin Orthop Rel Res 347:243–249, 1998.
145. RD Stout, KP Ferguson, YN Li, DW Lambe Jr. Staphylococcal exopolysaccharides inhibit lymphocyte proliferative responses by activation of monocyte prostaglandin production. Infect Immun 60:922–927, 1992.
146. MC Hudson, WK Ramp, NC Nicholson, AS Williams, MT Nousiainen. Internalization of *Staphylococcus aureus* by cultured osteoblasts. Microb Pathog 19:409–419, 1995.
147. AM Lowe, DT Beattie, RL Deresiewicz. Identification of novel staphylococcal virulence genes by *in vivo* expression technology. Mol Microbiol 27:967–976, 1998.
148. A Lammers, PJ Nuijten, HE Smith. The fibronectin binding proteins of *Staphylococcus aureus* are required for adhesion to and invasion of bovine mammary gland cells. FEMS Microbiol Lett 180:103–109, 1999.
149. BE Menzies, I Kourteva. Internalization of *Staphylococcus aureus* by endothelial cells induces apoptosis. Infect Immun 66:5994–5998, 1998.
150. BC Kahl, M Goulian, W van Wamel, M Herrmann, SM Simon, G Kaplan, G Peters, AL Cheung. *Staphylococcus aureus* RN6390 replicates and induces apoptosis in a pulmonary epithelial cell line. Infect Immun 68:5385–5392, 2000.
151. JK Ellington, SS Reilly, WK Ramp, MS Smeltzer, JF Kellam, MC Hudson. Mechanisms of *Staphylococcus aureus* invasion of cultured osteoblasts. Microb Pathog 26:317–323, 1999.
152. KW Bayles, CA Wesson, LE Liou, LK Fox, GA Bohach, WR Trumble. Intracellular *Staphylococcus aureus* escapes the endosome and induces apoptosis in epithelial cells. Infect Immun 66:336–342, 1998.
153. CA Wesson, J Deringer, LE Liou, KW Bayles, GA Bohach, WR Trumble. Apoptosis induced by *Staphylococcus aureus* in epithelial cells utilizes a mechanism involving caspases 8 and 3. Infect Immun 68:2998–3001, 2000.
154. SS Reilly, MC Hudson, JF Kellam, WK Ramp. *In vivo* internalization of *Staphylococcus aureus* by embryonic chick osteoblasts. Bone 26:63–70, 2000.
155. HD Gresham, JH Lowrance, TE Caver, BS Wilson, AL Cheung, FP Lindberg. Survival of *Staphylococcus aureus* inside neutrophils contributes to infection. J Immunol 164:3713–3722, 2000.
156. AT Giraudo, H Rampone, A Calzolari, R Nagel. Phenotypic characterization and virulence of a sae agr mutant of *Staphylococcus aureus*. Can J Microbiol 42:120–123, 1996.

157. D McDevitt, P Vaudaux, TJ Foster. Genetic evidence that bound coagulase of *Staphylococcus aureus* is not clumping factor. Infect Immun 60:1514–1523, 1992.
158. JS Blevins, AF Gillaspy, TM Rechtin, BK Hurlburt, MS Smeltzer. The Staphylococcal accessory regulator (*sar*) represses transcription of the *Staphylococcus aureus* collagen adhesin gene (*cna*) in an *agr*-independent manner. Mol Microbiol 33:317–326, 1999.
159. DS Piriz, FH Kayser, B Berger-Bachi. Impact of sar and agr on methicillin resistance in *Staphylococcus aureus*. FEMS Microbiol Lett 141:255–260, 1996.
160. P Moreillon, JM Entenza, P Francioli, D McDevitt, TJ Foster, P Francois, P Vaudaux. Role of *Staphylococcus aureus* coagulase and clumping factor in pathogenesis of experimental endocarditis. Infect Immun 63:4738–4743, 1995.
161. JM van der Vijver, MM van Es-Boon, MF Michel. A study of virulence factors with induced mutants of *Staphylococcus aureus*. J Med Microbiol 8:279–287, 1975.
162. MN Rhem, EM Lech, JM Patti, D McDevitt, M Hook, DB Jones, KR Wilhelmus. The collagen-binding adhesin is a virulence factor in *Staphylococcus aureus* keratitis. Infect Immun 68:3776–3779, 2000.
163. QY Zhang, D DeRyckere, P Lauer, M Koomey. Gene conversion in *Neisseria gonorrhoeae*: evidence for its role in pilus antigenic variation. Proc Natl Acad Sci USA 89:5366–5370, 1992.
164. BE Britigan, MS Cohen, PF Sparling. Gonococcal infection: a model of molecular pathogenesis. N Engl J Med 312:1683–1694, 1985.
165. S Ram, FG Mackinnon, S Gulati, DP McQuillen, U Vogel, M Frosch, C Elkins, HK Guttormsen, LM Wetzler, M Oppermann, MK Pangburn, PA Rice. The contrasting mechanisms of serum resistance of *Neisseria gonorrhoeae* and group B *Neisseria meningitidis*. Mol Immunol 36:915–928, 1999.
166. M Larribe, MK Taha, A Topilko, C Marchal. Control of *Neisseria gonorrhoeae* pilin gene expression by environmental factors: involvement of the *pilA*/*pilB* regulatory genes. Microbiology 143:1757–1764, 1997.
167. PA Rice, DL Kasper. Characterization of serum resistance of *Neisseria gonorrhoeae* that disseminate. Roles of blocking antibody and gonococcal outer membrane proteins. J Clin Invest 70:157–167, 1982.
168. CR Gregg, MA Melly, CG Hellerqvist, JG Coniglio, ZA McGee. Toxic activity of purified lipopolysaccharide of *Neisseria gonorrhoeae* for human fallopian tube mucosa. J Infect Dis 143:432–439, 1981.
169. DL Goldenberg, JI Reed, PA Rice. Arthritis in rabbits induced by killed *Neisseria gonorrhoeae* and gonococcal lipopolysaccharide. J Rheumatol 11:3–8, 1984.
170. LM Wetzler, K Barry, MS Blake, EC Gotschlich. Gonococcal lipooligosaccharide sialylation prevents complement-dependent killing by immune sera. Infect Immun 60:39–43, 1992.
171. LG Rahme, FM Ausubel, H Cao, E Drenkard, BC Goumnerov, GW Lau, S Mahajan-Miklos, J Plotnikova, MW Tan, J Tsongalis, CL Walendziewicz, RG Tompkins. Plants and animals share functionally common bacterial virulence factors. Proc Natl Acad Sci USA 97:8815–8821, 2000.
172. R Ramphal, S Vishwanath. Why is *Pseudomonas* the colonizer and why does it persist? Infection 15:281–287, 1987.

173. M Hobbs, ES Collie, PD Free, SP Livingston, JS Mattick. PilS and PilR, a two-component transcriptional regulatory system controlling expression of type 4 fimbriae in *Pseudomonas aeruginosa*. Mol Microbiol 7:669–682, 1993.
174. MS Strom, S Lory. Structure-function and biogenesis of the type IV pili. Annu Rev Microbiol 47:565–596, 1993.
175. A Glessner, RS Smith, BH Iglewski, JB Robinson. Roles of *Pseudomonas aeruginosa las* and *rhl* quorum-sensing systems in control of twitching motility. J Bacteriol 181:1623–1629, 1999.
176. GA O'Toole, R Kolter. Flagellar and twitching motility are necessary for *Pseudomonas aeruginosa* biofilm development. Mol Microbiol 30:295–304, 1998.
177. J Davies, A Dewar, A Bush, T Pitt, D Gruenert, DM Geddes, EW Alton. Reduction in the adherence of *Pseudomonas aeruginosa* to native cystic fibrosis epithelium with anti-asialoGM1 antibody and neuraminidase inhibition. Eur Respir J 13:565–570, 1999.
178. A Singh, L Hazlett, RS Berk. Characterization of pseudomonal adherence to unwounded cornea. Invest Ophthalmol Vis Sci 32:2096–2104, 1991.
179. TR De Kievit, BH Iglewski. Quorum sensing, gene expression, and *Pseudomonas* biofilms. Methods Enzymol 310:117–128, 1999.
180. DG Davies, MR Parsek, JP Pearson, BH Iglewski, JW Costerton, EP Greenberg. The involvement of cell-to-cell signals in the development of a bacterial biofilm. Science 280:295–298, 1998.
181. A Boyd, AM Chakrabarty. Role of alginate lyase in cell detachment of *Pseudomonas aeruginosa*. Appl Environ Microbiol 60:2355–2359, 1994.
182. JW Costerton, PS Stewart, EP Greenberg. Bacterial biofilms: a common cause of persistent infections. Science 284:1318–1322, 1999.
183. H Anwar, JL Strap, JW Costerton. Eradication of biofilm cells of *Staphylococcus aureus* with tobramycin and cephalexin. Can J Microbiol 38:618–625, 1992.
184. H Anwar, JL Strap, JW Costerton. Kinetic interaction of biofilm cells of *Staphylococcus aureus* with cephalexin and tobramycin in a chemostat system. Antimicrob Agents Chemother 36:890–893, 1992.
185. BD Hoyle, J Alcantara, JW Costerton. *Pseudomonas aeruginosa* biofilm as a diffusion barrier to piperacillin. Antimicrob Agents Chemother 36:2054–2056, 1992.
186. MJ Wick, AN Hamood, BH Iglewski. Analysis of the structure-function relationship of *Pseudomonas aeruginosa* exotoxin A. Mol Microbiol 4:527–535, 1990.
187. MJ Wick, DW Frank, DG Storey, BH Iglewski. Structure, function, and regulation of *Pseudomonas aeruginosa* exotoxin A. Annu Rev Microbiol 44:335–363, 1990.
188. J Coburn. *Pseudomonas aeruginosa* exoenzyme S. Curr Top Microbiol Immunol 175:133–143, 1992.
189. H Fu, J Coburn, RJ Collier. The eukaryotic host factor that activates exoenzyme S of *Pseudomonas aeruginosa* is a member of the 14-3-3 protein family. Proc Natl Acad Sci USA 90:2320–2324, 1993.
190. JP Pearson, C Van Delden, BH Iglewski. Active efflux and diffusion are involved in transport of *Pseudomonas aeruginosa* cell-to-cell signals. J Bacteriol 181:1203–1210, 1999.

191. JP Pearson, EC Pesci, BH Iglewski. Roles of *Pseudomonas aeruginosa las* and *rhl* quorum-sensing systems in control of elastase and rhamnolipid biosynthesis genes. J Bacteriol 179:5756–5767, 1997.
192. YY Adar, S Ulitzur. GroESL proteins facilitate binding of externally added inducer by LuxR protein-containing *E. coli* cells. J Biolumin Chemilumin 8:261–266, 1993.
193. AM Albus, EC Pesci, LJ Runyen-Janecky, SE West, BH Iglewski. Vfr controls quorum sensing in *Pseudomonas aeruginosa*. J Bacteriol 179:3928–3935, 1997.
194. M Whiteley, MR Parsek, EP Greenberg. Regulation of quorum sensing by RpoS in *Pseudomonas aeruginosa*. J Bacteriol 182:4356–4360, 2000.
195. T de Kievit, PC Seed, J Nezezon, L Passador, BH Iglewski. RsaL, a novel repressor of virulence gene expression in *Pseudomonas aeruginosa*. J Bacteriol 181:2175–2184, 1999.
196. SL McKnight, BH Iglewski, EC Pesci. The *Pseudomonas* quinolone signal regulates *rhl* quorum sensing in *Pseudomonas aeruginosa*. J Bacteriol 182:2702–2708, 2000.
197. EC Pesci, JB Milbank, JP Pearson, S McKnight, AS Kende, EP Greenberg, BH Iglewski. Quinolone signaling in the cell-to-cell communication system of *Pseudomonas aeruginosa*. Proc Natl Acad Sci USA 96:11229–11234, 1999.
198. O Geisenberger, M Givskov, K Riedel, N Hoiby, B Tummler, L Eberl. Production of *N*-acyl-L-homoserine lactones by *P. aeruginosa* isolates from chronic lung infections associated with cystic fibrosis. FEMS Microbiol Lett 184:273–278, 2000.
199. GA O'Toole, KA Gibbs, PW Hager, PV Phibbs, R Kolter. The global carbon metabolism regulator Crc is a component of a signal transduction pathway required for biofilm development by *Pseudomonas aeruginosa*. J Bacteriol 182:425–431, 2000.
200. ML Vasil, UA Ochsner. The response of *Pseudomonas aeruginosa* to iron: genetics, biochemistry and virulence. Mol Microbiol 34:399–413, 1999.
201. HA Barton, Z Johnson, CD Cox, AI Vasil, ML Vasil. Ferric uptake regulator mutants of *Pseudomonas aeruginosa* with distinct alterations in the iron-dependent repression of exotoxin A and siderophores in aerobic and microaerobic environments. Mol Microbiol 21:1001–1017, 1996.
202. DJ Hassett, ML Howell, UA Ochsner, ML Vasil, Z Johnson, GE Dean. An operon containing *fumC* and *sodA* encoding fumarase C and manganese superoxide dismutase is controlled by the ferric uptake regulator in *Pseudomonas aeruginosa*: *fur* mutants produce elevated alginate levels. J Bacteriol 179:1452–1459, 1997.
203. DJ Hassett, PA Sokol, ML Howell, JF Ma, HT Schweizer, U Ochsner, ML Vasil. Ferric uptake regulator (Fur) mutants of *Pseudomonas aeruginosa* demonstrate defective siderophore-mediated iron uptake, altered aerobic growth, and decreased superoxide dismutase and catalase activities. J Bacteriol 178:3996–4003, 1996.
204. UA Ochsner, ML Vasil. Gene repression by the ferric uptake regulator in *Pseudomonas aeruginosa*: cycle selection of iron-regulated genes. Proc Natl Acad Sci USA 93:4409–4414, 1996.
205. PV Dunlap. Mechanism for iron control of the *Vibrio fischeri* luminescence system: involvement of cyclic AMP and cyclic AMP receptor protein and modulation of DNA level. J Biolumin Chemilumin 7:203–214, 1992.

206. HV Winteler, D Haas. The homologous regulators ANR of *Pseudomonas aeruginosa* and FNR of *Escherichia coli* have overlapping but distinct specificities for anaerobically inducible promoters. Microbiology 142:685–693, 1996.
207. H Arai, T Kodama, Y Igarashi. Cascade regulation of the two CRP/FNR-related transcriptional regulators (ANR and DNR) and the denitrification enzymes in *Pseudomonas aeruginosa*. Mol Microbiol 25:1141–1148, 1997.
208. R Cassels, B Oliva, D Knowles. Occurrence of the regulatory nucleotides ppGpp and pppGpp following induction of the stringent response in staphylococci. J Bacteriol 177:5161–5165, 1995.
209. WA Haseltine, R Block, W Gilbert, K Weber. MSI and MSII made on ribosome in idling step of protein synthesis. Nature 238:381–384, 1972.
210. F Jorgensen, M Bally, V Chapon-Herve, G Michel, A Lazdunski, P Williams, GS Stewart. RpoS-dependent stress tolerance in *Pseudomonas aeruginosa*. Microbiology 145:835–844, 1999.
211. PC Loewen, B Hu, J Strutinsky, R Sparling. Regulation in the rpoS regulon of *Escherichia coli*. Can J Microbiol 44:707–717, 1998.
212. MJ Schurr, V Deretic. Microbial pathogenesis in cystic fibrosis: co-ordinate regulation of heat-shock response and conversion to mucoidy in *Pseudomonas aeruginosa*. Mol Microbiol 24:411–420, 1997.
213. KT Hughes, K Mathee. The anti-sigma factors. Annu Rev Microbiol 52:231–286, 1998.
214. MJ Schurr, H Yu, JM Martinez-Salazar, JC Boucher, V Deretic. Control of AlgU, a member of the sigma E-like family of stress sigma factors, by the negative regulators MucA and MucB and *Pseudomonas aeruginosa* conversion to mucoidy in cystic fibrosis. J Bacteriol 178:4997–5004, 1996.
215. JC Boucher, H Yu, MH Mudd, V Deretic. Mucoid *Pseudomonas aeruginosa* in cystic fibrosis: characterization of *muc* mutations in clinical isolates and analysis of clearance in a mouse model of respiratory infection. Infect Immun 65:3838–3846, 1997.
216. S Jin, K Ishimoto, S Lory. Nucleotide sequence of the *rpoN* gene and characterization of two downstream open reading frames in *Pseudomonas aeruginosa*. J Bacteriol 176:1316–1322, 1994.
217. MN Starnbach, S Lory. The *fliA* (*rpoF*) gene of *Pseudomonas aeruginosa* encodes an alternative sigma factor required for flagellin synthesis. Mol Microbiol 6:459–469, 1992.
218. LG Rahme, EJ Stevens, SF Wolfort, J Shao, RG Tompkins, FM Ausubel. Common virulence factors for bacterial pathogenicity in plants and animals. Science 268:1899–1902, 1995.
219. C Blumer, S Heeb, G Pessi, D Haas. Global GacA-steered control of cyanide and exoprotease production in *Pseudomonas fluorescens* involves specific ribosome binding sites. Proc Natl Acad Sci USA 96:14073–14078, 1999.
220. J Trueta, JD Morgan. The vascular contribution to osteogenesis: studies by the injection method. J Bone Joint Surg 42B:97–109, 1960.
221. T Hobo. Zur pathogenese de akuten haematatogenen Osteomyelitis, mit Beruckishtigun der Vitalfarbungslehre. Acta School Med Univ Imp Kioto 4:1–29, 1922.

222. RT Morrissy, DW Haynes. Acute hematogenous osteomyelitis: a model with trauma as an etiology. J Pediatr Orthop 9:447–456, 1989.
223. GM Caputo, PR Cavanagh, JS Ulbrecht, GW Gibbons, AW Karchmer. Assessment and management of foot disease in patients with diabetes. N Engl J Med 331:854–860, 1994.
224. JA Smith, JJ O'Connor. Nasal carriage of *Staphylococcus aureus* in diabetes mellitus. Lancet 2:776–777, 1966.
225. LA Lavery, SC Walker, LB Harkless, K Felder-Johnson. Infected puncture wounds in diabetic and nondiabetic adults. Diabetes Care 18:1588–1591, 1995.
226. E Bohm, C Josten. What's new in exogenous osteomyelitis? Pathol Res Pract 188:254–258, 1992.
227. G Cierny. Chronic osteomyelitis: results of treatment. Instr Course Lect 39:495–508, 1990.
228. EL Pesanti, JA Lorenzo. Osteoclasts and effects of interleukin 4 in development of chronic osteomyelitis. Clin Orthop 355:290–299, 1998.
229. JT Mader, M Ortiz, JH Calhoun. Update on the diagnosis and management of osteomyelitis. Clin Podiatr Med Surg 13:701–724, 1996.
230. JT Mader, GL Brown, JC Guckian, CH Wells, JA Reinarz. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 142:915–922, 1980.
231. Y Kharbanda, RS Dhir. Natural course of hematogenous pyogenic osteomyelitis (a retrospective study of 110 cases). J Postgrad Med 37:69–75, 1991.
232. JM Buckholz. The surgical management of osteomyelitis: with special reference to a surgical classification. J Foot Surg 26:S17–S24, 1987.
233. A Ben-Yehuda, ME Weksler. Host resistance and the immune system. Clin Geriatr Med 8:701–711, 1992.
234. FR Roisman, DT WaIz, AE Finkelstein. Superoxide radical production by human leukocytes exposed to immune complexes: inhibitory action of gold compounds. Inflammation 7:355–362, 1983.
235. JY Wang, BH Wicklund, RB Gustilo, DT Tsukayama. Prosthetic metals impair murine immune response and cytokine release *in vivo* and *in vitro*. J Orthop Res 15:688–699, 1997.
236. S Santavirta, YT Konttinen, V Bergroth, M Gronblad. Lack of immune response to methyl methacrylate in lymphocyte cultures. Acta Orthop Scand 62:29–32, 1991.
237. S Santavirta, YT Konttinen, T Saito, M Gronblad, E Partio, P Kemppinen, P Rokkanen. Immune response to polyglycolic acid implants. J Bone Joint Surg 72B:597–600, 1990.
238. BD Brause. Infections associated with prosthetic joints. Clin Rheum Dis 12:523–536, 1986.
239. SG Sourmelis, FD Burke, JP Varian. A review of total elbow arthroplasty and an early assessment of the Liverpool elbow prosthesis. J Hand Surg 11B:407–413, 1986.
240. SH Dougherty, RL Simmons. Endogenous factors contributing to prosthetic device infections. Infect Dis Clin North Am 3:199–209, 1989.

241. MD Kalmeijer, E van Nieuwland-Bollen, D Bogaers-Hofman, GA de Baere. Nasal carriage of *Staphylococcus aureus* is a major risk factor for surgical-site infections in orthopedic surgery. Infect Control Hosp Epidemiol 21:319–323, 2000.
242. PJ Gill, E Goddard, DW Beatty, EB Hoffman. Chronic granulomatous disease presenting with osteomyelitis: favorable response to treatment with interferon-gamma. J Pediatr Orthop 12:398–400, 1992.
243. AI Tauber, N Borregaard, E Simons, J Wright. Chronic granulomatous disease: a syndrome of phagocyte oxidase deficiencies. Medicine 62:286–309, 1983.
244. CJ White, JI Gallin. Phagocyte defects. Clin Immun Immunopath 40:50–61, 1986.
245. ML Weber, A Abela, L de Repentigny, L Garel, N Lapointe. Myeloperoxidase deficiency with extensive candidal osteomyelitis of the base of the skull. Pediatrics 80:876–879, 1987.
246. H Donabedian, JI Gallin. The hyperimmunoglobulin E recurrent-infection (Job's) syndrome: a review of the NIH experience and the literature. Medicine 62:195–208, 1983.
247. KS Yoon, RHJ Fitzgerald, S Sud, Z Song, PH Wooley. Experimental acute hematogenous osteomyelitis in mice. II. Influence of *Staphylococcus aureus* infection on T-cell immunity. J Orthop Res 17:382–391, 1999.
248. S Sasaki, S Nishikawa, T Miura, M Mizuki, K Yamada, H Madarame, YI Tagawa, Y Iwakura, A Nakane. Interleukin-4 and interleukin-10 are involved in host resistance to *Staphylococcus aureus* infection through regulation of gamma interferon. Infect Immun 68:2424–2430, 2000.
249. O Hultgren, M Kopf, A Tarkowski. Outcome of *Staphylococcus aureus*-triggered sepsis and arthritis in IL-4-deficient mice depends on the genetic background of the host. Eur J Immunol 29:2400–2405, 1999.
250. JJ Boelens, T van der Poll, J Dankert, SA Zaat. Interferon-gamma protects against biomaterial-associated *Staphylococcus epidermidis* infection in mice. J Infect Dis 181:1167–1171, 2000.
251. B Koch, P Lemmermeier, A Gause, H Wilmowsky, J Heisel, M Pfreundschuh. Demonstration of interleukin-1beta and interleukin-6 in cells of synovial fluids by flow cytometry. Eur J Med Res 1:244–248, 1996.
252. M Osiri, K Ruxrungtham, S Nookhai, Y Ohmoto, U Deesomchok. IL-1beta, IL-6 and TNF-alpha in synovial fluid of patients with non-gonococcal septic arthritis. Asia Pac J Allergy Immunol 16:155–160, 1998.
253. M Verdrengh, A Tarkowski. Granulocyte-macrophage colony-stimulating factor in *Staphylococcus aureus*-induced arthritis. Infect Immun 66:853–855, 1998.
254. E Sakiniene, T Bremell, A Tarkowski. Inhibition of nitric oxide synthase (NOS) aggravates *Staphylococcus aureus* septicaemia and septic arthritis. Clin Exp Immunol 110:370–377, 1997.
255. A Abdelnour, T Bremell, R Holmdahl, A Tarkowski. Role of T lymphocytes in experimental *Staphylococcus aureus* arthritis. Scand J Immunol 39:403–408, 1994.
256. M Puliti, C von Hunolstein, F Bistoni, P Mosci, G Orefici, L Tissi. Influence of interferon-gamma administration on the severity of experimental group B streptococcal arthritis. Arthritis Rheum 43:2678–2686, 2000.

257. YX Zhao, IM Nilsson, A Tarkowski. The dual role of interferon-gamma in experimental *Staphylococcus aureus* septicaemia versus arthritis. Immunology 93:80–85, 1998.
258. S Roy, J Bhawan. Ultrastructure of articular cartilage in pyogenic arthritis. Arch Pathol 99:44–47, 1975.
259. P Riegels-Nielsen, N Frimodt-Moller, M Sorensen, JS Jensen. Antibiotic treatment insufficient for established septic arthritis. *Staphylococcus aureus* experiments in rabbits. Acta Orthop Scand 60:113–115, 1989.
260. RL Smith, DJ Schurman, G Kajiyama, M Mell, E Gilkerson. The effect of antibiotics on the destruction of cartilage in experimental infectious arthritis. J Bone Joint Surg 69A:1063–1068, 1987.
261. EM Knights. Infectious arthritis. J Foot Surg 21:229–233, 1982.
262. JD Nelson, WC Koontz. Septic arthritis in infants and children: a review of 117 cases. Pediatrics 38:966–971, 1966.
263. M Mitchell, B Howard, J Haller, DJ Sartoris, D Resnick. Septic arthritis. Radiol Clin North Am 26:1295–1313, 1988.
264. J Rosenthal, GG Bole, WD Robinson. Acute nongonococcal infectious arthritis: evaluation of risk factors, therapy, and outcome. Arthritis Rheum 23:889–897, 1980.
265. SA Al-Suleiman, EM Grimes, HS Jonas. Disseminated gonococcal infections. Obstet Gynecol 61:48–51, 1983.
266. FL Sapico. Microbiology and antimicrobial therapy of spinal infections. Orthop Clin North Am 27:9–13, 1996.
267. KK Holmes, GW Counts, HN Beaty. Disseminated gonoccocal infection. Ann Intern Med 74:979–993, 1971.
268. KK Kerle, JR Mascola, TA Miller. Disseminated gonococcal infection. Am Fam Physician 45:209–214, 1992.

2
Staging and Staging Application in Osteomyelitis

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I. INTRODUCTION: STAGING

Osteomyelitis can be classified by duration, pathogenesis, location, extent, and host status. There is no universally accepted classification system for osteomyelitis, although a number of classifications have been suggested to help guide therapy and to allow for comparison of published results.

The first osteomyelitis staging system was described in 1970 by Waldvogel (1). He described three categories of osteomyelitis: hematogenous, contiguous focus, and osteomyelitis associated with vascular insufficiency (1). Hematogenous osteomyelitis is predominantly encountered in the pediatric population: 85% of cases occur in patients younger than 17 years of age. In children, the bone infection usually affects the long bones, whereas in adults the lesion is usually located in the thoracic or lumbar vertebrae. Hematogenous osteomyelitis is more common in males of any age (2).

Osteomyelitis secondary to a contiguous focus of infection can derive from either a direct infection of bone from a source outside the body (i.e., soft tissue trauma, open fracture, or surgery) or the continuous spread of infection from an adjacent focus (i.e., soft tissue infection, dental abscess, or decubitus ulcer). In age distribution, contiguous focus osteomyelitis is biphasic. The infection occurs in younger individuals secondary to trauma and related surgery and in older adults secondary to decubitus ulcers and infected joint arthroplasties (1).

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Osteomyelitis associated with vascular insufficiency is usually seen in individuals with diabetes mellitus. Of the 31 patients in Waldvogel's study with this form of osteomyelitis, 25 were diabetic, 5 had severe atherosclerosis not related to diabetes, and 1 had vasculitis secondary to rheumatoid arthritis (1). All of the infections affected the toes, metatarsals, tarsals, or hindfoot. The patients in this group ranged between 40 and 70 years of age.

Of all classification systems, that of Waldvogel remains the major classification system for osteomyelitis. However, that classification is an etiological classification system and does not readily lend itself to guiding surgical or antibiotic therapy. Other classification systems have been developed to emphasize different clinical aspects of osteomyelitis.

Ger's classification system, published in 1977, addresses the physiological characteristics of the wound as they relate to osteomyelitis. His categories include simple sinus, chronic superficial ulcer, multiple sinuses, and multiple skin-lined sinuses (3). If the wound is not appropriately managed, the bone infection cannot be arrested. Early coverage of open tibial fractures with soft tissue prevents the later development of osteomyelitis, ulceration, and, perhaps, nonunion.

Kelly's classification system was published in 1984 (4). Kelly noted that osteomyelitis in the adult can be divided into four categories: hematogenous osteomyelitis, osteomyelitis in a united fracture (fracture with union), osteomyelitis in a nonunion (fracture with nonunion), and postoperative osteomyelitis without fracture (4). Kelly's classification system emphasizes the cause of the infection and its relationship to fracture healing.

In 1984, Weilan and colleagues defined chronic osteomyelitis as a wound with exposed bone, positive bone culture, findings and drainage for more than 6 months (5). A similar wound with drainage of less than 6 months in duration was not considered to be a site of chronic osteomyelitis. They further divided the infection on the basis of soft tissue and the location of bone involved. Type I osteomyelitis was defined as open, exposed bone without evidence of osseous infection but with evidence of soft tissue infection. Type II osteomyelitis showed circumferential, cortical, and endosteal infection. The radiographs demonstrated a diffuse inflammatory response, increased bone density, and spindle-shaped sclerotic thickening of the cortex. Other radiographic findings included areas of bony resorption and often a sequestrum with a surrounding involucrum. Type Ill osteomyelitis revealed cortical and endosteal infection associated with a segmental bone defect.

Gordon and Chin's classification of osteomyelitis was published in 1988 (6). The researchers classified infected tibial nonunions and segmental defects on the basis of the osseus defects. Type A includes tibial defects and nonunions without significant segmental loss. Type B includes tibial defects greater than 3 cm with an intact fibula. Type C includes tibial defects of greater than 3 cm in patients whose fibula was not intact. Gordon and Chin's classification correlates with the prognosis for successful free muscle transportation.

May and associates' system of classification, published in 1989 (7), focuses on the status of the tibia after soft tissue and skeletal débridement. The system is useful in determining the length of rehabilitation that will be needed, under ideal conditions, before the patient will be able to ambulate without upper extremity aids. Type I osteomyelitis is defined as an intact tibia and fibula capable of withstanding functional loads (rehabilitation time of 6 to 12 weeks). Type II osteomyelitis involves an intact tibia with bone graft only needed for structural support (rehabilitation time of 3 to 6 months). Type III osteomyelitis involves a tibial defect 6 cm long or less with an intact fibula (rehabilitation time of 6 to 12 months). Type IV has a tibial defect greater than 6 cm and an intact fibula rehabilitation time of 12 to 18 months). Type V osteomyelitis has tibial defect greater than 6 cm long with no usable intact fibula (rehabilitation time of 18 months or more). May and coworkers' classification system and the estimated time for rehabilitation assist the decision making process involved in the treatment of post-traumatic tibial osteomyelitis. However, many factors, including age, metabolic status, mobility of the patient's foot and ankle, neurovascular integrity, and patient's motivation, can greatly affect the time necessary for rehabilitation.

The Cierny-Mader classification (Table 1), published in 1984, is based on the anatomical characteristics of the bone infection and the physiological characteristics of the host (8). Cierny-Mader staging allows stratification of long bone osteomyelitis and permits the development of comprehensive treatment guidelines for each of the 12 stages.

The classification is determined by the condition of the disease process regardless of its cause, regionality, or chronicity. The anatomical types of osteomyelitis are medullary, superficial, localized, and diffuse (8). Stage 1, or medullary, osteomyelitis denotes infection confined to the intramedullary surfaces of the bone. Hematogenous osteomyelitis and infected intramedullary rods are examples of this anatomical type. Stage 2, or superficial, osteomyelitis, a true contiguous focus infection of bone, occurs when an exposed infected necrotic surface of bone lies at the base of a soft tissue wound. Stage 3, or localized, osteomyelitis is usually characterized by a full-thickness cortical sequestration that can be removed surgically without compromising bony stability. Stage 4, or diffuse, osteomyelitis is a through-and-through process that usually requires an intercalary resection of the bone to arrest the disease process. Diffuse osteomyelitis includes those infections with a loss of bony stability either before or after débridement surgery.

The patient is classified as an A, B, or C host (Table 1). An A host represents a patient with normal physiological, metabolic, and immunological capabilities (8). The B host is either systemically compromised, locally compromised, or both. When the morbidity of treatment is worse than that imposed by the disease itself, the patient is given the C host classification. The terms *acute*

Table 1 The Cierny-Mader Staging System[a]

Anatomical type
Stage 1: medullary osteomyelitis
Stage 2: superficial osteomyelitis
Stage 3: localized osteomyelitis
Stage 4: diffuse osteomyelitis
Physiological class
A Host: normal host
B Host:
Systemic compromise (Bs)
Local compromise (Bl)
Systemic and local compromise (Bls)
C Host: Treatment worse than disease
Systemic or local factors that affect immune surveillance, metabolism, and local vascularity
Systemic (Bs)
Malnutrition
Renal, hepatic failure
Diabetes mellitus
Chronic hypoxia
Immune disease
Malignancy
Extremes of age
Immunosuppression or immune deficiency
Local (Bl)
Chronic lymphedema
Venous stasis
Major vessel compromise
Arteritis
Extensive scarring
Radiation fibrosis
Small vessel disease
Neuropathy
Tobacco abuse [≥two packs per day]

[a] Bs, B-host, systemic compromise.
Bl, B-host, local compromise.
Bls, B-host, local and systemic compromise.

and *chronic osteomyelitis* are not used in this staging system since areas of macronecrosis must be removed regardless of the acuity or chronicity of an uncontrolled infection. The stages are dynamic and interact according to the pathophysiological characteristics of the disease. They may be altered by

successful therapy, host alteration, or treatment. This classification system aids in the understanding, diagnosis, and treatment of bone infections in children and adults.

Host factors are primarily involved with containment of the infection once it is introduced adjacent to or into the bone (8). A systemically and/or locally compromised host does not contain the infection as well as a normal host, and the infection may permeate the bone. The compromised host is more difficult to manage and treat than a normal host. On occasion, host factors may predispose the host to the development of osteomyelitis. These diseases include sickle cell anaemia, chronic granulomatous disease, and diabetes mellitus (9). Host deficiencies that lead to bacteremia favor the development of stage 1 osteomyelitis.

II. APPLICATION OF STAGING: CIERNY-MADER CLASSIFICATION

All of the staging systems described have obvious merits. Since the Cierny-Mader staging allows stratification of long bone osteomyelitis and permits the development of comprehensive treatment guidelines for each stage, the Cierny-Mader classification is used as a model for a discussion of the diagnosis and treatment of long bone osteomyelitis.

A. Diagnosis

The diagnosis of long bone osteomyelitis rests on the isolation of the pathogen(s) from the bone lesion, blood, or joint cultures (10). In hematogenous osteomyelitis (stage 1), positive blood or joint culture results can often obviate the need for a bone biopsy when there is radiographic or radionuclide scan evidence of osteomyelitis.

Thus, except in stage 1 osteomyelitis, in which positive blood or joint fluid culture results may suffice, antibiotic treatment of osteomyelitis should be based on meticulous bone cultures taken at débridement surgery or from deep bone biopsy specimens (11,12). If possible, cultures should be obtained before antibiotics are initiated or after the patient has been off antibiotic therapy for at least 24 to 48 hours. Sinus tract cultures are not reliable for predicting organisms other than *Staphylococcus aureus* as a cause of osteomyelitis (13). *S. aureus* and coagulase-negative *Staphylococcus* sp. are the most common organisms isolated from patients with osteomyelitis. In the immunocompromised patient the physician must also consider other organisms including fungi and mycobacteria.

Leukergy, sedimentation rates, C-reactive protein level, and leukocyte counts are frequently elevated before therapy in the acute disease (14–16). The white blood cell count rarely exceeds $15{,}000/mm^3$ in acute osteomyelitis, and the

leukocyte count is usually normal in patients with chronic osteomyelitis. The sedimentation rates, C-reactive protein level, and leukocyte counts may fall with appropriate therapy; however, these values may be elevated after each débridement surgery. A sedimentation rate and C-reactive protein level that return to normal during the course of therapy are favorable prognostic signs. However, these laboratory determinations are not reliable in the compromised host, as these patients are constantly challenged by minor illnesses and peripheral inflammatory lesions that may elevate these indices.

Radiographic changes in early stage 1 osteomyelitis are often difficult to interpret and lag at least 2 weeks behind the evolution of infection (17). The earliest radiographic changes are soft tissue swelling, periosteal thickening or elevation or both, and focal osteopenia. These findings are subtle and may be missed. The more diagnostic lytic changes are delayed and often associated with an indolent infection of several months' duration. Later, when the patient is undergoing appropriate antimicrobial therapy, radiographic improvement may lag behind clinical recovery. In superficial osteomyelitis (stage 2), the outer cortex of the bone is involved. There may be periosteal thickening or sclerosis. In localized (stage 3) and diffuse (stage 4) osteomyelitis, the radiographic changes usually show soft tissue swelling, osteopenia, lytic changes, and sclerosis. Small and large sequestrum may also be present. Because of the degree of the sclerosis and nonspecific radiographic changes, it is often difficult to gauge the extent of infection by visualizing the radiograph. Gauging the extent of infection may require careful clinical and, ultimately, surgical evaluation. In stage 4 osteomyelitis, it is often difficult to distinguish an infected nonunion from one that is not infected.

Radionuclide scans (18,19), computed tomography (20,21), or magnetic resonance imaging (22,23) may be done when the diagnosis of osteomyelitis is equivocal or to help gauge the extent of bone and soft tissue infection. In general, it is not usually necessary to obtain these scans for long bone osteomyelitis.

B. Treatment

Appropriate therapy of osteomyelitis includes adequate drainage, thorough débridement, obliteration of dead space, wound protection, and specific antimicrobial coverage (10,11). If the patient is a compromised host, an effort is made to correct or improve the host defect(s) (Table 2). In particular, attention should be paid to good nutrition and to a smoking cessation program along with dealing with specific abnormalities such as control of diabetes. Thus, an attempt is made to improve the nutritional, medical, and vascular status of the patient and to provide optimal care for any underlying disease.

Table 2 Patient Management: Methods of Host Alteration

Patient education: no smoking
Nutritional supplementation
Alcohol abuse
Diabetes mellitus
Immune compromise
Malnutrition
Renal/hepatic failure
Hyperbaric oxygen: Cierny-Mader 3–4 Bl, poor granulation beds, refractory[a] osteomyelitis
Special considerations
Chemical suppression: discontinue or alter medications
Diabetes mellitus: tight blood glucose control
Local compromise: pressure garments, local or microvascular tissue transfers
Major vessel disease: arterial bypass surgery
Pressure sores: force distribution
Sepsis–toxicity: emergency decompression or drainage

[a] B1, B-host, local compromise.

1. Antibiotic management

After cultures are obtained, a parenteral antimicrobial regimen is begun to cover the clinically suspected pathogens. Once the organism is identified, specific antibiotic(s) class(es) can be selected by appropriate sensitivity methods (24). Because of the need for prolonged therapy, antibiotics used in the treatment of bone and joint infection must be nontoxic, convenient to administer, and cost-effective.

Stage 1 osteomyelitis in children usually can be treated with antibiotics alone. Antibiotic therapy alone is possible because bones of children are very vascular and have an effective immune and metabolic response to infection. Stage 1 osteomyelitis in adults is more refractory to therapy and is usually treated with antibiotics and surgery. The patient is treated for 6 weeks with appropriate parenteral and oral antimicrobial therapy, dated from the initiation of therapy or after the last major débridement surgery. If the initial medical management fails and the patient is clinically compromised by a recurrent infection, medullary and/or soft tissue débridement is necessary in conjunction with another 4-week course of antibiotics.

Stage 1 osteomyelitis may be due to an infected intramedullary rod. If the bone is stable, the rod can be removed. The patient is given a 4-week course of antibiotics dated from rod removal. If the bone is unstable, the patient is placed on

suppressive oral antibiotic therapy until bony stability is achieved. Once stability is obtained, the rod is removed and the patient is given a 6-week course of patenteral and oral antibiotics dated from rod removal.

Oral antibiotic therapy can be utilized for treatment of osteomyelitis. However, it is recommended that the patient initially receive 2 weeks of parenteral antibiotic therapy prior to changing to an oral regimen (25,26). High doses of the quinolone class of antibiotics have been reported to cause articular cartilage damage in young animals, generating some concern about the long-term use of these agents in infants and children (27,28). Therefore, under most circumstances, pediatric patients should not be given the quinolone class of antibiotics. Oral quinolone therapy is widely used in the treatment of adult osteomyelitis.

In stage 2 osteomyelitis, the patient may be treated with a 2-week course of antibiotics after superficial débridement and soft tissue coverage. The arrest rate is approximately 80%.

In stages 3 and 4 osteomyelitis, the patient is traditionally treated with 6 weeks of parenteral and antimicrobial therapy dated from the last major débridement surgery (10,11). Without adequate débridement most antibiotic regimens fail regardless of the duration of therapy. Even when all necrotic tissue has been adequately débrided, the remaining bed of tissue must be considered contaminated with the responsible pathogen(s). Therefore, it is important to treat the patient for at least four weeks with antibiotics. With good débridement surgery, the arrest rate is approximately 90%. Outpatient intravenous therapy using peripherally inserted central catheter (PICC) lines or long-term intravenous access catheters, such as Hickman or Groshong catheters, decreases hospitalization time (29–31).

Oral therapy using quinolones for gram-negative organisms is currently being used in adult patients with osteomyelitis (32–34). The second-generation quinolones (ciprofloxacin, ofloxacin) have poor activity against *Streptococcus* sp., *Enterococcus* sp., and anaerobic bacteria (35). The third-generation (levofloxacin, gatifloxacin) quinolones have excellent *Streptococcus* sp. activity, but minimal anaerobic coverage (36). The fourth-generation (trovafloxacin mesylate) quinolone has excellent *Streptococcus* sp. and anaerobic organism coverage (36,37). Trovafloxacin has been found to produce severe liver toxicity in a small number of patients and is only used for inpatient treatment. None of the quinolones has reliable *Enterococcus* sp. coverage. The current quinolones have variable *S. aureus* and *S. epidermidis* coverage, and resistance to the second-generation quinolones is increasing (38). Polymicrobic coverage of methicillin-sensitive *S. aureus* should be obtained with another oral antibiotic such as clindamycin or ampicillin-sulbactam (Unasyn). Before changing to an oral regimen, it is recommended that the patient initially receive 2 weeks of parenteral antibiotic therapy and that the organism(s) be sensitive to the oral regimen. The patient must be compliant and have close outpatient follow-up.

A combination of parenteral and oral antibiotics has been used in some situations. Methicillin-sensitive and methicillin-resistant *S. aureus* osteomyelitis have been successfully treated with semisynthetic penicillin-rifampin and vancomycin-rifampin, respectively (39).

Streamlining from parenteral to oral therapy may be an effective alternative strategy for the treatment of osteomyelitis in adults. In a historical control study, Swiontkowski and associates (40) gave 5 to 7 days of parenteral therapy followed by 6 weeks of oral therapy. Treatment was successful in 91% of these patients. In a randomized study, Shirtliff and colleagues (41) gave 4 weeks of parenteral antibiotic therapy versus 2 weeks of parenteral therapy followed by 4 weeks of oral antibiotic therapy for the treatment of patients with long bone osteomyelitis. The patients who received parenteral antibiotic therapy had an arrest rate of 84.3%. In the parenteral-to-oral antibiotic therapy group the arrest rate was 89.5%. Before changing to an oral regimen, an initial parenteral antibiotic therapy for at least 6 weeks is recommended. Additionally, the patient must be compliant and agree to close outpatient follow-up.

2. Surgical management

Surgical management of osteomyelitis can be very challenging. The principles of treating any infection are equally applicable to the treatment of infection in bone. These include adequate drainage, extensive débridement of all necrotic tissue, obliteration of dead spaces, stabilization, and adequate soft tissue coverage and restoration of an effective blood supply (10). The goal of débridement is to leave healthy, viable tissue. However, even when all necrotic tissue has been adequately débrided, the remaining bed of tissue must be considered contaminated with the responsible organism. The challenge in treating osteomyelitis, as compared to infection of soft tissue alone, involves bone débridement.

Débridement surgery is the foundation of osteomyelitis treatment. Débridement should be direct, atraumatic, and executed with reconstruction in mind. All dead or ischemic hard and soft tissue is excised unless a noncurative procedure has been chosen. If complete excision threatens bone stability, external fixation may be necessary before or during débridement surgery. At débridement, surgical excision of the bone is carried down to uniform Haversian or cancellous bleeding, termed the *paprika sign* (8).

Adequate débridement may leave a large bony defects or dead space. Appropriate management of dead space created by débridement surgery is mandatory in order to arrest the disease and maintain the integrity of the skeletal part. The goal of dead space management is to replace dead bone and scar tissue with durable vascularized tissue. Complete wound closure should be attained whenever possible. Suction irrigation systems are not recommended because of

the high incidence of associated nosocomial infections and the unreliability of these setups (42,43). Secondary intention healing is discouraged since the scar tissue that fills the defect may later become avascular.

Local tissue flaps or free flaps may be used to fill dead space (44–46). An alternative technique is to place cancellous bone grafts beneath local or transferred tissues where structural augmentation is necessary. Careful preoperative planning is critical to the conservation of the patient's limited canellous bone reserves. Open cancellous grafts without soft tissue coverage are useful when a free tissue transfer is not a treatment option and local tissue flaps are inadequate (47).

Antibiotic-impregnated acrylic beads may be used to sterilize and temporarily maintain dead space (48–51). The beads are usually removed within 2 to 4 weeks and replaced with a cancellous bone graft. The most commonly used antibiotics in beads are vancomycin, tobramycin, and gentamicin. Local delivery of antibiotics (amikacin, clindamycin) into dead space has been achieved with an implantable pump (52).

If movement is present at the site of infection, measures must be taken to achieve permanent stability of the skeletal unit. Stability may be achieved with plates, screws, rods, and/or an external fixator. External fixation is preferred to internal because of the tendency of medulllary rods to become secondarily infected and to spread the extent of the infection.

The Ilizarov external fixator allows bone reconstruction of segmental defects and difficult infected nonunions (53). This external fixation method utilizes the theory of distraction histogenesis, whereby bone is fractured in the metaphyseal region and slowly lengthened. The growth of new bone in the metaphyseal region pushes a segment of healthy bone into the defect left by surgery. The Ilizarov technique is used for difficult cases of osteomyelitis when stabilization and bone lengthening are necessary (54). The method may also be used to compress nonunions and correct malunions. The technique is labor intensive and requires an extended period of treatment averaging 9 months in the device. The Ilizarov pins usually become infected and the device is painful. The Ilizarov is commonly used in a small group of patients for reconstruction of difficult deformities that result from osteomyelitis. The Ilizarov external fixation method is utilized by most tertiary care hospitals.

Infected pseudarthrosis with segmental osseous defects may also be treated by débridement and microvascular bone transfers (55). Vascularized bone transfer is a useful procedure for the treatment of infected segmental osseous defects of long bones of more than 3 cm in length. Vascularized bone transfers can be placed after 1 month of inactive sepsis.

Adequate soft tissue coverage of the bone is necessary to arrest osteomyelitis. Small soft tissue defects may be covered with a split-thickness skin graft. In the presence of a large soft tissue defect or with an inadequate soft tissue envelope, local muscle flaps and free vascularized muscle flaps may be placed in a one-or two-stage procedure (56). Local and free muscle flaps, when combined

with antibiotics and surgical débridement of all nonviable osseous and soft tissue for chronic osteomyelitis, have a success rate ranging from 66% to 100% (57). Local muscle flaps and free vascularized muscle transfers improve the local biological environment by introducing a blood supply important in host defense mechanisms, antibiotic delivery, and osseous and soft tissue healing.

The Cierny-Mader classification of osteomyelitis not only stratifies the disease and host condition, but also provides guidelines for the surgical management of the disease. In medullary osteomyelitis (stage 1), the nidus of infection is entirely within the medullary canal of the bone. It usually is caused by blood-borne bacteria or the introduction of surgical hardware such as an intramedullary nail. Because of the location, surgical treatment is usually more straightforward than in other types of bone involvement. In pediatric patients without hardware, surgical therapy is usually not necessary. In adults with primary or secondary stage 1 osteomyelitis, thorough intramedullary reaming and unroofing are usually done with or without bone grafting. Soft tissues are reapproximated and the limb is protected by external means (brace or cast) until structural integrity of the bone is re-established by normal remodeling.

In superficial osteomyelitis (stage 2), the surface of the bone is exposed because of an overlying soft tissue defect. The superficial cortex becomes involved with the infection and eventually becomes sequestered (stage 3 progression) if treatment is delayed. The most important aspect of treatment is soft tissue coverage after adequate débridement to bleeding cortex. This may be a simple problem involving local tissue, or it may require free tissue transfer.

Localized osteomyelitis (stage 3) combines the problems of both stages 1 and 2. The treatment involves the modalities employed for both of these categories of disease. Bone is sequestered, medullary extension of the infection is common, and major soft tissue defects may be present. These patients may require external fixation for structural support while the bone graft incorporates into normal bone. Complex reconstruction of both bone and soft tissue is frequently necessary.

Diffuse osteomyelitis (stage 4) combines the problems of stages 1, 2, and 3. Instability is a problem before or after surgery. Therefore, treatment often must be directed to establishing structural stability and obliterating débridement gaps by means of cancellous bone grafts or the Ilizarov technique. Free flaps and vascularized bone grafts are other possible treatment modalities. All of the modalities previously discussed may have a place in the treatment of diffuse osteomyelitis.

III. SUMMARY

Long bone osteomyelitis is traditionally staged by the Waldvogel classification system, an etiological system that does not readily lend itself to guiding surgical

or antibiotic therapy. As a result, classifications have been developed to emphasize different clinical aspects of osteomyelitis. These classifications include those of Kelly, Weiland and associates, Ger, Gordon and Chiu, May and coworkers, and Cierny and associates. Most of these systems apply to osteomyelitis at any site, but the Gordon and Chiu and May and colleagues systems are limited to tibial disease. The Cierny-Mader classification is based on the anatomical characteristics of bone infection and the physiological characteristics of the host; the classification permits the development of comprehensive treatment guideline for each stage.

REFERENCES

1. FA Waldvogel, G Medoff, MM Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations, and unusual aspects. N Engl J Med 282:198–206, 260–266, 316–322, 1970.
2. R David, BJ Barron, JE Madewell. Osteomyelitis, acute and chronic. Radiol Clin North Am 25:1171–1201, 1987.
3. R Ger. Muscle transposition for treatment and prevention of chronic post-traumatic osteomyelitis of the tibia. J Bone Joint Surg 59A:784–791, 1977.
4. PJ Kelly. Infected nonunion of the femur and tibia. Orthop Clin North Am 15:481–490, 1984.
5. AJ Weiland, JR Moore, RK Daniel. The efficacy of free tissue transfer in the treatment of osteomyelitis. J Bone Joint Surg 66A: 181–193, 1984.
6. L Gordon, EJ Chiu. Treatment of infected non-unions and segmental defects of the tibia with staged microvascular muscle transplantation and bone grafting. J Bone Joint Surg 70A:377–386, 1988.
7. JW May, JB Jupiter, AJ Weiland, HS Byrd. Clinical classification of post-traumatic tibial osteomyelitis. J Bone Joint Surg 71A:1422–1428, 1989.
8. G Cierny, JT Mader, H Pennick. A clinical staging system of adult osteomyelitis. Contemp Orthop 10:17–37, 1985.
9. ER Wald. Risk factors for osteomyelitis. Am J Med 78 (supp1):206–212, 1985.
10. JT Mader, JH Calhoun. Osteomyelitis. In: GL Mandell, RG Douglas, JE Bennett Jr, eds. Principlcs and Practice of Infectious Diseases. New York: Churchill Livingstone, 1995:1039–1051.
11. G Cierny, JT Mader. Adult chronic osteomyelitis. Orthopedics 7:1557–1564, 1984.
12. CR Perry, RL Pearson, GA Miller. Accuracy of cultures of material from swabbing of the superficial aspect of the wound and needle biopsy in the preoperative assessment of osteomyelitis. J Bone Joint Surg 73A: 745–749, 1991.
13. PA Mackowiak, SR Jones, JW Smith. Diagnostic value of sinus tract cultures in chronic osteomyelitis. JAMA 239:2772–2775, 1978.
14. I Otremski, RJ Newman, PJ Kahn, J Stadler, N Kariv, Y Skornik, G Goldman. Leukergy: a new diagnostic test for bone infection. J Bone Joint Surg 75B: 734–736, 1993.

15. I Roine, I Faingezicht, A Argnedas, JF Herrera, F Rodriguez. Serial serum C-reactive protein to monitor recovery from acute hematogenous osteomyelitis in children. Pediatr Infect Dis J 14:40–44, 1995.
16. L Unkila-Kallio, MJ Kallio, J Eskola, H Peltola. Serum C-reactive protein, erythrocyte sedimentation rate, and white blood cell count in acute hematogenous osteomyelitis of children. Pediatrics 93:59–62, 1994.
17. WP Butt. The radiology of infection: Clin Orthop 96:20–30, 1973.
18. R Lisbona, L Rosenthall. Observations of the sequential use of ^{99m}Tc phosphate complex and ^{67}Ga imaging in osteomyelitis, cellulitis, and septic arthritis. Radiology 123:123–129, 1977.
19. SL Propst-Proctor, MF Dillingham, IR McDougall, D Goodwin. The white blood cell scan in orthopedics. Clin Orthop l68:157–165, 1982.
20. JP Kuhn, PE Berger. Computed tomographic diagnosis of osteomyelitis. Radiology 130:503–506, 1979.
21. SE Seltzer. Value of computed tomography in planning medical and surgical treatment of chronic osteomyelitis. J Comp Assist Tomog 8:482–487, 1984.
22. WA Erdman, F Tamburro, HT Jayson, PT Weatherall, KB Ferry, RM Peshock. Osteomyelitis: characteristics and pitfalls of diagnosis with MR imaging. Radiology 180:533–539, 1991.
23. J Tehranzadeh, F Wang, M Mesgarzadeh. Magnetic resonance imaging of osteomyelitis. Crit Rev Diagn Imaging 33:495–534, 1992.
24. HM Ericcson, JC Sherris. Antibiotic sensitivity testing: Report of an international collaborative study. Acta Pathol Microbiol Scand 227(suppl B):1–90, 1971.
25. JD Nelson. A critical review of the role of oral antibiotics in the management of hematogenous osteomyelitis. In: RS Remington, MN Swartz, eds. Current Clinical Topics in Infectious Diseases. Vol. 4. New York: McGraw-Hill, 1983:64–74.
26. TR Tetzloff, GH McCracken, FD Nelson. Oral antibiotic therapy for skeletal infections in children. II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr 92:485–490, 1978.
27. W Christ, T Lehnert, B Ulbrich. Specific toxicologic aspects of the quinolones. Rev Infect Dis 10(suppl 1):141–146, 1988.
28. DG Mayer. Overview of toxicological studies. Drugs 34(suppl 1):150–153, 1987.
29. L Couch, G Cierny, JT Mader. Inpatient and outpatient use of the Hickman catheter for adults with osteomyelitis. Clin Orthop 219:226–235, 1987.
30. DR Graham, MM Keldermans, LW Klemm, NJ Semenza, ML Shafer. Infectious complications among patients receiving home intravenous therapy with peripheral, central, or peripherally placed central venous catheters. Am J Med 91: S95–S100, 1991.
31. RO Hickman, CD Buckner, RA Clift, JE Sanders, P Stewart, ED Thomas. A modified right atrial catheter for access to the venous system in marrow transplant recipients. Surg Gynecol Obstet 148:871–875, 1979.
32. JT Mader. Fluoroquinolones in bone and joint infections. In: WE Sanders Jr, CC Sanders, eds. Fluoroquinolones in the Treatment of Infectious Diseases. Glenview, IL: Physicians & Scientists, 1990:71–86.

33. DP Lew, FA Waldvogel. Quinolones and osteomyelitis: state-of-the-art. Drugs 49(suppl) 2:100–111, 1995.
34. JT Mader, JS Cantrell, JH Calhoun. Oral ciprofloxacin compared with standard parenteral antibiotic therapy for chronic osteomyelitis in adults. J Bone Joint Surg 72A:104–110, 1990.
35. DR Schamberg, WI Dillon, MS Terpenning, KA Robinson, SF Bradley, CA Kauffman. Increasing resistance of enterococci to ciprofloxacin. Antimicrob Agents Chemother 36:2533–2535, 1992.
36. ME Ernst, EJ Ernst, ME Klepser. Levofloxacin and trovafloxacin: the next generation of fluoroquinolones. Am J Health Syst Pharm 54:2569–2584, 1997.
37. AJ Wagstaff, JA Balfour. Grepafloxacin. Drugs 53:817–824, 825–827, 1997.
38. HM Blumberg, D Rimland, DJ Carroll, P Terry, IK Wachsmuth. Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant *Staphylococcus aureus*. J Infect Dis 163:1279–1285, 1991.
39. CW Norden, R Bryant, D Palmer, JZ Montgomerie, J Wheat. Chronic osteomyelitis caused by *Staphylococcus aureus*: controlled clinical trial of nafcillin therapy and nafcillin-rifampin therapy. South Med J 79:947–951, 1986.
40. MF Swiontkowski, DP Hanel, NB Vedder, JR Schwappach. A comparison of short- and long-term intravenous antibiotic therapy in the postoperative management of adult osteomyelitis. J Bone Joint Surg 81B:1046–1050, 1991.
41. ME Shirtliff, D Mohan, JH Calhoun, JT Mader. Four week intravenous antibiotic therapy versus two week intravenous antibiotic therapy versus two week intravenous plus four week oral antibiotic therapy in the treatment of long bone osteomyelitis. Musculoskeletal Infection Society Annual Meeting. Snowmass, CO, 1997.
42. DK Clawson, FJ Davis, ST Hansen. Treatment of chronic osteomyelitis with emphasis on closed suction-irrigation technique. Clin Orthop 96:88–97, 1973.
43. RM Letts, E Wong. Treatment of acute osteomyelitis in children by closed-tube irrigation: a reassessment. Can J Surg 18:60–63, 1975.
44. JP Anthony, SJ Mathes, BS Alpert. The muscle flap in the treatment of chronic lower extremity osteomyelitis: results in patients over 5 years after treatment. Plast Reconstr Surg 88:311–318, 1991.
45. JW May Jr, JB Jupiter, GG Gallico 3rd, DM Rothkopf, P Zingarelli. Treatment of chronic traumatic bone wounds. Microvascular free tissue transfer: a 13-year experience in 96 patients. Ann Surg 214:241–250, 1991.
46. PE Ruttle, PJ Kelley, PG Arnold, GB Irons, RH Fitzgerald. Chronic osteomyelitis treated with a muscle flap. Orthop Clin North Am 15:451–459, 1984.
47. LJ Papineau, A Alfageme, JP Dalcourt, L Pilon. Osteomyelite chronique: excision et greffe de spongieux a l'air libre apres mises a plat extensives. Int Orthop 3:165–176, 1979.
48. K Adams, MSL Couch, G Cierny, J Calhoun, JT Mader. *In vitro* and *in vivo* evaluation of antibiotic diffusion from antibiotic-impregnated polymethylmethacrylate (PMMA) beads. Clin Orthop 276:244–252, 1992.
49. JH Calhoun, JT Mader. Antibiotic beads in the management of surgical infection. Am J Surg 157:443–449, 1989.

50. SL Henry, D Seligson, P Mangino, GJ Popham. Antibiotic-impregnated beads. Part I. Bead implantation versus systemic therapy. Orthop Rev 20:242–247, 1991.
51. KJ Wilson, G Cierny, KR Adams, JT Mader. Comparative evaluation of the diffusion of tobramycin and cefotaxime out of antibiotic-impregnated polymethylmethacrylate beads. J Orthop Res 6:279–286, 1988.
52. CR Perry, K Davenport, MK Vossen, Local delivery of antibiotics via an implantable pump in the treatment of osteomyelitis. Clin Orthop 226:222–230, 1988.
53. SA Green. Osteomyelitis. The Ilizarov perspective. Orthop Clin North Am 22:515–521, 1991.
54. JH Calhoun, DM Anger, JT Mader. The Ilizarov technique in the treatment of osteomyelitis. Texas Med 87:56–59, 1991.
55. A Minami, K Kaneda, H Itoga, Treatment of infected segmental defect of long bone with vascularized bone transfer. J Reconstr Mierosurg 8:75–82, 1992.
56. AE Beris, PN Soucacos, TA Xenakis, S Zaravelas, G Mitsionis, Z Dailiana. Latissimus dorsi free transfer for coverage of extensive soft tissue defects. Acta Orthop Scand 264(suppl):31–34, 1995.
57. LB Gayle, WC Lineaweaver, A Oliva, PP Siko, BS Alpert, GM Buncke, K Yim, HJ Buncke. Treatment of chronic osteomyelitis of the lower extremities with debridement and microvascular muscle transfer. Clin Plast Surg 19:895–903, 1992.

3

Musculoskeletal Infection in Systemically and Locally Immunocompromised Hosts

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I. INTRODUCTION

Osteomyelitis in immunocompromised hosts is associated with poor prognosis and high rates of morbidity and mortality. The immunocompromised state comprises a variety of conditions, including congenital and acquired immunodeficiency and underlying disease. Immunocompromised patients usually have impaired humoral- or cellular-mediated immunity secondary to disorders such as poorly controlled diabetes mellitus, end-stage renal disease, acquired immunodeficiency syndrome (AIDS), sickle cell or aplastic anemia, and iatrogenic immunosuppression in organ transplantation, vasculitis, or malignancy. Human immunodeficiency virus disease and increasing success in transplantation medicine, cancer therapy, and rheumatological therapy have contributed to the increased prevalence of immunocompromise in the general population. Predicated on the underlying immune system defect, many diverse microbes, including those handled routinely by the immunocompetent host, can become pathogens.

Orthopedic physicians should develop a systematic approach for patients with compromised immune systems who have soft tissue and bone and joint infections. The approach should include historical and physical findings pertinent

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to these patients, with attention to details that are atypical or specific to the immunocompromised state: a diagnostic work-up applicable to most patients with immune system dysfunction, a knowledge of common clinical scenarios of immunosuppression, focusing on unique presentations, and treatment strategies that include disposition options.

II. OVERVIEW OF THE IMMUNE SYSTEM

The immune system is a complex, multisystem network that protects the human body from pathogenic invasion by microorganisms and tumors (1,2). When part of the immune system functions in a compromised state, infectious complications can be sudden and fulminant, or even fatal. A defect at one site in the system can elicit dysfunction throughout the whole system.

The first-line host defenses against microorganisms consist of various physical barriers such as skin, mucosa, secretory substances, and normal flora. The complexity of the system increases greatly at the level of cellular and molecular defenses. The principal components of the adaptive immune responses are T and B lymphocytes. B cells produce immunoglobulins that are critical for phagocytosis, bind to bacterial toxins, and prohibit microorganism entry from respiratory and alimentary tracts. T cells are the primary effectors of cell-mediated immunity. Subsets of T cells become cytotoxic killer cells able to lyse infected host cells or foreign cells.

Other T cells regulate a host of immune responses by producing cytokines, such as interferon-γ (IFN), tumor necrosis factor (TNF), and granulocyte colony-stimulating factor (G-CSF), that activate and modulate macrophages, B lymphocytes, and other T lymphocytes. Phagocytic cells ingest and destroy bacteria, fungi, and some large viruses; they also serve as activation centers for other components of the immune response. Phagocytic cells are either fixed or mobile and are widely distributed throughout the body. Mobile cells include granulocytes and monocytes. Fixed cells are primarily macrophages, including some specialized types, such as alveolar cells, Kupffer's cells, and spleen and lymph node histiocytes. The spleen provides a site for the phagocytosis of intravascular pathogens and for the initial antibody synthesis in response to intravenous antigens. Additional functions include production of humoral factors (complement proteins and tuftsin) and the coordination of B-cell/T-cell interaction. The complement cascade and other inflammatory response mediators (e.g., bradykinins and the fibrinolytic system) are also involved in competent immune function by integrating and accelerating the immune response and recruiting additional cellular and molecular help.

The activation of the immune system by microorganisms can be summarized as follows: Macrophages ingest and process an antigen. The macrophage then presents the antigen on its cell membrane surface, along with the additional protein markers, to a helper lymphocyte ($CD4^+$). At the same time, the

macrophage also produces interleukin-1. When presented with this array, the helper lymphocyte becomes activated; activation, in turn, modulates several parallel pathways. The helper cell can produce additional cytokines that act on monocyte-macrophage cells, attracting them to the inflammatory site and allowing them to kill intracellular microbes. The helper cell can also activate B lymphocytes, facilitating their transformation into immunoglobulin-producing plasma cells. Granulocytes, attracted by the inflammatory cascade, migrate from the bloodstream to the site and ingest bacteria opsonized by these immunoglobulins. Finally, the helper cell can activate $CD8^+$ T lymphocytes, transforming them into cytotoxic cells.

III. OSTEOMYELITIS IN IMMUNOCOMPROMISED PATIENTS

Human disease such as osteomyelitis is a status of interaction between the host and pathogens. Thus, the final outcome of osteomyelitis is determined by a net effect of several host factors and pathogens. Infection in bone is very difficult to eradicate, even in a patient with a normal immune response. In the immunocompromised host, the course of osteomyelitis may be altered by host factors that affect immune surveillance, metabolism, and local vascularity (3). Usually, a small focus of acute osteomyelitis evolves into chronic disease.

A. Congenital Immune Deficiency and Osteomyelitis

Predisposition to infection as a consequence of either qualitative or quantitative defects in one or more natural defense mechanisms of the body has long been recognized. Until the arrival of the acquired immunodeficiency syndrome, the term *immunocompromised host* was used almost exclusively to describe infectious complications in a small group of patients with congenital deficiency of the immune system (Table 1). These patients usually experienced acute osteomyelitis

Table 1 Congenital Immunodeficiency

Congenital immunodeficiency	Immune defect
Severe combined immunodeficiency (SCID)	Decreased serum immune globulin level
DiGeorge syndrome	T-cell deficiency
Common variable immunodeficiency and selective immunoglobulin A (IgA) deficiency	IgA deficiency
Chronic granulomatous disease (CGD)	Neurophils incapable of making superoxide; impaired phagocyte function
Congenital complement deficiencies	Complement deficiency

Table 2 Organisms in Musculoskeletal Infection of Immunocompromised Hosts

Organism	Common	Unusual
Bacterial	*Staphyloccus aureus*	*Salmonella* spp.
	Pseudomas auruginosa	*Clostridium* spp.
	Streptococcus spp.	*Nocardia* spp.
	Enterococcus spp.	*Actinomyces* spp.
	Escherichia coli	*Neisseria gonococcus*
		Haemophilus influenzae
Fungal		Zygomycetes (*Apophysomyces elegans*)
		Phaeohyphomycosis
		Cryptococcosis
	Candida spp.	Histoplasmosis
		Blastomycosis
		Coccidioidomycosis
		Fusarium spp.
Mycobacterium spp.		Atypical *Mycobacterium* spp., e.g.,
		M. marinum,
		M. kansasii,
	Mycobacterium tuberculosis	*M. avium* complex,
		M. fortuitum,
		M. chelonae
Others		*Rickettsia* spp.
		Pneumocystis carinii
		Treponema pallidum

at a young age. Predicated on the underlying immune system defect, many diverse microbes, including those handled routinely by the immunocompetent host, can become pathogens. The common organisms responsible for osteomyelitis in immunocompromised patients are listed in Table 2. The immunological diagnosis is suggested by the unusual nature of the organisms isolated and confirmed by appropriate laboratory studies.

B. Systemic and Local Immunosuppression from an Underlying Process

A large number of disease processes can cause immune system dysfunction (Table 3). Malnutrition is well-documented cause of T-cell dysfunction. Globally depressed immune function after extensive burns or trauma is also well recognized. The discussion that follows highlights some of the diseases more commonly seen in the patient who has osteomyelitis.

Table 3 Immunocompromised States with Underlying Diseases or Conditions and Their Associated Immune Dysfunction

Acquired immunodeficiency	Immune defect
Malnutrition	Phagocytic defects/cell-mediated defects/humoral defects
Diabetics	Impaired chemotaxis, phagocytosis, opsonization
Uremia	Impaired cell-mediated and humoral immunity
COPD	Impaired cell-mediated immunity
Malignancy	Impaired cell-mediated and humoral immunity, neutropenia
Multiple myeloma	IgG deficiency
Vasculitis	Complement deficiencies/impaired phagocytosis
Corticosteroid and immuno-suppression	Cell-mediated immunity
Asplenic/Sickle cell	Increased susceptibility to encapsulated organism
AIDS/IVDA	Lymphopenia and CD4 depletion
Alcoholism with cirrhosis	Impaired opsonization, chemotaxis macrophage dysfunction
Trauma (Burns, multisystem injury)	Barrier, humoral deficiency/cell-mediated defects

[a] COPD, chronic obstructive pulmonary disease; AIDS, acquired immunodeficiency syndrome; IVDA, intravenous drug abuse; IgG, immunoglobin G.

IV. OSTEOMYELITIS, CONCEPT AND STAGING

Bone infections were originally classified by the system of Waldvogel (4) as either hematogenous osteomyelitis or osteomyelitis secondary to a contiguous focus of infection. Contiguous-focus osteomyelitis has been further subdivided into osteomyelitis with or without vascular insufficiency. Hematogenous and contiguous-focus osteomyelitis have been further divided into acute or chronic disease. Acute disease appears as a suppurative infection accompanied by edema, vascular congestion, and small vessel thrombosis. In early acute disease, the vascular supply to the bone is compromised by infection extending into the surrounding soft tissue. When both the medullary and periosteal blood supplies are compromised, large areas of dead bone (sequestra) may be formed. Within this necrotic and ischemic tissue, the bacteria may be difficult to eradicate even after an intense host response, surgery, antibiotic therapy, or all of these. Clinically, acute osteomyelitis evolves into chronic disease. The hallmarks of chronic disease are a nidus of infected dead bone or scar tissue, an ischemic soft tissue envelope, and a refractory clinical course.

An alternative classification system has been developed by Cierny and Mader (5) (Table 4). This classification takes into consideration the quality of the host, the anatomical nature of the disease, treatment factors, and prognostic factors. This staging system combines four anatomical disease types and three physiological host categories to define 12 distinct clinical stages of osteomyelitis.

Table 4 Cierny-Mader Classification System of Osteomyelitis

Anatomical class	
Stage 1: medullary	
Stage 2: superficial	
Stage 3: localized	
Stage 4: diffuse	
Physiological class	
A host: normal host	
B host: systemic compromise (Bs); local compromise (Bl)	
C host: treatment worse than disease	
Physiological class: systemic or local factors that affect immune surveillance, metabolism, and local vascularity	
Systemic (Bs)[a]	
1Bs.	Malnutrition
2Bs.	Renal, liver failure
3Bs.	Diabetes mellitus
4Bs.	Chronic hypoxia
5Bs.	Malignancy
6Bs.	Extremes of age
7Bs.	Immune disease
8Bs.	Immunosuppression or immune deficiency
9Bs.	Asplenic patients: Functional asplenia and sickle cell disease
10Bs.	HIV/AIDS
11Bs.	IVDA
12Bs.	ETOH
13Bs.	Tobacco abuse
Local (Bl)	
1Bl.	Chronic lymphedema
2B1.	Venous stasis
3Bl.	Major vessel compromise.
4Bl.	Arteritis
5Bl.	Extensive scarring
6Bl.	Radiation fibrosis
7Bl.	Small vessel disease
8Bl.	Neuropathy

[a] HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency virus; IVDA, intravenous drug abuse; ETOH, Alcohol abuse.

Stage 1, or medullary osteomyelitis, equates with early hematogenous osteomyelitis in which the primary lesion is endosteal. Pediatric stage 1 usually can be treated with antibiotics alone. Adult stage 1 osteomyelitis is usually treated with cortical unroofing and intramedullary reaming. An infected intramedullary rod in a stable bone is an example of stage 1 osteomyelitis. In this case, the infected intramedullary rod must be removed, followed by intramedullary reaming.

In stage 2, or superficial osteomyelitis, the bone infection results from an adjacent soft tissue infection and represents a true contiguous-focus lesion. An exposed, infected necrotic outer surface of the bone lies at the base of a soft tissue wound. Stage 2 osteomyelitis requires superficial débridement and coverage with a local or microvascular flap.

Stage 3, or localized osteomyelitis, is characterized by full-thickness cortical sequestration that can be surgically removed without compromising stability of the infected bone. Stage 3 osteomyelitis requires débridement, saucerization, and possibly a bone graft to improve stability.

Stage 4, or diffuse osteomyelitis, represents a through-and-through section of the bone and usually requires segmental resection of the bone. The stage 4 patient may also have bone infection on both sides of a nonunion or a major joint. Diffuse osteomyelitis includes those infections with a loss of bony stability either before or after débridement surgery. Stage 4 osteomyelitis requires débridement, dead space management, and stabilization.

In the Cierny-Mader system, patients are classified as A, B, or C hosts. A hosts are those patients with normal physiological metabolic, and immunological capabilities. B hosts are patients who are locally compromised, systematically compromised, or both. It is important to improve the factors and diseases that made the patient a B host. The goal of host modification is to make a B host as much like an A host as possible. The final category, or C host, represents the patient for whom the treatment of the bone infection is worse than the osteomyelitis itself.

This staging system has been used to determine optimal treatment protocols and prognoses and to compare therapy results between institutions. The stages are dynamic and may be altered by the outcome of therapy or a change in the host's status.

A. Systemic Immunocompromised States

1. Malnutrition

The immune system is governed by a large number of influences. Malnutrition frequently contributes to the immunocompromise seen in hospitalized patients. Clinical and epidemiological studies have established that malnutrition is a risk factor for infection (6). Globally, protein-energy malnutrition is the most frequent

cause of immunodeficiency. Studies document major impairment of the T-cell and complement systems in severe protein energy malnutrition, and less profound, but probably significant, effects on B-cells and immunoglobulins, particularly secretory immunoglobulin A (*S*IgA). Although mild to moderate malnutrition also alters the T-cell system and may predispose a patient to infection, there is less evidence to suggest that complement is similarly affected. Many other factors alter immune responses, including vitamins, calories, and trace minerals.

Nutritional status has a profound impact on the immune function and the immune system may be modulated by the use of specific modes of nutritional support. Nutritional support corrects malnutrition and can reverse the associated immunocompromise. In selected malnourished or severely injured patients, early nutritional support has been shown to improve outcome and decrease the incidence of infectious complications after major surgery or trauma (7). Developing an understanding of nutritional needs and the role of nutrition in immune function is essential to prevention and treatment of nutrition-related immunocompromise. Evidence from 1998 suggests that the route (enteral versus parenteral) of providing nutritional support can affect immune competence (8). Intervention trials may show a role of key nutrients in not only maintaining normal immune competence, but also modulating immunological outcomes in critically ill patients.

2. End–stage renal disease

Infection remains a leading cause of death in patients with chronic renal failure. Approximately one-fifth of patients with end-stage renal disease die of bacterial infection and septicemia (9). Multiple immune defects have been described in this disease. Immunodeficiency occurs because of disruption of mucocutaneous barriers and granulocyte/phagocyte dysfunction and defects in cellular immunity and humoral immunity. The cutaneous barrier is compromised by uremic pruritus with excoriation, epidermal and sweat gland atrophy, dryness, and vesicular eruptions, all of which increase risk for cellulitis. Granulocyte dysfunction is manifested by reduced mobility, chemotaxis, adherence, phagocytosis, and intracellular bactericidal activity.

Impairment of cellular immunity is probably the most important cause of compromise in renal failure. The primary problem is the host's oversuppression of lymphocytes in the face of normal numbers of cells. Depressed activation and proliferation of T lymphocytes occur, causing lymphopenia and a reduced absolute number of peripheral blood lymphocytes. These lymphocyte abnormalities appear early in the course of renal failure and cannot be reversed by hemodialysis.

In addition to the impairment of cellular immunity, defects in humoral immunity are present. Uremic patients can synthesize normal amounts of Ig despite reduced B lymphocyte counts, but certain IgG subclass antibodies are

depressed, resulting in the poor protective effect of vaccines. Lymphocytes taken from uremic patients appear to function well in nonuremic serum; conversely, lymphocytes from normal serum function poorly in uremic serum.

Staphyloccus aureus infections are most common because 60% of patients on hemodialysis are chronic carriers (10). Furthermore, the carriage rate of *S. aureus* increases as time on dialysis increases. Fungal infections caused by *Candida* species are common. In addition, infections caused by *Cryptococcus*, *Histoplasma*, *Coccidioides*, and *Mycobacteria* species and *Nocardia* species occur with increased frequency.

Osteomyelitis can occur as a complication of hemodialysis (11,12). Since *S. aureus* and *S. epidermidis* are common blood isolates in hemodialysis patients in whom indwelling cannulae allow portals for bacterial entry, bone infections are probably hematogenous in origin. The ribs and the thoracic vertebral column are the most common sites of involvement. The diagnosis of osteomyelitis is usually made 12 to 72 months after the initiation of hemodialysis. Surgical intervention and antibiotic treatment can result in an arrest of the infection. The infection may not be recognized, as the clinical signs and radiograph findings may mimic those of renal osteodystrophy.

3. Diabetes mellitus

Diabetic patients have increased susceptibility to infection when compared with euglycemic patients because of defects in immune function, vascular insufficiency related to microangiopathy and macroangiopathy, and wound neglect that is due to peripheral sensory neuropathy.

Neutrophil function is impaired in diabetic patients through decreased adherence to bacteria, impaired chemotaxis and phagocytosis, and diminished intracellular killing of organisms (13). Furthermore, opsonization is deficient because glucose binds to complement C3 and reduces its activity. In addition, complement C4 level is reduced in 25% of diabetic patients. These defects predispose diabetic patients to purulent bacterial infections with gram-positive and gram-negative organisms (14,15). These defects are exacerbated by periods of poor glycemic control, and conversely, phagocytosis is improved with euglycemia. Monocytes exhibit impaired phagocytosis during periods of hyperglycemia as well.

Lower extremity ulcers are a serious complication of diabetes mellitus. More than 4% of the population, 16 million people in the United States, have diabetes; among these, 15% experience a foot ulcer at some point of their lifetime. One-third to two-thirds of these patients have osteomyelitis in their lifetime. Because of the presence of ischemia and diminished sensation in the feet of many diabetic patients, soft tissue ulcerations commonly form beneath weight-bearing bony prominences. Minor trauma in the presence of neuropathy and

impaired vasculature and healing can cause soft-tissue infections in the feet that almost always precede osteomyelitis. Highly characteristic locations for ulcerations are in the plantar soft tissues beneath the metatarsal heads, the phalanges, and the calcaneus. Infection spreads first to the periosteum and then to the cortex and may finally disrupt medullary bone. Not surprisingly, approximately 95% of diabetic patients with osteomyelitis in the foot have associated ulcers.

Local findings consist of swelling, erythema, and sometimes pain. Indolent ulcers and frank cellulitis are seen in more than 50% of cases. Erosive lesions in radiographic film are typical and air may be present in the soft tissues. The bone scan is of very limited value because of generalized poor perfusion in the area and the frequency of concurrent soft-tissue infection. Diabetic foot osteomyelitis is usually polymicrobic (16). The most common organisms responsible for osteomyelitis in diabetic patients are staphylococci, streptococci, and the Enterobacteriaceae. Anaerobes (e.g., *Peptostreptococcus* spp.) are also often isolated. Surgical treatment is often required and severe cases may lead to amputation.

4. Chronic hypoxia

Experimental findings show that hypoxic hypoxia brings about consistent changes in the immunobiological status of patients that are directly correlated with the level of hypoxia (17). Secondary immunodeficiency (SID) was diagnosed in 80.7% of 57 cases of chronic obstructive pulmonary disease (COPD) patients and was associated with reduced quantitative and functional parameters of T lymphocytes and imbalance in subpopulations of regulatory T lymphocytes (18). Immune globulin subclass level deficiencies were also found in COPD patients taking long-term, low-dose corticosteroid therapy.

Patients with severe COPD who are treated with long-term systemic corticosteroids are at a higher risk for the development of invasive aspergillosis as a result of altered mononuclear phagocytic function and abnormalities in the effective adherence, chemotaxis, and recruitment of phagocytic cells. Vertebral *Aspergillus* spp. osteomyelitis in patients with COPD who were treated with systemic corticosteroids has been reported (19).

5. Malignancy

Patients with cancer often have multiple immune defects that predispose them to infection (20,21). These defects include neutropenia, impairment in T-cell and B-cell function, and splenic dysfunction or splenectomy. Defects in physical barriers (skin and mucous membrane) and use of long-term intravascular catheters also predispose these patients to infection.

a.) *Neutropenia.* *Neutropenia* is defined as a neutrophil count, including band forms, of less than $1000/mm^3$. It usually develops as a result of cytotoxic chemotherapy or the disease process itself, especially in hematological malig-

nancies. Neutropenia predisposes cancer patients to the development of certain bacterial and fungal infections.

b.) *Impairment of Cell-Mediated Immunity in the Cancer Patient.* T-cell defects resulting in impaired cell-mediated immunity commonly develop in cancer patients as a result of cancer chemotherapy or corticosteroid treatment. The cancer itself produces impairment in cellular immunity in patients with Hodgkin's disease, non-Hodgkin's lymphoma, and hairy cell leukemia. The patient becomes susceptible to infection with intracellular pathogens, including bacteria, fungi, parasites, and viruses. Impaired cell-mediated immunity in cancer patients may result in reactivation of *Histoplasma capsulatum* and *Coccidioides immitis* with resultant disseminated disease. Infections with *Candida* species are also common in cancer patients with defective cell-mediated immunity, but disseminated disease is less likely than in patients with neutropenia. In cancer patients on high-dose corticosteroids aspergillosis may also develop, but it is much less likely than in organ transplantation recipients or patients with prolonged neutropenia.

c.) *Humoral Immune* (*B-Cell*) *Defects in the Cancer Patient.* Hypogammaglobulinemia is common in patients with chronic lymphocytic leukemia and myeloma. Low immune globulin levels predispose these patients to infections with encapsulated bacteria, especially *S. pneumoniae*, *H. influenzae*, and *N. meningitidis*, and occasionally other streptococci. Regular infusions of human polyclonal intravenous immune globulin may decrease the incidence of infection in these patients but may not result in improvement in quality or duration of life and is probably not cost-effective.

6. Extremes of age (geriatric patients)

Aging is associated with a decline in immune response, particularly of cytokine production (22,23) and T-cell-mediated function (24). These factors are well documented and contribute to an increased incidence of infectious and neoplastic diseases in this patient population.

Osteomyelitis secondary to contiguous focus of infection can occur in elderly adults without vascular insufficiency (secondary to pressure ulcers) or with vascular insufficiency. Most cases of osteomyelitis secondary to a contiguous focus of infection are seen in patients above the age of 50, presumably as a result of precipitating factors such as diabetes mellitus, peripheral vascular disease, and atherosclerosis. The long bones of the lower extremities are frequently involved since these are often the sites of fracture and open reduction. Pressure sores (decubitus ulcers) may overlie and produce a focus of osteomyelitis. The diagnosis of osteomyelitis must be strongly considered if a pressure sore does not respond to local therapy. The skull and mandible bones are also frequent

sites of osteomyelitis after neurosurgery, oral surgery, or dental infection. Sternal osteomyelitis is an uncommon, but highly morbid complication of median sternotomy incision for open heart surgery.

Although classically described as a disease of children, hematogenous osteomyelitis is being reported with increased frequency in the older age group (25–28). The common types of hematogenous osteomyelitis that are seen in the elderly include vertebral and long bone osteomyelitis. Positive blood culture findings occur in approximately 40% of cases of vertebral osteomyelitis. Genitourinary tract infections that seed the bloodstream are the most common precipitators of vertebral osteomyelitis. Respiratory infections and bacteremia from indwelling venous or arterial catheters also predispose to vertebral osteomyelitis.

7. Immune disease (collagen vascular disease)

Phagocytosis defects, dysfunction of the macrophage-monocyte, complement deficiencies, hypergammaglobulinemia, and T-cell lymphopenia ($CD4^+$ cells) are commonly seen in collagen vascular diseases such as systemic lupus erythematosus (SLE) (29,30). Multiple studies have pinpointed use of corticosteroids, usually with prednisone doses greater than 20 mg daily, as a predictor of infections.

Bacterial skin infections usually are manifested as cellulitis or skin abscesses. Unusual organisms such as *Escherichia coli*, *S. pyogenes*, and *Candida* spp. can be the cause of cellulitis, but *S. aureus* and hemolytic streptococcus are the most common. Gangrene, osteomyelitis, abscess, infected vasculitic ulcers, or infected wounds are frequently seen. Opportunistic infections such as those by coagulase negative *Staphylococus* spp., *Candida* spp., and other fungi can occur as skin infections. Septic arthritis, usually occurring in the knee, has been reported from multiple pathogens in SLE, although *S. aureus* is the most common cause. Unusual joints, such as the manubriosternal, have been reported to have septic arthritis. Multiple investigators have reported cases caused by *N. gonococcus* and *N. meningitidis*. Patients with systemic lupus erythematosus are at increased risk of *Salmonella* spp. infection because of insufficiency of the reticuloendothelial system caused by either immunosuppressive therapy or inadequate opsonization. Septic arthritis and osteomyelitis caused by *Salmonella* spp. have been reported (31).

8. Immunosuppression (bone marrow and stem cell transplantation)

Bone marrow and stem cell transplantation is increasingly common in the treatment of a variety of solid and hematological malignancies, as well as metabolic and genetic disorders. Infection and graft-versus-host disease (GVHD) are common and remain the major sources of morbidity and mortality

in bone marrow transplantation patients. Infections occur as a direct result of the predictable suppression of host defenses (32,33). The severity and type of infection depend on the type of transplantation, the degree of histocompatibility mismatch, GVHD, therapy used, and preexisting viral and fungal infections.

In bone marrow transplantation, native marrow is purposely destroyed by chemotherapy; reconstitution of the marrow and restoration of immunocompetence take months to years and the patient's vulnerability to infection is enormous at the outset and remains compromised in minor ways even years later. Both humoral and cellular immunity defects recover slowly and some persist for several years.

Osteomyelitis in the bone marrow transplantation patient can be caused by bacterial, invasive fungus, and atypical mycobacterium (34,35). In rare instances, osteomyelitis can follow marrow aspiration from the sternum or marrow harvest from the iliac crest.

9. Immunosuppression (solid organ transplantation and immunesuppresant)

The successful rehabilitation of patients with end-stage renal, hepatic, and cardiac failure through organ transplantation is one of the advancements of biomedical science. Lifelong immunosuppression is usually needed for recipients of solid organ transplantation. The mainstay of transplantation immunosuppression is cyclosporine, which suppresses interleukin-2 production and results in potent immunosuppression of T helper-inducer cells but does not affect the suppressor T-cell subset. The T cells enhance antibody recognition and production by B cells, so that cyclosporine inhibits both cellular and humoral immunity (36–38).

Steroids shut down the acute phase of the immune response by limiting leukocyte kinetics. Decreased lymphokine production and inhibited lymphocyte aggregation at the site of immune insult are both found (39,40). Steroids also limit granulocyte and macrophage function. Short-term or pulse therapy generates minimal risk, and generally steroid therapy must be long term to allow infectious complications to arise. Larger doses also increase risk. The intensity and duration of immunosuppressive therapy affect the frequency of infection. Transplantation patients typically receive maximal dosage of these agents in the first 6 months after transplantation, corresponding with a peak in the risk of opportunistic infection. If chronic rejection develops, long-term immunosuppressive therapy becomes necessary, again increasing risk.

Musculoskeletal infection is not unusual in transplantation patients. Most of the pathogens associated specifically with impaired cellular immunity are intracellular. Osteomyelitis caused by invasive fungus and atypical mycobacterium is frequently seen in steroid-dependent or solid organ transplantation patients (41,42).

Chronic granulomatous disease is a syndrome characterized by abnormal neutrophil oxidative metabolism. Affected persons experience recurrent severe infection of various organs including bone. Noncaseating granulomas are the most common histopathological feature of this disease. Even if *S. aureus* is one of the most common pathogens in these patients, uncommon organisms causative of bone infection, such as *Aspergillus* spp. and *Nocardia* spp. are frequently reported.

10. Asplenic patients, functional asplenia, and sickle cell disease

Patients become asplenic through surgical removal of the spleen (most commonly because of trauma) or functional loss of splenic activity (sickle cell disease). Splenectomy or functional asplenia predisposes a patient to overwhelming pneumococcal infection and fulminant infection with other encapsulated organisms such as *H. influenzae*, *N. meningitidis*, and *Capnocytophaga canimorsus* after dog bites. Infants and children are most susceptible to postsplenectomy infections. Adult patients who have splenectomy, especially as part of treatment for underlying malignancy, are less susceptible to infection than children but still carry a higher risk than the normal population. Patients with sickle cell disease are usually functionally asplenic by early childhood. In addition, opsonic function in these patients is often depressed. Other hemoglobinopathies carry similar risks. Aplastic anemia also occurs in sickle cell patients.

One large series reviewing sickle cell disease and osteomyelitis reported that 20 of 70 patients with complete hemoglobin defects had at least one hospitalization for the treatment of osteomyelitis during a 10-year period (43). In essentially all cases, the infecting organisms were gram-negative rods. *Salmonella* spp. accounted for approximately 80% of the gram-negative organisms. In the same hospital series, 1 of 117 patients with normal hemoglobin levels who had osteomyelitis exhibited a *Salmonella* spp. infection of the bone. In a second series of osteomyelitis patients with sickle cell disease, *S. aureus* was the most common pathogen, followed by *Salmonella* spp. and *Proteus mirabilis* (44).

Although osteomyelitis in sickle cell anemia may occur in any bone, it occurs most frequently in the medullary cavity of long bones. The differentiation of bone infection from bone infarction in sickle cell patients is a challenge. Fever, a toxic appearance, and an elevated erythrocyte sedimentation rate (ESR) are all more commonly associated with osteomyelitis than with bone infarction. Plain radiographs are not helpful in distinguishing between the two entities. Skeletal scintigraphy may help make the diagnosis. The best method appears to be ^{99}Tc methylene-diphosphonate (MDP), followed by gallium or indium scanning. Although both infection and infarction may show increased uptake on the technetium scan, the gallium or indium scan should be “hot” with osteomyelitis

but "cold" with sickle cell infarction. Another approach is to note the response to conservative therapy—bone infarctions usually improve within 24 to 48 hours, whereas bone infection worsens. Sickle cell disease patients may have multiple sites of bone infection. Since the presenting symptoms are often insidious and mimic those of marrow crisis, early cultures of blood and stool offer clues to the correct diagnosis. Presumptive antibiotic therapy in patients suspected of having osteomyelitis should include antibiotics effective against *Salmonella* spp.

People known to be at risk should receive a pneumococcal vaccine. Some authorities recommend immunization against *H. influenzae* type B and meningococci as well. Antimicrobial prophylaxis (twice daily penicillin V or amoxicillin) is generally limited to children less than 2 years of age.

11. Human immunodeficiency virus type 1

Human immunodeficiency virus type 1 (HIV-1) is a human retrovirus that infects lymphocytes and other cells bearing the CD4 cell marker. Infection leads to lymphopenia and CD4 cell depletion, impaired cell-mediated immunity, and polyclonal B-cell activation with impaired B-cell response to new antigens. Over time, this immune dysfunction gives rise to AIDS, which is characterized by opportunistic infections and malignancies. The time from onset of HIV infection to development of AIDS varies from months to years, with a median incubation period of 10 years. The virus is transmitted sexually or parenterally. Therapy for HIV infection and AIDS includes antiretroviral therapy, prophylaxis for and treatment of infections, and treatment of neoplasia.

Patients with AIDS have profound cell-mediated immunity defects. In patients who have HIV, a variety of common and opportunistic organisms may cause infections of bones, joints, muscles, subcutaneous tissues, and skin. Septic arthritis is most common in patients with HIV infection. Isolated septic arthritis, septic arthritis with osteomyelitis, and septic bursitis have been reported (45–47). Thirty percent of new patients admitted with acute arthritis in Rwanda had septic arthritis and 82% of them were HIV-positive. The clinical picture seen is predominantly monoarticular; the hip joint is most commonly affected. Involvement of the sternoclavicular joint is common, especially in cases when the patient is an intravenous drug abuser. *Staphylococcus aureus* and *Pseudomonas* spp. are the most frequently isolated agents; *Gonococcus* spp., *Salmonella* spp., and tuberculous arthritis were also found and several uncommon opportunistic organisms have been isolated as well. Pneumococcal septic arthritis, *Haemophilus influenzae*, *Salmonella* spp., tuberculous arthritis and spondylodiscitis, and most cases of atypical mycobacteria are seen with CD4 counts less than 100 mm. Frequently, there are multiple sites involved and concomitant skin infection is common. Opportunistic fungal infections with articular involvement in patients with AIDS have been reported. Chronic syphilitic polyarthritis that mimicks

systemic lupus erythematosus–rheumatoid arthritis, improves with penicillin, and is manifested as the initial presentation of HIV infection also has been reported (48).

Osteomyelitis in the HIV patient is usually a more serious infection, which also affects young individuals with lower CD4 counts (49,50). *Staphylococcus aureus* is the most commonly isolated agent. Osteomyelitis due to *Mycobacterium tuberculosis* is also frequently reported (51) and may reflect the high prevalence of tuberculosis in the HIV population in the United States.

A thorough clinical examination and aggressive diagnostic measures such as bone biopsy are usually required to establish the diagnosis and to initiate the appropriate therapeutic regimen in patients with osteomyelitis. One unusual, but particularly characteristic, form of osteomyelitis in HIV-positive patients is bacillary angiomatosis (52), an infectious disease caused by a gram-negative rickettsia-like organism that frequently leads to osteolytic bone lesions.

12. Intravenous drug use

Immune system dysfunction in intravenous drug abuse (IVDA) patients probably plays a minor role in infection compared with the repeated parental introduction of contaminated material. Studies have shown that the major functional defect is in cell-mediated immunity (53,54). Despite this finding, the incidence of infection typical of T-cell deficiency is rare when AIDS is factored out. Not much has been done to define the degree and significance of neutrophil-monocyte dysfunction in these patients.

Infection is the most common cause of death in hospitalized intravenous drug abuse patients. Skin and soft-tissue infection, especially abscesses, are common causes of infection in this subpopulation (55). Osteomyelitis is also a complication of intravenous drug addiction (56,57). Clinical symptoms and signs of infection may be subtle and include localized pain. Fever is often absent. The infection is commonly found in the vertebrae, pubis, and clavicles but may occur in any bone. *P. aeruginasa*, *S. aureus*, *S. epidermidis*, gram-negative rods, and *Candida* spp. are the most commonly isolated pathogens. The risks of AIDS to users who expose themselves to another's blood or body fluids are well known. Occult bacteremia and major illness also occur in these patients, with a reported frequency of 11% in otherwise healthy patients. Blood cultures should be obtained on these patients. If blood cultures are positive along with radiographic evidence of osteomyelitis, then bone cultures are mandatory to make a correct bacteriological diagnosis.

13. Alcoholism

Alcohol consumption predisposes to infection through impaired development and direct suppression of the immune system, alterations in blood flow, depression of mental status, and delay in seeking medical care. Alcoholic cirrhosis has been

associated with a variety of immune defects (58–60). Impaired opsonization and impaired neurophil chemotaxis have been found. Macrophage dysfunction also has been described. Neutropenia has been described in 4% to 8% of hospitalized alcoholics and corrects after a few days of abstinence (61–63). Both acute and chronic ethanol ingestion inhibit antibody response to new antigens. Total serum globulin concentration is elevated as a consequence of increased production by lymphocytes, but cutaneous delayed hypersensitivity, lymphocyte sensitization to new antigens, and natural killer (NK) cell activity are all depressed. These effects are often compounded by other factors associated with alcoholism, such as malnutrition, impaired drug liver metabolism, and cigarette smoking, and increase the risk of injury.

Osteomyelitis in these alcoholic patients commonly involves the mandible and long bones (64–66). Traumatic and chronic osteomyelitis is often seen because of the increased risk of injury. Given all these factors, it is not surprising that osteomyelitis in alcoholics has a poorer prognosis than in nondrinkers.

14. Tobacco abuse

Despite the known health risks associated with cigarettes, millions of Americans continue to smoke. Among the 3800 chemicals that have been identified in the tobacco smoke there are many biologically active compounds. Smoking is associated with cancers occurring in the oral cavity, esophagus, larynx, lung, and distant organs such as the pancreas, bladder, and kidney. Cigarette smoking is a risk factor for the development of atherosclerosis acting through activation of leukocytes and endothelial cell damage. Nicotine is a vasoconstrictor that reduces nutritional blood flow to the skin, resulting in tissue ischemia. The association between cigarette smoking and nonunion (67–69) and delayed wound healing (70) is well recognized in clinical practice, although extensive controlled studies have yet to be performed.

The immunosuppressive effects associated with prolonged exposure to chemical substances are often accompanied by an increased susceptibility to challenge with infectious agents and certain forms of neoplasia. The genotoxic effects of cigarette smoking on lymphocytes and various quantitative and functional changes in lymphocytes subpopulations have been frequently observed (71). Tobacco smoking can affect the human immune system and cause a decrease in serum immunoglobulin (IgA and IgG) concentrations together with reduction of the absolute number of $CD16^{+}$ lymphocytes. Moreover, it was found that in men with a long-term smoking habit, the level of serum lysozyme was lowered (72). The occurrence of the alterations described, especially in long-term cigarette smokers, may help explain the disturbances that depend on impaired cell-mediated immunity encountered in smokers.

B. Local Immunocompromised States

1. Chronic lymphedema

Lymphedema arises when an intrinsic fault develops within the lymph-conducting pathways (primary lymphedema) or as a consequence of surgery (secondary lymphedema). Primary lymphedema may occur at any phase of life, but it most commonly appears at puberty. Secondary lymphedema is encountered more often. The most prevalent worldwide cause of lymphedema is filariasis, which is particularly common in Southeast Asia. In the United States, postsurgical lymphedema of the extremity prevails.

Lymphedema is often diagnosed by its characteristic clinical presentation. In some cases, ancillary tests might be necessary to establish the diagnosis, particularly in the early stages of the disease and in edemas of mixed cause. Available modalities include isotopic lymphoscintigraphy, indirect and direct lymphography, magnetic resonance imaging, computed tomography, and ultrasonography. Complications of chronic limb lymphedema include recurrent cellulitis and lymphangiosarcoma. Most patients are treated conservatively, by means of various forms of compression therapy, including complex physical therapy, pneumatic pumps, and compressive garments. Volume reducing surgery is performed rarely. Lymphatic microsurgery is currently experimental.

2. Venous stasis

Venous insufficiency is a multifactorial abnormality that has an important impact on the quality of life of the patient. The primary factor of venous disease is an abnormal wall distensibility, which seems to be correlated with genetic factors. Facilitating factors include hormonal impregnation and prolonged hydrostatic load that result in valvular incompetence, which, combined with the augmented hydrostatic load, lead to varicosis and venous stasis. Ensuing tissue hypoxia and local edema favor inflammation and infection, which ultimately favor the occurrence of ulcers.

Manifestations of chronic venous insufficiency include mild to severe swelling, aching to frank leg pain, leg heaviness, dilated superficial veins and/or dilated tributaries of the saphenous vein system, skin changes, and ultimately ulceration. The need for diagnostic testing may be minimal if the ulcer typifies the usual venous ulcer in persons recognized to be at high risk.

Management includes nonsurgical and surgical procedures, wound débridement, and electrical stimulation. The mainstay of treatment for venous ulcers is compression therapy, exercise, and leg elevation at rest. Compression to the lower extremities is used to increase healing of venous stasis ulcers by improving the blood supply and reducing edema and distension. Compression wraps are

available in elastic or nonelastic materials and in single to multilayer systems requiring varying types of application and exerting different levels of compression.

3. Major vessel compromise

Osteomyelitis in the diabetic foot is a difficult problem with multiple causes. Ischemia is often a contributing factor in the diabetic foot ulcer; thus, determination of the vascular status of the tissue at the infection site is crucial. Although several methods can be used to determine the vascular status, measurement of cutaneous oxygen tensions and pulse pressure are the most common techniques. Cutaneous oxygen tension is obtained by using a modified Clark electrode applied to the skin surface (73). Cutaneous oxygen tensions provide guidelines for determining the location of adequately perfused tissue (74,75). The values are also helpful in predicting the benefit of local débridement surgery and in selecting surgical margins where healing can be expected to occur (76).

Management decisions are based on risk factors and disease history. Comprehensive management includes exercise, discontinuation of smoking, and optimal control of diabetes. The management of hyperlipidemia and hypertension and appropriate application of anticoagulant/antiplatelet drugs are important. Methods of surgical management include bypass with autogenous or synthetic material in addition to reconstructive surgery with patch angioplasty or extra-anatomic bypass, amputation, percutaneous transluminal angioplasty/stents, thrombolytic infusion, atherectomy, intraluminal ultranography, and angioscopy.

4. Arteritis

One of the common underlining conditions of nonhealing leg ulcer is vasculitis. Two groups of vasculitic disorders that share varying degrees of vascular inflammation and necrosis are arteritis (lupus, erythematosus, periarteritis nodosa, dermatomyositis). Because there is an increased inflammatory response to trauma, particularly of the skin, in patients with vasculitis, an alteration in wound healing in the patient with arteritis is expected. Leg ulcers associated with vasculitis are due to inadequate tissue oxygenation at the local level, are typically chronic, are slow to heal, and commonly recur. Studies suggest that revascularization and vein surgery improve the healing of leg ulcers in patients with collagen vascular disease (77). Hyperbaric oxygen therapy has been demonstrated to be beneficial in several series (78,79).

5. Extensive scarring

Abnormal dermal scarring, which affects a large number of people, is aesthetically disfiguring and can be functionally disabling. Hypertrophic scars and keloids are often the sequelae of deep injury to the skin. These lesions are characterized by excessive collagen, in the form of discrete nodules, and an excess of microvessels, most of which are partially or totally occluded as a result of an excess of endothelial cells. The occlusion contributes to a measurable hypoxia. Hypertrophic scars and keloids contain elevated levels of fibronectin, immunoglobulins, other plasma proteins, histamine, type III collagen, and chondroitin-4-sulfate. PO_2 levels are lower than in normal skin and PCO_2 levels are higher. Granulation tissue from deep injury contains predisposed patterns for nodule formation, excessive numbers of fibroblasts, and high levels of fibronectin and demonstrates excessive synthesis of fibroblast products and microvascular occlusion. The stimulator for excessive synthesis activity is postulated to be related to a state of hypoxia. It has been postulated that resolution of the lesions is affected when microvascular patency is restored and PO_2 levels return to normal. Degradation of excess collagen takes place when collagenase and/or lysosomal hydrolases are unmasked, activated, or released. The cause of the hypertrophic scar and keloid (and thus their resolution) is believed to be directly related to the quality of the microvessels and the leakage and deposition of blood products into the wound and lesion (80,81).

Existing medical and surgical strategies to prevent or to treat scars are frequently disappointing and more effective therapies are needed. Corticosteroids are still the first-line therapeutics. Tamoxifen, which has been used extensively in the treatment of breast cancer over the last 20 years, was shown in 2002 to inhibit the proliferation of fibroblasts cultured from keloid biopsies (118).

6. Radiation fibrosis

Radiation fibrosis is a frequent sequel of therapeutic or accidental radiation overexposure in normal human tissues. One of the main fundamental problems yet unsolved in fibrotic tissues is the origin of the chronic activation of myofibroblasts within these tissues. It has been postulated that this chronic activation results from a continuous production of activating factors. In this context, fibrosis could be defined as a wound where continuous signals for tissue repair are emitted. Cytokines and growth factors probably play a central role in this process; among them, transforming growth factor-1 (TGF-1) is considered a master switch for the fibrotic program (82,83). It has been postulated that deregulation of this TGF-signaling pathway may occur in tissue fibrosis. Both overactivity of activating proteins and downregulation of inhibitory proteins may be linked to the chronic TGF overexpression in fibrosis.

Understanding that TGF-1 is a key factor in fibrogenesis offered a new possible target for therapeutic agents with potential antifibrotic effects. Until very recently, fibrotic tissue was considered dead, irreversible tissue that could not be cured. Drugs of several categories have been tried in the management of fibroproliferative disorders, including anti-inflammatory agents (steroids, colchicine, D-penicillamine), drugs acting on blood flow (heparin, pentoxifylline), and interferons. Corticosteroids are still the first-line therapeutics, even though they essentially reduce symptoms associated with inflammatory reactions. Several drugs were effective in preventing the occurrence of fibrosis in experimental models, whereas few were able to reduce an established fibrotic tissue. Among the latter, several, including interferons, produced significant clinical improvement in various fibrotic disorders but were associated with toxicity and side effects.

In 2001, new data challenged the postulate of the irreversibility of established radiation fibrosis. Liposomal Cu/Zn superoxide dismutase (SOD) was shown to be the first agent effective in reducing long-standing radiation fibrosis in patients treated by radiotherapy (84).

7. Small vessel disease

During the past few years, rapid advancement has been made in our understanding of the mechanisms and molecules involved in the pathogenesis of diabetic microvasculopathy. This is particularly true with regard to diabetic microvasculopathy and the role of the angiogenesis- and vasopermeability-inducing molecule vascular endothelial growth factor (VEGF). VEGF appears to play a central role in mediating diabetic vasculopathy in many organs (85). Improved understanding of the molecular mechanisms underlying these processes has permitted development of novel therapeutic interventions, several of which are now in human clinical trials.

8. Neuropathy

Diabetic peripheral neuropathy is the most frequent neuropathy in Western countries. The pathophysiological characteristics of diabetic neuropathy remain to be fully understood. The prevalence of diabetic neuropathy varies from 10% within 1 year of diagnosis of diabetes to 50% in patients with diabetes for more than 25 years. Neuropathy initiates the pathophysiological pathway to leg ulceration and amputation and by itself it is sufficient cause for painful paresthesia, sensory ataxia, and Charcot deformity. The symmetrical, distally pronounced, and predominantly sensory neuropathy is far more frequent than the symmetrical neuropathy with predominant motor weakness or the asymmetrical neuropathy. The painless neuropathy is manifested with impaired light touch sensation, position sense, and vibratory perception and diminished or absent

ankle deep tendon reflexes. The painful sensory diabetic neuropathy primarily affects small nerve fibers and accounts for decreased temperature perception and paresthesias.

Clinical trial evidence for the efficacy of screening strategies demonstrated reduced outcomes of amputation and ulceration. Consequently, screening and early identification of the neuropathic process offer a crucial opportunity for the patient with diabetes actively to alter the course of suboptimal glycemic control and to implement improved foot care before the onset of significant morbidity. Currently, four standard simple screening maneuvers (i.e., 10-g Semmes-Weinstein monofilament examination [SWME], superficial pain, vibration testing by the on-off method, and vibration testing by the timed method) are appropriate for the detection of neuropathy in diabetic patients.

The most important therapy is to attempt optimal blood glucose control, to reduce body weight, and hyperlipidemia, as well as symptomatic pain treatment and aggressive foot care.

V. MEDICAL APPROACH TO THE IMMUNOCOMPROMISED PATIENT

A. History and Physical Examination

The symptoms and signs of musculoskeletal infection that can be present in any given compromised host span a wide spectrum. Table 5 outlines the historical information that should be collected in immunocompromised hosts with soft tissue and bone infection. The history should include a review of the immunocompromised state: duration of the immunocompromise; past infections and current and previous therapies, especially chemotherapy; and use of immunosuppressive drugs and antibiotics. A history of long-term, broad-spectrum antibiotic use also predisposes to fungal infection. A history of transfusion adds related diseases (hepatitis B and C) to the differential.

Table 5 History of the Immunocompromised State

Underlying immune deficiency, autoimmune disease, functional immune deficiency
Dose, duration, and temporal sequence of immunosuppressive therapy
Metabolic conditions (uremia, malnutrition, diabetes, alcoholism, cirrhosis)
Current/past infections (HIV, CMV, EBV, hepatitis B and C)[a]
Current/past therapies (including antibiotics and immunosuppressant)
Transfusion history (hepatitis)
Fever (duration and degree)
Local symptom (pain, swelling, draining)

[a] HIV, human immunodeficiency virus; CMV, cytomegalovirus; EBV, Epstein-Barr virus.

The physical examination should be complete because the findings present for a given infection can be subtle. Examination of the skin can reveal local tenderness, warmth, and erythema. Invasive cutaneous fungal lesions in transplantation patients may have a distinct presentation. Tenderness is usually absent in diabetic peripheral neuropathy, except in the acute phase. Examination should also attend to sites of barrier compromise (e.g., Foley catheter, indwelling line, wounds, and prosthetic devises), which may lead to repeated episodes of bacteremia or fungemia that can cause hematogenous osteomyelitis. On physical examination, fever is uncommon, and foot ulceration need not expose the bone for osteomyelitis to be present.

B. Diagnostic Tests

The orthopedic clinic work-up of the patient with fever and immunosuppression requires a high level of suspicion and involves a minimal battery of routine tests, augmented by the clinical findings. Any site of potential infection suggested by the history and physical examination should be imaged or cultured as possible. In the absence of localizing symptoms or signs, a minimal work-up includes urinalysis, chest radiograph, radiograph of the affected limb, and wound culture. Generally, basic blood testing is also ordered. A complete blood count (CBC) is necessary to determine the degree of granulocytopenia, if any, present. Impaired renal function is not uncommon in this patient group, and liver function tests can be useful as well. Blood cultures are obtained in febrile patients. Nasal cultures for detection of the patient's *S. aureus* carriage state are an important modality in the immunocompromised population. In the transplantation patient, cyclosporin or FK 506 levels are usually obtained. Specific immunological tests for patients with suspected congenital immune deficiency or vasculitis should be requested. Tuberculin (TB) skin test, fungal serological evaluation, RPR, and HIV tests may provide important clues to diagnosis.

C. Clinical Diagnosis

Clinical diagnosis of osteomyelitis is difficult. Cellulitis is pervasive, but nonspecific for osteomyelitis. Sinus tracts or exposed bone are the highly sensitive clinical markers for osteomyelitis. On laboratory analysis, the erythrocyte sedimentation rate may be normal and bacteremia is uncommon. To confuse the diagnosis, further neuropathic joint disease may mimic, or be superimposed upon, osteomyelitis.

D. Radiological Evaluation

The radiological evaluation of musculoskeletal infection is the subject of substantial controversy, but certain principles can be agreed upon. In all cases of suspected osteomyelitis, radiography should be the initial screening imaging examination of choice. When radiograph results are positive for osteomyelitis, as manifested by cortical erosion and periosteal new bone adjacent to an ulceration and cellulitis, further imaging studies often are not needed. However, radiographs generally do not yield positive results in these cases for 10 to 20 days after the onset of symptoms. The evaluation of diabetic pedal osteomyelitis generally has a disappointing sensitivity of 43% to 75% and specificity of 69% to 83%.

Computed tomography (CT) can be a useful method to detect early osseous erosions, as well as to document the presence of a sequestrum, foreign body, subcutaneous gas, or occult fracture. However, CT does not allow distinction among edema, suppuration, granulation tissue, and postoperative fibrosis.

The three-phase bone scan is an excellent way to exclude osteomyelitis in uncomplicated situations because of its low false-negative result rate. Unfortunately, it has a low specificity when applied to diabetic feet because of radiopharmaceutical accumulation in neuropathic bones. White blood cells (WBCs) may be labeled with radioactive tracers to increase the specificity of conventional bone scintigraphy, such as indium-111. Indium-111–WBC scans are time-consuming, have poor spatial resolution for distinguishing bone from soft tissue infection, and may yield false-positive findings in cases of fracture or neuropathic osteoarthropathy. The cost of this scan is higher than that of a magnetic resonance imaging (MRI) examination with intravenous contrast material.

MRI is highly sensitive in determining the presence and extent of inflammation. In particular, MRI can help delineate whether an infection is limited to bones, joints, or soft tissues, or whether several of these structures are affected (86,87). Such an evaluation allows planning of the degree or location of débridement or the level of amputation, so that the viability of adjacent tissues may be preserved. The diagnosis of osteomyelitis by MRI is made by detecting low T_1 and high T_2 (or Short Tau Inverson Recovery (STIR)) signal intensity in the bone marrow, with enhancement after intravenous injection of contrast material. Since these signal intensity abnormalities are also present in diabetic patients with neuropathic osteoarthropathy, additional imaging findings must be looked for in this population including extension of a sinus tract from the skin to bone, cortical interruption, rim-enhancing abscess within the marrow, and sequestrum formation. The diagnosis of osteomyelitis in the feet of diabetics has a reported sensitivity and specificity of 82% and 80%, respectively, compared with 89% and 94%, respectively, in nondiabetics.

E. Treatment of Osteomyelitis in the Immunocompromised Host

Successful treatment of osteomyelitis depends on multidisciplinary approach (88,89), combining both medical and surgical approaches. The major task in the treatment of osteomyelitis in the immunocompromised host involves the modification of the host status, which includes improving the patient's nutritional, medical (better diabetes control, blood pressure), and vascular (bypass) status and treating underlying diseases (Table 6).

1. Antimicrobial therapy

The ideal antibiotic for treating osteomyelitis in the immunocompromised patient should be one with low toxicity, chemical stability at the site of infection, and relatively high bone penetration.

Therapy usually starts with broad-spectrum antibiotic treatment of suspected osteomyelitis before culture results are available. The first priority is in adequately covering *Staphylococcus* species with a penicillinase-resistant penicillin such as nafcillin or newer β-lactam antibiotics. In patients with penicillin allergy, clindamycin is a good alternative. *Streptococcus* spp. are usually sensitive to antibiotics used to combat staphylococci. Quinolones, third- or fourth-generation cephalosporins, or imipenem-cilastatin is the usual choice for broad gram-negative coverage. Beyond initial broad-spectrum therapy, prospective treatment against anaerobic bacteria, *Pseudomonas* spp., fungal organisms, *Mycobacterium tuberculosis*, or atypical *Mycobacterium* spp. must be based on clinical suspicion and specific tests.

Table 6 Adjunctive Therapy for Osteomyelitis in Immunocompromised Patients

Therapy	Patient group
Nutrition supplementation	Malnutrition
	Alcohol abuse
	Diabetes mellitus
	Renal/hepatic failure
Advice on smoking cessation	Smoking
Pressure garments	Local compromise
Vascular bypass	Major vessel disease
Discontinuation or alteration of medications	Chemical immunosuppression
Tight blood glucose control	Poorly controlled diabetes
Hyperbaric oxygen	Cierny-Mader stage 3–4Bs1*
	Poor granulation bed
	Refractory osteomyelitis

*B-host, local and systemic compromise.

2. Surgical débridement

In most cases of osteomyelitis, antibiotic therapy alone does not cure the infection and surgical débridement of infected necrotic bone, adequate drainage, and obliteration of dead space are necessary. This is especially true when osteomyelitis is caused by direct inoculation into bone or spreads from a contiguous focus of infection. If the area of osteomyelitis is small, aspiration or resection of the bone abscess may be both a diagnostic and a therapeutic procedure.

Treatment of chronic osteomyelitis is a difficult surgical problem. The implantation of antibiotic-impregnated beads (90) into infected bone can sterilize and temporally close a dead space, so that bone grafts can be successfully used in chronic osteomyelitis. The most common antibiotic choices in beads are vancomycin, tobramycin, and gentamicin.

Adequate soft tissue coverage of the bone is necessary to arrest the osteomyelitis. The Ilizarov fixator is effective in the reconstruction of difficult bone deformities that result from osteomyelitis (91). Soft tissue coverage may be achieved by split-thickness grafts or local vascularized muscle flaps (92,93).

3. Immunomodulation

Immunomodulation, as the term implies, can be used to designate either suppression or augmentation of an immune response. Suppressing the function of the immune system may be important in cases of inflammation and in augmentation of the immune response when increased resistance to disease is present.

a.) *Granulocyte Colony-Stimulating Factor.* The human recombinant granulocyte colony-stimulating factor (G-CSF), also known as *filgrastim*, is a central mediator of the endogenous response to infection. This factor increases the release of neutrophils from the bone marrow and improves neutrophil function. G-CSF is approved for use in the prevention of infection-related complications in patients with nonmyeloid malignancies during antineoplastic therapy associated with high risk of severe neutropenia. Moreover, data from human studies show that G-CSF downregulates inflammation (94). The efficacy of G-CSF in the treatment of severe infections in nonneutropenic patients is under investigation. Favorable results have been reported in the treatment of pneumococcal meningitis and nosocomial pneumonia (95,96). Enhanced neutrophil functions in diabetic patients with foot infections in vitro (97) and in an animal model of osteomyelitis (98) also have been reported.

In 1997 and 2001 two randomized clinical studies assessed the safety and efficacy of G-CSF as adjunctive therapy for diabetic foot infection (99,100). The first study demonstrated an improved clinical outcome in the group treated with G-CSF. The second study showed that the administration of G-CSF for 3 weeks

for limb-threatening diabetic foot infection was associated with a lower rate of amputation. G-CSF has also been successfully used in the treatment of osteomyelitis in patients with phagocitic defects (101).

b.) *Nutrition and Vitamins.* The nutritional status of the patient plays an important role in resistance mechanisms against disease-causing organisms and may influence the outcome of osteomyelitis in immunocompromised patients.

Optimal function of the host defense system depends upon an adequate supply of antioxidative micronutrients. Intervention into the functionally deficient antioxidant micronutrient status can act as the appropriate preventative or therapeutic treatment with higher efficacy and fewer adverse effects than direct pharmacological modulation of single immune functions by specific mediators. Many antioxidants can be obtained directly from the diet (e.g., ascorbic acid, α-tocopherol, carotenoids, and polyphenolic flavonoids). The antioxidative vitamins, ascorbic acid, and the tocopherols, are important not only for limiting tissue damage but also for preventing overproduction of cytokine. Glutathione is a major endogenous antioxidant and is important for lymphocyte replication. Two vitamins, vitamin B_6 and riboflavin, participate in the maintenance of glutathione status. Ascorbic acid and tocopherols exert anti-inflammatory effects in studies in humans and animals. In humans, dietary supplementation with ascorbic acid, tocopherols, and vitamin B_6 enhances a number of aspects of lymphocyte function. The effect is most apparent in the elderly.

A study reported a significant reduction of plasma ascorbic acid levels in patients with chronic osteomyelitis receiving antibiotic treatment (102). Treatment with ampicillin, chloramphenicol, cefotaxime, gentamicin, benzyl, procaine-penicillin combination, co-trimoxazole, and streptomycin significantly reduced plasma vitamin C levels in vitro. There was moderate, but insignificant, reduction in plasma vitamin C levels with clindamycin. The cause of this reduction of plasma vitamin C levels by antibacterial agents in vitro is not yet understood. A supplement of vitamin C may be required for patients on antibacterial agents.

c.) *Immunomodulation Effects of Antibiotics.* Besides their antimicrobial effect, antibiotics are reported to have effects on immunomodulation. Investigations are ongoing to study antibiotics for their potential activity as immunomodulators (103–105) over and above their primary bactericidal or bacteristatic activity. Graded doses of various antibiotics have been tested for their ability to affect functions such as chemotaxis, phagocytic ingestion, and killing as well as particular biochemical mechanisms, such as generation of superoxide. Among the cephalosporins, cefodizime shows the greatest positive immunomodulating activity, which is due to the unique nature of the three-sided chain. Cefotaxime has an immunodepressing effect in vitro. The oral cephalosporin cefaclor appears to have a beneficial effect on polymorphonuclear neutrophils (PMN) function;

macrolides and quinolones display synergy with the immune system. An understanding of the immunomodulating effects of antimicrobial regimens would be clinically useful in the selection of antibiotics to prevent posttransplantation complications and optimize antimicrobial, antiviral, and antitumor therapies.

4. Hyperbaric oxygen therapy

Hyperbaric oxygen has been used as adjunctive therapy for difficult cases of osteomyelitis for more than 30 years. The direct effect of hyperbaric oxygenation is to increase oxygen tension to tissue beds. In osteomyelitis, the oxygen tension in medullary bone falls to about 17 to 23 mmHg, rendering the bone hypoxic. High tissue oxygen tensions appear to be directly toxic to strictly anaerobic bacteria. These organisms lack the enzyme superoxide dismutase and are sensitive to the superoxide radicals present in highly oxygenated tissue. In contrast, aerobic bacteria can degrade superoxide radicals rapidly by increasing their superoxide dismutase levels in an oxygen-rich environment. It appears that hyperbaric oxygen may be effective in the treatment of aerobic infections by increasing the oxygen-dependent intercellular killing of the polymorphonuclear leukocytes. Fibroblast proliferation, collagen production, and angiogenesis also are suboptimal in hypoxic conditions and appear to be enhanced by hyperbaric oxygen therapy.

Using a rabbit model of *Staphylococcus aureus* osteomyelitis, Mader and colleagues (106,107) showed the oxygen tension in osteomyelitic bone to be 23 mmHg. At 23 mmHg, there was a reduced ability of phagocytes to kill bacteria compared with killing in normal bone at an oxygen tension of 45 mmHg. When the rabbits were subjected to 100% oxygen at 2 ATA, the oxygen tension in osteomyelitic bone increased to 109 mmHg and phagocytic killing of *S. aureus* was restored. Thus, hyperbaric oxygen therapy allows the return of intramedullary oxygen tensions to normal or supranormal levels, resulting in normalization of phagocytic killing. In addition, hyperbaric oxygen has been demonstrated to augment the bactericidal action of the aminoglycoside class of antibiotics, which perform poorly in hypoxic conditions.

Studies by other authors (108–110) also suggest that similarly enhanced phagocytic killing may also be the mechanism by which hyperbaric oxygen therapy is beneficial in *Staphylococcus epidermidis*, *Pseudomonas aeruginosa*, and *Escherichia coli* osteomyelitis.

Adjunctive hyperbaric oxygen therapy may offer additional benefit for treatment infection caused by Mucormycosis (111) and the human immunodeficiency virus (112).

5. Prevention

The immunocompromised host is an individual whose defense mechanisms against infectious agents are altered in such a significant way that he or she is abnormally susceptible to infectious agents in general and bacterial "opportunists" in particular. The type of infection and etiological agents vary with the nature and the severity of the immune defect. The goal of prophylactic treatments is to prevent the occurrence or recurrence of infections in order to reduce the infectious morbidity and mortality rates when the nature or severity of immunosuppression makes these complications probable. Besides the strict application of the so-called universal precautions, specific measures, including early identification and early intervention, remain the basis of the prevention of musculoskeletal infections in the immunocompromised host.

For example, pressure ulcers are a common problem for older persons. Complications associated with pressure ulcers include infection and even death of some patients. Pressure is the primary pathogenic factor, but shearing forces, friction, and moisture are also important. Immobility, nutritional status, and age-related factors seem to be significant risk factors. Preventive care includes use of assessment tools to identify high-risk patients, frequent repositioning, air or foam mattresses that reduce pressure over bony prominence, as well as careful attention to optimizing the patient's overall condition.

a.) *Deoxyribonucleic Acid–Based Immunotherapy.* Vaccines with live or attenuated microorganisms, as well as purified recombinant protein and synthetic peptide-based vaccines, present potential problems in the immunocompromised host. These problems include the risk for severe infection due to the attenuated organism in the vaccine, the patient's weak immune response, and high costs. Moreover, side effects are a concern in immunocompromised patients. Such problems can be circumvented by gene immunization (113), which uses plasmid DNA encoding antigens from microorganisms and leads to protective humoral- and cellular-mediated immunity. A number of DNA-based vaccines have proved effective in animal models for the prevention of nosocomial infectious organisms such as methicillin-resistant *S. aureus* (MRSA) (114), *P. aeruginosa* (115), *Streptococcus* spp. (116), and *Mycobacterium tuberculosis* (117).

VI. SUMMARY

The treatment of osteomyelitis involves many different interventions. Osteomyelitis in immunocompromised hosts has a poor prognosis and a high incidence of complications. A systematic approach to the susceptible patient leads to an earlier diagnosis with improved survival rate and outcome. Successful treatment of

osteomyelitis is predicated upon accurate classification of stage, identification of the offending organism, surgical débridement, modification of host condition, and prompt initiation of antibiotic therapy.

REFERENCES

1. EC Tramont, DL Hoover. General or nonspecific host defense mechanisms. In: GL Mandell, JE Bennett, R Dolin, eds. Principles and Practice of Infectious Diseases. 4th ed. New York: Churchill Livingstone, 1995.
2. FP Heinzel. Antibodies. In: GL Mandell, JE Bennett, R Dolin, eds. Principles and Practice of Infectious Diseases. 4th ed. New York: Churchill Livingstone, 1995.
3. M Glauser. Alterations of host defenses: the key to the multifaceted spectrum of infections in immunocompromised patients. Recent Results Cancer Res 121:321, 1991.
4. FA Waldvogel, G Medoff, MN Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations and unusual aspects. N Engl J Med 282(4):198–206, 1970.
5. G Cierny, JT Mader, H Pennick. A clinical staging system of adult osteomyelitis. Contemp Orthop 10:17–37, 1985.
6. GT Keusch. Host defense mechanisms in protein energy malnutrition. Adv Exp Med Biol 135:183–209, 1981.
7. C Chuntrasakul, S Siltharm, V Chinswangwatanakul, T Pongprasobchai, S Chockvivatanavanit, A Bunnak. Early nutritional support in severe traumatic patients. J Med Assoc Thai 79(1):21–26, 1996.
8. S Mercadante. Parenteral versus enteral nutrition in cancer patients: indications and practice. Support Care Cancer 6(2):85–93, 1998.
9. WF Keane, MF Maddy. Host defenses and infectious complications in maintenance hemodialysis patients. In: JF Maher, ed. Replacement of Renal Function by Dialysis. Dordrecht: Kluwer Academic, 1989.
10. GF Moxley, TL Moffatt, WF Falls Jr. Hemodialysis-related osteomyelitis. South Med J 73(3):376–379, 1980.
11. JD Spencer. Bone and joint infection in a renal unit. J Bone Joint Surg 68B(3):489–493, 1986.
12. MA Parker, CU Tuazon. Cervical osteomyelitis: Infection due to Staphylococcus epidermidis in hemodialysis patients. JAMA 240(1):50–51, 1978.
13. V Esmann. The polymorphonuclear leukocyte in diabetes mellitus. J Clin Chem Clin Biochem 21:561, 1983.
14. LA Lavery, M Sariaya, H Ashry, LB Harkless. Microbiology of osteomyelitis in diabetic foot infections. J Foot Ankle Surg 34(1):61–64, 1995.
15. MP Moutschen, AJ Scheen, PJ Lefebvre. Impaired immune response in diabetes mellitus: analysis of the factors and mechanisms involved: relevance to the increased susceptibility of diabetic patients to specific infections. Diabetes Metab 18:187, 1992.

16. Calhoun JH, Mader JT, Sanford JP. Infection in the diabetic foot. Hosp Pract 27(3A):81–84, 87–90, 99, 1992.
17. OA Malysbeva, VS Shirinskii, VS Kozhevnikov, EV Evsiukova, NM Starostina. Immune status of patients with chronic bronchitis and neurocirculatory asthenia. Ter Arkh 72(12):30–35, 2000.
18. VS Shirinskii, IA Sennikova. The problem of secondary immunodeficiencies in patients with chronic bronchitis. Ter Arkh 65(3):35–38, 1993.
19. M Martinez, AS Lee, WC Hellinger, J Kaplan. Vertebral Aspergillus osteomyelitis and acute diskitis in patients with chronic obstructive pulmonary disease. Mayo Clin Proc 74(6):579–583, 1999.
20. AS Rosenberg, AE Brown. Infection in the cancer patient. Dis Mon 39:507, 1993.
21. SC Schimpff. Infections in the cancer patient: diagnosis, prevention and treatment. In: GL Mandell, JE Bennett, R Dolin, eds. Principles and Practice of Infectious Diseases. 4th ed. New York: Churchill Livingstone, 1995.
22. H Bruunsgaard, M Pedersen, BK Pedersen. Aging and proinflammatory cytokines. Curr Opin Hematol 8(3):131–136, 2001.
23. L Rink, I Cakman, H Kirchner. Altered cytokine production in the elderly. Mech Ageing Dev 102(2–3):199–209, 1998.
24. A Globerson, RB Effros. Ageing of lymphocytes and lymphocytes in the aged. Immunol Today 21(10):515–521, 2000.
25. JT Mader, ME Shirtliff, S Bergquist, JH Calhoun. Bone and joint infections in the elderly: practical treatment guidelines. Drugs Aging 6(1):67–80, 2000.
26. HA Mousa, MG Abaid. Acute haematogenous osteomyelitis: microbial conversion and unusual age presentation. East Mediterr Health J 6(1):89–92, 2000.
27. EJ Carragee. Pyogenic vertebral osteomyelitis. J Bone Joint Surg 79A(6):874–880, 1997.
28. EI Jokinen, TT Mottonen, PJ Hannonen, HS Arvilommi. Association of in vitro immune functions with the severity of the disease in rheumatoid arthritis. Br J Rheumatol 32(7):550–555, 1993.
29. M Guma, R Krakauer. CD4+ lymphocytopenia in systemic lupus erythematosus. Ann Intern Med 120(2):168–169, 1994.
30. MJ Walport, KA Davies, BJ Morley, M Botto. Complement deficiency and autoimmunity. Ann N Y Acad Sci 815:267–281, 1997.
31. U Picillo, G Italian, MR Marcialis, F Ginolfi, G Abbate, MA Tufano. Bilateral femoral osteomyelitis with knee arthritis due to Salmonella enteritidis in a patient with systemic lupus erythematosus. Clin Rheumatol 20(1):53–56, 2001.
32. CA Sable, GR Donowitz. Infections in bone marrow transplant recipients. Clin Infect Dis 18:273, 1994.
33. JD Myers. Infections associated with bone marrow transplantation. In: S Gorbach, ed. Infectious Diseases. Philadelphia: WB Saunders, 1992.
34. JR Wingard, SU Beals, GW Santos, WG Merz, R Seral. *Aspergillus* infections in bone marrow transplant recipients. Bone Marrow Transplant 2:175–181, 1987.
35. C Watanabe, S Yajima, T Taguchi, K Toya, Y Fujii, T Hongo, T Ohzeki. Successful unrelated bone marrow transplantation for a patient with chronic granulomatous

disease and associated resistant pneumonitis and Aspergillus osteomyelitis. Bone Marrow Transplant 28(1):83–87, 2001.
36. RH Rubin. Infection in the renal and liver transplant patient. In: RH Rubin, LS Young, eds. Clinical Approach to Infection in the Compromised Host. 2nd ed. New York: Plenum Press, 1988.
37. P Sweny, AK Burroughs. Infections in solid organ transplantation. Curr Opin Infect Dis 7:436, 1994.
38. WY Qunibi, MB al-Siba, S Taher, EJ Harder, E de Vol, O al-Furayh, HE Ginn. Mycobacterial infection after renal transplantation: report of 14 cases and review of the literature. Q J Med 77:1039–1060, 1990.
39. DT Boumpas, F Paliogianni, ED Anastassiou, JE Balow. Glucocorticosteroid action on the immune system: molecular and cellular aspects. Clin Exp Rheumatol 9:413, 1991.
40. GA Rook. Glucocorticoids and immune function. Baillieres Best Pract Res Clin Endocrinol Metab 13(4):567–581, 1999.
41. TC Pruitt, LO Hughes, RD Blasier, RE McCarthy, CM Glasier, GJ Roloson. Atypical mycobacterial vertebral osteomyelitis in a steroid-dependent adolescent: A case report. Spine 18(16):2553–2555, 1993.
42. JG Pirofsky, CT Huang, KB Waites. Spinal osteomyelitis due to Mycobacterium avium-intracellulare in an elderly man with steroid-induced osteoporosis. Spine 18(13):1926–1929, 1993.
43. CA Engh, JL Hughes, RC Abrams, JW Bowerman. Osteomyelitis in the patient with sickle cell disease. J Bone Joint Surg 53A:1–15, 1971.
44. CH Epps Jr, DD Bryant III, MJ Coles, O Castro. Osteomyelitis in patients who have sickle-cell disease: diagnosis and management. J Bone Joint Surg 73A:1281–1294, 1991.
45. EA Melamed, C Zinman, HD Reis. Musculoskeletal infections in HIV-positive patients. Harefuah 131(5–6):181–184, 1996.
46. D Vassilopoulos, P Chalasani, RL Jurado, K Workowski, CA Agudelo. Musculoskeletal infections in patients with human immunodeficiency virus infection. Medicine (Baltimore) 76(4):284–294, 1997.
47. RA Hughes, IF Rowe, D Shanson, AC Keat. Septic bone, joint and muscle lesions associated with human immunodeficiency virus infection. Br J Rheumatol 31(6):381–388, 1992.
48. LH Calabrese. Human immunodeficiency virus (HIV) infection and arthritis. Rheum Dis Clin North Am 19(2):477–488, 1993.
49. IM Fox, K Brady. Acute hematogenous osteomyelitis in intravenous drug users. J Foot Ankle Surg 36(4):301–305, 1997.
50. AD McNaghten, MR Adams, MS Dworkin. Case 23-2000: osteomyelitis in HIV-infected patients. N Engl J Med 344(1):66–67, 2001.
51. R Hirsch, SM Miller, S Kazi, TR Cate, JD Reveille. Human immunodeficiency virus-associated atypical mycobacterial skeletal infections. Semin Arthritis Rheum 25(5):347–356, 1996.
52. A Olive, X Tena, A Raventos, J Romeu, JC Lorenzo, I Ojanguren, Perez R. Bone bacillary angiomatosis in an HIV-infected patient. Br J Rheumatol 35(9):901–904, 1996.

53. D Shine, B Moll, E Emeson, I Spigland, C Harris, CB Small, G Friedland, SH Weiss, AJ Bodner. Serologic, immunologic, and clinical features of parenteral drug users from contrasting populations. Am J Drug Alcohol Abuse 13(4):401–412, 1987.
54. MA Fletcher, NG Klimas, RO Morgan. Immune function and drug treatment in anti-retrovirus negative intravenous drug users. Adv Exp Med Biol 335:241–246, 1993.
55. DM Novick, M Ochshorn, V Ghali, TS Croxson, WD Mercer, N Chiorazzi, MJ Kreek. Natural killer cell activity and lymphocyte subsets in parenteral heroin abusers and long-term methadone maintenance patients. J Pharmacol Exp Ther 250(2):606–610, 1989.
56. A Lafont, A Olive, M Gelman, J Roca-Burniols, R Cots, J Carbonell. Candida albicans spondylodiscitis and vertebral osteomyelitis in patients with intravenous heroin drug addiction: report of 3 new cases. J Rheumatol 21(5):953–956, 1994.
57. J Belzunegui, F Rodriguez-Arrondo, C Gonzalez, R Queiro, M Martinez de Bujo, JJ Intxausti, JR De Dios, M Figueroa. Musculoskeletal infections in intravenous drug addicts: report of 34 cases with analysis of microbiological aspects and pathogenic mechanisms. Clin Exp Rheumatol 18(3):383–386, 2000.
58. YK Liu. Effects of alcohol on granulocytes and lymphocytes. Semin Hematol 17:130, 1980.
59. RR MacGregor. Alcohol and immune defense. JAMA 256:1474, 1986.
60. TR Jerrells. Immunodeficiency associated with ethanol abuse. Adv Exp Med Biol 288:229–236, 1991.
61. FJ Dunne. Alcohol and the immune system. Br Med J 298(6673):543–544, 1989.
62. SJ Ewald, C Huang, L Bray. Effect of prenatal alcohol exposure on lymphocyte populations in mice. Adv Exp Med Biol 288:237–244, 1991.
63. RH Morse. Consultation: tibial pain and alcoholism. J La State Med Soc 137(6):16–18, 1985.
64. M Silbermann, PL Maloney, HC Doku. Mandibular osteomyelitis in the patient with chronic alcoholism: etiology, management, and statistical correlation. Oral Surg Oral Med Oral Pathol 38(4):530–534, 1974.
65. B Wallner, JM Friedrich, C Pietrzyk. Bone lesions in chronic pancreatitis. Rofo Fortschr Geb Rontgenstr Nuklearmed 149(3):289–293, 1988.
66. HT Davies, RJ Carr. Osteomyelitis of the mandible: a complication of routine dental extractions in alcoholics. Br J Oral Maxillofac Surg 28(3):185–188, 1990.
67. F Chen, AL Osterman, K Mahony. Smoking and bony union after ulna-shortening osteotomy. Am J Orthop 30(6):486–489, 2001.
68. JB Kinsella, CH Rassekh, ZD Wassmuth, JA Hokanson, KH Calhoun. Smoking increases facial skin flap complications. Ann Otol Rhinol Laryngol 108(2):139–142, 1999.
69. WF Reus III, LB Colen, DJ Straker. Tobacco smoking and complications in elective microsurgery. Plast Reconstr Surg 89(3):490–494, 1992.
70. P Moszczynski, Z Zabinski, P Moszczynski Jr, J Rutowski, S Slowinski, Z Tabarowski. Immunological findings in cigarette smokers. Toxicol Lett 118(3):121–127, 2001.

71. DA Hughes, PL Haslam, PJ Townsend, M Turner-Warwick. Numerical and functional alterations in circulatory lymphocytes in cigarette smokers. Clin Exp Immunol 61(2):459–466, 1985.
72. F Mili, WD Flanders, JR Boring, JL Annest, F Destefano. The associations of race, cigarette smoking, and smoking cessation to measures of the immune system in middle-aged men. Clin Immunol Immunopathol 59(2):187–200, 1991.
73. VA Spence, PT McCollum, WF Walker. Transcutaneous oxygen measurements (TcpO2). Br J Surg 71(6):481–482, 1984.
74. GM Andreozzi, S Signorelli, G Butto, C Scrofani. Transcutaneous measurement of oxygen pressure in the diagnosis of vascular involvement in diabetes. J Mal Vasc 13(2):178, 1988.
75. KS Christensen, M Klarke. Transcutaneous oxygen measurement in peripheral occlusive disease. An indicator of wound healing in leg amputation. J Bone Joint Surg Br 68(3):423–426, 1986.
76. K Ito, S Ohgi, T Mori, B Urbanyi, V Schlosser. Determination of amputation level in ischemic legs by means of transcutaneous oxygen pressure measurement. Int Surg 69(1):59–61, 1984.
77. J Hafner, E Schneider, G Burg, PC Cassina. Management of leg ulcers in patients with rheumatoid arthritis or systemic sclerosis: the importance of concomitant arterial and venous disease. J Vasc Surg 32(2):322–329, 2000.
78. R Gerard, P Fredenucci, J Bourde, L Barthelemy, J Lamy, A Jouve, A Appaix. Hyperbaric oxygen in the treatment of arteriopathies. Arch Mal Coeur Vaiss 60(4):472–483, 1967.
79. I Monies-Chass, D Herer, U Alon, HJ Birkhahn. Hyperbaric oxygen in acute ischaemia due to allergic vasculitis. Anaesthesia 31(9): 1221–1224, 1976.
80. JC Murray. Keloids and hypertrophic scars. Clin Dermatol 12(1):27–37, 1994.
81. EE Tredget, B Nedelec, PG Scott, A Ghahary. Hypertrophic scars, keloids, and contractures: the cellular and molecular basis for therapy. Surg Clin North Am 77(3):701–730, 1997.
82. HP Rodeman, M Bamberg. Cellular basis of radiation-induced fibrosis. Radiother Oncol 35: 83–90, 1995.
83. MW Skwarchuk, EL Travis. Changes in histology and fibrogenic cytokines in irradiated colorectum of two murine strains. Int J Radiat Oncol Biol Phys 42:169–178, 1998.
84. S Delanian, M Martin, A Bravard, C Luccioni, JL Lefaix. Cu/Zn superoxide dismutase modulates phenotypic changes in cultured filbroblasts from human skin with chronic radiotherapy damage. Radiother Oncol 58(3):325–331, 2001.
85. LP Aiello, JS Wong. Role of vascular endothelial growth factor in diabetic vascular complications. Kidney Int 58(suppl 77):S113–S119, 2000.
86. CD Marcus, VJ Ladam-Marcus, J Leone, D Malgrange, FM Bonnet-Gausserand, BP Menanteau. MR imaging of osteomyelitis and neuropathic osteoarthropathy in the feet of diabetics. Radiographics 16(6):1337–1348, 1996.
87. SD Croll, GG Nicholas, MA Osborne, TE Wasser, S Jones. Role of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. J Vasc Surg 24(2):266–270, 1996.

88. JT Mader, D Mohan, J Calhoun. A practical guide to the diagnosis and management of bone and joint infections. Drugs 54(2):253–264, 1997.
89. JT Mader, M Ortiz, JH Calhoun. Update on the diagnosis and management of osteomyelitis. Clin Podiatr Med Surg 13(4):701–724, 1996.
90. JT Mader, J Calhoun, J Cobos. In vitro evaluation of antibiotic diffusion from antibiotic-impregnated biodegradable beads and polymethylmethacrylate beads. Antimicrob Agents Chemother 41(2):415–418, 1997.
91. JH Calhoun, DM Anger, J Mader, BR Ledbetter. The Ilizarov technique in the treatment of osteomyelitis. Tex Med 87(12):56–59, 1991.
92. JH Calhoun, WJ Gogan, V Beraja, RJ Howard, JR Oliphant. Dynamic axial fixation for immobilization of cross-leg flaps in chronic osteomyelitis. Ann Plast Surg 23(4):354–356, 1989.
93. DN Fish, JA Goulet, T Stevenson. Chronic osteomyelitis of the calcaneus: treatment with a vascularized muscle flap. Orthopedics 16(1):81–85, 1993.
94. T Hartung. Anti-inflammatory effects of granulocyte colony-stimulating factor. Curr Opin Hematol 5(3):221–225, 1998.
95. F de Lalla, R Nicolin, L Lazzarini. Safety and efficacy of recombinant granulocyte colony-stimulating factor as an adjunctive therapy for Streptococcus pneumoniae meningitis in non-neutropenic adult patients: a pilot study. J Antimicrob Chemother 46(5):843–846, 2000.
96. G Meyanci, H Oz. Combination of granulocyte colony-stimulating factor and antibacterial drugs for the treatment of ventilatory associated nosocomial pneumonia. Middle East J Anesthesiol 16(1):91–101, 2001.
97. DW Maher, GJ Lieschke, M Green, J Bishop, R Stuart-Harris, M Wolf, WP Sheridan, RF Kefford, J Cebon, I Olver. Filgrastim in patients with chemotherapy-induced febrile neutropenia, Ann Intern Med 121:492–501, 1994.
98. M Subasi, A Kapukaya, C Kesemenli, H Kaya, I Sari. Effect of granulocyte-macrophage colony-stimulating factor on treatment of acute osteomyelitis. An experimental investigation in rats. Arch Orthop Trauma Surg 121(3):170–173, 2001.
99. A Gough, M Clapperton, N Rolando, V Foster, J Philpott-Howard, ME Edmonds. Randomised placebo-controlled trial of granulocyte-colony stimulating factor in diabetic foot infection. Lancet 350(9081):855–859, 1997.
100. F de Lalla, G Pellizzer, M Strazzabosco, Z Martini, G Du Jardin, L Lora, P Fabris, P Benedetti, G Erle. Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection. Antimicrob Agents Chemother 45(4):1094–1098, 2001.
101. H Isotani, Y Fukumoto, H Kawamura, M Sasada, K Hattori, T Fujiwara, Y Kobayashi. Treatment with rhG-CSF for osteomyelitis in a patient with p47-phox-deficient chronic granulomatous disease. Ann Hematol 75(5–6):243–246, 1997.
102. ZO Alabi, KD Thomas, O Ogunbona, IA Elegbe. The effect of antibacterial agents on plasma vitamin C levels. Afr J Med Med Sci 23(2):143–146, 1994.
103. JM Hamilton-Miller. Immunopharmacology of antibiotics: direct and indirect immunomodulation of defence mechanisms. J Chemother 13(2):107–111, 2001.

104. MT Labro. Cefodizime as a biological response modifier: a review of its in-vivo, ex-vivo and in-vitro immunomodulatory properties. J Antimicrob Chemother 26(suppl C):37–47, 1990.
105. W Roszkowski, HL Ko, K Roszkowski, J Jeljaszewicz, G Pulverer. Antibiotics and immunomodulation: effects of cefotaxime, amikacin, mezlocillin, piperacillin and clindamycin. Med Microbiol Immunol (Berl) 173(5):279–289, 1985.
106. JT Mader, JC Guckian, DL Glass, JA Reinarz. Therapy with hyperbaric oxygen for experimental osteomyelitis due to Staphylococcus aureus in rabbits. J Infect Dis 138(3):312–318, 1978.
107. JT Mader, KR Adams, WR Wallace, JH Calhoun. Hyperbaric oxygen as adjunctive therapy for osteomyelitis. Infect Dis Clin North Am 4(3):433–440, 1990.
108. JC Davis, JD Heckman, JC DeLee, FJ Buckwold. Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. J Bone Joint Surg 68A(8):1210–1217, 1986.
109. TJ Bray. Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. J Bone Joint Surg 69A(8):1303, 1987.
110. DS Herman. Hyperbaric oxygen therapy and its role in the treatment of chronic osteomyelitis: a preliminary report involving refractory osteomyelitis in the foot. J Foot Surg 24(4):293–300, 1985.
111. L Couch, F Theilen, JT Mader. Rhinocerebral mucormycosis with cerebral extension successfully treated with adjunctive hyperbaric oxygen therapy. Arch Otolaryngol Head Neck Surg 114(7):791–794, 1988.
112. MR Reillo, RJ Altieri. HIV antiviral effects of hyperbaric oxygen therapy. J Assoc Nurses AIDS Care 7(1):43–45, 1996.
113. CJ Pachuk, DE McCallus, DB Weiner, C Satishchandran. DNA vaccines—challenges in delivery. Curr Opin Mol Ther 2(2):188–198, 2000.
114. A Ohwada, M Sekiya, H Hanaki, KK Arai, I Nagaoka, S Hori, S Tominaga, K Hiramatsu, Y Fukuchi. DNA vaccination by mecA sequence evokes an antibacterial immune response against methicillin-resistant Staphylococcus aureus. J Antimicrob Chemother 44(6):767–774, 1999.
115. J Gabelsberger, B Knapp, S Bauersachs, UI Enz, BU von Specht, H Domdey. A hybrid outer membrane protein antigen for vaccination against Pseudomonas aeruginosa. Behring Inst Mitt 98:302–314, 1997.
116. H Bercovier, C Ghittino, A Eldar. Immunization with bacterial antigens: infections with streptococci and related organisms. Dev Biol Stand 90:153–160, 1997.
117. DP Fonseca, B Benaissa-Trouw, M van Engelen, CA Kraaijeveld, H Snippe, AF Verheul. Induction of cell-mediated immunity against *Mycobacterium tuberculosis* using DNA vaccines encoding cytotoxic and helper T-cell epitopes of the 38-kilodalton protein. Infect Immun 69(8):4839–4845, 2001.
118. MA Kuhn, X Wang, WG Payne, F Ko, MC Robson. Tamoxifen decreases fibroblast function and downregulates $TGF_{\beta 2}$ in dupuytren's affected palmar fascia. J Surg Res 103:146–152, 2002.

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Prophylaxis of Musculoskeletal Infection

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I. INTRODUCTION

Bacterial contamination is a component of every surgical incision. Whether or not contamination causes infection is determined by interplay between the patient's immune system and the number and virulence of contaminating organisms. One of the methods available to the orthopedic surgeon for reducing bacterial load and lowering the incidence of wound infection is the use of prophylactic antibiotics.

In this chapter we review the history and current rationale for the use of prophylactic antibiotics in orthopedic surgery. We also address the timing of antibiotic prophylaxis, the role of intraoperative dosage, the duration of prophylaxis, and the choice of agent for prophylaxis. In addition, we discuss the use of antibiotic prophylaxis for arthroscopic surgery, total joint replacements, and gunshot wounds. The use of prophylactic antibiotics for open fractures is discussed in Chapter 5.

II. HISTORY AND RATIONALE

The first studies examining the use of prophylactic antibiotics in orthopedic surgery suggested that their use led to a higher rate of postoperative infection (1). In 1957, Tachdjian and Compere (2) retrospectively studied the infection rate in 1900 cases that received prophylactic antibiotics and 1100 cases that did not. The antibiotics used were penicillin, penicillin and streptomycin, erythromycin,

erythromycin and sulfonamide, and tetracycline-oxytetracycline-chlortetracycline. The antibiotic group had 112 infections (5.9%) versus 29 infections (2.6%) in the control group. On the basis of these results, the authors recommended against the use of prophylactic antibiotics. However, the retrospective nature of the study allowed for the possibility that the higher infection rate seen in the antibiotic group was the result of the surgeon's decision to give prophylactic antibiotics only to patients who were at a greater risk for infection.

A prospective study arguing against the use of prophylactic antibiotics followed in 1960. In a series of 500 consecutive patients, Olix and associates (3) assigned every other patient 400,000 units of penicillin G and 0.5 gram of dihydrostreptomycin every 12 hours for 3 to 7 days after surgery. When compared to the control group, the antibiotic group had a 5.9% increased incidence of wound infection. The authors did not specify when the antibiotics were given in relation to the skin incision. The timing of administration could have played a role in the higher incidence of wound infection.

In 1970, Fogelberg and colleagues (4) published a prospective study demonstrating a decrease in postoperative wound infections with the use of prophylactic penicillin after mold arthoplasties and spinal fusions. Every other patient in a series of 232 consecutive cases of a single surgeon received two preoperative and one intraoperative dose of penicillin. The penicillin was continued until the fifth postoperative day. The infection rate in the patients receiving penicillin was 1.7% compared to 8.9% in the control group, a statistically significant difference. On the basis of these results, the authors concluded that prophylactic penicillin was effective in lowering the incidence of wound infection in clean orthopedic procedures, especially those of long duration or those with a high frequency of deep sequestered hematomas.

This study was followed by a much larger, double-blind, prospective study published by Pavel and coworkers (5) in 1974. One thousand ninety-one patients undergoing clean orthopedic procedures lasting more than 30 minutes were randomized into either an antibiotic or a placebo group. The antibiotic group received 1 g of cephaloridine intramuscularly one hour prior to surgery and 1 g intravenously over 4 hours during and after the operation. Twenty-five (2.8%) of the 887 patients in the cephaloridine group had wound infections compared to 35 (5%) of the 704 patients in the placebo group, a difference that was statistically significant. These results confirmed that an effective antibiotic, given preoperatively and continued intraoperatively, significantly reduces the rate of postoperative infection.

Since the publication of Pavel and coworkers' classic study, numerous other studies have confirmed the efficacy of various prophylactic antibiotic combinations in all types of clean orthopedic surgery. In 1996, Boxma and associates (6) conducted a prospective, randomized, double-blind, placebo-controlled study of 2195 patients with closed limb fractures in the Dutch Trauma Trial. The 1105

patients in the antibiotic group received a single, preoperative 2 g dose of ceftriaxone. Ceftriaxone was chosen because of its broad spectrum of activity and long-acting pharmacokinetic profile, which allows for bactericidal levels up to 24 hours after dosage. In 36 (3.6%) of the patients in the ceftriaxone group deep or superficial wound infections developed, whereas infections developed in 79 (8.3%) of the 1090 patients in the placebo group. The rate of nosocomial infections, either urinary or respiratory, was 10.2% in the placebo group compared to 2.3% in the ceftriaxone group. Gram-positive bacteria were found in 74.5% of the wound infections, whereas gram-negative bacteria alone were responsible for 65% of the nosocomial infections. These results clearly demonstrate the efficacy of prophylactic antibiotics in reducing wound infections after operative treatment of closed fractures.

The authors also performed a cost-effectiveness analysis based on their data. Patients who had wound infections spent an average of 36 additional days in the hospital, with approximately $22,000 in additional charges. On the basis of the decreased rate of infection with prophylactic antibiotics, they estimated that if all 2195 patients in the study received prophylaxis the cost savings would have been $486 per patient.

In 2000, Gillespie and Walenkamp (7) performed a systematic review and meta-analysis of all studies completed in the past 25 years involving antibiotic prophylaxis of patients undergoing surgery for treatment of closed long bone fractures. They identified 22 studies that involved 8307 patients who had internal fixation or replacement arthroplasty after a fracture. Data from 1896 participants in 10 trials comparing a preoperative dose and two or more postoperative doses of parenteral antibiotics with a placebo or no treatment showed a 0.36 (95% confidence interval [CI] 0.21–0.65) reduction in the risk of deep wound infections. There was also a 0.48 (CI 0.28–0.81) decrease in the relative risk of superficial wound infections and a decrease of 0.66 (CI 0.43–1.0) in the relative risk of urinary tract infections. Trials that compare a single preoperative dose of parenteral antibiotic with a placebo or no treatment showed risk reductions of 0.40 (CI 0.24–0.67) in deep wound infections, 0.69 (CI 0.50–0.95) in superficial wound infections, and 0.63 (0.53–0.76) in urinary tract infections. On the basis of these results, the authors concluded that antibiotic prophylaxis for closed fracture surgery is effective. They also concluded that, in light of this evidence, further trials comparing prophylactic antibiotics to placebo are not ethical. Furthermore, any trials comparing the effectiveness of different antibiotic regimens would have to be extremely large to produce statistically significant results given the overall low rate of infection with any antibiotic prophylaxis.

The large number of studies demonstrating the effectiveness of prophylactic antibiotics in clean orthopedic surgery procedures has made their use the standard of care; however, there continues to be controversy surrounding the timing of administration, duration of prophylaxis, and choice of agent.

III. TIMING OF PROPHYLACTIC ANTIBIOTICS

In light of multiple studies demonstrating the ineffectiveness of prophylactic antibiotics published in the 1950s, Burke (8) examined the effect of timing on the effectiveness of antibiotic prophylaxis. Using guinea pigs, he inoculated 2-cm skin incisions with *Staphylococcus aureus* and gave the animals various antibiotics before, during, or after the time of bacterial contamination. He found that incisions in animals that received the antibiotics 1 hour prior to inoculation were clinically and microscopically indistinguishable from incisions inoculated with dead bacteria. There was minimal inflammation of the incision if the antibiotics were given at the same time as bacterial exposure. The degree of inflammation continued to increase with delayed antibiotic administration. Furthermore, if the antibiotics were given 3 hours or more after inoculation there was no difference between the incisions of treated animals and those of animals that did not receive any antibiotics. Burke's results suggested that, in order for prophylactic antibiotics to be maximally effective, the antibiotics need to be present in the wound at the time of incision.

The role of timing in the administration of antibiotic prophylaxis in surgery involving bone was further studied by Bowers and colleagues in 1970 (9). They used an experimental model that consisted of making 1- by 3-cm cortical windows in canine femurs followed by marrow removal to ensure formation of a hematoma. When cephaloridine was given 30 minutes before the incision, they found high drug levels in the subsequent hematomas. With continued postoperative dosage, bactericidal levels could be maintained for more than 64 hours. In dogs whose hematomas were injected with staphylococci, doses of cephaloridine given 30 minutes preoperatively followed by 48 hours of postoperative dosage resulted in hematomas that showed no clinical signs of infection and were sterile on subsequent culture. If the antibiotics were not given preoperatively, but started within the first 24 hours postoperatively, there were no clinical signs of infection; however, wound aspirates grew out bacteria. When the antibiotics were given more than 24 hours postoperatively, there was no difference between these dogs and those that did not receive any antibiotics. Both sets of animals displayed clinical signs of infection and had positive aspirate culture results. This study demonstrates that, in surgery involving bone hematomas, prophylactic antibiotics are most effective when given preoperatively. The results suggest that improper timing of antibiotic administration with regard to the surgical incision may have led to the lack of success of prophylactic antibiotics in several of the early studies.

In a prospective study in vivo, Classen and coworkers (10) examined the timing of prophylactic antibiotic administration and the rate of surgical wound infection. They studied 2847 patients who had clean or "clean-contaminated" procedures. The patients were divided into groups based on the timing of antibiotic administration. The early group received antibiotics 2 to 24 hours before surgery ($n = 369$), the preoperative group received prophylaxis 0 to 2

hours before the incision ($n = 1708$), the perioperative group received antibiotics within 3 hours of the incision ($n = 282$), and the postoperative group received prophylaxis 3 to 24 hours after the incision.

The majority of the procedures in this study were not orthopedic, 6% were total knee arthroplasties, and 5% were total hip arthroplasties. The patients who received antibiotics preoperatively had the lowest rate of infection at 0.6% compared to 3.8% for the early group, 3.3% for the postoperative group, and 1.4% for the perioperative group. The authors concluded that (1) the timing of prophylactic antibiotic administration has a significant impact on its effectiveness and (2) antibiotics should be administered 0 to 2 hours before the surgical incision.

Johnson (11) examined the issue of timing of antibiotic prophylaxis and tourniquet inflation in 22 patients who had total knee arthroplasty. The patients were randomly assigned to receive 1.5 grams of cefuroxime intravenously 5, 10, 15, or 20 minutes before inflation of the tourniquet. All 22 patients were found to have bactericidal concentrations of antibiotic in their bone; however, 6 of the 7 patients given cefuroxime 5 minutes before tourniquet inflation had inadequate levels in the subcutaneous fat. All 15 patients had adequate levels in subcutaneous fat when 10 minutes or more elapsed between drug administration and tourniquet inflation. The author concluded that, in order to ensure adequate prophylaxis, the antibiotic should be given at least 10 minutes before inflation of the tourniquet.

In summary, on the basis of the animal studies of Burke and Bowers and coworkers it is clear that prophylactic antibiotics are most effective when they are present in the tissues at the time of the surgical procedure. The antibiotics should be administered within the 2 hours before the skin incision and at least 10 minutes before inflation of the tourniquet.

IV. INTRAOPERATIVE DOSAGE

Additional intraoperative doses of antibiotic should be given during prolonged procedures at intervals one to two times the half-life of the drug to maintain adequate levels throughout the operation (12). Meter and associates (13) found that, even with blood loss of 2000 mL, it is not necessary to shorten the dose interval of cefazolin to less than 4 hours.

V. DURATION OF PROPHYLAXIS

There are several theoretical reasons to limit the duration of prophylactic antibiotics, including (1) a decrease in the risk of adverse drug reactions, (2) a decrease in the development of resistant organisms, and (3) a decrease in cost. Many of the original studies recommending prophylactic antibiotics in orthopedic surgery used up to 7 days of antibiotic administration.

In 1983, Nelson and colleagues (14) compared 1-day to 7-days of antibiotic prophylaxis in patients undergoing total hip arthroplasties, total knee arthroplasties, and hip fracture repair. Three hundred fifty-four patients were divided into two groups. Both groups received one dose of antibiotic 20 minutes before incision. In the 7-day group ($n = 172$), the antibiotic was continued intravenously every 6 hours for 3 days and then orally for 4 days, whereas the 1-day group ($n = 186$) received only 24 hours of antibiotic. The drug used was nafcillin or, in the case of allergy, cefazolin. The 24-hour group had three (1.6%) deep wound infections; the 7-day group had four (2.3%) infections. The authors concluded that there is no difference in efficacy between 1 and 7-day courses of prophylactic antibiotics.

Williams and Gustilo (15) confirmed these results when they retrospectively reviewed the incidence of infection in 1791 total joint arthroplasties performed over 7 years. For the first 4 years, they used 3 days of antibiotic prophylaxis in 1341 joint replacements with an infection rate of 0.6%. Over the following 3 years, the authors used two grams of cefazolin preoperatively and 1 gram every 8 hours for 24 hours postoperatively in 450 total joint arthroplasties and had an infection rate of 0.67%. On the basis of these results, the authors recommended only 24 hours of antibiotic prophylaxis.

In their (previously mentioned) review, Gillespie and Walenkamp (7) examined several studies that compared single-dose prophylaxis with multiple-dose prophylaxis. Although the results in this area are conflicting, the authors concluded that single-dose prophylaxis is effective if the agent used provides minimal inhibitory concentration over a 12-hour period. The Dutch Trauma Trial (6), which showed a significant decrease in infection with a single dose of ceftriaxone, strongly supports this conclusion. If the antibiotic chosen for prophylaxis has a shorter half-life, then additional doses providing coverage for at least 12 hours should be used.

VI. CHOICE OF AGENT

The ideal prophylactic antibiotic is active against common wound pathogens, has a relatively long serum half-life, penetrates the bone and soft tissue well, causes no adverse reactions, and is inexpensive (16). The goal of prophylaxis is not to ensure coverage of every conceivable pathogen, but to inhibit the most likely organisms to be encountered adequately. The primary bacterial contaminants in clean orthopedic surgery are *Staphylococcus aureus* and *Staphylococcus epidermidis* (16). The antistaphylococcal synthetic penicillin derivatives, such as nafcillin, provide adequate protection against gram-positive bacteria but are ineffective against gram-negative rods that occasionally cause postoperative infection. The first-generation cephalosporins are effective against the majority of staphylococci as well as other gram-positive organisms, the majority of clinically important aerobic gram-negative bacilli, and nonbacteroid anaerobes (16). The first-generation cephalosporins provide better gram-positive coverage

than second- and third-generations drugs, making them better suited for orthopedic surgical prophylaxis.

The studies demonstrating the effectiveness of prophylactic antibiotics have been conducted with numerous agents. No one drug has been shown conclusively to be superior. The most common choice for prophylaxis in the United States is the first-generation cephalosporin cefazolin. Its spectrum of activity, pharmacokinetics, cost, and safety make it an excellent choice. Compared to the other first-generation cephalosporins, cefazolin has a higher peak level and longer half-life in both bone and serum (17). The longer half-life allows for less frequent administration, which makes cefazolin less expensive to use than other first-generation cephalosporins (16).

The half-life of cefazolin is not long enough to allow for one-time dosage as was done with ceftriaxone in the Dutch Trauma Trial. Additionally, there are several arguments against using ceftriaxone as a prophylactic antibiotic. Ceftriaxone is a third-generation cephalosporin, and, as previously mentioned, first-generation cephalosporins have superior gram-positive coverage to third-generation drugs. In many hospitals, ceftriaxone is the first-line agent for several types of infections, including meningitis. Induction of resistance after widespread use of this drug as a prophylactic agent would be a legitimate concern.

The main adverse effects of cefazolin, and all of the other first-generation cephalosporins, are hypersensitivity reactions (16). These include rash, utricaria, eosinophilia, drug fever, angioedema, and anaphylaxis. These reactions tend to be rare and are normally reversible with cessation of the drug (18).

We recommend 1 gram of intravenous cefazolin given up to 2 hours before skin incision. An additional 1-gram dose should be administered if the duration of surgery exceeds 4 hours. The antibiotic can then be continued at 500 mg intravenously every 8 hours for 24 hours postoperatively. In patients with a history of severe allergic reaction (urticaria, angioedema, or anaphylaxis) to a penicillin or cephalosporin, vancomycin is an appropriate alternative for prophylaxis. One gram should be administered intravenously up to 2 hours before incision followed by 1 g every 12 hours for 24 hours. One of the major disadvantages of vancomycin is its association with the "red man syndrome." This syndrome, which may include flushing, puritis, chest pain, or hypotension, is related to the infusion rate and should not be misinterpreted as an allergic reaction precluding further use of the drug (18).

In institutions with a prevalence of methacillin-resistant *Staphylococcus aureus* (MRSA) greater than 10%–20% or a high incidence of coagulase-negative *Staphylococcus* spp., vancomycin can be used as the first-line prophylactic agent. In Europe, the glycopeptide teicoplanin is emerging as a viable alternative to vancomycin. Recent studies have demonstrated equivalent or superior effectiveness in comparisons with MRSA. Mini and coworkers (19) performed a meta-analysis of four randomized trials comparing teicoplanin to cephalosporins for antibiotic prophylaxis in orthopedic surgery. They found similar rates of infection

and adverse events. Teicoplanin appears to be as efficacious as vancomycin with fewer adverse effects and no requirement for routine serum monitoring (20). One advantage of teicoplanin is that its long half-life (36–172 hours) allows for one 400 mg dose before surgery. Unfortunately, this drug is not currently available in the United States. In order to avoid increased resistance to the glycopeptide antibiotics, the use of these drugs should be restricted to patients with allergies to cephalosporins or institutions with high rates of MRSA.

VII. ANTIBIOTIC PROPHYLAXIS FOR ARTHROSCOPY

One category of procedures in which the routine use of prophylactic antibiotics is not recommended is arthroscopic surgery that does not involve the placement of foreign materials. Wieck and associates (21) performed a prospective, double-blind study of 437 patients who had arthroscopic procedures. Patients were randomized to receive either 1 g of cefazolin or placebo for prophylaxis. None of the patients in either group had a deep wound infection, but one patient did have an allergic reaction to cefazolin that required treatment with diphenhydramine hydrochloride (Benadryl). The short duration of the procedures combined with the decreased area of tissue exposure make the use of prophylactic antibiotics unnecessary.

VIII. ANTIBIOTIC PROPHYLAXIS IN TOTAL JOINT REPLACEMENT SURGERY

Infection is one of the most devastating complications of total joint replacement surgery. Treatment of infection almost always requires additional surgical procedures and often replacement of the prosthesis. Consequently, the role of prophylactic antibiotics for patients receiving total joint replacements has been studied extensively. The efficacy and recommendations for prophylactic antibiotics in patients having primary joint replacements are the same as those for patients having other clean orthopedic procedures. However, the following three areas deserve special attention: the tuning of prophylactic antibiotic administration in patients who have revision joint surgery, the use of antibiotic-impregnated bone cement as prophylaxis for primary joint replacements, and the need for antibiotic prophylaxis in patients with total joint replacements who have procedures that cause transient bacteremia.

Traditionally, prophylactic antibiotics have been withheld for patients undergoing revision surgery for total joint replacements until tissue surrounding the prosthesis could be collected for culture. Given that the majority of revisions

are aseptic, Hanssen and Osmon have questioned this practice (22). They suggest that, in patients for whom there is a high clinical likelihood of infection, or those with confirmed infection, antibiotics should be held until cultures are obtained. However, all other patients who have revisions should be given antibiotics before skin incision in order to derive maximal effectiveness from the prophylaxis.

Since the use of antibiotic-impregnated bone cement is limited primarily to patients undergoing treatment of total joint infections, this topic is discussed in Chapters 9 and 10. However, we do wish to point out a large, retrospective study addressing the use of such cement as prophylaxis for primary joint arthroplasties. In 1997, Espehaug and associates (23) reviewed 10,905 primary cemented total hip arthroplasties performed in Norway between 1987 and 1995. The authors compared infection rates for patients receiving antibiotic-containing cement plus systemic antibiotic prophylaxis, systemic antibiotic prophylaxis alone, antibiotic-containing cement prophylaxis alone, or no antibiotic prophylaxis. Patients who received prophylaxis both systemically and in the cement had the lowest rate of revision due to infection. Those receiving only systemic antibiotic prophylaxis had a revision rate 4.3 times higher and those receiving only antibiotic-impregnated bone cement had a revision rate 6.3 times higher. The revision rate for patients receiving no antibiotic prophylaxis was 11.5 times higher. The authors concluded that systemic antibiotics combined with antibiotic-impregnated cement provides the best prophylaxis for total hip arthroplasties. However, before the use of antibiotic-impregnated bone cement can be recommended for routine primary joint arthroplasties, prospective, randomized trials are needed to study the rate of infection and the risk of increased microbial resistance (22).

The issue of prophylactic antibiotic administration for patients with joint arthroplasties undergoing procedures that may cause transient bacteremia remains controversial. Deacon and colleagues (24) reviewed the site of primary infection or procedure that was reported to have led to infection in 180 hematogenously spread prosthetic joint infections. They found that only 34 (19%) of these infections were caused by a procedure and that the major predisposing condition for hematogenous infection was an acute or chronic infectious process elsewhere in the body. They concluded that, except for patients with predisposing factors for late infection, such as rheumatoid arthritis or hemophilia, prophylactic antibiotics are unnecessary for patients with joint replacements who are having procedures.

Ainscow and Denham (25) studied 1000 patients who received 1112 joint replacements between 1966 and 1980. The patients were not instructed to take prophylactic antibiotics for dental or surgical procedures and were followed for an average of 6 years. Only 2 or 3 of these 1000 patients had hematogenous joint infections and 2 of them had rheumatoid arthritis. None of the infections occurred in the 224 patients who had dental or operative procedures.

There is some evidence to suggest that all patients are more susceptible to hematogenous prosthetic joint infections in the first 2 years after insertion of their joint. Hanssen and Osmon (22) found that the rate of deep wound infections in prosthetic joints is highest in the first 3 months after implantation and then gradually decreases to a stable rate of incidence 18 to 24 months after surgery. They suggest that the initial increased rate of infection is due not only to local factors affecting the wound, but also to an increased susceptibility to hematogenous infection during this period. They recommend that patients postpone any elective procedures that may cause transient bacteremia during the first 2 years after joint replacement.

Despite the conflicting evidence, antibiotics are frequently prescribed for prophylaxis before dental procedures because of the frequency of such procedures, the well-defined occurrence of bacteremia, and the data supporting the use of prophylactic antibiotics to prevent endocarditis after dental procedures (24). A 1994 survey showed that a majority of dentists ($n = 36$) and orthopedists ($n = 44$) believe that patients with prosthetic joints should receive prophylactic antibiotics before dental procedures (66% and 81%, respectively) (26).

Waldman and coworkers (27) retrospectively reviewed 3490 patients treated with total knee arthroplasties between 1982 and 1993. Sixty-two of these patients had developed late infections and 7 (11%) of these infections were strongly associated with dental procedures. All of the dental procedures that caused infection were extensive in nature, lasting between 75 and 205 minutes. The majority of these patients had a systemic disease, either diabetes or rheumatoid arthritis, that predisposed them to infection. The authors concluded that patients with total knee arthroplasties with underlying conditions that increase their risk for infection should receive prophylactic antibiotics when they have extensive dental procedures.

Jacobson and colleagues (28) and Gillespie (29), among others, have performed extensive cost analyses on the subject. However, there is no clear, reliable outcome because the estimates of the rate of infection after dental procedures performed with and without antibiotics are based on extremely limited and questionable data. Prophylaxis can appear more or less cost-effective than no prophylaxis with small variations in the rates of infections or choice of antibiotic (24).

An expert panel from the American Dental Association and the American Academy of Orthopaedic Surgeons released an advisory statement in 1997 concerning antibiotic prophylaxis for patients with joint arthroplasties undergoing dental work (30). The statement stratifies dental procedures into two groups, which are based on a high or low association with bacteremia (Table 1). Patients with a variety of systemic conditions are described as at increased risk for hematogenous joint infection (Table 2). Of note, the panel considers all patients to be high-risk within the first 2 years of joint placement. The statement recommends the use of prophylactic antibiotics in high-risk patients undergoing high-

Table 1 Risk of Bacteremia with Various Dental Procedures

High incidence	Low incidence
Dental extractions	Restorative dentistry (operative and prosthodontic) with or without retraction cord
Periodontal procedures including surgery, subgingival placement of antibiotic fibers/strips, scaling and root planing, and probing recall maintenance	Local anesthetic injections (nonintraligamentary)
Dental implant placement and reimplantation of avulsed teeth	Intracanal endodontic treatment; placement and buildup
Endodontic (root canal) instrumentation or surgery only beyond the apex	Placement of rubber dam
Initial placement of orthodontic bands, but not brackets	Postoperative suture removal
Intraligamentary local anesthetic injections	Placement of removable prosthodontic/orthodontic appliances
Prophylactic cleaning of teeth or implants when bleeding is anticipated	Taking of oral impressions
	Fluoride treatments
	Taking of oral radiographs
	Orthodontic appliance adjustment

risk procedures. Since all patients are considered high-risk for the first 2 years, they should all receive prophylactic antibiotics for high-risk dental procedures during this period. After 2 years, only patients who are predisposed to infection should be given prophylaxis. Patients should not be given prophylaxis for low-risk dental procedures. The statement also contains recommendations of antibiotic regimens for dental prophylaxis (Table 3).

The American Society for Gastrointestinal Endoscopy does not recommend antibiotic prophylaxis for any endoscopic procedures in patients with prosthetic joints (31). Although there are no published guidelines for patients undergoing cystoscopy, Deacon and colleagues recommend prophylactic antibiotics only when preprocedure urine analysis indicates the presence of infection (24). In this situation, the choice of antibiotic should be directed by sensitivity testing of organisms from a urine culture.

Table 2 Patients at Increased Risk of Hematogenous Total Joint Infection

First 2 years after joint replacement
Inflammatory arthropathies: rheumatoid arthritis, systemic lupus erythematosus
Disease-, drug- or radiation-induced immunosuppression
Insulin-dependent (type 1) diabetes
Previous prosthetic joint infections
Malnourishment
Hemophilia

Table 3 Suggested Antibiotic Prophylaxis Regimens

Patients not allergic to penicillin: amoxicillin, cephalexin, or cephradine 2 g orally 1 hour before procedure
Patients not allergic to penicillin and unable to take oral medications: ampicillin 2 g or cefazolin 1 g intramuscular or intravenous 1 hour before procedure
Patients allergic to penicillin: clindamycin 600 mg orally 1 hour before procedure
Patients allergic to penicillin and unable to take oral medications: clindamycin 600 mg intravenous 1 hour before procedure

IX. GUNSHOT WOUNDS

The use of prophylactic antibiotics after gunshot wounds causing injury to the musculoskeletal system remains controversial. It is generally accepted that high-velocity, high-energy gunshot wounds should be considered open injuries and treated with immediate and aggressive irrigation and débridement (32). Antibiotics should be administered according to open-fracture protocols.

Treatment of low-velocity, low-energy gunshot wounds is primarily dictated by the bone injuries. These injuries can be considered closed fractures. If a fracture can be easily managed nonoperatively, surgical treatment should not be used since it can increase the risk of infection by further disruption of the soft tissues (32). If the nature of the fracture indicates operative treatment, then prophylactic antibiotics should be given as in any other orthopedic procedure. Cefazolin, administered within 2 hours before the skin incision and continued every 8 hours for 24 hours, remains the ideal agent.

Patients treated nonoperatively probably do not require antibiotics unless they have grossly contaminated wounds. However, because contamination is not always apparent, the current consensus favors prophylactic antibiotics in this situation (32). Hansraj and associates (33) suggest 48 hours of antibiotic coverage for fractures caused by gunshot wounds that are treated nonoperatively. They found a cost savings of $2,348 per patient when using ceftriaxone instead of cefazolin. Although the cost of cefazolin was nearly five times lower, the use of ceftriaxone was less expensive because its longer half-life allowed for 24 instead of 48 hours of hospitalization.

In a prospective, randomized trial, Knapp and colleagues (34) compared 3 days of intravenous cephapirin sodium and gentamicin to 3 days of oral ciprofloxacin in patients with fractures caused by low-velocity gunshot wounds. They found a 2% infection rate in both sets of patients and concluded that oral antibiotics are effective for prophylaxis after low-velocity gunshot wounds. These results confirmed the earlier findings of Woloszyn and coworkers (35) that 7 to 10 days of oral cephalexin is as effective as intravenous antibiotics in preventing infection after low-velocity gunshot wounds.

On the basis of these studies, we recommend 72 hours of oral ciprofloxacin prophylaxis for low-velocity gunshot wound patients with nonsurgical musculoskeletal injuries, if the patient can obtain the medication. Many gunshot wound patients do not have access to or cannot afford outpatient ciprofloxacin. We recommend 1 g of intravenous cefazolin before discharge from the emergency department. This is clearly an area in which the ideal agent for prophylaxis and length of antibiotic coverage need further clarification.

Tetanus prophylaxis with 0.5 mL of tetanus toxoid is indicated for all gunshot wound patients who have not had a booster within the past 5 years or are unsure of their immunization history. Those who are not completely immunized (fewer than three previous immunizations) should be given toxoid in addition to 250–500 units of human tetanus immune globulin (32).

X. SUMMARY

There is ample evidence to recommend the use of prophylactic antibiotics in patients who have clean orthopedic surgical procedures, with the exception of arthroscopic procedures that do not involve the placement of foreign material. For maximal effectiveness, the prophylaxis should be administered within the 2 hours preceding the skin incision and the dosage repeated to maintain bacteriocidal levels for 12 hours. There is no need for continued dosage more than 24 hours after surgery. Cefazolin is an appropriate choice for prophylaxis; vancomycin is reserved for cases in which there is a high risk of MRSA or allergy to cefazolin.

There is very little to be gained from additional studies comparing the use of prophylactic antibiotics to that of placebos. Future studies comparing the efficacy of various prophylactic antibiotic regimens need to be extremely large in order to demonstrate significant effect, since the baseline rate of infection is very low with any form of effective prophylaxis. The role of prophylaxis against MRSA deserves additional study since the prevalence of MRSA in the hospital setting is likely to continue to rise in the future.

For patients with total joint replacements who have dental procedures, the current recommendations are for the use of prophylactic antibiotics for all patients who have procedures with a high risk of bacteremia for the first 2 years after arthroplasty and only for patients at an increased risk of infection thereafter. These recommendations are likely to continue to change in the future as the true risk of hematogenous infection after dental procedures is elucidated.

REFERENCES

1. CS Oshi, WV Carrion, FT Hoaglund. Use of parenteral prophylactic antibiotics in clean orthopaedic surgery: a review of the literature. Clin Orthop 296:249–255, 1993.

2. MO Tachdjian, EL Compere. Postoperative wound infections in orthopaedic surgery: evaluation of prophylactic antibiotics. J Int Coll Surg 28:797, 1957.
3. ML Olix, TJ Klung, WS Smith. Prophylactic antibiotics in elective operations on bones, joints and tendons. J Bone Joint Surg 42A:538, 1960.
4. EV Fogelberg, EK Zitzmann, FE Stinchfield. Prophylactic penicillin in Orthopaedic Surgery. J Bone Joint Surg 52A:95–98, 1970.
5. A Pavel, RL Smith, A Bakkard, AJ Larsen: Prophylactic antibiotics in clean orthopaedic surgery. J Bone Joint Surg 56A:777–782, 1974.
6. H Boxma, T Broekhuizen, P Patka, H Oosting. Randomised control trial of single dose antibiotic prophylaxis in surgical treatment of closed fractures: the Dutch Trauma Trial. Lancet 347:1133–1137, 1996.
7. WJ Gillespie, G Walenkamp. Antibiotic prophylaxis for proximal femoral and other closed long bone fractures. Cochrane Database Syst Rev 1:CD000244, 2001.
8. JF Burke. The effective period of preventive antibiotic action in experimental incisions and dermal lesions. Surgery 50:161–168, 1961.
9. WH Bowers, FC Wilson, WB Greene. Antibiotic prophylaxis in experimental bone infections. J Bone Joint Surg 55A:795–807, 1973.
10. DC Classen, RS Evans, SL Pestotnik, SD Horn, RL Menlove, JP Burke. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 326:281–286, 1992.
11. DP Johnson. Antibiotic prophylaxis with cefuroxime in arthroplasty of the knee. J Bone Joint Surg 69B:787–789, 1987.
12. EP Dellinger, PA Gross, TL Barrett, PJ Krause, WJ Martone, JE McGowan, RL Sweet, RP Wenzel. Quality standard for antimicrobial prophylaxis in surgical procedures. Clin Infec Dis 18:422–427, 1994.
13. JJ Meter, DW Polly, RP Brueckner, JJ Tenuta, L Asplund, WJ Hopkinson. Effect of intraoperative blood loss on the serum level of cefazolin in patients managed with total hip arthroplasty. J Bone Joint Surg 78A:1201–1205, 1996.
14. CL Nelson, TG Green, RA Porter, RD Warren. One day versus seven days of preventive antibiotic therapy in orthopedic surgery. Clin Orthop 176:258–263, 1983.
15. DN Williams, RB Gustilo. The use of preventive antibiotics in orthopaedic surgery. Clin Orthop 190:83–88, 1984.
16. RH Fitzgerald, RL Thompson. Cephalosporin antibiotics in the prevention and treatment of musculoskeletal sepsis. J Bone Joint Surg 65A:1201–1205, 1983.
17. BA Cunha, HR Gossling, HS Pasternak, CH Nightingale, R Quintilani. The penetration characteristics of Cefazolin, Cephalothin and Cephradine into bone in patients undergoing total hip replacement. J Bone Joint Surg 59A:856, 1977.
18. CP Page, JM Bohnen, R Fletcher, AT McManus, JS Solomkin, DH Wittmann. Antimicrobial prophylaxis for surgical wounds: guidelines for clinical care. Arch Surg 128:79–88, 1993.
19. E Mini, S Nobili, P Periti. Methicillin-resistant staphylococci in clean surgery: is there a role for prophylaxis? Drugs 54(suppl 6):39–53, 1997.
20. MJ Wood. The comparative efficacy and safety of teicoplanin and vancomycin. J Antimicrob Chemother 37:209–222, 1996.

21. JA Wieck, JK Jackson, TJ O'Brien, RB Lurate, JM Russell, JD Dorchak. Efficacy of prophylactic antibiotics in arthroscopic surgery. Orthopedics 20:133–134, 1997.
22. AD Hanssen, DR Osmon. The use of prophylactic antimicrobial agents during and after hip arthroplasty. Clin Orthop 369:124–138, 1999.
23. B Espehaug, LB Engesaeter, SE Vollset, LI Havelin, N Langeland. Antibiotic prophylaxis in total hip arthroplasty: review of 10905 primary cemented total hip replacements reported to the Norwegian arthroplasty register, 1987–1995. J Bone Joint Surg 79B:590–595, 1997.
24. JM Deacon, AJ Pagliaro, SB Zelicof, HW Horowitz. Prophylactic use of antibiotics for procedures after total joint replacement. J Bone Joint Surg 78A:1755–1770, 1996.
25. DAP Aniscow, RA Denham. The risk of haematogenous infection in total joint replacements. J Bone Joint Surg 66B:580–582, 1984.
26. MK Shrout, F Scarbrough, BJ Powell. Dental care and the prosthetic joint patient: a survey of orthopaedic surgeons and general dentists. J Am Dent Assoc. 125:429–435, 1994.
27. BJ Waldman, MA Mont, DS Hungerford. Total knee arthroplasty infections associated with dental procedures. Clin Orthop 343:164–172, 1997.
28. JJ Jacobson, SO Schweitzer, CJ Kowalski. Chemoprophylaxis of prosthetic joint patients during dental treatment: a decision-utility analysis. Oral Surg Oral Med Oral Pathol 72:167–177, 1991.
29. WJ Gillespie. Infection in total joint replacement. Infect Dis Clin North Am 4:465–484, 1990.
30. Advisory statement. Antibiotic prophylaxis for dental patients with total joint replacements. American Dental Association. American Academy of Orthopaedic Surgeons. J Am Dent Assoc 128:1004–1008, 1997.
31. American Society for Gastrointestinal Endoscopy. Antibiotic prophylaxis for gastrointestinal endoscopy. Gastrointest Endos 42:630–635, 1995.
32. CS Bartlett, DL Helfet, MR Hausman, E Strauss. Ballistics and gunshot wounds: effects on musculoskeletal tissues. J Am Acad Orthop Sur 8:21–36, 2000.
33. KK Hansraj, LD Weaver, AO Todd, SM Taylor, MD Griffin, KS Dukhram, TP Judd, MS Hansraj. Efficacy of Ceftriaxone versus cefazolin in the prophylactic management of extra-articular cortical violation of bone due to low-velocity gunshot wounds. Orthop Clin North Am 26:9–17, 1995.
34. TP Knapp, MJ Patzakis, J Lee, PR Seipel, K Abdollahi, RB Reisch. Comparison of intravenous and oral antibiotic therapy in the treatment of fractures caused by low-velocity gunshots: A prospective, randomized study of infection rates. J Bone Joint Surg 78A:1167–1171, 1996.
35. JT Woloszyn, GM Uitvlugt, ME Castle. Management of civilian gunshot fractures of the extremities. Clin Orthop 226:247–251, 1988.

5
Open Fractures

Current Concepts of Management

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I. INTRODUCTION

Open fractures represent injuries of considerable severity with variable potential for an adverse prognosis. These injuries continue to constitute a challenging problem, despite advances in the care of musculoskeletal injuries. The orthopedic surgeon can play a critical role in determination of the final outcome by prompt and judicious intervention. Therefore, a thorough understanding of the management principles of open fractures is mandatory.

A. Historical Perspective

In recent history, open fractures were considered injuries of grave prognosis. Preservation of life was frequently an unattainable goal, and amputation of the extremity was routine. In the l9th century, Billroth reported a mortality rate of approximately 50% in patients with open fractures of the lower leg (1). The treatment of fractures secondary to gunshot wounds consisted of immediate amputation. In the American Civil War, 26% of patients died; the mortality rate reached 54% among those with thigh amputations (2). Guidelines for contaminated tissue resection, foreign body removal, and prevention of primary wound closure later than 8 hours after the injury were proposed at the end of the First World War (3).

Considerable improvements of open fracture care have emerged in the past three decades. These include increased understanding of infection and fracture biological principles, improved implants and devices for fracture stabilization, microsurgical procedures for revascularization of dysvascular extremities, and reconstruction of the soft tissue envelope.

Thus, we now aim to prevent clostridial myonecrosis, prevent infection at the fracture site, achieve fracture union, and restore function.

B. Definition

A fracture is characterized as open when it is accompanied by soft tissue disruption that establishes communication of the fracture site with the outside environment.

C. Etiological and Pathophysiological Characteristics

Open fractures are usually the result of high-energy trauma. Motorcycle, motor vehicle, and pedestrian injuries account for the majority of cases (4,5). The consequences of a high-energy injury that results in an open fracture should not be viewed only in the context of the fractured bone. The surrounding soft tissues, the whole extremity, and, even more importantly, the whole patient should be considered.

1. Bone

High-energy trauma can result in comminution, displacement, periosteal stripping, and denudation of bone fragments from their soft tissue attachments. Even extrication and loss of fragments are possible. Thus, the structural integrity of the bone is severely compromised and viability of the osseous fragments is endangered.

2. Soft Tissues

The soft tissues are disrupted to a variable degree in all open fractures. This disruption has several adverse consequences:

1. Loss of coverage: Bone, articular cartilage, tendons, and nerves may be exposed to a variable degree. Desiccation and irreversible structural damage occur. In addition, hardware is left exposed and infection is facilitated.
2. Compromised vascularity: Soft tissue injury compromises vascularity at the fracture site and predisposes to a diminished healing potential. In

addition, the host defense mechanism response to the contamination insult is impaired.

3. Communication of fracture with environment: Contamination with infectious microorganisms is an unavoidable complication of all open fractures (6–8). Furthermore, the wound may also be contaminated with foreign material introduced during the injury, which serves as a nidus for infection. The fracture hematoma occupies the zone of injury, extends along fascial planes, fills dead spaces, and serves as a culture medium for microorganisms, in addition to any devitalized tissues present.

3. Extremity

The injury may have further consequences on the extremity. Neurovascular compromise may be present, endangering limb viability. It should also be remembered that the presence of an open fracture wound does not preclude development of compartment syndrome, which has been reported to occur in 9% of cases, especially in injuries with a severe crushing component (9).

4. Patient

Open fractures can be accompanied by potentially life-threatening trauma of other organ systems, or by musculoskeletal injuries at other body regions. Associated injuries involving intra-abdominal organs, chest, skull, pelvis, and major blood vessels have been described in 50% of open fracture patients (4). Thus, detailed evaluation of the patient who has an open fracture by the trauma team and appropriate resuscitation are necessary.

II. PRINCIPLES OF MANAGEMENT

The main principles of open fracture management include the following:

Evaluation of the injury
Use of antimicrobials
Soft tissue considerations
Skeletal fixation
Early bone grafting

A. Evaluation of the injury

Careful assessment of the open fracture includes the mechanism of injury, the neurovascular status of the extremity, the condition of the soft tissues, the presence of contamination, and the fracture characteristics.

The severity of injury can vary considerably among cases. Therefore, a classification system of open fractures, based on the assessment indicated, is useful to describe the injury, provide guidelines for treatment, determine prognosis, and aid in the comparison of various treatment modalities for research purposes.

The classification system of Gustilo and Anderson, subsequently modified by Gustilo, Mendoza, and Williams, has been widely used (8,10). This classification comprises the following types:

Type I: Puncture wound of 1 cm or less, with minimal contamination or muscle crushing.

Type II: Laceration more than 1 cm long with moderate soft tissue damage and crushing. Bone coverage is adequate and comminution is minimal.

Type IIIA: Extensive soft tissue damage, often due to a high-velocity injury with a severe crushing component. However, bone coverage is adequate. Massively contaminated wounds, and severely comminuted or segmental fractures, are included in this subtype.

Type IIIB: Extensive soft tissue damage with periosteal stripping and bone exposure, usually associated with massive contamination and severe bone comminution. Flap coverage is required.

Type IIIC: Arterial injury requiring repair.

However, the reliability of this classification has been questioned. Brumback and Jones evaluated the responses of 245 orthopedic surgeons who were also asked to classify 12 open fractures of the tibia on the basis of videotaped case presentations. The average agreement among the observers for all 12 fractures was 60% overall, and specifically 66% for academic orthopedic surgeons and 59% for residents and fellows (11).

In fact, on admission of the patient to the emergency department, the true extent and severity of the injury cannot be accurately assessed. Therefore, classification of the fracture should be done only in the operative room, after exploration and débridement of the wound. We want to emphasize the importance of contamination and crushing in classifying an open fracture. These are important factors that should not be mistakenly overlooked in a wound of small size.

B. Use of Antimicrobials

Prevention of subsequent infection is a major focus of the treatment of open fractures. Around 50% to 70% of patients with open fractures have bacterial contamination of their wounds. Antibiotics are not used as “prophylaxis” in these wounds, but rather as treatment of wound contamination. Presumptive antibiotic therapy has been shown to decrease the risk of the development of infection in

patients with open fractures. Patzakis and colleagues showed a decrease of infection rate from 13.9% to 2.3% when patients with open fractures were treated with a cephalosporin. The single most important factor in reducing the infection rate is the early administration of antibiotics (6).

However, the organisms initially present in the wound are usually not the organisms that cause later infection. Most infections are caused by organisms found in the hospital environment, such as staphylococci and aerobic gram-negative bacilli. In highly contaminated open fractures and those from special environmental circumstances, other organisms can be found. Anaerobes, especially *Clostridium perfringen*, are a special concern in patients who have highly contaminated fractures. Other anaerobes and enteric gram-negative bacilli may be associated with open fractures in a farm or barnyard environment.

The choice of which antibiotic to use should be governed by what are thought to be the likely organisms to cause infection. The optimal regimen of systemic antibiotics and the optimal length of therapy remain controversial. Antibiotic regimens that have been recommended include cefazolin plus gentamicin or tobramycin, ticarcillin/clavulanate, or a quinolone such as ciprofloxacin. Special circumstances of extensive environmental exposure may require the regimens with broader-spectrum coverage, including coverage of anaerobes. The length of antibiotic therapy is generally 3 days, although some authors have suggested that 1 day is adequate (12,13). Prolonged therapy may select for resistant organisms.

Many physicians have used local administration of antibiotics in irrigation fluid routinely during surgery. A standard irrigation consists of 8 liters of sterile saline solution, followed by 2 liters of antibiotic fluid consisting of 50,000 units of bacitracin and 1 million units of polymyxin per liter of saline solution. Although topical antibiotics are used routinely in irrigation fluid, their efficacy has never been scientifically demonstrated in open fracture management.

Local therapy with antibiotic-impregnated polymethylmethacrylate (PMMA) beads provides high local levels of antibiotic while minimizing systemic toxicity. Osterman and colleagues found that adding tobramycin-impregnated PMMA beads to a regimen of intravenous penicillin, cefazolin, and tobramycin decreased the infection rate of open fractures from 12% to 3.7% (14). Currently, many surgeons use a bead pouch, with tobramycin-impregnated PMMA beads placed in the open surgical wound after irrigation and débridement, and covered with an Opsite dressing. Elution of antibiotic from the beads requires fluid in the wound and is related to the size of the beads (smaller beads elute more antibiotic) and the concentration of antibiotic in the cement.

One of the greatest problems for the future is the growing frequency of antimicrobial resistance in bacteria. Methicillin-resistant *Staphylococcus aureus* has been known for decades, but its incidence is growing, even among nonhospitalized patients. Multidrug-resistant gram-negative bacilli are becoming

an increasing problem, limiting the treatment options that are available. Vancomycin-resistant *Enterococcus faecium* has become a major problem in nosocomial infections in the United States but thus far has been rarely seen in osteomyelitis. The greatest concern is the development of vancomycin-resistant *Staphylococcus aureus*, which has now been identified in patients in Japan, the United States, and Europe. Although this has not yet been reported as a cause of osteomyelitis, bone infections with this organism could be catastrophic since it is resistant to the standard antibiotics used in empirical therapy.

C. Soft Tissue Considerations

Wound management includes irrigation and débridement, and subsequently either wound closure if adequate coverage can be achieved with the soft tissues available, or soft tissue reconstruction with local or free muscle flaps.

Thorough irrigation and surgical débridement are the most important principles in open fracture management. Removal of all devitalized tissues and foreign material from the wound is key to the prevention of infection, since they promote the growth of microorganisms and at the same time constitute a barrier for the host's defense mechanisms.

Irrigation mechanically removes foreign bodies and reduces the bacterial concentration. Although consensus exists on the necessity of irrigation, the irrigation solution and the pressure with which it should be delivered remain controversial. High pressure pulsatile lavage was associated in experimental studies with a detrimental effect on early new bone formation (15) and damage to bone architecture with bacterial seeding into the intramedullary canal (16). Low-pressure lavage, however, may not be as effective in removing adherent bacteria if more than 6 hours has elapsed since the injury (17). However, no clinical studies have addressed the effects of different irrigation methods on infection and fracture healing. We advocate irrigating the wound with 10 liters of saline solution by gravity tubing.

Radical débridement to eliminate all nonviable tissue and foreign material is critical in the management of open injuries. Débridement should be performed in the operating room. A tourniquet is applied to the extremity, to be used only when necessary. Débridement without inflation of the tourniquet can make identification of viable tissues easier and prevent additional tissue damage secondary to ischemia. However, Godina has advocated the judicious use of the tourniquet to facilitate visualization of the extent of injury in a bloodless field (18).

When the injury wound is insufficient for thorough assessment of the injury, such as in type I and II open fractures, the existing wound should be extended to facilitate débridement. It should be extended so as to respect the vascularity of soft tissue flaps, and facilitate fracture fixation and anticipated reconstructive procedures, whenever possible.

Skin and subcutaneous tissues are sharply débrided back to bleeding edges. Muscle is débrided until bleeding is visualized. Viable muscle can be identified by its bleeding, color, and contractility. Bone fragments devoid of soft tissue attachments are avascular and should be discarded, unless they constitute part of an articular surface. Hemostasis should be achieved. Débridement should be performed at 24- to 48-hour intervals, according to the degree of contamination and soft tissue damage, until a clean wound with viable tissues and no signs of infection is present. In injuries with extensive soft tissue damage requiring flap coverage, débridement should be also repeated at the time of the procedure.

The optimal time for wound closure is still debated. Primary wound closure, after a thorough débridement, prevents secondary contamination and has been associated with slightly decreased, but not statistically significant, infection rates (7). However, the main disadvantage of primary closure is the potential for gas gangrene. Gas gangrene (clostridial myonecrosis) is a catastrophic complication that may lead not only to loss of the limb, but to death of the patient as well (19). Primary wound closure, inadequate débridement, and inadequate antibiotic therapy are the factors that increase the risk of this complication (20).

Delayed wound closure, within 3–7 days, prevents anaerobic conditions in the wound, permits drainage, allows for repeat débridements at 24- to 48-hour intervals, gives time to tissues of questionable viability to declare themselves, and facilitates use of the antibiotic beadpouch technique. Sealing of the wound with OpSite prevents secondary contamination and makes delayed wound closure even more preferable.

However, the additional surgical wound, created in order to assess the condition of the bone and soft tissues and facilitate débridement, can be safely closed primarily in type I and II open fractures, leaving the injury wound open. If the injury wound is directly over the bone, it can be closed, and the wound away from the fracture site left open. This technique proved useful in our experience and we have coined the term *partial wound closure* to describe it (21). In type III injuries, we advocate leaving the wound open in its entirety.

When extensive damage to the soft tissues is present, as in type IIIB open fractures, usually occurring at the tibia, adequate coverage may not be possible and soft tissue reconstruction should be performed. The importance of a viable soft tissue envelope cannot be overemphasized. The soft tissue envelope is a source of vascularity at the fracture site; therefore, it promotes fracture healing, delivery of antibiotics, and action of the host defense mechanisms. It provides durable coverage, which prevents secondary contamination of the wound and desiccation of bone, articular cartilage, tendons, and nerves, which would be irreversibly damaged if exposed.

The selection of coverage depends on the location and magnitude of the soft tissue defect (22–24). Soft tissue reconstruction is usually achieved with local

or free muscle transfers, and a microvascular surgeon should always evaluate an open fracture with extensive soft tissue damage and participate in its management.

Local pedicle muscle flaps include the gastrocnemius for proximal third tibia fractures and the soleus for middle third fractures. In distal third tibia fractures free muscle flaps are necessary. The latissimus dorsi, the rectus abdominis, and the gracilis muscle may be transferred (25,26). In our opinion, free muscle flaps may be considered even in more proximally located fractures for two reasons. First, the local muscles usually participate in the zone of injury; thus their condition and viability may not be optimal. Interestingly, Pollak and colleagues concluded that use of a free flap in limbs with a severe osseous injury was significantly less likely to lead to wound complications necessitating operative treatment when compared to a rotational flap (26). Second, even if they are not damaged, their transfer deprives the already traumatized leg of their function (27). On the other hand, free muscle transfer is more demanding, technically for the surgeon and physiologically for the patient. In injuries with exposed tendons, fasciocutaneous flaps, such as the radial forearm flap, are preferred to facilitate tendon gliding.

Soft tissue reconstruction should be performed early, within the first 7 days. Delays beyond 7 to 10 days have been associated with increased flap and infectious complications (28,29). Early flap coverage decreased the deep infection rate from 69% (9 of 13 wounds) to 18% (2 of 11) in a study by Fisher and associates (28). Cierny and associates observed a 50% infection rate (6 of 12 wounds) with delayed coverage, but only 4% (1 of 24) with early muscle transfer (29). Godina even argued in favor of flap coverage within 72 hours. He observed flap failure in less than 1% (1/134) of early cases compared to 12% (20/167) in patients operated from 4 to 90 days. The infection rate was only 1.5% (2/134) in the early group, whereas it increased to 17.5% (29/167) in the other group (18). The experience of Gopal and associates with an early aggressive protocol in type IIIB and IIIC open fractures was also satisfactory. In their series, deep infection developed in 6% (4/63) of fractures that were covered within 72 hours, in contrast to 29% (6/21) in the ones with coverage beyond 72 hours (25).

It should be stressed that in all these studies the antibiotic bead pouch had not been used, and therefore secondary contamination was a major factor contributing to the infectious complications.

D. Salvage or Amputation?

Salvage and reconstruction of a severely traumatized extremity, although possible with the advances in microsurgical techniques, are not always indicated. The treating surgeon may be confronted with the dilemma of salvage versus amputa-

tion of a nonviable extremity with a type IIIC open fracture or a mangled extremity with a IIIB fracture.

The appropriate decision is difficult, since recovery of function in a salvaged but severely injured extremity may be limited or absent. Thus, multiple reconstructive procedures with associated morbidity and prolonged hospitalization may be too expensive a price to pay for the end result of a useless and painful limb. Moreover, leg prostheses offer satisfactory restoration of function, especially for below-knee amputations. Georgiadis and coworkers concluded that early below-knee amputation resulted in faster recovery and reduced long-term disability in comparison with successful limb salvage (30).

In deciding how best to treat the mangled extremity, a variety of factors, broadly classified as patient and extremity factors, should be considered. Patient factors include the general condition and age of the patient. Associated injuries resulting in cardiopulmonary or hemodynamic compromise, as well as preexisting medical problems, are weighed against a lengthy salvage procedure, especially in a patient of advanced age. Conditions adversely affecting the blood vessels, such as diabetes mellitus, vasculitis, and smoking, increase the risk of anastomosis failure and should be taken into consideration. The occupation, functional requirements, and socioeconomic background of the patient are important, since the salvage attempt is accompanied by prolonged disability time, increased psychological distress, and financial demands (30).

Important extremity factors comprise the time since the injury, the severity of the injury, and the previous functional status of the extremity. Warm ischemia time greater than 6 hours leads to irreversible changes in cellular structure of muscle. Even if vascularity is reestablished, tissue necrosis may not be prevented. Systemic risks of revascularizing a limb with prolonged ischemia must also be considered and addressed. These include acidosis, hyperkalemia, and rhabdomyolysis. Severe crushing and avulsion are associated with a compromised functional result. Tibial nerve disruption deprives the sole of the foot of protective sensation. Finally, the previous condition of the extremity should be considered. A history of major trauma, neurological disease, or congenital deformity resulting in impaired function may not justify a salvage attempt.

Specialized scoring systems, such as the mangled extremity severity score (MESS), appear to offer guidelines for decision making in lower extremity injuries (31). However, the final decision should be an individualized one, based on sound judgment and assessment of patient and extremity parameters (32). The patient should be informed of the potential risks and benefits of surgery and the possibility of early or late amputation. Warm ischemia time greater than 6 hours in a crush injury and complete tibial nerve disruption in adults constitute absolute contraindications for a revascularization and salvage attempt (33). In this setting, amputation is not a failure, but rather a step toward stabilization of the patient and rehabilitation of the extremity.

E. Skeletal Fixation

Stable fracture fixation is necessary in open fractures. Fracture stability prevents further injury to the soft tissues and, despite the presence of implants, enhances the host response to infectious organisms (34). In addition, stable fixation facilitates wound and patient care and allows early motion and functional rehabilitation of the extremity, which are even more important in the presence of traumatized soft tissues.

Fracture stabilization can be accomplished with intramedullary nailing, external fixation, or plate and screw fixation. The choice of method depends on the fractured bone, the location of the fracture (intra-articular, metaphyseal, diaphyseal), the soft tissue injury, and the surgeon's expertise.

Intramedullary nailing has been found by numerous investigators to be an effective method of stabilization of diaphyseal fractures of the lower extremity (35–38). Statically interlocked intramedullary nailing maintains length and alignment of the fracture bone, is biomechanically superior to other methods, and does not interfere with soft tissue management. However, it is technically more demanding, and it disrupts the endosteal bone circulation to a variable degree, depending on whether the medullary canal receives reaming.

Reamed intramedullary nailing is the method of choice for open femur fractures. Brumback and associates observed no infections in 62 type I, II, and IIIA open fractures, whereas infection developed in 3 of 27 (11%) type IIIB open femur fractures (35). Unreamed intramedullary nailing is widely used for open tibia fractures (36–38), but controversies exist regarding the optimal method of fixation of these fractures.

External fixation can be helpful in wounds with severe soft tissue damage and contamination, as in type IIIB and IIIC open fractures, since no hardware is implanted and the vascularity of the fracture is not disturbed. It is applied in a technically easy, safe, and expedient way, with minimal blood loss, at a site distant to the injury and does not interfere with wound management. External fixation is particularly suitable for diaphyseal tibia fractures, because of the subcutaneous location of the bone. In addition, ring or transarticular fixators may be used for periarticular fractures. The disadvantages of the technique are the necessity for patient compliance and the associated complications of pin tract infections and malunion. However, these complications can be minimized with an external fixator protocol that includes use of half-pins inserted after predrilling, meticulous pin tract care, and use of the external fixator as the definitive method of fixation with early bone grafting if indicated.

By maintaining the fixator as the definitive treatment until fracture healing, the surgeon can prevent the loss of alignment that frequently occurs when the fixator is prematurely removed (39) and the high infection rate that accompanies delayed intramedullary nailing (28,40). Conversion of external fixation to

intramedullary nailing, if the surgeon believes it will improve fracture stabilization, should be performed only within the first week after the injury to prevent infectious complications. Otherwise, the fixator should be the definitive fracture fixation.

Many reports in the literature have demonstrated the efficacy of external fixation as definitive treatment and the value of early bone grafting in these severe injuries (39,41,42). Behrens and Searls evaluated a series of 75 tibia injuries of which 54 were open fractures. Pin tract infection occurred in 9 of 75 cases (12%), with one ring sequestrum (1.3%). One loss of reduction occurred (1.3%) (41). Edwards and colleagues, in a prospective series of 202 type III open tibia fractures, concluded that the infection rate was reduced to 9% by thorough débridement and delayed union and angulation were reduced with early grafting (39). Marsh and associates, in a prospective study of 101 type II and III fractures, observed that 96 fractures (96%) healed; the 93 had less than 10° of angulation in any plane. There were only six fracture site infections (42). Thus, external fixation can be useful for type IIIB and type IIIC fractures, especially with heavily contaminated wounds.

Plate and screw fixation is useful in intra-articular and metaphyseal fractures, because it allows restoration of joint congruency and orientation, and in upper extremity diaphyseal fractures without massive contamination. Plate and screw fixation has the advantage of accurate restoration of the anatomical features. Screw fixation can be used for fixation of intra-articular fragments, either alone or in conjunction with a ring or transarticular fixator.

III. CONTROVERSIES IN OPEN FRACTURE FIXATION

The optimal fixation method for open tibia fractures remains controversial. The two main debates concern intramedullary nailing versus external fixation and unreamed versus reamed nailing. The management protocol of type IIIC fractures is another issue that has not been clearly defined.

A. Choice of Fixation

Few studies have compared the two techniques in a prospective, randomized fashion. Tornetta and associates compared external fixation with unreamed nails in 29 type IIIB open tibial fractures. All fractures healed and there was no difference in infectious complications between the two techniques (36). In another prospective series of 174 open tibial fractures, Henley and coworkers concluded that the severity of soft tissue injury rather than the choice of implant appears to be the predominant factor influencing bone healing and injury site infection. However, half-pin external fixators appeared to be less efficacious than

unreamed interlocking intramedullary nails in maintaining limb alignment and were associated with a pin tract infection in 50% of cases (37). A meta-analysis by Bhandari and associates on the management of open tibia fractures demonstrated that unreamed nails, compared with external fixators, reduced the risk of reoperation, malunion, and superficial infection (38).

Intramedullary nailing is cosmetically preferred by patients and does not require the same high level of patient compliance as external fixation. However, no advantage has been demonstrated in terms of fracture healing and injury site infection, and the potential problems of pin tract infections and malunion can be minimized with the external fixator protocol described.

Unreamed nailing is considered advantageous because of the greater preservation of endosteal blood supply and the increased room for revascularization when compared to reamed nailing (43). In addition, it is not associated with mechanical, thermal, or embolic bone damage (44). Because of this, unreamed nailing is considered the preferred technique in open tibia fractures, especially since these fractures have an already compromised periosteal vascularity, which is due to the effect of the injury (36,37,45).

However, the unreamed technique allows the insertion of small-diameter implants only. Reamed nailing, by utilizing nails of larger diameter, improves stability at the fracture site and reduces implant failure. Furthermore, cortical circulation is gradually reconstituted after reamed nailing (43).

Clinical experience with reamed nailing in open tibia fractures is limited. Keating and colleagues reported a reduction in infection rates achieved by combining reamed nailing with the bead pouch technique. There were four deep infections (16%) in 25 fractures treated before the use of the bead pouch and two (4%) deep infections in 53 fractures when the bead pouch was used (46).

Two prospective, randomized studies compared reamed to unreamed nailing in open tibia fractures and observed higher infection rates in reamed nailing, although the differences were not statistically significant. In a study by Keating and coworkers, infection developed in 2.5% (1/40) of fractures treated with unreamed nailing, versus 4.4% (2/45) of the ones treated with the reamed technique (47). Finkemeier and associates observed an infection rate of 4% in unreamed nailing and of 5.3% in reamed nailing (48). Both studies noted a reduced screw failure rate in the reamed group.

No advantages were clearly demonstrated in the reamed technique, whereas the satisfactory results of unreamed nailing have been clearly demonstrated by many authors, even in complex cases (36,37,45). We previously reported an infection rate of 15% (5/33) in severe open tibia fractures that were treated by unreamed nailing in conjunction with free or local muscle flaps (45). Therefore, until further studies evaluate the two techniques, it would be preferable to insert tibial nails without reaming to minimize damage to bone vascularity.

B. Timing of Fixation of IIIC Open Fractures

Type IIIC open fractures by definition have an arterial injury that requires repair. However, the management priorities are not well established. Should fracture fixation precede or follow arterial repair?

Arterial repair, followed by stabilization, minimizes ischemia time and soft tissue damage and was recommended as the best approach by Ashworth and colleagues (49). Prompt reconstitution of arterial flow to the extremity prevents the prolongation of ischemia that would have resulted had the fracture been fixed first. Muscle tissue sustains irreversible changes after 6 hours of warm ischemia time, and a greater delay is considered a contraindication for revascularization. Thus, minimization of the duration of ischemia is very important, especially when extensive soft issue damage and crushing are present. Traumatized muscle is more vulnerable to the effects of ischemia, and its survival limit may be less than 6 hours.

However, in the absence of skeletal fixation, the length, alignment, and rotation of the fractured bone are not corrected and the soft tissue relationships and tension are altered. Thus, it is difficult to evaluate the necessity for bone grafts and their optimal length. Moreover, without fracture site stability, the microvascular anastomosis is not protected from inadvertent damage. Although definitive fracture fixation before the arterial repair has been preferred by some authors (50), rapid, provisional fixation with an external fixator and conversion to the definitive fixation method after the arterial repair appear to be a better option (51).

Arterial intraluminal shunts offer a viable alternative. They allow prompt revascularization of the extremity and permit definitive fixation without the detrimental effect of prolonged ischemia (52). Clinical studies prospectively comparing the different protocols are needed to establish the best course of action.

C. Early Bone Grafting

In the presence of bone defects or delayed healing, we advocate early bone grafting. The preferred timing for bone grafting ranges in the literature from 2 to 6 weeks after soft tissue coverage (39,53). We elect to wait for 6 weeks after a soft tissue transfer to ensure the absence of infection and the restoration of the soft tissue envelope. Then, the existing defect is bone grafted. Early bone grafting is also beneficial when healing is delayed and no callus is apparent on radiographs by 8–12 weeks. Grafts are applied either at the fracture site beneath a flap or posterolaterally, away from the site of injury.

IV. SUMMARY

Open fractures are high-energy injuries that should be treated on an emergent basis and the patient should be evaluated for associated injuries and resuscitated appropriately. Injury assessment and classification should be done intraoperatively and be based on the degree of contamination and soft tissue damage. Early, systemic, wide-spectrum antibiotic therapy should be initiated, and we recommend a 3-day combination therapy with a cephalosporin and an aminoglycoside, supplemented with penicillin or ampicillin for farm and vascular injuries. Local antibiotic delivery with the bead pouch technique is effective and prevents secondary wound contamination. Thorough irrigation and débridement with elimination of dead tissues and foreign material are critical and the wound should not be closed primarily to prevent the complication of gas gangrene. Partial wound closure is preferred for type I and type II fractures, whereas wounds in type III fractures are initially left open. Delayed primary wound closure should be performed within 3 to 7 days. In the presence of extensive soft tissue damage, soft tissue coverage is accomplished with local or free muscle flaps. In selected cases with severe injuries, amputation may be a treatment option. Stable fracture fixation should be achieved with a method suitable for the bone and soft tissue characteristics. If external fixation is used, it should remain as the definitive method of treatment. Early bone grafting is indicated for bone defects or delayed union. A treatment plan guided by the principles summarized achieves the goals of prevention of infection and clostridial myonecrosis, fracture healing, and restoration of function in most of these challenging injuries.

REFERENCES

1. W Billroth. Clinical Surgery. London: The New Sydenham Society, 1881.
2. C Colton. The history of fracture treatment. In: BD Browner, AM Levine, JB Jupiter, PG Trafton, eds. Skeletal Trauma. Vol 1. Philadelphia: WB Saunders, 1998:3–31.
3. General principles guiding the treatment of wounds of war: Conclusions adopted by the Inter-Allied Surgical Conference held in Paris, March and May 1917. London: H.M. Stationery Office, 1917.
4. RB Gustilo. Management of open fractures: An analysis of 673 cases. Minn Med 54:185–189, 1971.
5. CM Court-Brown, S Rimmer, U Prakash, MM McQueen. The epidemiology of open long bone fractures. Injury 29:529–534, 1998.
6. MJ Patzakis, JP Harvey Jr, D Ivler. The role of antibiotics in the management of open fractures. J Bone Joint Surg 56A:532–541, 1974.
7. MJ Patzakis, J Wilkins. Factors influencing infection rate in open fracture wounds. Clin Orthop 243:36–40, 1989.

8. RB Gustilo, JT Anderson. Preventjon of infection in the treatment of one thousand and twenty-five open fractures of long hones: retrospective and prospective analyses. J Bone Joint Surg 58A:453–458, 1976.
9. SS Blick, RJ Brumback, A Poka, AR Burgess, NA Ebraheim. Compartment syndrome in open tibial fractures. J Bone Joint Surg 68A:l348–1353, 1986.
10. RB Gustilo, RM Mendoza, DN Williams. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. J Trauma 24:742–746, 1984.
11. RJ Brumback, AL Jones. Interobserver agreement in the classification of open fractures of the tibia. The results of a survey of two hundred and forty-five orthopaedic surgeons. J Bone Joint Surg 76A:1162–1166, 1994.
12. EP Dellinger, SD Miller, MJ Wertz, M Grypma, B Droppert, PA Anderson. Risk of infection after open fracture of the arm or leg. Arch Surg 123:1320–1327, 1988.
13. EP Dellinger, ES Caplan, LD Weayer, MJ Wertz, BM Droppert, N Hoyt, R Brumback, A Burgess, A Poka, SK Benirschke. Duration of preventive antibiotic administration for open extremity fractures. Arch Surg 123:333–339, 1988.
14. PA Ostermann, D Seligson, SL Henry. Local antibiotic therapy for severe open fractures. A review of 1085 consecutive cases. J Bone Joint Surg 77B:93–97, 1995.
15. DR Dirschl, GP Duff, LE Dahners, M Edin, BA Rahn, T Miclau. High pressure pulsatile lavage irrigation of intrarticular fractures: effects on fracture healing. J Orthop Trauma 12:460–463, 1998.
16. M Bhrndari, A Adili, RJ Lachowski. High pressure pulsatile lavage of contaminated human tibiae: an in vitro study. J Orthop Trauma 12:479–484, 1998.
17. M Bhandari, EH Schemitsch, A Adili, RJ Lachowski, SG Shaughnessy. High and low pressure pulsatile lavage of contaminated tibial fractures: an in vitro study of bacterial adherence and bone damage. J Orthop Trauma 13:526–533, 1999.
18. M Godina. Early microsurgical reconstruction of complex trauma of the extremities. Plast Reconstr Surg 78:285–292, 1986.
19. MJ Patzakis. Clostridial myonecrosis. Instr Course Lect 39:491–493, 1990.
20. MJ Patzakis, LD Dorr, W Hammond, D Ivler. The effect of antibiotics, primary and secondary closure on clostridial contaminated open fracture wounds in rats. J Trauma 18:34–37, 1978.
21. MJ Patzakis, J Wilkins, TM Moore. Considerations in reducing the infection rate in open tibial fractures. Clin Orthop 178:36–41, 1983.
22. R Sherman, J Ecker. Soft tissue coverage. In: BD Browner, AM Levine, JB Jupiter, PG Trafton, eds. Skeletal Trauma. Vol 1. Philadelphia: WB Saunders, 1998:419–448.
23. MI Yaremchuk. Acute management of severe soft tissue damage accompanying open fractures of the lower extremity. Clin Plast Surg 13:621–629, 1986.
24. C Zalavras, LE Shepherd, F Sharpe, M Stevanovic. Management of the mangled upper extremity. In: KN Malizos, ed. Reconstructive Microsurgery. Georgetown, Landes Bioscience, 2002.
25. S Gopal, S Majumder, AG Batchelor, SL Knight, P De Boer, RM Smith. Fix and flap: the radical orthopaedic and plastic treatment of severe open fractures of the tibia. J Bone Joint Surg 82B:959–966, 2000.

26. AN Pollak, ML McCarthy, AR Burgess. Short-term wound complications after application of flaps for coverage of traumatic soft-tissue defects about the tibia. The Lower Extremity Assessment Project (LEAP) Study Group. J Bone Joint Surg 82A:1681–1691, 2000.
27. IA Kramers-de Quervain, JM Lauffer, K Kach, O Trentz, E Stussi. Functional donor-site morbidity during level and uphill gait after a gastrocnemius or soleus muscle-flap procedure. J Bone Joint Surg 83A:239–246, 2001.
28. MD Fischer, RB Gustilo, TF Varecka. The timing of flap coverage, bone-grafting, and intramedullary nailing in patients who have a fracture of the tibial shaft with extensive soft-tissue injury. J Bone Joint Surg 73A:1316–1322, 1991.
29. G Cierny III, HS Byrd, RE Jones. Primary versus delayed soft tissue coverage for severe open tibial fractures: a comparison of results. Clin Orthop 178:54–63, 1983.
30. GM Georgiadis, FF Behrens, MJ Joyce, AS Earle, AL Simmons. Open tibial fractures with severe soft-tissue loss: limb salvage compared with below-the-knee amputation. J Bone Joint Surg 75A:1431–1441, 1993.
31. K Johansen, M Daines, T Howey, D Helfet, ST Hansen Jr. Qbjective criteria accurately predict amputation following lower extremity trauma. J Trauma 30:568–572, 1990.
32. P Tornetta III, SA Olson. Amputation versus limb salvage. Instr Course Lect 46:511–518, 1997.
33. RH Lange, AW Bach, ST Hansen Jr, KH Johansen. Open tibial fractures with associated vascular injuries: prognosis for limb salvage. J Trauma 25:203–208, 1985.
34. P Worlock, R Slack, L Harvey, R Mawhinney. The prevention of infection in open fractures: an experimental study of the effect of fracture stability. Injury 25:31–38, 1994.
35. RJ Brumback, PS Ellison Jr, A Poka, R Lakatos, GH Bathon, AR Burgess. Intramedullary nailing of open fractures of the femoral shaft. J Bone Joint Surg 71A:1324–1331, 1989.
36. P Tornetta III, M Bergman, N Watnik, G Berkowitz, J Steuer. Treatment of grade-IIIb open tibial fractures: a prospective randomised comparison of external fixation and non-reamed locked nailing. J Bone Joint Surg 76B:13–19, 1994.
37. MB Henley, JR Chapman, J Agel, EJ Harvey, AM Whorton, MF Swiontkowski. Treatment of type II, IIIA, and IIIB open fractures of the tibial shaft: a prospective comparison of unreamed interlocking intramedullary nails and half-pin external fixators. J Orthop Trauma 12:1–7, 1998.
38. M Bhandari, GH Guyatt, MF Swiontkowski, EH Schemitsch. Treatment of open fractures of the shaft of the tibia. J Bone Joint Surg 83B:62–68, 2001.
39. CC Edwards, SC Simmons, BD Browner, MC Weigel. Severe open tibial fractures: results treating 202 injuries with external fixation. Clin Orthop 230:98–115, 1988.
40. JM McGraw, EV Lim. Treatment of open tibial-shaft fractures: external fixation and secondary intramedullary nailing. J Bone Joint Surg 70A:900–911, 1988.
41. F Behrens, K Searls. External fixation of the tibia: basic concepts and prospective evaluation. J Bone Joint Surg 68B:246–254, 1986.

42. JL Marsh, JV Nepola, TK Wuest, D Osteen, K Cox, W Oppenheim. Unilateral external fixation until healing with the dynamic axial fixator for severe open tibial fractures. J Orthop Trauma 5:341–348, 1991.
43. EH Schemitsch, MJ Kowalski, MF Swiontkowski, D Senft. Cortical bone blood flow in reamed and unreamed locked intramedullary nailing: a fractured tibia model in sheep. J Orthop Trauma 8:373–382, 1994.
44. S Olerud. The effects of intramedullary reaming. In: BD Browner, CC Edwards, eds. The Science and Practice of Intramedullary Nailing. Philadelphia: Lea & Febiger, 1987:61–66.
45. LE Shepherd, WM Costigan, RJ Gardocki, AD Ghiassi, MJ Patzakis, MV Stevanovic. Local or free muscle flaps and unreamed interlocked nails for open tibial fractures. Clin Orthop 350:90–96, 1998.
46. JF Keating, PA. Blachut, PJ O'Brien, RN Meek, H Broekhuyse. Reamed nailing of open tibial fractures: does the antibiotic bead pouch reduce the deep infection rate? J Orthop Trauma 10:298–303, 1996.
47. JF Keating, PJ O'Brien, PA Blachut, RN Meek, HM Broekhuyse. Locking intramedullary nailing with and without reaming for open fractures of the tibial shaft: a prospective, randomized study. J Bone Joint Surg 79A:334–341, 1997.
48. CG Finkemeier, AH Schmidt, RF Kyle, DC Templeman, TF Varecka. A prospective, randomized study of intramedullary nails inserted with and without reaming for the treatment of open and closed fractures of the tibial shaft. J Orthop Trauma 14:187–193, 2000.
49. EM Ashworth, MC Dalsing, JL Glover, MK Reilly. Lower extremity vascular trauma: a comprehensive, aggressive approach. J Trauma 28:329–336, 1988.
50. D Seligson, PA Ostermann, SL Henry, T Wolley. The management of open fractures associated with arterial injury requiring vascular repair. J Trauma 37:938–940, 1994.
51. WM Iannacone, R Taffet, WG DeLong Jr, CT Born, RM Dalsey, LS Deutsch. Early exchange intramedullary nailing of distal femoral fractures with vascular injury initially stabilized with external fixation. J Trauma 37:446–451, 1994.
52. JA Nunley, LA Koman, JR Urbaniak. Arterial shunting as an adjunct to major limb revascularization. Ann Surg 193:27l–273, 1981.
53. SS Blick, RJ Brumback, R Lakatos, A Poka, AR Burgess. Early prophylactic bone grafting of high-energy tibial fractures. Clin Orthop 240:21–41, 1989.

6
Adult Long Bone Osteomyelitis

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I. INTRODUCTION

Osteomyelitis is a term used to describe infection in bone. The root words *osteon* (bone) and *myelo* (marrow) are combined with *-itis* (inflammation) to define the clinical state in which bone is infected with microorganisms. Osteomyelitis can be classified by duration (acute or chronic), by pathogenesis (trauma, hematogenous, surgery, or true contiguous spread), by site (spine, hip, tibia, foot, etc.), by extent (size of defect), and by type of patient (infant, child, adult, or compromised host). Bone infections are currently classified etiologically by the Waldvogel system (1–3) as either hematogenous osteomyelitis or osteomyelitis secondary to a contiguous focus of infection. Contiguous focus osteomyelitis has been further subdivided into osteomyelitis with or without vascular insufficiency.

In the Waldvogel classification, osteomyelitis may be acute or chronic. Acute disease is characterized by a suppurative infection accompanied by edema, vascular congestion, and small vessel thrombosis. The vascular supply to the bone is compromised as the infection extends into the surrounding soft tissue. Large areas of dead bone or sequestra may be formed when the medullary and periosteal blood supplies are reduced. Reactive new bone may form around infected bone and is termed *involucrum*. Established or chronic infection comprises a nidus of infected dead bone or scar tissue and an ischemic soft

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tissue envelope. If established osteomyelitis is not medically and surgically treated, it leads to an indolent refractory infection.

An alternative classification system to the Waldvogel classification has been developed by Cierny and Mader (4,5). The Cierny-Mader staging system (Table 1) is based on the anatomical characteristics of the bone infection and the physiological processes of the host. The classification is determined by the status of the disease process regardless of its cause, regionality, or chronicity. The anatomical types of osteomyelitis arc medullary, superficial, localized, and diffuse. *Stage 1*, or *medullary*, *osteomyelitis* denotes infection confined to the intramedullary surfaces of the bone. Hematogenous osteomyelitis and infected intramedullary rods are examples of this anatomical type (Fig. 1). *Stage 2*, or *superficial*, *osteomyelitis*, a true contiguous focus infection of bone, occurs when an exposed infected necrotic surface of bone lies at the base of a soft tissue wound (Fig. 2a,b). *Stage 3*, or *localized*, *osteomyelitis* is usually characterized by full-

Table 1 Cierny-Mader Staging System[a]

Anatomical type	
Stage 1 Medullary osteomyelitis	
Stage 2 Superficial osteomyelitis	
Stage 3 Localized osteomyelitis	
Stage 4 Diffuse osteomyelitis	
Physiological class	
A Host: normal host	
B Host: systemic compromise (Bs)	
Local compromise (Bl)	
System and local compromise (Bls)	
C Host: treatment worse than disease	
Systemic and local factors that affect immune surveillance, metabolism, and local vascularity	
Systemic (Bs)	Local (Bl)
Malnutrition	Chronic lymphedema
Renal, hepatic failure	Venous stasis
Diabetes mellitus	Major vessel compromise
Chronic hypoxia	Arteritis
Immune disease	Extensive scarring
Malignancy	Radiation fibrosis
Extremes of age	Small vessel disease
Immunosuppression or immune deficiency	Neuropathy
Asplenic patients	
HIV/AIDS	
ETOH and/or tobacco abuse	

[a] HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome; ETOH, Alcohol abuse.

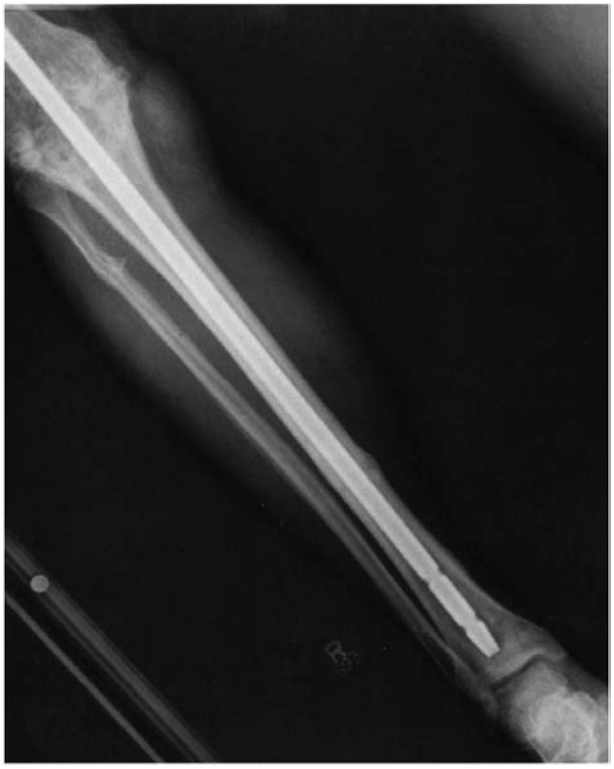
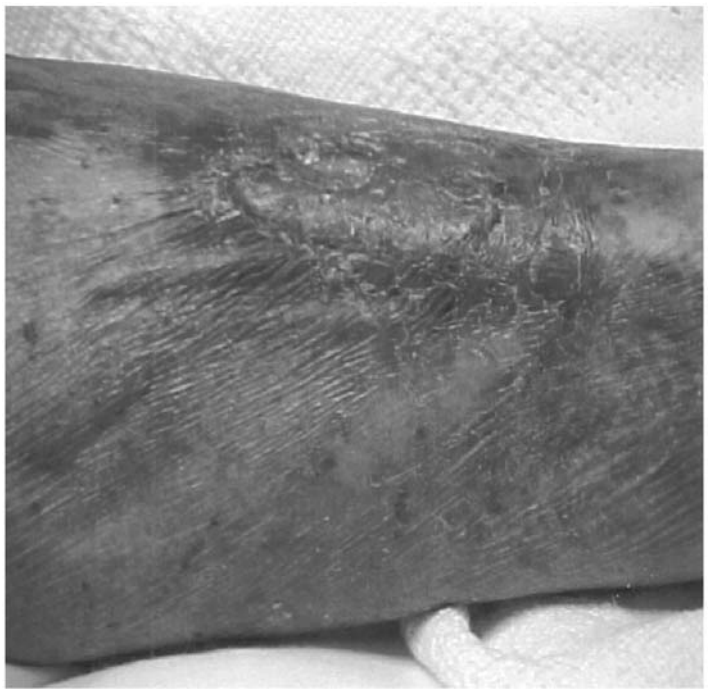


Figure 1 Stage 1, or medullary, osteomyelitis seen here in an infected medullary rod.

thickness cortical sequestration that can be removed surgically without compromising bony stability (Fig. 3). *Stage 4*, or *diffuse*, *osteomyelitis* is a through-and-through process that usually requires an intercalary resection of the bone to arrest the disease process. Diffuse osteomyelitis includes those infections in which there is a loss of bony stability either before or after débridement surgery (Fig. 4).

The patient is classified as an A, B, or C host. An A host is a patient with normal physiological, metabolic, and immunological capabilities. The B host is either systemically compromised, locally compromised, or both. When the morbidity of treatment is worse than that imposed by the disease itself, the patient is given the C host classification. The terms *acute* and *chronic osteomyelitis* are not used in the Cierny-Mader staging system because areas of macronecrosis must be removed regardless of the acuity or chronicity of an uncontrolled infection. The stages are dynamic and interact according to the pathophysiological processes of the disease. They may be altered by successful therapy, host alteration, or treatment. This classification system aids in the understanding, diagnosis, and treatment of bone infections in children and adults.

(a)



(b)

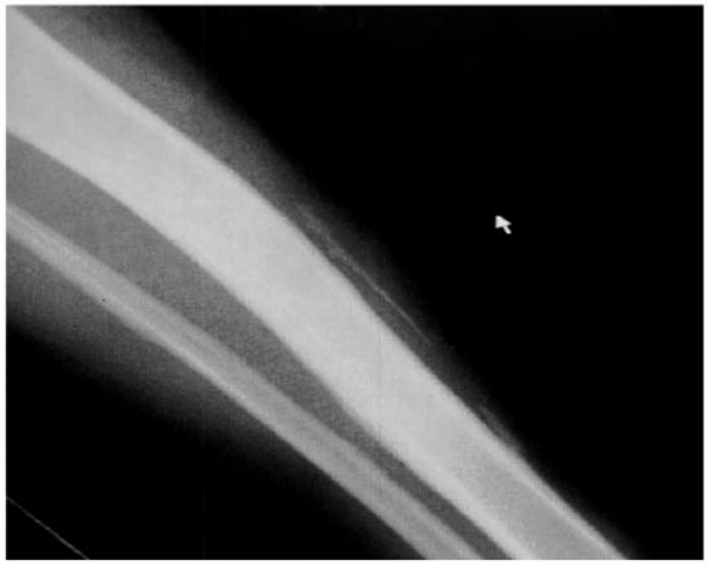


Figure 2 Early stage 2, or superficial, osteomyelitis. a.) Soft tissue appearance overlying the osteomyelitis. b.) A periosteal reaction can be seen at the base of a soft tissue wound.

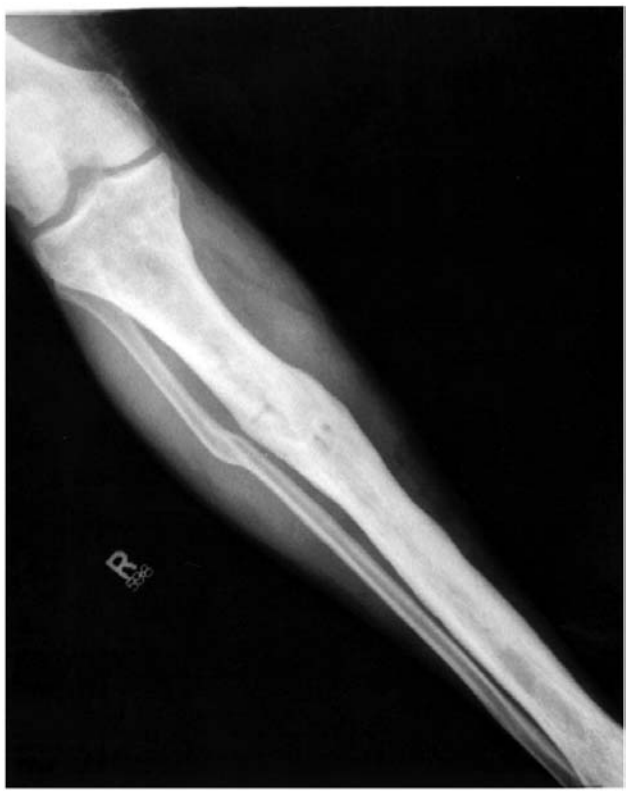


Figure 3 Stage 3, or localized, osteomyelitis involving both cortical and medullary bone without compromising bone stability. A marked periosteal reaction is present along with sclerosis and lytic changes. Soft tissue swelling can be seen as well.

II. ETIOLOGICAL CHARACTERISTICS

In hematogenous osteomyelitis, a single pathogenic organism is almost always recovered from the bone (Table 2). In infants, *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Escherichia coli* are most frequently isolated from blood or bones. However, in children above 1 year of age, *Staphylococcus aureus*, *Streptococcus pyogenes*, and *Haemophilus influenzae* are most commonly isolated (6). The incidence of *Haemophilus influenzae* infection decreases after age 4. However, the overall incidence of *H. influenzae* as a cause of osteomyelitis

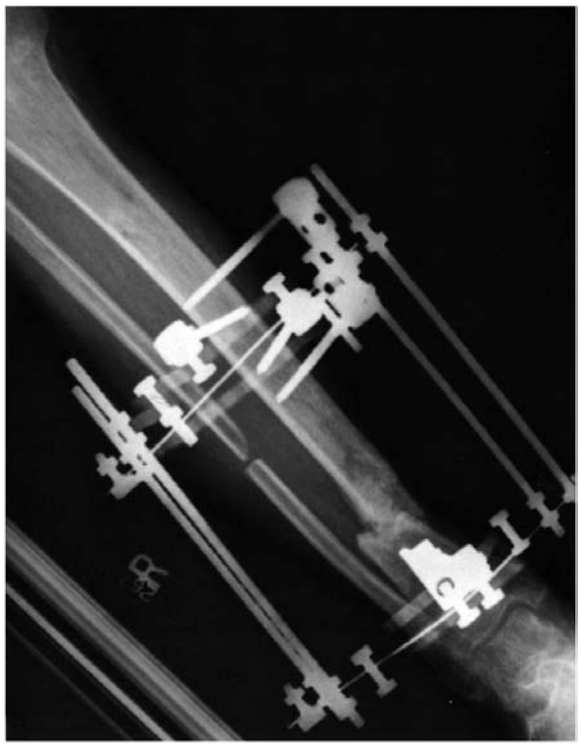


Figure 4 Stage 4, or diffuse, osteomyelitis seen here in an infected non-union treated with an Ilizarov external fixator.

is decreasing because of the new *H. influenzae* vaccine now given to children (7). In adults, *Staphylococcus aureus* is the most common organism isolated.

Multiple organisms are usually isolated from the infected bone in contiguous focus osteomyelitis (Table 2). *Staphylococcus aureus* remains the most commonly isolated pathogen. However, gram-negative bacilli and anaerobic organisms are also frequently isolated.

Skeletal tuberculosis is the result of hematogenous spread of *Mycobacterium tuberculosis* early in the course of a primary infection. Rarely, skeletal tuberculosis may be a contiguous infection from an adjacent caseating lymph node. Atypical mycobacteria including *M. marinum*, *M. avium-intracellulare*, *M. fortuitum*, and *M. gordonae* all have been associated with osteoarticular infections. Bone infections may also be caused by a variety of fungal organisms including coccidioidomycosis, blastomycosis, cryptococcus, and sporotrichosis.

Table 2 Osteomyelitis: Commonly Isolated Organisms

Hematogenous osteomyelitis (monomicrobic infection): Cierny-Mader stage 1		
Infant	Childhood	Adults
<1 year	1–16 years	>16 years
Group B *Streptococcus* spp.	*Staphylococcus aureus*	*Staphylococcus aureus*
Staphylococcus aureus	*Streptococcus pyogenes*	*Staphylococcus epidermidis*
Escherichia coli	*Haemophilus influenzae*	Gram-negative bacilli
		Pseudomonas aeruginosa
		Serratia marcescens
		Escherichia coli
Contiguous focus osteomyelitis (polymicrobic infection): Cierny-Mader stages 2, 3, and 4		
Staphylococcus aureus		
Staphylococcus epidermidis		
Streptococcus pyogenes		
Enterococcus species		
Gram-negative bacilli		
Anaerobes		

III. SOURCE OF INFECTION

Osteomyelitis may be caused by hematogenous spread or by a contiguous focus of infection. Contiguous focus osteomyelitis has been further subdivided into osteomyelitis with or without vascular disease. Hematogenous osteomyelitis usually involves the metaphysis of long bones in children or the vertebral bodies in adults. The most common causes of contiguous focus osteomyelitis are trauma, perioperative infections, nonsurgically induced contiguous infections, and infected foreign bodies. Contiguous focus osteomyelitis with vascular disease commonly occurs in the bones of the feet in patients who have severe ischemic or neuropathic disease such as diabetes mellitus.

IV. EPIDEMIOLOGICAL CHARACTERISTICS

The epidemiological features of osteomyelitis include several broad trends. The incidence of hematogenous osteomyelitis is decreasing in many populations. In Glasgow, Scotland, 275 cases of acute hematogenous osteomyelitis in children below 13 years of age were reviewed from 1970 to 1990. During the same period the population of children below 13 in Glasgow, Scotland, fell by an average of 2% per year. When comparing 1970 with 1990, there was a fall from 64 to 19 cases of acute hematogenous osteomyelitis. The number of cases of osteomyelitis

involving long bones decreased while osteomyelitis from all other sites remained the same. The incidence of *Staphylococcus aureus* infections decreased from 55% to 31% over the 20-year period. In contrast to that of hematogenous osteomyelitis, the incidence of contiguous focus osteomyelitis is increasing, probably as a result of motor vehicle accidents and the increasing use of orthopedic hardware and total joint arthroplasties. There is an increased incidence of contiguous focus osteomyelitis in males versus females. Finally, osteomyelitis occurs with a higher frequency in immunocompromised patients (8).

V. HOST FACTORS

Host factors are primarily involved with containment of the infection once it is introduced adjacent to or into the bone. On occasion, host factors may predispose the host to the development of osteomyelitis. Thus, host deficiencies that lead to bacteremia favor the development of hematogenous osteomyelitis. Host deficiencies involved with direct inoculation of organisms and/or contiguous spread of infection from an adjacent area of soft tissue infection are primarily involved with the lack of containment of the initial infection. Three patient groups with an unusual susceptibility to acute skeletal infections are those with sickle cell anemia, chronic granulomatous disease, and diabetes mellitus (9,10). Many systemic and local factors influence the ability of the host to elicit an effective response to infection and treatment (Table 1).

The functional impairment caused by the disease, reconstruction operations, and metabolic consequences of aggressive therapy influence the selection of candidates for treatment. A draining sinus with minimal pain and/or dysfunction is not itself an indication for surgical treatment. At times, the procedures required to arrest or palliate the disease are of such magnitude for the compromised host that treatment can lead to loss of function, limb, or life. The condition of the host and the relative disability caused by osteomyelitis are elements of the Cierny-Mader classification (Table 1).

VI. PATHOLOGICAL CHARACTERISTICS

Pathogenic organisms reach the bone by direct extension from neighboring infected soft tissues, through penetrating wounds, open fractures, or the bloodstream.

Acute osteomyelitis produces a suppurative infection accompanied by edema, vascular congestion, and small vessel thrombosis. In early acute disease, the vascular supply to the bone is compromised by infection extending into the surrounding soft tissue. When both the medullary and periosteal blood supplies

are compromised, large areas of dead bone (sequestra) may be formed. However, if treated promptly and aggressively with antibiotics and, possibly, surgery, acute osteomyelitis can be arrested before dead bone, the hallmark of chronic disease, develops. Once the infection is established, fibrous tissue and chronic inflammatory cells form around the granulations and dead bone. After the infection is contained, there is a decrease in the vascular supply, and the metabolic demands of an effective inflammatory response cannot be satisfied. The coexistence of infected, nonviable tissues and an ineffective host response leads to the chronicity of this disease. Clinically and histologically, acute osteomyelitis blends into chronic disease (11).

Necrosis of normal tissues is an important feature of osteomyelitis. Dead bone is absorbed by the action of granulation tissue developing at its surface. Absorption takes place earliest and most rapidly at the junction of living and necrotic bone. If the area of the dead bone is small, it is entirely destroyed by granulation tissue, leaving a cavity behind. The necrotic cancellous bone in localized osteomyelitis, even though extensive, is usually absorbed. Some of the dead cortex (cortical bone) is gradually detached from living bone to form a sequestrum. The organic elements in the dead bone are largely broken down by the action of proteolytic enzymes elaborated by host defense cells, mainly the macrophages or the polymorphonuclear leukocytes. Because of lost blood supply, dead bone appears whiter than living bone. Cancellous bone is absorbed rapidly and may be completely sequestrated or destroyed in 2 to 3 weeks, but necrotic cortex may require 2 weeks to 6 months for separation. After complete separation, termed *sequestration*, the dead bone is slowly eroded by granulation tissue and absorbed.

The surviving bone in the field of osteomyelitis usually becomes osteoporotic during the active period of infection. Osteoporosis is the result of both the inflammatory reaction and disuse atrophy. New bone formation is another characteristic pathological feature of osteomyelitis but usually occurs in subacute and chronic osteomyelitis (11).

Pathological features of chronic osteomyelitis are the presence of necrotic bone, the formation of new bone, and the exudation of polymorphonuclear leukocytes joined by large numbers of lymphocytes, histocytes, and, occasionally, plasma cells. The hallmark of chronic osteomyelitis is infected dead bone found within a compromised soft tissue envelope. New bone formation is also a characteristic feature of chronic osteomyelitis. New bone forms from the surviving fragments of periosteum, endosteum, and cortex in the region of the infection and is produced by a vascular reaction to the infection. New bone may be formed along the intact periosteal and endosteal surfaces. New bone may form from the periosteum, forming an encasing sheath of live bone surrounding the dead bone under the periosteum. The live encasing bone is known as *involucrum*. Involucrum is irregular and is often perforated by openings through which pus may

track into the surrounding soft tissues and eventually drain to the skin surfaces, forming a drain sinus tract. The involucrum may gradually increase in density and thickness to form part or all of a new shaft. New bone increases in amount and density for weeks or months, according to the size of the bone and extent and duration of infection. Endosteal new bone may proliferate and obstruct the medullary canal. After host defense or surgical removal of the sequestrum, the remaining cavity may be filled with new bone, especially in children. However, in adults, the cavity may persist or the space may be filled with fibrous tissue, which may connect with the skin surface via a sinus tract (11).

VII. PATHOPHYSIOLOGICAL CHARACTERISTICS

Primary hematogenous osteomyelitis occurs mainly in infants and children. The most common site of hematogenous seeding is the metaphysis, particularly in the hip and tibia, because of the anatomical characteristics of the growing metaphysis. The growth plate separates the epiphyseal blood supply from the metaphyseal vessels. The metaphyseal arteries end at the growth plate by connecting with large sinusoidal veins. The blood flow slows here and allows bacteria to proliferate, especially if there has been slight trauma with resultant hematoma formation. In infants, medullary infection may spread to the epiphysis and joint surfaces through capillaries that cross the growth plate. The adjacent joint is usually infected in infants with osteomyelitis. In children the infection is confined to the metaphysis and diaphysis. The joint is spared unless the metaphysis is intracapsular. Cortical perforation at the proximal radius, humerus, or femur can lead to infection of the elbow, shoulder, or hip joint, respectively, regardless of the age of the patient (1). The infection can also cause elevation of the periosteum and the formation of a so-called Brodie's abscess.

Hematogenous long bone osteomyelitis is rarely found in the adult population. When it occurs, adult hematogenous osteomyelitis may be primary infection or a reactivation of a primary infection that occurred during infancy or childhood. Primary infections are usually found in compromised hosts. The infection begins in the diaphysis but may spread to involve the entire medullary canal. Extension into the joint may occur since the growth plate has matured and once again shares vessels with the metaphysis. As the periosteum firmly adheres to the bone in adults, cortical penetration usually leads to a soft tissue abscess. In time, sinus tracts, which connect the sequestered nidus of infection to the skin via soft tissue extension, may form.

Osteomyelitis in the adult may result from the reactivation of a quiescent focus of hematogenous osteomyelitis initially developed in infancy or childhood. Reactivation of hematogenous osteomyelitis in adults generally has a metaphyseal localization.

Contiguous focus osteomyelitis in adults is usually caused by direction inoculation of organisms (trauma), nosocomial infection from surgery, and true contiguous infection from an adjacent infected wound. In the trauma patient, additional factors that contribute to the subsequent development of osteomyelitis are the presence of hypotension, inadequate débridement of a fracture site, malnutrition, alcoholism, and smoking. Because they cannot contain the initial infection, patients with systemic or metabolic disorders that impair their ability to fight infection are prone to the development and progression of osteomyelitis.

Recently, a number of studies have pointed out some critical factors in the pathogenesis of osteomyelitis. The importance of the host inflammatory response has been stressed. Prostaglandin production in infected bone has been an object of investigation. Prostaglandin E production has been shown to be 5- to 30-fold higher in infected bone than in normal bone (12). The production of large amounts of prostaglandin has been postulated to be responsible for bone resorption and sequestrum formation in osteomyelitis (13). Experimental treatment of rabbit osteomyelitis with sodium salicylate has been shown to prevent bone destruction and sequestration (14). Experimental treatment of osteomyelitis in rats with ibuprofen has been shown to reduce prostaglandin production in infected bone and concurrently reduce gross bone abnormality and radiographic changes, without any change in the bacterial counts (15,16). Granulocyte-macrophage colony-stimulating factor (GM-CSF), a recombinant growth factor with anti-inflammatory and prophagocytic properties, has significantly improved the outcome of experimental acute osteomyelitis in rats (17). Effective phagocytosis has been shown to be an important factor for host defense in patients with osteomyelitis. Intramedullary oxygen tensions in infected bone have been demonstrated to be lower than in normal bone; oxygen tensions less than 30 mmHg impair normal phagocytic function. Hyperbaric oxygen therapy has significantly improved oxygen tensions in intramedullary bone and in experimentally infected rabbits (18,19).

Some bacterial factors have been recognized to be important in the pathogenesis of osteomyelitis. Since the pathogen must colonize the target tissue in order to initiate infection, adequate molecules are required to adhere to the bone matrix, to the extracellular matrix, and to implanted medical devices. *Staphylococcus* spp. have a large variety of adhesive proteins and glycoproteins that mediate binding with bone components (20,21). An important factor in the pathogenesis of osteomyelitis is the formation of a glycocalyx surrounding the infecting organisms. This glycocalyx protects the organisms from the action of phagocytes as well as access by most antimicrobials. Evidence indicates that a surface negative change of devitalized bone or metal implants promotes organism adherence and subsequent glycocalyx formation (22).

Another way to elude host defense is bacterial intracellular location, as demonstrated with staphylococci in osteoblasts and osteocytes in an in vivo model (23).

VIII. CLINICAL MANIFESTATIONS

A. Signs and Symptoms

Children who have hematogenous osteomyelitis may have acute signs of infection, including abrupt fever, irritability, lethargy, and local signs of inflammation. However, 50% of children have vague complaints, including pain of the involved limb of 1 to 3 months in duration and minimal, if any, temperature elevation. Children with hematogenous osteomyelitis usually have normal soft tissue enveloping the infected bone and are capable of a very effective response to infection. Thus, children have the potential to resorb large sequestra and generate a significant periosteal response to the infection. This latter feature leads to substantial formation of bone at the margin of the infection (involucrum). The involucrum provides skeletal continuity and lessens the development of nonunion and pathological fractures. In children, the joint is usually spared from infection unless the metaphysis is intracapsular as is found at the proximal radius, humerus, or femur (24,25).

Adults who have primary infection or reactivation of hematogenous osteomyelitis usually report vague symptoms consisting of nonspecific pain and few constitutional symptoms of 1 to 3 months in duration. However, acute clinical symptoms of fever, chills, swelling, and erythema over the involved bone(s) are occasionally seen. The source of bacteremia may be a trivial skin infection or a more serious infection such as acute or subacute bacterial endocarditis. Hematogenous osteomyelitis that involves either long bones or vertebrae is an important complication of injection drug abuse (6).

Patients who have contiguous focus osteomyelitis often experience localized bone and joint pain, erythema, swelling, and drainage around the area of trauma, surgery, or wound infection. Signs of bacteremia such as fever, chills, and night sweats may be present in the acute phase of osteomyelitis, but not in the chronic phase.

Both hematogenous and contiguous focus osteomyelitis can progress to a chronic condition. Local bone loss, areas of dead necrotic bone (sequestrum), and bony sclerosis are common. Persistent drainage and/or sinus tracts are often found adjacent to the area of infection. The patient usually reports chronic pain and drainage. If present, fever is low grade. The sedimentation rate is usually elevated, reflecting chronic inflammation, but the leukocyte count is usually normal. The chronic disease is usually either not progressive or slowly progressive. If a sinus tract becomes obstructed, the patient may have a localized abscess and or an acute soft tissue infection.

B. History and Physical Examination

A thorough history, review of systems, past medical history, and physical examination must be obtained to identify systemic disease and to evaluate the

integrity and condition of the musculoskeletal component involved. The patient must be able to tolerate rigorous surgical, medical, and rehabilitation protocols. Underlying disease may render the patient a poor surgical candidate. The symptom complex assessment is carefully documented for future reference. Any history of allergies or drug toxicity is obtained.

In patients who have hematogenous osteomyelitis, the general examination evaluates potential entry sites of the infecting organisms including endocarditis. In patients with contiguous focus osteomyelitis, the wound is closely examined. In those with contiguous focus osteomyelitis with generalized vascular disease, the blood supply and sensation are carefully evaluated.

On examination of the limb, any previous operations must be noted, including scars, previous flap designs, and remaining options for local flap coverage. Local signs of stasis, hypoxia, and induration are noted. Range of motion above and below the infected segment is recorded.

During history taking and physical examination, the physician must assess the patient as a surgical candidate, the degree of bone necrosis, the extent of bone and soft tissue involvement, and the potential for rehabilitation. Methods of host improvement should be discussed with a patient who is systemically or locally compromised (Table 3).

IX. LABORATORY STUDIES

Although hematological studies do not confirm the diagnosis of osteomyelitis, they may be useful in assessing the response to treatment. The leukocyte count

Table 3 Patient Management: Methods of Host Alteration

Patient education: no smoking
Nutritional supplementation
Malnutrition
Alcohol abuse
Immune compromise
Renal/hepatic failure
Diabetes
Hyperbaric oxygen: Cierny-Mader Bl, extensive granulation beds, refractory osteomyelitis
Special considerations
Local compromise: pressure garments, local or microvascular tissue transfers
Pressure sores: force distribution
Diabetes: blood glucose control
Major vessel disease: arterial bypass surgery
Chemical suppression: discontinuation or alteration of medications
Sepsis and toxicity: emergency decompression or drainage

may be elevated in acute osteomyelitis but is often normal in more chronic cases. The sedimentation rate is usually elevated in both acute and chronic osteomyelitis. Elevated sedimentation rates and leukocyte counts generally fall with appropriate therapy, but both may increase acutely after débridement surgery. A sedimentation rate that returns to normal during the course of therapy is a favorable prognostic sign (26–30). Laboratory studies to monitor the nutritional status of the patient and any toxic effects of antibiotic treatment regimens are also necessary. Baseline laboratory studies including a complete blood count, chemical levels, liver function tests, erythrocyte sedimentation rate, urinalysis, serum albumin level, and total iron binding capacity should be obtained initially and monitored regularly while the patient is on antibiotic therapy. Total iron binding capacity, prealbumin, and albumin are markers of the nutritional status of the patient with osteomyelitis.

X. DIAGNOSIS

A. Microbiological Documentation

The diagnosis and determination of the cause of long bone osteomyelitis rest on the isolation of the pathogen(s) from the bone lesion or blood or joint culture. In Cierny-Mader stage 1, or hematogenous, osteomyelitis, positive blood or joint culture findings can often obviate the need for a bone biopsy when there is radiographic or scan evidence of osteomyelitis.

Except in hematogenous osteomyelitis, in which positive blood or joint fluid culture results may suffice, antibiotic treatment of osteomyelitis should be based on meticulous cultures of bone taken at débridement surgery or from deep bone biopsies. If possible, cultures should be obtained before antibiotics are initiated. Sinus tract cultures are not reliable for predicting which organisms will be isolated from infected bone (31,32). However, sinus tract cultures that grow *S. aureus* show a positive correlation with bone cultures. In most cases, antibiotic treatment of osteomyelitis should be based on meticulous cultures taken at débridement surgery or from deep bone biopsies and antibiotic susceptibilities (33,34).

Conventional microbiological techniques are usually used for the diagnosis of osteomyelitis. However, some authors have established that the use of improved techniques for pus processing and culturing may yield a higher percentage of isolated strains (35). A lysis-centrifugation technique has been described to improve the sensitivity of pus cultured from osteomyelitis samples (36). Removed hardware requires mild ultrasonication to provide optimal bacterial removal (37). Polymerase chain reaction (PCR), a well-known technique of gene amplification, has been used in the diagnosis of bone infection due to unusual or difficult pathogens, such as *Mycoplasma penumoniae* (38), *Brucella*

spp. (39), *Bartonella henselae* (40), and both tuberculous and nontuberculous *Mycobacterium* spp. (41). PCR has detected *Mycobacterium tuberculosis* in formaldehyde solution-fixed, paraffin-embedded tissue samples from patients with Pott's disease (42). Even if PCR is not a routine technique for the diagnosis of osteomyelitis, it can be potentially useful in this setting. PCR has been shown to be more sensitive than culture in the detection of infection in a hip prosthesis (37). Adaptation of the bacteria to the environment by the production of biofilm has been postulated as an unfavorable condition for the successful isolation of organisms by current culture techniques (37). Finally, PCR can detect the bacterial genome even when culture findings are negative because of concurrent antibiotic treatment. PCR identification of an organism can be useful when antibiotic discontinuation is not feasible at the time of attempting to make a diagnosis.

B. Radiographs and Scans

In hematogenous osteomyelitis, radiographic changes usually reflect the destructive process but lag at least 2 weeks behind the evolution of infection. The earliest changes are swelling of the soft tissue, periosteal thickening and/or elevation, and focal osteopenia. At least 50%–75% of the bone matrix must be destroyed before radiographs show lytic changes. The more diagnostic lytic changes are delayed and associated with a subacute and chronic osteomyelitis. Radiographic improvement may lag behind clinical recovery, even when the patient is receiving appropriate antimicrobial therapy (43). In contiguous focus osteomyelitis, the radiographic changes are subtle, often found in association with other nonspecific radiographic findings, and require a careful clinical correlation to achieve diagnostic significance.

C. Radionuclide Studies

Radionuclide scans may be obtained when the diagnosis of osteomyelitis is ambiguous or when it is necessary to gauge the extent of bone and soft tissue inflammation. In general, it is not usually necessary to obtain these scans for the diagnosis of long bone osteomyelitis. The actual mechanism of bone labeling with radiopharmaceuticals is still unclear. The technetium polyphosphate ^{99m}Tc scan demonstrates increased isotope accumulation in areas of increased blood flow and reactive new bone formation (44). In biopsy-confirmed cases of hematogenous osteomyelitis, the finding is usually positive as early as 48 hours after the initiation of the bone infection (45). Negative ^{99m}Tc scan results in documented cases of osteomyelitis may reflect impaired blood supply to the infected area (46). A negative technetium polyphosphate ^{99m}Tc scan finding effectively rules out the diagnosis of osteomyelitis

A second class of radiopharmaceuticals used for the evaluation of osteomyelitis includes gallium citrate. Gallium attaches to transferrin, which leaks from the bloodstream into areas of inflammation. The gallium scan also shows increased isotope uptake in areas concentrating polymorphonuclear leukocytes, macrophages, and malignant tumors (47). Since the gallium citrate scan does not show bone detail well, distinguishing between bone and soft tissue inflammation is often difficult; a comparison with a ^{99m}Tc scan helps to resolve this problem (48). Gallium citrate is also found to accumulate in areas of infected and noninfected nonunions (47). Because gallium accumulates in areas of inflammation, it has a high sensitivity and low specificity for the diagnosis of osteomyelitis.

Indium-labeled leukocyte scans are more useful in the evaluation of acute osteomyelitis. Indium leukocyte scan results are positive in approximately 40% of cases of acute osteomyelitis and 60% of cases of septic arthritis (49). Patients with chronic osteomyelitis usually have equivocal or negative indium-labeled leukocyte scan findings.

D. Computed Tomography

Computed axial tomography (CT) may play a role in the diagnosis of osteomyelitis. Increased marrow density occurs early in the infection (49), and intramedullary gas has been reported in patients with hematogenous osteomyelitis (50). The CT scan result can also help in identifying areas of necrotic bone and assessing the involvement of the surrounding soft tissues. One disadvantage of this study is the scatter phenomenon, which occurs when metal is present in or near the area of bone infection. This scatter results in a significant loss of image resolution.

E. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been recognized as a useful modality for diagnosing the presence and scope of musculoskeletal sepsis (51–53). The resolution of MRI makes it useful in differentiating between bone and soft tissue infection, often a problem with radionuclide studies (54). Unlike the radionuclide studies, MRI is not useful for whole-body examinations. Metallic implants in the region of interest may produce focal artifacts, thereby decreasing the quality of the image (55). Initial MRI screening usually consists of a T_1-weighted and a T_2-weighted spin-echo pulse sequence. In a T_1-weighted study, edema is dark and fat is bright. In a T_2-weighted study, the reverse is true. The typical appearance of acute osteomyelitis is a localized area of abnormal marrow with decreased signal intensity on T_1-weighted images and increased signal intensity on T_2-weighted images. On occasion there may be decreased signal intensity on T_2-weighted images (55). Posttraumatic or surgical scarring of the marrow is seen as a region of

decreased signal intensity on T_1-weighted images with no change of the T_2-weighted image. Sinus tracts are seen as areas of high signal intensity on the T_2-weighted image, extending from the marrow and bone through the soft tissues and out of the skin. Cellulitis is seen as diffuse areas of intermediate signal in the T_1-weighted images of the soft tissues, with increased signal on the T_2-weighted images of the same area. The MRI scan has the highest sensitivity and specificity for the diagnosis of osteomyelitis. However, because of its expense, it should only be requested when the diagnosis of osteomyelitis is equivocal.

XI. DIFFERENTIAL DIAGNOSIS

A number of conditions may present symptoms and signs similar to those of osteomyelitis. Malignant and benign tumors including Ewing's sarcomas, osteosarcomas, fibrous histiocytomas, fibrosarcomas, lymphomas, and benign giant cell bone cysts may be confused with osteomyelitis. Patients with leukemia may have bony infiltrates, which may resemble osteomyelitis. Bone infarcts secondary to sickle cell anemia or other hemoglobinopathies may resemble osteomyelitis. (56). Noninfected nonunions and old trauma may likewise mimic osteomyelitis. In the conditions detailed, results of radiographs and scans may be consistent with osteomyelitis, but the patients generally lack symptoms and signs of infection, including fever, erythema, and drainage. The correct diagnosis is usually based on histological features and culture results.

XII. TREATMENT

Appropriate therapy of osteomyelitis includes adequate drainage, thorough débridement, obliteration of dead space, wound protection, and specific antimicrobial coverage. If the patient is a compromised host, an effort is made to correct or improve the host defect(s) (Table 3). In particular attention should be paid to good nutrition and to a smoking cessation program besides dealing with specific abnormalities such as control of diabetes. Thus, an attempt is made to improve the nutritional, medical, and vascular status of the patient and to provide optimal care for any underlying disease.

A. Antibiotic Management

After cultures are obtained, a parenteral antimicrobial regimen is begun to cover the clinically suspected pathogens. Once the organism is identified, a specific antibiotic class(es) can be selected by appropriate sensitivity methods.

If possible, antibiotics should not be initiated until the results of the bone bacterial culture and sensitivities are known. However, if immediate débridement

surgery is required, empirical broad-spectrum antibiotics can be started. The antibiotics may be modified, if necessary, when results of the débridement cultures and sensitivities are available.

Since bone takes 3 to 4 weeks to revascularize after débridement surgery, antibiotics are used to treat live infected bone and to protect bone undergoing revascularization. The patient is treated with 4 to 6 weeks of antimicrobial therapy dated from the last major débridement surgery (57,58). Outpatient intravenous therapy with intravenous access catheters such as a peripherally inserted central catheter (PICC), Hickman catheter, or Groshong catheter makes outpatient intravenous antibiotic treatment possible (59–61).

Oral therapy using quinolones for gram-negative organisms is currently being utilized in adult patients with osteomyelitis (62–64). The second-generation quinolones (ciprofloxacin, ofloxacin) have poor activity against *Streptococcus* spp., *Enterococcus* spp., and anaerobic bacteria (65). The third-generation (levofloxacin, gatifloxacin) quinolones have excellent *Streptococcus* spp. activity, but minimal anaerobic coverage (66). The fourth-generation quinolone trovafloxacin has excellent *Streptococcus* spp. and anaerobic organism coverage (66,67). Trovafloxacin is only approved for inpatient treatment and must be used with caution because, in rare cases, it can lead to serious liver toxicity. None of the quinolones has reliable *Enterococcus* spp. coverage. The current quinolones have variable *S. aureus* and *S. epidermidis* coverage, and resistance to the second- and third-generation quinolones is increasing (68). Coverage of methicillin-sensitive *S. aureus* should be obtained with another oral antibiotic such as clindamycin or ampicillin-sulbactam (Unasyn). It is recommended that before a change to a nonquinolone oral regimen the patient initially receives 2 weeks of parenteral aptibiotic therapy and the organism(s) be sensitive to the oral regimen. The patient must be compliant and have close outpatient follow-up. Because of their excellent oral absorption, the quinolones are changed to an oral route as soon as the patient is able to take oral medications.

A combination of parenteral and oral antibiotics has been used in some situations. Methicillin-sensitive and methicillin-resistant *S. aureus* osteomyelitis has been successfully treated with a semisynthetic penicillin-rifamipin and vancomycin-rifampin, respectively (69).

In general, it is not necessary to follow serum-cidal levels (70) because most treatment failures are due to a lack of adequate surgical débridement rather than antibiotic efficacy (57). It may be necessary to follow serum levels in cases of relatively resistant organisms or to gauge the efficacy of oral antibiotic therapy.

1. Antibiotic treatment by Cierny-Mader stage

Stage 1 (Table 4) osteomyelitis in children usually can be treated with antibiotics alone. Antibiotic therapy alone is possible because children's bone is highly

Table 4 Osteomyelitis: Initial Antibiotic Therapy

Hematogenous osteomyelitis (monomicrobic infection): Cierny-Mader stage 1	
Long Bone	
Children	Nafcillin[a] or clindamycin[a]
Adults	Nafcillin[a] or clindamycin[a] + levofloxacin
Vertebral	Nafcillin[a] + cefotaxime
Continguous focus osteomyelitis (polymicrobic infection): Cierny-Mader stages 2A,B, 3A,B, 4A,B	
Long bone	Clinidamycin[a] + levofloxacin
Mandibular	Clindamycin
Pelvic	Ampicillin/sulbactam + levofloxacin
Contiguous focus osteomyelitis with vascular diseases (polymicrobic infection) Cierny-Mader stages 2B, 3B, 4B	
Diabetic foot osteomyelitis	Clindamycin or ampicillin/ Sulbactam + Levofloxacin

[a] Vancomycin when methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *S. epidermidis* (MRSE), or *Enterococcus* sp. suspected.

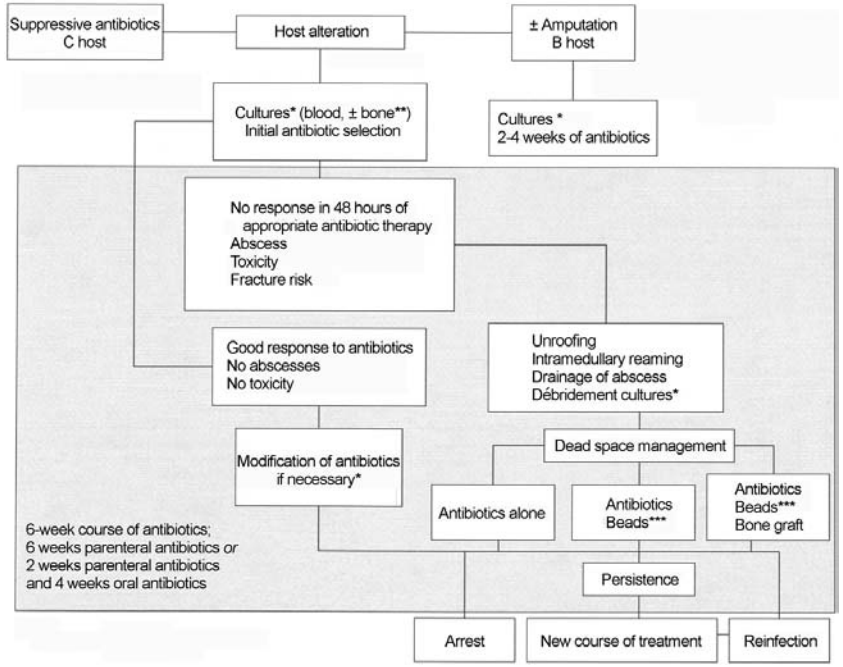
vascular and has a very effective response to infection. Stage 1 (Table 4) osteomyelitis in adults is more refractory to therapy and is usually treated with antibiotics and surgery. The patient is treated for 4 weeks with appropriate parenteral antimicrobial therapy, dated from the initiation of therapy or the last major débridement surgery. If the initial medical management fails and the patient is clinically compromised by a recurrent infection, medullary and/or soft tissue débridement is necessary in conjunction with another 4-week course of antibiotics.

Oral antibiotic therapy can be used for treatment of pediatric stage 1 osteomyelitis. However, it is recommended that the child initially receive 1 to 2 weeks of parenteral antibiotic therapy before changing to an oral regimen. High doses of the quinolone class of antibiotics have been reported to cause articular cartilage damage in young animals, generating some concern regarding the long-term use of these agents in infants and children. Therefore, in most circumstances, pediatric patients should not be given the quinolone class of antibiotics.

In stage 2 osteomyelitis (Table 5), the patient may be treated with a 2-week course of antibiotics after superficial débridement and soft tissue coverage. The arrest rate is approximately 80%.

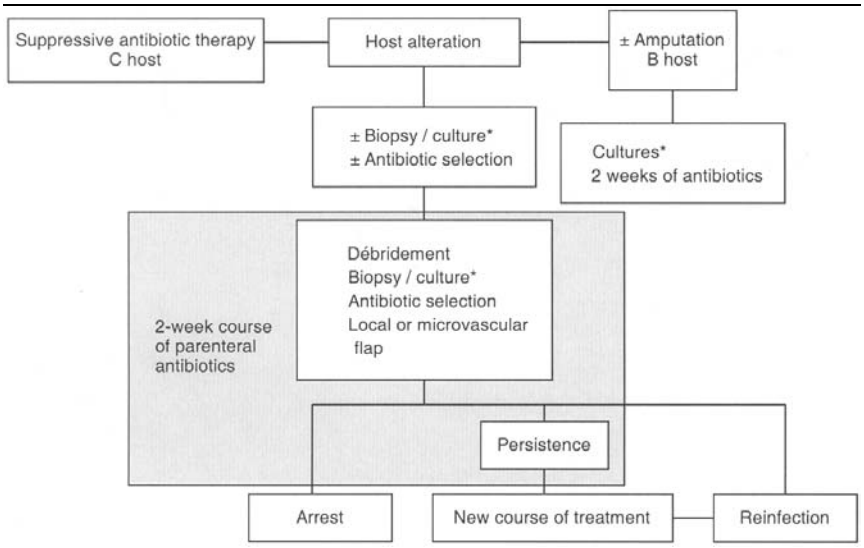
In stages 3 (Table 6) and 4 (Table 7) osteomyelitis, the patient is treated with 4 to 6 weeks of antimicrobial therapy dated from the last major débridement surgery. Without adequate débridement most antibiotic regimens fail regardless of duration of therapy. Even when all necrotic tissue has been adequately débrided, the remaining bed of tissue must be considered contaminated with the responsible

Table 5 Treatment Algorithm for Cierny-Mader Stage 1 Long Bone Osteomyelitis



*Modify antibiotics on culture and sensitivity results.
**If blood cultures are positive with radiographic or scan evidence of osteomyelitis, then bone cultures are not necessary.
***Beads are removed at 2–3 weeks and replaced with cancellous bone. A bead exchange may be done at 2–3 weeks later and replaced with cancellous bone.

Table 6 Treatment Algorithm for Cierny-Mader Stage 2 Long Bone Osteomyelitis

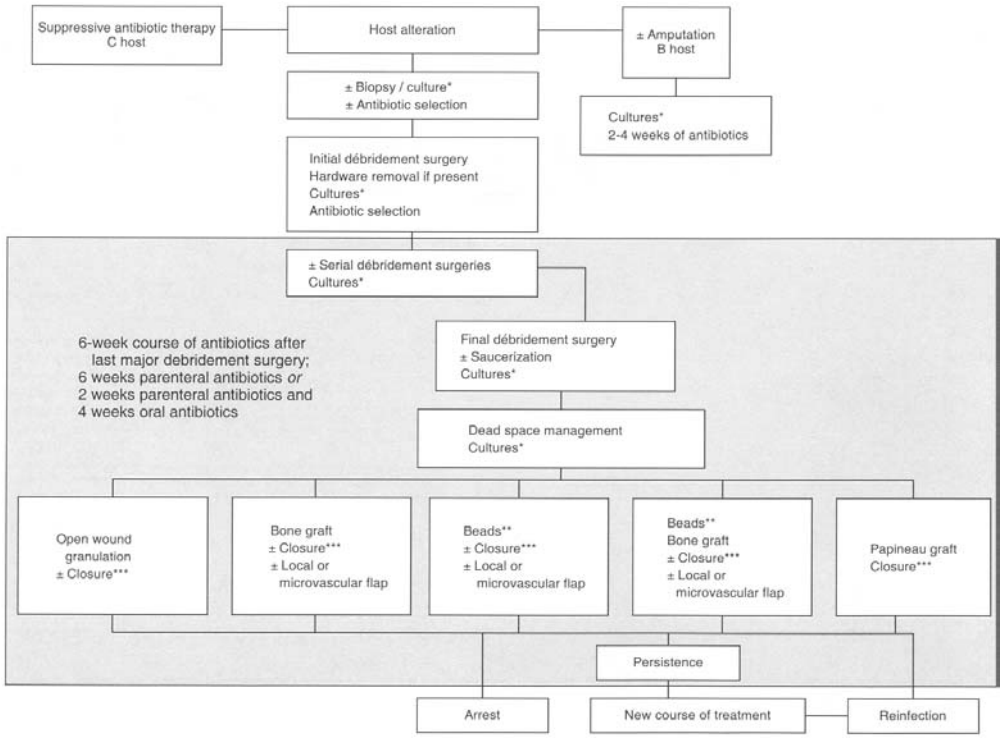


* Modify antibiotics on culture and sensitivity results.

pathogen(s). Therefore, it is important to treat the patient for at least 4 weeks with antibiotics (1). The arrest rate is approximately 90%. Outpatient intravenous therapy using long-term intravenous access catheters, such as Hickman or Groshong catheters, decreases hospitalization time. Oral therapy by the quinolone class of antibiotics is currently being utilized in adult patients with osteomyelitis. The currently available quinolones have relatively poor activity against *Enterococcus* spp. and anaerobes. The quinolones have modest activity against *Staphylococcus aureus* and *S. epidermidis*, but resistance is increasing. Coverage of aerobic gram-positive organisms should be obtained with other antibiotics such as clindamycin or ampicillin and a β-lactamase inhibitor. Before a change to an oral regimen, it is recommended that the patient initially receive 2 weeks of nonquinolone parenteral antibiotic therapy. Because of their excellent oral absorption, the quinolones are changed to an oral route as soon as the patient is able to take oral medications. The patient must be compliant and agree to close outpatient follow-up.

Because of the need for prolonged therapy, antibiotics used in the treatment of bone and joint infection must be nontoxic, convenient to administer, and cost-effective. Bone concentration of the treatment antibiotic may be an important factor in eradicating the organism from the bone. Using a rabbit model for *Staphylococcus aureus* osteomyelitis, the authors found clindamycin to have the greatest bone-to-serum ratio, followed by vancomycin, nafcillin, moxalactam, tobramycin, cefazolin, and cephalothin. The significance of bone antibiotic

Table 7 Treatment Algorithm for Cierny-Mader Stage 3 Long Bone Osteomyelitis



* Modify antibiotics on culture and sensitivity results.

* Beads are removed at 2–3 weeks and replaced with cancellous bone. A bead exchange may be done at 2–3 weeks; the new beads are removed 2–3 weeks later and replaced with cancellous bone.

***Closure includes primary closure or split thickness skin graft.

concentrations is unclear; clindamycin gave the best treatment results in experimental *Staphylococcus aureus* osteomyelitis (71).

B. Suppressive Antibiotic Therapy

When surgical treatment of osteomyelitis is not feasible, antibiotic suppressive therapy is usually given to control the disease and to prevent flare-ups. This therapy is usually administered by the oral route. Ideal drugs for suppression must possess good bioavailability, low toxicity, and adequate bone penetration. The causative microorganism must be susceptible to the antibiotic(s) used for suppression. Suppressive therapy does not exempt the physician from the need for a microbiological diagnosis and susceptibility testing. Suppressive therapy has been extensively studied in the setting of infected orthopedic implants. Rifampin (in combination with other antibiotics), fusidic acid, ofloxacin, and co-trimoxazole have been administered to patients with infected hip or knee arthroplasties in numerous studies (34,72–74). In these studies, suppressive antibiotic treatment was administered for 6 to 9 months. After discontinuation of treatment, a cure (i.e., no recurrence of infection during the follow-up period) was achieved for nearly 60% of patients (34). Failures were thought to be due to persistence of the infection or to resistance to the suppression antibiotic. Efficacy of suppressive therapy is probably due to prolonged action against low-replicating bacteria or their action against organisms (planktonic organism) liberated from the glycocalyx.

Suppressive therapy is traditionally administered for 6 months. If recurrence of the infection occurs after discontinuation, a new suppressive regimen is begun and administered sine die. If possible the regimen is culture directed.

C. Surgical Management

Surgical management of osteomyelitis can be very challenging. The principles of treating any infection are equally applicable to the treatment of infection in bone. These include adequate drainage, extensive débridement of all necrotic tissue, obliteration of dead spaces, adequate soft tissue coverage, and restoration of an effective blood supply. The goal of débridement is to leave healthy, viable tissue. Débridement of bone is executed to the point where punctate bleeding, which is termed the "paprika sign," is noted. However, even when all necrotic tissue has been adequately débrided, the remaining bed of tissue must be considered contaminated with the responsible organism. In 2001 the importance of the extent of surgical débridement in both normal and compromised hosts was reinvestigated (75). B hosts treated with marginal resection (i.e., with a clearance margin less than 5 mm) had a higher rate of recurrence than normal hosts. The

extent of resection appears therefore to be much more important in B hosts, whereas in normal hosts a marginal resection may be acceptable.

The challenge in treating osteomyelitis, as compared to infection of soft tissue alone, involves bone débridement. Adequate débridement may leave a large bony defect termed *dead space*. Appropriate management of any dead space created by débridement surgery is mandatory to arrest the disease and to maintain the integrity of the bone part. The goal of dead space management is to replace dead bone and scar tissue with durable vascularized tissue (57,58). Secondary-intention healing is discouraged, since the scar tissue that fills the defect may later become avascular. Complete wound closure should be attained whenever possible. Local tissue flaps or free flaps may be used to fill dead space (76–80). An alternative technique is to place cancellous bone grafts beneath local or transferred tissues where structural augmentation is necessary. Careful preoperative planning is critical to the conservation of the patient's limited cancellous bone reserves. Open cancellous grafts without soft tissue coverage are useful when a free tissue transfer is not a treatment option and local tissue flaps are inadequate (81). Antibiotic-impregnated acrylic beads may be used to sterilize and maintain dead space temporarily (Fig. 5). The beads are usually removed within 2 to 4

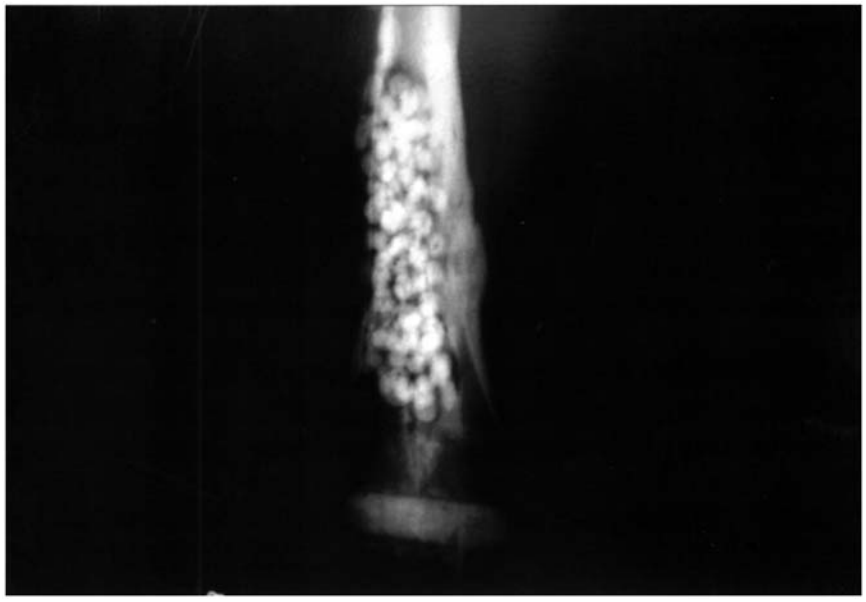


Figure 5 Antibiotic-impregnated beads used to sterilize and maintain dead space after débridement surgery.

weeks and replaced with a cancellous bone graft (58,82–87). The most commonly used antibiotics in beads are vancomycin, tobramycin, and gentamicin. Antibiotics (clindamycin, amikacin) have also been delivered directly into dead space with an implantable pump (88).

If movement is present at the site of infection, measures must be taken to achieve permanent stability of the skeletal unit. Stability may be achieved with plates, screws, rods, and/or an external fixator. External fixation is preferred to internal fixation because of the tendency of medullary rods to become secondarily infected and to spread the extent of the infection. A type of external fixator allows bone reconstruction of segmental defects and difficult infected nonunions (89). The Ilizarov external fixation method utilizes the theory of distraction histogenesis, whereby bone is fractured in the metaphyseal region and slowly lengthened. The growth of new bone in the metaphyseal region pushes a segment of healthy bone into the defect left by surgery. The Ilizarov technique is used for difficult cases of osteomyelitis when stabilization and bone lengthening are necessary. The method may also be used to compress nonunions and correct malunions. The technique is labor intensive and requires an extended period of treatment, averaging 8.5 months in the device. Calhoun and associates (90) successfully reconstructed 92% of patients with chronic osteomyelitis with segmental defects, ranging from simple nonunions to 8-cm gaps. The Ilizarov pins usually become infected and the device is painful. The Ilizarov technique is commonly used for a small group of patients for reconstruction of difficult deformities that result from osteomyelitis. The Ilizarov external fixation method is utilized by most tertiary care hospitals.

Adequate soft tissue coverage of the bone is necessary to arrest osteomyelitis. Small soft tissue defects may be covered with a split-thickness skin graft. In the presence of a large soft tissue defect or an inadequate soft tissue envelope, local muscle flaps and free vascularized muscle flaps may be placed in a one- or two-stage procedure. Local and free muscle flaps, when combined with antibiotics and surgical débridement of all nonviable osseous and soft tissue for chronic osteomyelitis, have a success rate ranging from 66% to 100%. Local muscle flaps and free vascularized muscle transfers improve the local biological environment by introducing a blood supply important in host defense mechanisms, antibiotic delivery, and osseous and soft tissue healing.

1. Surgical treatment by Cierny-Mader stage

The Cierny-Mader classification of osteomyelitis not only stratifies the disease and host condition, but also provides guidelines for the surgical management of the disease. In stage 1 osteomyelitis (Table 5), the nidus of infection is entirely within the medullary canal of the bone. It is usually caused by blood-borne bacteria or the introduction of surgical hardware such as an intramedullary nail.

Because of the location, surgical treatment is usually more straightforward than in other types of bone involvement. In pediatric patients without hardware, surgical therapy is usually not necessary. In adults with primary or secondary stage 1 osteomyelitis, thorough intramedullary reaming and unroofing are usually done with or without bone grafting. Soft tissues are reapproximated and the limb is protected by external means (brace or cast) until structural integrity of the bone is reestablished by normal remodeling.

In stage 2 osteomyelitis (Table 6), the surface of the bone is exposed as a result of an overlying soft tissue defect. The superficial cortex becomes involved with the infection and eventually becomes sequestered (stage 3 progression) if treatment is delayed. The most important aspect of treatment is soft tissue coverage after adequate débridement to bleeding cortex, This may be a simple problem involving local tissue, or it may require free tissue transfer. Stage 3 osteomyelitis (Table 7) combines the problems of both stages 1 and 2; treatment involves the modalities employed for both of these categories of disease. Bone is sequestered, medullary extension of the infection is common, and major soft tissue defects may be present as well. These patients may require external fixation for structural support while the bone graft incorporates. Complex reconstruction of both bone and soft tissue is frequently necessary.

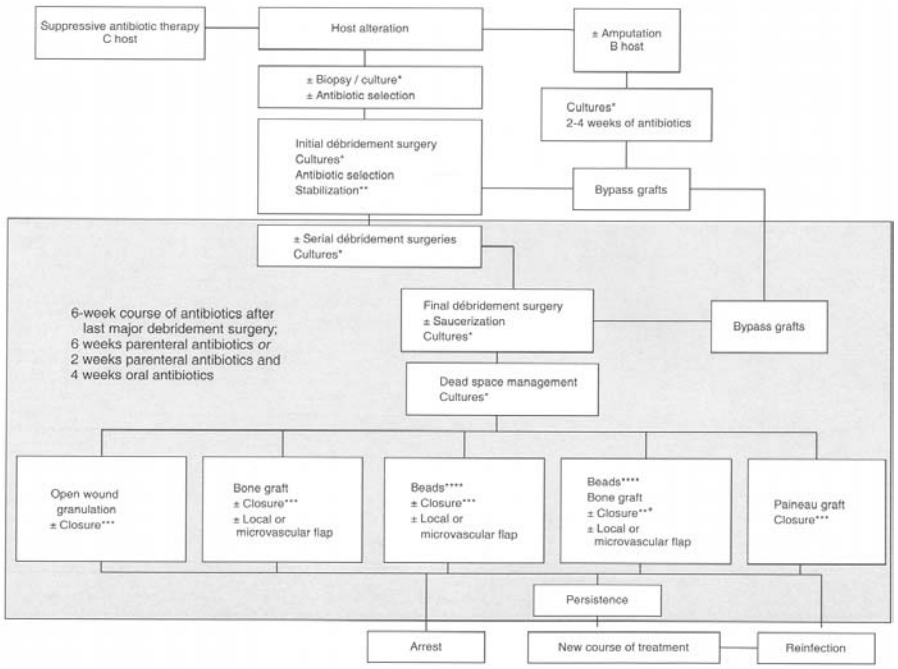
Stage 4 osteomyelitis (Table 8) combines problems of stages 1, 2, and 3. Instability is a problem before or after surgery. Therefore, treatment often must be directed toward establishing structural stability and obliterating débridement gaps by means of cancellous bone grafts or the Ilizarov technique. Free flaps and vascularized bone grafts are other possible treatment modalities. All of the modalities discussed may have a place in the treatment of diffuse osteomyelitis.

D. Therapy of Osteomyelitis Secondary to Contiguous Focus Infection with Vascular Diseases

Because of the relative inability of the host to participate in the eradication of the infectious process, osteomyelitis secondary to contiguous focus infection with vascular disease is difficult to treat (see Chapter 11). These infections are insidious and are often beyond simple salvage by the time the patient seeks medical therapy.

Determination of the vascular status of the tissue at the infection site is crucial in the evaluation of these patients. Although several methods can be used to determine the vascular status, measurement of cutaneous oxygen tensions and pulse pressures is most commonly employed. Cutaneous oxygen tensions are obtained by using a modified Clark electrode applied to the skin surface. Cutaneous oxygen tensions provide guidelines for determining the location of adequately perfused tissue (91). The values are also helpful in predicting the benefit of local débridement surgery and in selecting surgical margins where

Table 8 Treatment Algorithm for Cierny-Mader Stage 4 Long Bone Osteomyelitis



* Modify antibiotics on culture and sensitivity results.
** Stabilization with external fixation (e.g., Ilizarov) or internal fixation (e.g., plates or intramedullary nails).
*** Closure includes primary closure or split thickness skin graft.
**** Beads are removed at 2–3 weeks and replaced with cancellous bone. A bead exchange may be done at 2–3 weeks; the new beads are removed 2–3 weeks later and replaced with cancellous bone.

healing can be expected to occur. Hyperbaric oxygen therapy may facilitate healing in areas where borderline oxygen tensions are present.

The patient may be managed with suppressive antibiotic therapy, antibiotic therapy without surgery (osteitis), local débridement surgery, or ablative surgery. The decision regarding treatment options used is based on tissue oxygen perfusion at the infection site, extent of the osteomyelitis, and patient preference (92,93).

The patient can be offered long-term suppressive antibiotic therapy when a definitive surgical procedure would lead to unacceptable patient morbidity or

disability or when a patient refuses local débridement or ablative surgery. Even with suppressive antibiotic therapy, in time, most of these patients require amputation of the involved bone.

Osteitis involves the outer cortex of the bone without intramedullary spread. Osteitis may be arrested with a 4- to 6-week course of antibiotic therapy without a definitive surgical procedure (94). In order to maintain the arrest of the infection, the contiguous soft tissue defect and infection must be resolved.

Local débridement surgery and a 4-week course of antibiotics may be used when a patient has localized osteomyelitis and good tissue oxygen perfusion. Unless good tissue oxygen tensions are present, the wound does not heal and ultimately requires an ablative procedure. Installation of antibiotic-impregnated methylmethacrylate beads to obliterate dead space may improve therapeutic responses.

The patient who has extensive osteomyelitis and poor tissue oxygen perfusion usually requires some type of ablative surgery. Digital and ray resections, transmetatarsal amputations, midfoot disarticulations, or Chopart, Lisfranc, and Syme amputations permit the patient to ambulate without a prosthesis. The amputation level is determined by the vascularity and potential viability of the tissues proximal to the site of infection and the requirements of a thorough débridement. The patient is given 4 weeks of antibiotics when infected bone is surgically transected. Two weeks of antibiotics is given when the infected bone is completely excised but some residual soft tissue infection remains. When the amputation is performed proximal to the bone and soft tissue infection, the patient is given 1 to 3 days of antibiotic therapy.

XIII. SUMMARY

Decreasing the known risk factors for the development of osteomyelitis should decrease the incidence of osteomyelitis. The basic mechanisms for the development of osteomyelitis are hematogenous dissemination, direct inoculation, and contiguous spread from an adjacent infection. The major risk factors for acute hematogenous osteomyelitis are circumstances that predispose to bacteremias. The major circumstances include infections of indwelling intravascular catheters, distant foci of infection, and intravenous drug abuse. The skin, respiratory tract, and urinary tract represent the distant sites of focal infection most commonly associated with acute osteomyelitis. The second major mechanism for the development of osteomyelitis is direct inoculation. The major direct inoculation injuries include animal and human bites and puncture wounds. Diagnostic procedures may also inadvertently result in the inoculation of neighboring osseous structures. Surgical procedures such as internal fixation of long bones and skeletal traction may lead to an infection of the bone. Osteomyelitis may

develop as a consequence of contiguous spread of infection from an adjacent soft tissue infection, particularly if vascular insufficiency is present. The major risk factors for the development of chronic infection of bone are inadequate or delayed management of acute osteomyelitis and unrecognized bone infection. Two groups of patients who have an increased susceptibility to acute skeletal infections are those with sickle cell anemia and those with chronic granulomatous disease. Prevention of osteomyelitis includes decreasing the incidence of bacteremias, inoculation injuries, and wound infections. Since achieving these goals completely is not possible, osteomyelitis will remain a major problem for the foreseeable future.

REFERENCES

1. FA Waldvogel, G Medoff, MN Swartz. Osteomyelitis: a review of clinical features, therapeutic considerations, and unusual aspect. N Engl J Med 282:198–206, 260–266, 316–322, 1970.
2. FA Waldvogel, H Vasey. Osteomyelitis: the past decade. N Engl J Med 303:360–370, 1980.
3. DP Lew, FA Waldvogel. Current concepts osteomyelitis. N Engl J Med 336:999–1007, 1997.
4. G Cierny, JT Mader, H Pennick. A clinical staging system of adult osteomyelitis. Contemp Orthop 10:17–37, 1985.
5. JT Mader, M Shirtliff, JH Calhoun. Staging and staging application osteomyelitis. Clin Infect Dis 25:1303–1309, 1997.
6. M Beronius, B Bergman, R Andersson. Vertebral oseomyelitis in Goteborg, Sweden: a retrospective study of patients during 1990–95. Scand J Infect Dis 33:527–532, 2001.
7. M De Jonghe, G Glaesener. Type B *Haemophilus influenzae* infection. Experience at the pediatric hospital of Luxembourg. Bull Soc Sci Med Grand Duche Luxemb 132:17–20, 1995.
8. WJ Gillespie. Epidemiology in bone and joint infection. Infect Dis Clin North Am 4:361–376, 1990.
9. CH Epps Jr, DD Bryant III, MJ Coles, O Castro. Osteomyelitis in patients who have sickle-cell disease: diagnosis and management. J Bone Joint Surg 73A:1281–1294, 1991.
10. MB Moutschen, AJ Scheen, PJ Lefebvre. Impaired immune responses in diabetes mellitus: analysis of the factors and mechanisms involved: relevance to the increased susceptibility of diabetic patients to specific infections. Diabetes Metab 18:187–201, 1992.
11. J Ciampolini, KG Harding. Pathophysiology of chronic bacterial osteomyelitis: why do antibiotics fail so often? Postgrad Med 76:479–483, 2000.

12. D Plotquin, S Dekel, S Katz, A Danon. Prostaglandin release by normal and osteomyelitic human bones. Prostaglandins Leukot Essent Fatty Acids 43:13–15, 1991.
13. M Corbett, S Dekel, B Puddle, RA Dickson, MJ Francis. The production of prostaglandins in response to experimentally induced osteomyelitis in rabbits. Prostaglandin Med 2: 403–412, 1979.
14. S Dekel, MJ Francis. The treatment of osteomyelitis of the tibia with sodium salycilate: an experimental study in rabbits. J Bone Joint Surg 63B: 178–184, 1981.
15. JP Rissing, TB Buxton, J Fisher, R Harris, RK Shockley. Arachidonic acid facilitates experimental chronic osteomyelitis in rats. Infect Immun 49:141–144, 1985.
16. JP Rissing, TB Buxton. Effect of ibuprofen on gross pathology, bacterial count, and levels of prostaglandin E2 in experimental staphylococcal osteomyelitis. J Infect Dis 154:627–630, 1986.
17. M Subasi, A Kapukaya, C Kesemenli, I Sari. Effect of granulocyte-macrophage colony-stimulating factor on treatment of acute osteomyelitis. Arch Orthop Trauma Surg 121:170–173, 2001.
18. JT Mader, GL Brown, JC Guckian, CU Wells, JA Reinarz. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 142: 915–922, 1980.
19. V Mendel, B Eichert, HJ Simanowski, HC Scholz. Therapy with hyperbaric oxygen and cefazolin for experimental osteomyelitis due to *Staphylococcus aureus* in rats. Undersea Hyperb Med 26:169–174, 1999.
20. A Johansson, JJ Flock, O Svensoon. Collagen and fibronectin binding in experimental staphylococcal osteomyelitis. Clin Orthop 382:241–246, 2001.
21. B Fischer, P Vaudaux, M Magnin, Y el Mesitikawy, RA Proctor, DP Lew, H Vasey. Novel animal model for studying the molecular mechanisms of bacterial adhesion to bone-implanted metallic devices: role of fibronectin in *Staphylococcus aureus* adhesion. J Orthop Res 14:914–920, 1996.
22. KJ Mayberre-Carson, B Tober-Meyer, JK Smith, DW Lambe Jr, JW Costerton. Bacterial adherence and glycocalyx formation in osteomyelitis experimentally induced with *Staphylococcus aureus*. Infect Immun 43(3): 825–833, 1984.
23. SS Reilly, MC Hudson, JF Kellam, WK Ramp. In vivo internalization of *Staphylococcus aureus* by embryonic chick osteoblasts, Bone 26:63–70, 2000.
24. LB Dahl, AL Hoyland, H Dramsdahl, PI Kaaresen. Acute osteomyelitis in children: a population-based retrospective study 1965 to 1994. Scand J Infect Dis 30:573–577, 1998.
25. RB Trobs, RP Moritz, U Buhligen, J Bennek, W Handrick, D Hormann, T Meier. Changing pattern of osteomyelitis in infants and children. Pediatr Surg Int 15: 363–372, 1999.
26. DJ Schulak, JM Rayhack, FG Lippert III, FR Convery. The erythrocyte sedimentation rate in orthopaedic patients. Clin Orthop 167:197–202, 1982.
27. EJ Carragee, D Kim, T van der Vlugt, D Vittum. The clinical use of the erythrocyte sedimentation rate in pyogenic vertebral osteomyelitis. Spine 22:2089–2093, 1997.
28. M Perry. Erythrocyte sedimentation rate and C reactive protein in the assessment of suspected bone infection—are they reliable inices? J R Coll Surg Edinb 41:116–118, 1996.

29. I Roine, I Faingezicht, A Arguedas, JF Herrera, F Rodriguez. Serial serum C-reactive protein to monitor recovery from acute hematogenous osteomyelitis in children. Pediatr Infect Dis 14:40–44, 1995.
30. L Unkilla-Kallio, MJ Kallio, J Eskola, H Peltola. Serum C-reactive protein, erythrocyte sedimentation rate, and white blood cell count in acute hematogenous osteomyelitis of children. Pediatrics 93:59–62, 1994.
31. PA Mackowiak, SR Jones, JW Smith. Diagnostic value of sinus tract cultures in chronic osteomyelitis. JAMA 239:2772–2775, 1978.
32. CR Perry, RL Pearson, GA Miller. Accuracy of cultures of material from swabbing of the superficial aspect of the wound and needle biopsy in the preoperative assessment of osteomyelitis. J Bone Joint Surg 73A:745–749, 1991.
33. G Cierny, JT Mader. Adult chronic osteomyelitis. Orthopedics 7:1557–1564, 1984.
34. HM Ericcson, JC Sherris. Antibiotic sensitivity testing: report of an international collaborative study. Acta Pathol Microbiol Scand 227(suppl B):1–90, 1971.
35. A Stein, JF Bataille, M Drancourt, G Curvale, JN Argenson, P Groulier, D Raoult. Ambulatory treatment of multidrug-resistant *Staphylococcus*-infected orthopedic implants with high-dose oral co-trimoxazole (trimethoprim-sulfamethoxazole). Antimicrob Agents Chemother 42:3086–3091, 1998.
36. A Zannier, M Drancourt, JP Franceschi, JM Aubaniac, D Raoult. Value of the technique of cellular lysis by thermic shock in the isolation of bacteria causing osteoarticular infections. Pathol Biol 39:543–546, 1991.
37. MM Tunney, S Patrick, MD Curran, G Ramage, D Hanna, JR Nixon, SP Gorman, RI Davis, N Anderson. Detection of prosthetic hip infection and revision arthroplasty by immunofluorescence microscopy and PCR amplification of the bacterial 16S rRNA gene. J Clin Microbiol 37:3281–3290, 1999.
38. B La Scola, G Michel, D Raoult. Use of amplification and sequencing of the 16S rRNA gene to diagnose *Mycoplasma pneumoniae* osteomyelitis in a patient with hypogammaglobulinemia, Clin Infect Dis 24:1161–1163, 1997.
39. P Morata, MI Queipo-Ortuno, JM Reguera, F Miralles, JJ Lopez-Gonzalez, JD Colmnero. Diagnostic yield of a PCR assay in focal complications of brucellosis. J Clin Microbiol 39:3743–3746, 2001.
40. SP Modi, SC Eppes, JD Klein. Cat-scratch disease presenting as multifocal osteomyelitis with thoracic abscess. Pediatr Infect Dis J 20:1006–1007, 2001.
41. JA Weigl, WH Haas. Postoperative *Mycobacterium avium* osteomyelitis confirmed by polymerase chain reaction. Eur J Pediatr 159:64–69, 2000.
42. RH Berk, M Yazici, N Atabey, OS Ozdamar, U Pabuccuoglu, E Alici. Detection of *Mycobacterium tuberculosis* in formaldehyde solution-fixed, paraffin-embedded tissue by polymerase chain reaction in Pott's disease. Spine 21:1991–1995, 1996.
43. WP Butt. The radiology of infection. Clin Orthop 96:20–30, 1973.
44. AG Jones, MD Francis, MA Davis. Bone scanning: radionuclide reaction mechanisms. Semin Nucl Med 6:3–18, 1976.
45. S Treves, J Khettry, FH Broker, RH Wilkinson, H Watts. Osteomyelitis: early scintigraphic detection in children. Pediatrics. 57:173–186, 1976.
46. LD Russin, LV Staab. Unusual bone-scan findings in acute osteomyelitis: case report. J Nucl Med 17:617–619, 1976.

47. M Deysine, H Rafkin, I Teicher, L Silver, R Robinson, J Manly, AH Aufses. Diagnosis of chronic and postoperative osteomyelitis with gallium 67 citrate scans. Am J Surg 129:632–635, 1975.
48. R Lisbona, L Rosenthall. Observations of the sequential use of ^{99m}Tc phosphate complex and ^{67}Ga imaging in osteomyelitis, cellulitis, and septic arthritis. Radiology 123:123–129, 1977.
49. SL Propst-Proctor, MF Dillingham, IR McDougall, D Goodwin. The white blood cell scan in orthopedics. Clin Orthop 168:157–165, 1982.
50. JP Kuhn, PE Berger. Computed tomographic diagnosis of osteomyelitis: Radiology 130:503–506, 1979.
51. LD Ma, FJ Frassica, DA Bluemke, EK Fishman. CT and MRI evaluation of musculoskeletal infection. Cri Rev Diagn Imaging 38:535–568, 1997.
52. WA Erdman, F Tamburro, HT Jayson, PT Weatherall, KB Ferry, RM Peshock. Osteomyelitis: characteristics and pitfalls of diagnosis with MR imaging. Radiology 180:533–539, 1991.
53. J Tehranzadeh, F Wang, M Mesgarzadeh. Magnetic resonance imaging of osteomyelitis. Crit Rev Diagn Imaging 33:495–534, 1992.
54. E Unger, P Moldofsky, R Gatenby, W Hartz, G Broder. Diagnosis of osteomyelitis by MR imaging. Am J Roentgenol 150:605–610, 1988.
55. MT Modic, W Pflanze, DHI Feiglin, G Berhobek. Magnetic resonance imaging of musculoskeletal infections. Radiol Clin North Am 24:247–258, 1986.
56. AL Wong, KM Sakamoto, EE Johnson. Differentiating osteomyelitis from bone infarction in sickle cell disease. Pediatr Emerg Care 17: 60–63, 2001.
57. G Cierny, JT Mader. The surgical treatment of adult osteomyelitis. In: CMC Evarts, ed. Surgery of the Musculoskeletal System. New York: Churchill Livingstone, 1983:15–35.
58. JT Mader, M Ortiz, JH Calhoun. Update on the diagnosis and management of osteomyelitis. Clin Podiatr Med Surg 13:53–61, 1996.
59. RO Hickman, CD Buckner, RA Clift, JE Sanders, P Stewart, ED Thomas. A modified right atrial catheter for access to the venous system in marrow transplant recipients. Surg Gynecol Obstet 148:871–875, 1979.
60. L Couch, G Cierny, JT Mader. Impatient and outpatient use of the Hickman catheter for adults with osteomyelitis. Clin Orthop 219:226–235, 1987.
61. DR Graham, MM Keldermans, LW Klemm, NJ Semenza, ML Shafer. Infectious complications among patients receiving home intravenous therapy with peripheral, central, or peripherally placed central venous catheters. Am J Med 91:95S–100S, 1991.
62. JT Mader. Fluoroquinolones in bone and joint infections, In: WE Sanders Jr, CC Sanders, eds. Fluoroquinolones in the Treatment of Infectious Diseases. Glenview, IL: Physicians & Scientists, 1990:71–86.
63. DP Lew, FA Waldvogel. Quinolones and osteomyelitis: state-of-the-art. Drugs 49(suppl) 2:100–111, 1995.
64. JT Mader, JS Cantrell, JH Calhoun. Oral ciprofloxacin compared with standard parenteral antibiotic therapy for chronic osteomyelitis in adults. J Bone Joint Surg 72(A):104–110, 1990.

65. DR Schamberg, WI Dillon, MS Terpenning, KA Robinson, SF Bradley, CA Kaufman. Increasing resistance of enterococci to ciprofloxacin. Antimicrob Agents Chemother 36:2533–2535, 1992.
66. ME Ernst, EJ Ernst, ME Klepser. Levofloxacin and trovafloxacin: the next generation of fluoroquinolones. Am J Health Syst Pharm 54:2569–2584, 1997.
67. AJ Wagstaff, JA Balfour. Grepafloxacin. Drugs 825–827, 1997.
68. HM Blumberg, D Rimland, DJ Carroll, et al. Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant *Staphylococcus aureus*. J Infect Dis 163:1279–1285, 1991.
69. CW Norden, R Bryant, D Palmer, JZ Montgomerie, J Wheat. Chronic osteomyelitis caused by *Staphylococcus aureus*: controlled clinical trial of nafcillin therapy and nafcillin-rifampin therapy. South Med J 79:947–951, 1986.
70. LB Reller, CW Stratton. Serum dilution test for bactericidal activity. II. Standardization and correlation with antimicrobial assays and susceptibility tests. J Infect Dis 136:196–204, 1977.
71. JT Mader, JH Calhoun. Osteornyelitis. In: GL Mandell, JE Bennett, R Dolin, eds. Principles and Practice of Infectious Diseases. 5th ed. Philadelphia: Churchill Livingstone: 2000:1181–1196.
72. JA Goulet, PM Pellicci, BD Brause, EM Salvati. Prolonged suppression of infection in total hip arthroplasty. J Arthroplasty 3:109–116, 1988.
73. M Drancourt, A Stein, JN Argenson, R Roiron, P Groulier, D Raoult. Oral treatment of *Staphylococcus* spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampicin. J Antimicrob Chemother 39:235–240, 1997.
74. J Segreti, JA Nelson, GM Trenholme. Prolonged suppressive antibiotic therapy for infected orthopedic prostheses. Clin Infect Dis 27:711–713, 1998.
75. AH Simpson, M Deakin, JM Latham. Chronic osteomyelitis: the effect of the extent of surgical resection on infection-free survival. J Bone Joint Surg 83B: 403–407, 2001.
76. PE Ruttle, PJ Kelley, PG Arnold, GB Irons, RH Fitzgerald. Chronic osteomyelitis treated with a muscle flap. Orthop Clin North Am 15:451–459, 1984.
77. JW May Jr, JB Jupiter, GG Gallico III, DM Rothkopf, P Zingarelli. Treatment of chronic traumatic bone wounds: microvascular free tissue transfer: a 13-year experience in 96 patients. Ann Surg 214:241, 1991.
78. JP Anthony, SJ Mathes, BS Alpert. The muscle flap in the treatment of chronic lower extremity osteomyelitis: results in patients over 5 years after treatment. Plast Reconstr Surg 88:311–318, 1991.
79. GB Irons Jr, MB Wood. Soft tissue coverage for the treatment of osteomyelitis of the lower part of the leg. Mayo Clin Proc 61:382–387, 1986.
80. JP Anthony, SJ Mathes. Update on chronic osteomyelitis. Clin Plast Surg 18:515–523, 1991.
81. LJ Papineau, A Alfageme, JP Dalcourt, L Pilon. Osteomyelite chronique: excision et greffe de sporigieux a l'air libre apres mises a plat extensives. Int Orthop 3:165–176, 1979.
82. DM Scott, JC Rotschafer, F Behrens. Use of vancomycin and tobramycin polymethylmethacrylate impregnated beads in the management of chronic osteomyelitis. Drug Intell Clin Pharmacol 22:480–483, 1988.

83. KJ Wilson, G Cierny, KR Adams, JT Mader. Comparative evaluation of the diffusion of tobramycin and cefotaxime out of antibiotic-impregnated polymethylmethacrylate beads. J Orthop Res 6:279–286, 1988.
84. K Adams, MSL Couch, G Cierny et al. In vitro and in vivo evaluation of antibiotic diffusion from antibiotic-impregnated polymethylmethacrylate (PMMA) beads. Clin Orthop 276:244–252, 1992.
85. JH Calhoun, JT Mader. Antibiotic beads in the management of surgical infection. Am J Surg 157:443–449, 1989.
86. SL Henry, D Seligson, P Mangino, GJ Popham. Antibiotic-impregnated beads. Part I. Bead implantation versus systemic therapy. Orthop Rev 20:242–247, 1991.
87. GJ Popham, P Mangino, D Seligson, SL Henry. Antibiotic-impregnated beads. Part II. Factors in antibiotic selection. Orthop Rev 20:331–337, 1991.
88. CR Perry, K Davenport, MK Vossen. Local delivery of antibiotics via an implantable pump in the treatment of osteomyelitis. Clin Orthop 226:222–230, 1988.
89. SA Green. Osteomyelitis: the Ilizarov perspective. Orthop Clin North Am 22:515–521, 1991.
90. JH Calhoun, DM Anger, JT Mader. The Ilizarov technique in the treatment of osteomyelitis. Tex Med 87:56–59, 1991.
91. FA Matsen, CR Wyss, LR Pedegana, RB Krugmire, CW Simmons, RV King, EM Burgess. Transcutaneous oxygen tension measurement in peripheral vascular disease. Surg Gynecol Obstet 150:525–528, 1980.
92. JH Calhoun, JT Mader. Osteomyelitis of the diabetic foot. In: SRG Frykberg, ed. The High Risk Foot in Diabetes Mellitus. New York: Churchill Livingstone, 1991:213–239.
93. JH Calhoun, J Cantrell, J Lacy, Y Hilliard, J Cobos, JT Mader. Treatment of diabetic foot infection: Wagner classification, therapy, and outcome. Foot Ankle 9:101–106, 1988.
94. DM Bamberger, GP Daus, DN Gerding. Osteomyelitis in the feet of diabetic patients: long-term results, prognostic factors, and the role of antimicrobial and surgical therapy. Am J Med 83:653–660, 1987.

7
Septic Arthritis

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I. INTRODUCTION

Septic arthritis is an inflammation of the joint space, synovial fluid, synovium, and articular cartilage caused by a variety of microorganisms. Acute infections are generally caused by pyogenic bacteria and called *acute bacterial* or *septic arthritis*. The process is generally acute and constitutes a medical emergency; if it is untreated for even 24 to 48 hours, permanent joint damage may result. Common pyogenic bacteria including *Staphylococcus aureus*, *Streptococcus* spp., *Haemophilus influenzae*, and *Neisseria gonorrhoeae* cause the vast majority of episodes. The aerobic gram-negative bacilli and anaerobes account for additional cases.

Chronic infections are most often caused by mycobacteria or fungi. Sterile or reactive arthritis is an inflammatory reaction that is generally secondary to infection in another part of the body. It may be associated with infection preceding hepatitis or postgastrointestinal infections with *Salmonella* or *Shigella* spp.

Nearly 10% of the patients who have nongonococcal bacterial arthritis may die with the infection and one-third of the survivors are afflicted with residual loss of function in the involved joint. It afflicts all age groups and has a predilection for immunocompromised patients. Important questions regarding the therapy of septic arthritis include the duration of antibiotic treatment, the mode of joint drainage, and the role of physical therapy.

II. MICROBIOLOGICAL CHARACTERISTICS

Virtually every bacterial organism has been reported to cause septic arthritis. The specific etiological agent in any given patient can be anticipated by identifying the patient's age, host factors, and presence of prior disease (Table 1). *Staphylococcus aureus* has been the most common cause of nongonococcal bacterial arthritis over the course of the last four decades (1,2). In 1990 an increased incidence of gram-negative organisms, especially *Escherichia coli* and *Pseudomonas aeruginosa*, in the elderly debilitated population was reported (3).

S. aureus causes most cases of bacterial arthritis in human immunodeficiency virus–(HIV)-positive patients who are intravenous drug users. However, HIV infection predisposes patients to joint infections with opportunistic as well as common pathogens (4–6).

In patients with sickle cell disease, *Salmonella* spp. as well as gram-positive and other gram-negative bacteria have been isolated from infected joints. In the neonate with prolonged hospitalization and instrumentation, coagulase-negative staphylococci, gram-negative enteric bacteria, and fungi have been isolated. *N. gonorrhoeae* is the most common cause of acute joint infection in young adults between 15 and 40 years of age in the United States.

Historically, *H. influenzae*, *S. aureus*, and group A streptococci were the most common causes of infectious arthritis in children below 2 years of age. However, the overall incidence of *H. influenzae* as a cause of septic arthritis is decreasing because of the *H. influenzae* type b (Hib) vaccine now given to children (7). A 1997 study of 165 cases of acute hematogenous osteomyelitis or septic arthritis treated in the years before and after the advent of the Hib vaccine demonstrated that musculoskeletal infections due to this bacterial species were reduced to nearly nonexistent levels (8). Therefore, the coverage of *H. influenzae* as part of the empirical antibiotic coverage may no longer be needed in the management of acute septic arthritis in Hib-vaccinated children. While *H.*

Table 1 Causative Organism in Septic Arthritis by Age in Years (Percentages)

	2 Yr	2–15 Yr	16–50 Yr	75 Yr
Staphylococcus aureus	35	50	15	75
Streptococcus pyogenes	15	20	5	5
Streptococcus pneumoniae	10	10	–	5
Haemophilus influenza, type B	35	2	–	–
Neisseria gonorrhoeae	–	10	10	–
Others	5	8	10	15
Gram-negative bacilli	5	7	9	15
Anaerobes	–	1	1	–

influenzae has lost its predominance as the most commonly identified gram-negative pathogen in pediatric populations, the normal oropharyngeal resident of young children *Kingella kingae* may have taken its place, specifically in patients less than 24 months of age (9–12). In fact, a 1998 study found that nearly half of the clinical isolates from acute septic arthritis patients less than 2 years old were *K. kingae* (11). However, these results have yet to be seen in other regions. Clinical data suggest that the organism may gain access to the bloodstream in the course of an upper respiratory infection or stomatitis (13). In children above the age of 2, *S. aureus*, streptococci, *H. influenzae*, and *N. gonorrhoea* have usually been isolated (14–16), but *H. influenzae* may have also lost its predominance in this patient age group as mentioned previously (10).

Microbiological associations exist with concomitant disease states. Septic arthritis after cases of infectious diarrhea may be caused by *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., or *Yersinia* spp. (17,18). However, these cases may reflect a form of reactive arthritis. A rare form of migrating polyarthritis may be caused by *Streptobacillus moniliformis*. In HIV-infected patients, *S. aureus* continues to be the most common isolate (approximately 30%) (6). However, there is an increased number of opportunistic pathogens isolated from this patient subset, including *Streptococcus pneumoniae*, mycobacterial species, and fungal species (14,16). Anaerobic bacteria have been seen primarily after surgical arthroplasty or traumatic injuries of the extremities (19). *Bacteroides* species appear to attack the sternoclavicular and sacroiliac joints. Table 2 summarizes the relationship between certain epidemiological situations and the infecting agents.

Table 2 Relationships Between Organisms and Underlying Epidemiological Conditions

Organisms	Epidemiological condition
Neisseria gonorrhoeae	Menstruation or pregnancy
Neisseria meningitis	Chronic meningococcemia
Haemophilus influenza	Children less than 2 years
Pasteurella multocida	Cat or dog bite
Eikenella corrodens	Human bite
Fusobacterium nucleatum	
Streptobacillus moniliformis	Rat bite
Borrelia burgdorferi	Tick exposure
Brucella spp.	Ingestion of nonpasteurized dairy products
Sporothrix schenkii	Injury: rose thorns, splinters, moist soil
Mycobacterium marinum	Trauma in aquatic environment
Staphylococcus aureus or	Intravenous drug abuse
Pseudomonas aeruginosa	
Mycobacterium kansasii	Monoarticular synovitis

III. PREDISPOSING CONDITIONS

Table 3 lists some of the predisposing factors for infectious arthritis. Intravenous (IV) drug abuse appears to be a risk factor for the development of bacterial arthritis. *S. aureus*, *P. aeruginosa*, and *Serratia marcescens* have been isolated. In these IV drug abusers there was an increased frequency of infection of the sacroiliac joints, sternal articulations, and pubic symphysis (20). Chronic inflammation and joint damage as seen in gout, osteoarthritis, and rheumatoid arthritis are predisposing factors for joint infection. Joint trauma, joint surgery, and presence of a joint prosthesis are also risk factors because damaged joints act as a nidus for bacterial infection. Patients with chronic underlying illnesses (systemic lupus erythematosus, diabetes, renal failure, HIV, etc.) have suppressed or defective immune functions and are susceptible to increased bacterial infections.

Table 3 Predisposing Factors in Infectious Arthritis

Adults
Immunosuppressive therapy
Joint trauma
Penetrating injury
Intra-articular injections (rare)
Preexisting arthritis
Osteoarthritis
Rheumatoid arthritis
Crystal-induced arthritis
Presence of joint prosthesis
Arthroscopic procedures (rare)
Serious chronic illness
Cancer
Systemic lupus erythematosus
Chronic liver disease
Diabetes
Human immunodeficiency virus
Hemoglobinopathy
Intravenous drug abuse
Children
Trauma
Contiguous osteomyelitis
Systemic illnesses

IV. PATHOGENESIS

There are three modes by which a joint space may be seeded in both children and adults; the most common cause is hematogenous. Roughly 50% of patients with septic arthritis have concomitant positive blood culture findings. A primary source such as otitis and endocarditis should be sought. Although not all episodes of bacteremia result in joint infection, the risk for the development of infection is increased by local factors in the joint (e.g., recent trauma, rheumatoid arthritis, preexisting joint disease) systemic factors in the host (e.g., parenteral drug abuse, corticosteriod use, immunosuppressive medication, malignancy) or finally properties of the infecting organism (e.g., gram-positive cocci as the etiological agent of nongonococcal septic arthritis).

A small percentage of cases result from direct inoculation of the joint space, either accidentally (e.g., atypical mycobacteria, actinomyces) or iatrogenically (e.g., arthrocentesis, instillation of corticosteroids). In children, septic arthritis can develop from a contiguous infection such as osteomyelitis. Septic arthritis may also result from the spread of a contiguous infection (*Mycobacterium tuberculosis*) in adults.

Once the synovium is seeded, the resulting inflammatory reaction may result in rapid destruction of the articular cartilage. The drainage to the joint results from increased intra-articular pressure and the release of proteolytic enzymes from the polymorphonuclear leukocytes, which degrade the cartilage (21,22). Since this cartilage is avascular and unable to regenerate, permanent damage results.

Endocrine factors seem to play an important role in the pathogenesis of gonococcal infectious arthritis. There is a greater incidence of gonococcal arthritis in women, and women are more susceptible to gonococcal bacteremia during pregnancy, in the postpartum period, and during the first week of the menstrual cycle. Rubella arthritis occurs primarily in postpubertal women and mumps arthritis is seen exclusively in postpubertal men (23).

Recovery from various systemic infections has been associated with a reactive arthritis related to the immune response. The postinfectious arthritis that follows gastrointestinal infections with *Shigella*, *Salmonella*, *Campylobacter*, and *Yersinia* spp. occurs most often in persons with human leukocyte antigen B27 (HLA-B27) histocompatibility antigen (24). Inpatients with hepatitis C infection arthritis secondary to antigen-antibody complex formation may develop.

V. CLINICAL FEATURE OF BACTERIAL ARTHRITIS

The clinical findings in gonococcal and nongonococcal infectious arthritis in adults are outlined in Table 4. The presenting symptoms in disseminated

Table 4 Comparison of Clinical Findings in Gonococcal and Nongonococcal Bacterial Arthritis

Gonococcal	Nongonococcal
Generally healthy young adults	Generally elderly or immunocompromised
Polyarticular arthritis (> 50% of cases)	Monoarticular arthritis (> 80% of cases)
Tenosynovitis common	Tenosynovitis rare
Rash common	Rash unusual
Blood culture results positive in < 10%	Blood culture results positive in > 50%
Joint culture results positive in < 25%	Joint culture results positive in > 90%
Rapid response to antibiotic treatment	Slow response to antibiotics and drainage
Generally good prognosis	Variable prognosis

Source: Modified from Ref. 39.

gonococcal infections may be insidious; migratory polyarthralgias, fever, dermatitis, urethral or vaginal discharge, and tenosynovitis are the most common findings. Only 30%–40% of these patients have the classic bacterial arthritis symptoms of fever, localized symptoms of warmth, pain, swelling, and tenderness over the involved joint. When tenderness in present, it is often diffuse in its periarticular location in contrast to the "point tenderness" often noted in acute osteomyelitis. Often, there is a palpable joint effusion, and most patients experience decreased active and passive motion of the involved joint, a sign that often distinguishes septic arthritis from bursitis or cellulitis (25). Radiographically the joint capsule may be distended with fluid, accompanied by soft tissue swelling; less commonly destructive changes in the bony structure are evident. The latter may occur with pyogenic arthritis in which there has been delay in diagnosis or in mycobacterial infection or in infections complicated by rheumatoid arthritis.

Septic arthritis is generally monoarticular and weight-bearing joints are most commonly affected (Table 5). Nearly half of the cases of septic arthritis in adults involve the knee joints, followed in descending order of frequency by the hip, elbow, ankle, wrist, shoulder, sternoclavicular joint, sacroiliac joint, and small joints of the hands and feet. Joints involved in acute pyogenic arthritis are usually warm, tender, and erythematous. Ninety percent of patients have joint effusions associated with general constitutional symptoms such as malaise and fever. Misleading symptoms may also be seen in bacterial arthritis of the hip and sacroiliac joints, where pain may be referred to the abdomen or knee. In older individuals with a history of chronic degenerative joint disease, a definitive diagnosis may be delayed because symptoms are erroneously attributed to the underlying condition rather than to an infectious process. In neonates, the clinical features of infectious arthritis are those of septicemia or fever of unknown origin.

Table 5 Frequency of Joint Involvement in Bacterial Arthritis

Site	Children (%)	Adults (%)
Knee	40	50
Hip	20	25
Ankle	15	7
Elbow	15	10
Wrist	5	7
Shoulder	5	5
Interphalangeal and metacarpal	1	1
Sternoclavicular	1	8
Sacroiliac	0	2

The clue to diagnosis here is a careful physical examination that may reveal localized swelling, pain on palpation or passive movement of the joint, and decreased movement of the extremity.

Pustular skin lesions similar to those commonly observed in disseminated gonococcemia have been described in patients with meningococcal arthritis (26,27) and in occasional patients with septic arthritis due to group A streptococci (28) and *H. influenzae* (12). Polyarticular nongonococcal infection occurs in 10%–20% of adults and children with septic arthritis (12). In contrast, more than one joint is involved in the majority of patients with gonococcal arthritis (29).

VI. DIAGNOSIS

The traditional "index of suspicion" remains the most important factor in the diagnosis of septic arthritis. Table 6 outlines the proper evaluation of a patient with suspected septic arthritis. The diagnosis is established by a complete history, including an epidemiological one; physical examination; and by examination and culture of the synovial fluid. Peripheral blood leukocyte counts are visually elevated in children but are often within normal limits in adults. Many patients display elevated C-reactive protein levels and erythrocyte sedimentation rates. A suspicion of septic arthritis mandates an arthrocentesis of the suspected joint and careful examination of the synovial fluid, if there is no contraindication (Table 7). Synovial fluid is analyzed for total and differential leukocyte count, crystals, glucose, and mucin clot (30). Other parameters include protein, complement, pH, color, and turbidity. However, there is significant overlap of all these findings among different types of inflammatory arthritis, for example septic, rheumatoid, gouty, and pseudogouty. In septic arthritis, the leukocyte count is usually greater than 50,000 per cubic millimeter with more than 90% of the cells polymorpho-

Table 6 Diagnostic Evaluation of a Patient with Septic Arthritis[a]

History
Physical examination
Joint fluid aspiration
Leukocyte count
Crystals
Synovial glucose level
Gram stain
Culture (aerobic, anaerobic, fungus, mycobacteria)
Culture other sites
Blood cultures
Blood tests
Peripheral WBC
Erythrocyte sedimentation rate
C-reactive protein
Blood sugar
Roentgenograms (routine, CT, MRI, radionuclide scans)
Response to treatment

[a] WBC, white blood cell count; CT, computed tomography; MRI, magnetic resonance imaging.

nuclear leukocytes. The glucose is less than 60% of simultaneous serum glucose, mucin clot is poor, and protein levels are elevated. The appearance is cloudy or turbid with a yellow to green hue.

Synovial fluid from any adult with monoarticular arthritis should be examined by compensated polarizing light microscopy for negatively birefringent (uric acid) and positively birefringent calcium pyrophosphate dihydrate crystals to

Table 7 Analysis of Synovial Fluid for Differing Forms of Infectious Arthritis

Condition	Leukocytes, n/mm	Predominant Cell Type	Glucose ratio, synovial fluid to blood	Diagnostic smear, % cases
Normal	200–600	Mononuclear	0.8–1.0	0
Bacterial arthritis	10,000–100,000	> 90% PMN[a]	< 0.5	> 90
Fungal arthritis	3,000–30,000	70% PMN	> 0.5	< 0.5
Tuberculous arthritis	10,000–20,000	50%–70% PMN[a]	0.5–1.0	< 20
Reactive	3,000–10,000	Mononuclear	0.8–1.0	0

[a] PMN, polymorphonuclear leukocyte cells.

rule out crystalline joint disease. However, simultaneous bacterial infection and crystalline disease has been reported (31).

The ultimate diagnosis of septic arthritis is made through identification of the infecting organism, either by Gram stain of the synovial fluid or through culture. Prior antibiotic therapy may result in a negative culture or Gram stain finding. If the Gram stain result is negative it is important to do an acid-fast stain for mycobacteria and a potassium hydroxide wet mount for fungi. Cultures of synovial fluid fail to grow organisms in a substantial number of patients in whom there is a clinical diagnosis of septic arthritis. Several reasons have been proposed for the inability to obtain positive culture results, including prior use of antibiotics, inadequate anaerobic cultures, standard of the microbiology laboratory, changing patterns of the organisms involved and their cultural characteristics, and failure to obtain blood for culture or to perform a sufficient number of arthrocentesis.

Skin lesions, particularly those that can be aspirated and examined on Gram stained smears, can provide a clue as to the presence of bacteremia (meningococcal, gonococcal, or staphylococcal) and indicate a specific organism.

Imaging studies of septic arthritis can only be used to support or refute a clinical suspicion of the disease and should not be used as an absolute diagnostic indicator. Radiographs taken in the first 7 to 10 days of infection are of little diagnostic help because they show only distention of the joint capsule and periarticular swelling. Initial films should nevertheless be obtained before arthrocentesis because one needs a baseline for comparison. Septic arthritis may be a consequence of preexisting osteomyelitis or the presence of intra-articular gas (rare) that would suggest *Clostridium* spp.; in prosthetic joint infections, it can often demonstrate loosening of the prosthesis, which would be revealed radiographically. Follow-up films are important in evaluating the extent of articular damage. The presence of chondrocalcinosis on radiography should not dissuade anyone from the diagnosis of septic arthritis.

Ultrasonography is capable of showing both intra- and extra-articular abnormalities not apparent by plain radiography and is a very powerful tool to detect early fluid effusions and to guide initial joint aspiration and drainage procedures (32,33). Even small collections of fluid (1–2 mL) can be accurately detected (33). Non–echo-free effusions (due to clotted hemorrhagic collections) are very characteristic of a septic joint. It has been suggested that the presence of only an echo-free effusion (caused by transient synovitis and fresh hemorrhagic effusions) may rule out the diagnosis of septic arthritis (33). This imaging technique is also useful for detecting collections of fluids in deep joints, including the hip. In addition, the status of the intra-articular compartment, joint capsule, bony surface, and adjacent soft tissues, and the patient's response to therapy can be monitored. When one considers that this imaging technique is also noninvasive, inexpensive, easy to use, and devoid of irradiation or any other known

complications, more clinicians should use ultrasonography in the diagnosis of septic arthritis in the future.

A triple-phase radionuclide bone scan is the best earliest radiographic diagnostic test for septic arthritis. It shows increased activity around an infected joint. However, these findings are nonspecific and can be detected in other forms of infectious arthropathies.

Like radiographs, computed tomography (CT) scans have limited use during the early stages of septic arthritis. However, these scans may allow the visualization of joint effusion, soft tissue swelling, and periarticular abscesses. In addition, they are more sensitive than plain radiographs in the imaging of joint space widening due to localized edema, bone erosions, foci of osteitis, and scleroses. This scanning technique may be useful in the diagnoses of arthritis cases that are difficult to assess, including infections of the hip, sacroiliac, and sternoclavicular joints. In addition, they may assist in guiding joint aspiration, selecting the surgical approach, and monitoring therapy in these difficult infections (34).

Magnetic resonance imaging (MRI) has become a useful diagnostic tool for the early determination of the extent of musculoskeletal infection (35,36). As with CT, MRI may be particularly useful in aiding the diagnosis of joint infections that are difficult to access, such as sacroiliitis (37). MRI displays greater resolution for soft tissue abnormalities than CT scans or radiographs and greater anatomical detail than radionuclide scans. The spatial resolution of MRI makes it useful in visualizing joint effusion and differentiating between bone and soft tissue infections. The main disadvantages to MRI are high cost, lack of universal availability, imaging interference due to metal implants, and lower resolution of calcified bone structures and cortex (38). However, neither CT nor MRI can differentiate between infectious and noninfectious joint effusions.

VII. DIFFERENTIAL DIAGNOSIS

The diagnosis of septic arthritis should be considered for any patient who has acute monoarticular arthritis (Table 8). A number of factors should be included in the differential diagnosis of septic arthritis:

1. Acute crystal-induced arthritis may resemble suppurative arthritis but can be distinguished readily by the presence of crystal in the synovial fluid.
2. Early rheumatoid arthritis, acute rheumatic fever, or Reiter's syndrome may mimic septic arthritis, particularly when only one or a few joints are involved. Joint fluid analysis is necessary to distinguish these processes from invasive infection.

Table 8 Differential Diagnosis of Septic Arthritis

Septic arthritis
Gonococcal
Nongonococcal
Nonsuppurative infectious arthritis
Mycobacteria
Fungal
Viral (hepatitis, rubella)
Syphilis
Mycoplasma
Lyme
Bacterial endocarditis
Sexually acquired reactive arthritis
Enteric arthritis
Acute rheumatic fever
Rheumatoid arthritis exacerbation
Crystal-induced arthritis
Septic bursitis
Polyarticular septic arthritis (PASA)

3. Acute arthritis involving one or several joints may occur in patients with sickle cell disease, usually along with other evidence of sickle cell crisis. Acute arthritis caused by sickle cell disease must also be distinguished from septic arthritis, osteomyelitis, aseptic bone infarctions, and gout. In acute arthritis that is caused by sickle cell disease, the synovial fluid finding is a noninflammatory process with a white blood cell (WBC) count of less than $1000/mm^3$ and mononuclear cells predominating (39).
4. Osteomyelitis must be considered in the differential diagnosis because it may have preceded joint involvement and may mimic septic arthritis by virtue of associated periarticular soft tissue swelling.
5. In any patient with rheumatoid arthritis in whom fever and disproportionate involvement of one or more joints develops bacterial infection should be suspected.
6. Unilateral sacroiliac pain with fever should point to a possible diagnosis of sacroiliac pyarthrosis.
7. Patients with septic bursitis experience fever and an acute painful swelling that may in some cases be mistaken for septic arthritis.
8. Trauma commonly precedes septic bursitis.
9. The diagnosis of Lyme arthritis in patients who live in endemic areas is based on a history of exposure to ticks, a history of erythema

chronicum migrans, or diagnostic serum titers of antibody to *Borrelia burgdorferi*.

10. Twenty-five percent of patients with infective endocarditis have an acute, sterile synovitis tenosynovitis, arthralgias, and myalgias (40). Bone or joint infections have been reported in 15% of cases in many series and are more common in intravenous drug users.

VIII. TREATMENT

Septic arthritis is a medical emergency that requires prompt diagnosis and treatment within 24 to 48 hours of onset of symptoms. Delaying therapy for more than 7 days commonly results in incomplete recovery, permanent disability, and death. Successful management consists of four elements: prompt diagnosis, appropriate antimicrobial therapy, drainage of the joint space, and rehabilitative therapy.

A. Antimicrobial Therapy

The clinical setting, epidemiological history, age of the patient, and results of the Gram stain of the joint fluid initially determine selection of antibiotics. Selection may later be modified on the basis of culture and sensitivity findings (Table 9).

The synovial tissue is very vascular and does not have a basement membrane. These characteristics facilitate the penetration of antimicrobial agents from blood into infected and uninfected inflamed joints. Synovial fluid concentrations of most antibacterials generally average at least 60% to 70% of serum drug concentrations at the time of peak serum concentrations and frequently exceed those in serum immediately before the subsequent systemic dose in patients with septic arthritis (41–43). In order for therapy to be effective, it is assumed that the antibacterial concentration attained in synovial fluid should exceed the usual amount required to inhibit the growth of the infecting bacteria.

Optimal concentrations of antibacterial agents in body fluids are particularly important in the immunocompromised host because recovery from the infected site depends to a large extent on the effectiveness of the antibacterials. In any host, a peak antibacterial concentration that exceeds the minimal inhibitory concentration of the infecting organism 5- to 10-fold and a measurable trough concentration has an excellent predictive value for a favorable outcome. Ceftriaxone should be used to treat gonococcal arthritis in most areas, since penicillin-resistant strains are being increasingly reported.

The route and duration of antibiotic therapy are still controversial in the treatment of septic arthritis. Parenteral antibiotics obtain adequate levels in the joint fluid, and intra-articular injection of antibiotics is not indicated for the

Table 9 Choice of Antibiotics in Therapy of Septic Arthritis[a]

Organism	Drug of choice	Dose (IV)	Alternative drug	Dose (IV)
Neisseria gonorrhoeae	Ceftriaxone	2 g q24 h	Doxycycline	100 mg q12 h
Staphylococcus aureus	Nafcillin	8–12 g, total 2–3 g q6 h	Vancomycin or imipenem	1 g q12 h
Streptococcus pneumoniae	Penicillin G Ceftriaxone	2 Million units q4–6 h 2 g q24 h	Erythromycin	0.5–1.0 g q6 h
Escherichia coli	Cefotaxime or	2 g q6–8 h	Imipenem or	0.5–1.0 g q6 h
Proteus mirabilis	Ceftriaxone	2 g q24 h	ciprofloxacin	400 mg IV q12 h
Pseudomonas aeruginosa	Ceftazidime and Tobramycin	2 g q24 h 8 mg/kg/qday		
No organisms seen Healthy young patient	Ceftriaxone	2 g q24 h	Imipenem	0.5–1.0 g q6 h
Older patient with underlying disease	Imipenem and Tobramycin	0.5–1 g q6 h 5 mg/kg/qday	Vancomycin[b] and ciprofloxacin	1 g q12 h and 400 mg q12 h

[a] Dosages for nonallergic patients with normal renal function. IV, intravenous.
[b] Vancomycin used only for methicillin-resistant *Staphylococcus* spp.

therapy of bacterial arthritis. In fact, intra-articular antibiotics may produce a chemical synovitis. Parenteral antibiotics should be given for 14 days or longer; the only exception is gonococcal arthritis, in which the organisms are usually very sensitive and 7 days suffices. However, when the organism is difficult to eradicate (such as *S. aureus* or gram-negative bacilli), parenteral treatment should be given for 4 weeks. Parenteral antibiotics can be changed to oral antibiotics if there is a good clinical response, but serum and synovial fluid concentrations of oral antibiotics must be bactericidal for effective therapy. For patients with nongonococcal infectious arthritis, most physicians administer antibiotics intravenously for 2 weeks, followed by 1 to 2 weeks of oral antibiotics. When the infection is difficult to eradicate, parenteral therapy is given for 4 weeks or for 2 weeks followed by a 4- to 6-week course of oral antibiotics. In gonococcal arthritis, parenteral therapy can be changed to oral therapy in 3 to 4 days if there is a good clinical response.

The effectiveness of treatment can be determined by serial examinations of the synovial fluid. Sterility should be achieved within a few days, but the leukocyte count may take a week to drop markedly. Few controlled studies assessing the optimal duration, dose, or route of administration of antibiotics in nongonococcal arthritis exist (41).

B. Surgical Therapy

Draining the infected joint allows removal of debris and toxin, which if allowed to accumulate would result in the destruction of the articular surfaces and the formation of adhesions. There are several methods available to achieve drainage, ranging from closed-needle aspiration to open drainage (Table 10). However, there are no universally accepted standards for drainage.

The joint should be aspirated by needle as often as required to remove pus, which contains enzymes that destroy cartilage. Repeated aspirations may be required for 7 to 10 days until the leukocyte count decreases and the synovial fluid remains sterile. Knees, ankles, wrists, and elbows usually can be drained adequately by needle aspiration. However, deep joints such as hips, shoulders, axial joints, and the sternoclavicular joint often necessitate open surgical drainage. Indications for open surgical drainage include the following:

1. Presence of loculations incompletely removed by repeated aspirations, especially when *S. aureus* is the pathogen
2. Persistently high neutrophil counts (>25,000 per cubic millimeter) in the joint fluid or positive culture results despite appropriate antibiotic treatment and multiple closed aspirations
3. Hip and other deep joint infections that cannot be aspirated with a needle

Table 10 Comparison of Drainage Procedures

	Aspiration	Tidal irrigation	Arthroscopy	Arthrotomy
Location	Bedside	Bedside	Operating room	Operating room
Anesthesia	Local	Local	Regional/general	Regional/general
Joint accessibility	Limited to large superficial joints; requires repeated aspirations	Limited to large superficial joints	Limited to large joints	All joints
Drainage capability	Modest	Modest	Excellent	Excellent
Adhesion lysis	No	No	Yes	Yes
Synovectomy	No	No	Yes	Yes
Morbidity	Minimal	Minimal	Moderate	Significant
Recovery time	Short	Short	Short	Prolonged
Cost	Inexpensive	Inexpensive	Modest	Expensive

After open drainage, the wound should be allowed to heal by secondary closure and antibiotic therapy should be continued for another week.

Arthroscopy and open arthrotomy should be considered when lysis of adhesions or synovectomy is being considered, when there is adjacent osteomyelitis, or when a trial of aspiration is unsuccessful (44–47). Arthroscopy can be also used to obtain synovial tissue for culture and histological testing when aspirated synovial fluid culture findings are negative and a bacterial identification is important to further treatment. This procedure is particularly valuable with fastidious organisms (44,48,49). Tidal irrigation, consisting of repeated distention and irrigation of the joint, may eliminate the need for surgical drainage (46).

C. Rehabilitation

Removable splints or casts, physical therapy, and active exercises are important for optimal recovery. Recently there has been support for early and aggressive mobilization after septic arthritis. However, weight bearing should be prevented until all signs of inflammation subside. Maintaining the joint in a position of maximal function by strict immobilization is not required. In fact, clinical observations have revealed deleterious effects of prolonged immobilization on synovial joints, including stiffness, pain, muscle atrophy, disuse osteoporosis, and later degenerative arthritis. Early continuous passive motion has the following benefits: prevention of adhesions and pannus formation, improvement in cartilage

nutrition through increased diffusion of synovial fluid, enhancement of clearance of enzymes in purulent exudate from the infected joint, and stimulation of chondrocytes to synthesize the various synovial matrix components (50,51). It has been recommended that passive range of motion be started during the first week of treatment, followed by active motion as soon as the patient permits it, usually within 1 or 2 weeks (50–52). Isometric exercise should be started on the first postoperative day, followed by range of motion exercise 1 or 2 days after removal of the drainage catheters (48).

Overall, the optimal time for initiating isometric exercise or range of motion exercise is not certain and remains controversial. Splinting versus continuous passive motion treatment for a joint with pyarthrosis is also controversial.

IX. COURSE OF ILLNESS AND PROGNOSIS

A permanent loss in joint function is seen in approximately 40% of patients with nongonococcal septic arthritis but ranges between 10% and 73% (2,53–55). Certain clinical findings are associated with poor prognosis (Table 11). The mortality rate associated with this disease is usually between 5% and 20% and is often a result of the transient or chronic bacteremia that causes most of the cases of septic arthritis and underlying host factors (malignancy, neonate, rheumatoid arthritis, etc.) (2,53–56). Septic arthritis in patients with rheumatoid arthritis (RA) has a mortality rate of about 20%, and a large proportion of survivors are left with diminished joint function. Case fatality rates are much higher among those with polyarticular septic nongonococcal arthritis (PASA) versus those with monoarticular infection (30% versus 4%, respectively) (57). Patients who have PASA have a very poor prognosis, which is due to the associated bacteremia and reduced ability to resist the infection. However, PASA may result in very high rates of mortality in patients infected with staphylococcal species (up to 56% mortality rate) and those with a concomitant diagnosis of rheumatoid arthritis (up to 49% mortality rate) (37).

Table 11 Predictors of Poor Outcome with Bacterial Arthritis

Age above 60 years
Infection in hip and shoulder
Severe underlying disease (rheumatoid arthritis, malignancy, etc.)
Duration of symptoms before treatment >1 week
Persistently positive culture results after 7-day course of appropriate therapy
Demonstrated bacteremia

The prognosis for patients suffering from gonococcal arthritis is very favorable with a rapid diminution of symptoms and a full return of joint function. In rare cases of DGI (1%–3%), complications such as endocarditis, pericarditis, osteomyelitis, pyomyositis, perihepatitis, and meningitis may occur.

The outcome in patients with septic arthritis due to some of the more virulent organisms such as superantigen-producing *S. aureus* and certain gram-negative bacilli is poor in spite of optimal therapy (58). The elderly demonstrate a high mortality rate (19%–23%) associated with septic arthritis since these patients often have preexisting medical conditions (e.g., diabetes mellitus) and joint diseases (e.g., osteoarthritis and rheumatoid arthritis) (3,59–61).

X. SPECIAL FORMS OF ARTHRITIS

In patients who experience fever, rash, lymphadenopathy, arthritis, or arthralgia, a viral cause should be considered. Arthropathy may be acute, subacute, or chronic. The most common viral diseases associated with arthropathy are rubella, mumps, hepatitis B, Epstein-Barr virus (associated with symptoms of infectious mononucleosis), parvovirus B19 (produces erythema infectiosum, (fifth disease), alpha viruses (Ross River virus in Australia, Chikungunya in Southeast Asia), and parvovirus (in the United Kingdom) (Table 12). Synovial fluid samples reveal an abundant presence of mononuclear leukocytes, and normal joint glucose and lactate levels are usually found (44,62). Clinical and epidemiological clues often lead the clinician to appropriate serological studies via antibody titers.

Tuberculosis Arthritis

Tuberculosis arthritis is a rare form of extrapulmonary tuberculosis that occurs in less than 1% of tuberculosis patients. However, with the advent of acquired immunodeficiency syndrome (AIDS) an increased incidence of articular involvement can be expected in these immunocompromised patients. Articular involvement is the result of either dissemination of infection from the original pulmonary primary focus or reactivation of a previously seeded by quiescent skeletal focus.

At present, patients suffering from tuberculosis arthritis who are not infected with HIV are 30 to 60 years of age, whereas we formerly saw it in children and adolescents. Both *M. tuberculosis* and atypical mycobacteria (*M. intracellulare* and *M. kansasii*) have been responsible for joint infection (28,63,64). Predisposing factors in the development of articular involvement include joint trauma, systemic illness (e.g., systemic lupus erythematosus, HIV, diabetes mellitus), narcotic addiction, and intra-articular injection of corticosteroids. Usually, the infection is monoarticular (spine, hips, knees, ankles) and is characterized by insidious onset, weight loss, and low-grade fever. Although

Table 12 Clinical and Epidemiological Features of Viral Arthritis

Viral agent	Occurrence/symptoms	Affected joints	Physical findings
Rubella	Adult females	Small joints of hands and feet, knees, wrists, and ankles	Joint pains near onset rash
Mumps	Adult males	Symmetrical polyarthritis of large and small joints	Joint pains within 1 week of parotids
Parvovirus B19	60% Adults, 10% children with erythema infectiosum	Metocarpophalangeal, proximal interphalangeal polyarthritis	Rash of EI
Hepatitis B	Preicteric phase	Symmetrical hands, knees, ankles	Urticaria
Arthropodiborne alpha virus Chikungunga ("that which bends up")	East Africa/India; abrupt onset of fever and chills	Large joints	Maculopapular rash over trunk and extensor surface extremities
Onyong-nyong (weakening of the joints)	East Africa (Uganda)	Symmetrical involvement of large joints	

examination of synovial fluid can detect acid-fast organisms in about 20% of culture-positive joint effusions, an open synovial biopsy definitely establishes the diagnosis. Resting of the inflamed joint during the acute stage followed by 18 to 24 months of antituberculosis therapy is the principal therapeutic measure. Débridement, synovectomy, or even joint fusion may be required if there has been extensive destructive change.

C. Fungal Arthritis

Fungal arthritis is rare and generally follows a chronic indolent course. Fungal arthritis can be divided into two groups: the mycostic agents that produce primary invasive systemic infections, such as *Histoplasma*, *Coccidioides*, and *Blastomyces* spp., and those that produce opportunistic infections, such as *Candida*, *Cryptococcus*, and *Sporothrix* spp. (65–68). Fungal arthritis is monoarticular; the knee is the most commonly affected joint, followed by the wrists and elbows. The patients have swollen joints, limited motion, chronic pain, and migratory arthritis. The definitive diagnosis is made by synovial biopsy and culture. The treatment of choice is still intravenous amphotericin B. Data are still lacking on the newer oral antifungals, fluconazole and itraconazole.

D. Syphilitic Arthritis

Arthritis can occur in congenital, secondary (rare), or tertiary syphilis. Children and teenagers with congenital syphilis may have only a painless synovitis with effusion in the knees and elbows. Neuropathic joint disease, most commonly involving the knees, and gummatous osteoarthritis of the large joints occur in tertiary syphilis. The treatment of choice is penicillin given in a dosage appropriate for the particular stage of syphilis.

E. Mycoplasma Arthritis

Septic arthritis has resulted from infection with *Mycoplasma hominis*, *Mycoplasma pneumoniae*, and *Ureaplasma urealyticum*. In some patients who have hypogammaglobulinemia polyarthritis resembling rheumatoid arthritis develops; in others acute septic arthritis develops (69). Mycoplasmas and ureaplasmas have been cultured from their joint fluids (70–72). The condition is responsive to antibiotic treatment with tetracycline or erythromycin.

F. Reactive Arthritis

An inflammatory joint response to extra-articular rather than intra-articular presence of microorganisms may be defined as *reactive arthritis* (73). Therefore,

although infection can be demonstrated at a distant site, joint inflammation occurs without traditional evidence of sepsis at the affected joint(s). Most cases are associated with the major histocompatibility complex antigen HLA-B27. Also, patients usually have recent microbial infections in distal sites that include the gastrointestinal (e.g., *Shigella* spp., *Salmonella* spp., *Campylobacter* spp., or *Yersinia* spp.), genitourinary (e.g., chlamydia and mycoplasmas), and respiratory (e.g., *Streptococcus pyogenes*) tracts (24). Patients have a sterile, inflamed joint and may also demonstrate enthesopathy, uveitis, conjunctivitis, or skin and mucous membrane lesions (28). Specifically, poststreptococcal reactive arthritis can follow group A streptococcal infection; it causes nonmigratory arthritis, lack of response to aspirin or nonsteroidal anti-inflammatory agents, and presence of extra-articular manifestations, including vasculitis and glomerulonephritis (74).

Studies in 1999 utilizing immunofluorescence, immunohistochemical, and polymerase chain reaction (PCR) techniques detected persistent microbial antigens within joints affected with reactive arthritis (73). These results may be explained by one hypothesis that describes the presence of bacteria and/or their antigens as a reflection of the persistence of small numbers of latent, nonculturable microbes in the joint space. This hypothesis may be valid in specific cases (e.g., chlamydia-triggered reactive arthritis) since the early administration of tetracycline therapy may reduce the length of disease and the associated articular damage (75). However, antibiotics are usually ineffective, especially when given at later stages of reactive arthritis. Therefore, another hypothesis is that the detection of microbial products may reflect only the natural filtering action of the synovium and the subsequent concentration of these products, thereby stimulating inflammation.

G. Prosthetic Joint Infections

The increased use of implanted prosthetic joints has provided a physiological niche for pathogenic organisms to cause septic arthritis. In fact, prosthetic joint implantation or replacement is the single most common cause of joint infections. The prevalence of infection after total knee or hip arthroplasty is estimated to be approximately 1%–2%; the incidence rate can climb to 4.4% in patients who have rheumatoid arthritis (76).

Prosthetic joint infections are manifested differently according to the length of time since placement of the device (77,78). Infections occurring within the first 3 months after surgery usually result from intraoperative wound contamination by coagulase-negative staphylococci. Typical signs of early joint infection are pain, erythema, wound drainage, hematoma formation, and superficial necrosis of the incision. Fever is an unreliable indicator of the presence of infection.

Late infections may occur from 3 months to many years after surgery. Such infections usually result from hematogenous seeding of the device followed by

bacterial production of a biofilm, which protects organisms from host immunity and antibiotics. Most patients have a prolonged indolent course of joint pain. Fever and leukocytosis are usually absent. The most common bacteria in late infection are *S. aureus*.

H. Septic Bursitis

Patients with septic bursitis report fever and an acute painful swelling that may in some cases be mistaken for septic arthritis. Skin trauma commonly precedes septic bursitis. The olecranon and the prepatellar bursae are the most common sites of septic bursitis. A skin wound can often be identified as the portal of entry, and most of these infections are due to *S. aureus*. The bursal fluid is usually purulent, the Gram stain smear result is often positive, and the synovial fluid culture result indicates a definite diagnosis. Antibiotics and drainage should be initiated immediately.

I. Lyme Disease

Lyme disease may produce a chronic monoarthritis, especially of the knee (79). Earlier cardinal symptoms include the typical erythema migrans skin lesion and transient polyarthralgias with virus-like features, including fever, headaches, and a variety of neurological signs. The chronic arthritis occurs at a median of 6 months after the erythema migrans. Joint effusions may be massive but often resolve without treatment and then recur. Chronic persistent synovitis develops in 20% of patients with untreated Lyme disease. The serological test results are confirmatory but many false-positive results may occur if the test is ordered for patients who do not manifest the typical clinical features of Lyme disease.

The diagnosis of Lyme arthritis in patients who live in endemic areas is based on a history of exposure to ticks and a history of erythema chronicum migrans. Culture of *Borrelia burgdorferi* from specimens in Varbour-Stoemer-Kelly medium permits a definitive diagnosis; an antibody response to *B. burgdorferi* by enzyme-linked immunosorbent assay (ELISA) is also available (80,81). Parenteral antibiotics are generally effective, but antibiotic failures do occur in chronic Lyme arthritis regardless of mode or duration of therapy.

J. Polyarticular Septic Arthritis

Acute bacterial arthritis is most often monoarticular. However, polyarticular infection occurs in 5% to 8% of pediatric cases and in 17% to 19% of nongonococcal adult cases. *N. gonorrhoeae*, *B. fragilis*, *H. influenzae*, *S. pneumoniae*, *Streptococcus* spp., and *S. aureus* are species with a predilection for polyarticular involvement; *S. aureus* accounts for half of all cases (57,82).

Prior disease in multiple joints predisposes to the development of polyarticular sepsis (e.g., 18%–35% of rheumatoid arthritis patients with joint infection have polyarticular involvement) (57). Polyarticular sepsis may not present florid systemic or local features (28,83), and poorer prognosis is related to older age (75 years), rheumatoid arthritis, or staphylococcal infection. The overall mortality rate (30%) has not changed over several decades.

K. Human Immunodeficiency Virus

Although patients infected with HIV demonstrate a higher prevalence of musculoskeletal infections than the general population (approximately 60 cases per 100,000 versus 2–10 cases per 100,000 yearly incidence rates, respectively), it is unclear whether this higher occurrence is due to the viral disease or to the increased incidence of intravenous drug abuse and multiple transfusions in this patient population (6,55,84). Intravenous drug users are at risk for septic arthritis and HIV infection (85). HIV-positive patients who were also intravenous drug users had involved sites other than the hips, knee, and sacroiliac and sternocostal joints and organisms isolated other than *S. aureus*, *C. albicans*, and *M. tuberculosis* (86–89). Most HIV-positive patients do not have profound immunodeficiency at the time of septic arthritis (86). *Salmonella* spp. septic arthritis has also been reported in patients with HIV infection (89).

L. Septic Arthritis in the Elderly

In 1990, 12% of the population of the United States, or 32 million people, was 65 or older. By the year 2050, 64 million Americans will be 65 and over (3,59). The older patient is more likely to display some of the systemic factors that impair host defense. The most common comorbidities among adults with septic arthritis are diabetes mellitus, cirrhosis, chronic renal failure, rheumatoid arthritis, and neoplastic disease (1). Other major risk factors for infectious complications are associated with the management of these chronic ilinesses, including invasive diagnostic procedures, surgical interventions, and use of immunosuppressive drugs.

The aging process in itself can lead to the decline of immune function and increased susceptibility to infectious diseases (61). The decline in immunity in the elderly causes a generalized reduction in the immune response to foreign antigens. The greater susceptibility to infections is due to the effects of age on the immune system and immune suppression caused by age-related illnesses. Specifically, the deficient immune response to foreign antigens results from the loss of thymic and T-lymphocyte function (mainly related to the production and response to interleukin 2 [IL-2]) and associated decrease in antibody production by B cells (90). Underlying joint disease (e.g., osteoarthritis or rheumatoid

arthritis) is another indicator that despite optimal treatment, the patient will have a poor prognosis (57,83). This poor prognosis is often due to a delayed diagnosis since the clinical symptoms of septic arthritis are often mistaken for symptoms related to the preexisting joint disease.

XI. CONTROVERSIES AND CONCLUSIONS

There are a number of unknowns in the treatment of septic arthritis, which are due to a lack of randomized double-blind comparative studies. They are as follows:

1. Route of administration and duration of treatment have not been established.
2. The preferred method of drainage (needle aspiration, open drainage, or arthroscopy) has not been adequately studied.
3. The advantages of splinting versus continuous passive motion treatment and the optimal time for initiating isometric and range of motion exercises are unknown.

With further study of some of the intricacies of septic arthritis treatment, some conclusions can be drawn:

1. Infectious arthritis attacks all age groups and has a predilection for immunocompromised patients.
2. The age of the patient and underlying medical condition provide important clues to the causative infectious agent.
3. Successful management depends on prompt diagnosis, appropriate antimicrobial therapy, and drainage of the joint space.
4. Initially, the choice of antibiotics is often empirical at the onset of therapy and may be changed when culture and sensitivity data are available.

REFERENCES

1. DL Goldenberg, JI Reed. Bacterial arthritis. N Engl J Med 312:764–771, 1985.
2. CJ Kaandorp, P Krijnen, HJ Moens, JD Habbema, D Van Schaardenburg. The outcome of bacterial arthritis: a prospective community-based study. Arthritis Rheum 40:884–892, 1997.
3. GM Vincent, JD Amirault. Septic arthritis in the elderly. Clin Orthop 251:241–245, 1990.
4. RI Rynes. Painful rheumatic syndromes associated with human immunodeficiency virus infection. Rheum Dis Clin North Am 17:79–87, 1991.

5. A Saraux, H Taelman, P Blanche, J Batungwanayo, J Clerinx, A Kagame, L Kabagabo, J Ladner, P Van de Perre, P Le Goff, J Bogaerts. HIV infection as a risk factor for septic arthritis. Br J Rheumatol 36:333–337, 1997.
6. D Vassilopoulos, P Chalasani, RL Jurado, K Workowski, CA Agudelo. Musculoskeletal infections in patients with human immunodeficiency virus infection. Medicine (Baltimore) 76:284–294, 1997.
7. M De Jonghe, G Glaesener. Type B *Haemophilus influenzae* infections. Experience at the Pediatric Hospital of Luxembourg (in French). Bull Soc Sci Med Grand Duche Luxem 132:17–20, 1995.
8. SG Bowerman, NE Green, GA Mencio. Decline of bone and joint infections attributable to *Haemophilus influenzae* type b. Clin Orthop Rel Res 341:128–133, 1997.
9. H Etesse-Carsenti, MF Masseyeff, J Entenza, F Monnot, F Giaume, A Barbarin, MJ Rosset, C Argenson, P Dellamonica. Contribution of bacterial detachment by enzymatic or physical methods to the diagnosis of foreign material infections and chronic osteomyelitis (in French). Pathol Biol 40:40–46, 1992.
10. JD Luhmann, SJ Luhmann. Etiology of septic arthritis in children: an update for the 1990s. Pediatr Emerg Care 15:40–42, 1999.
11. DW Lundy, DK Kehl. Increasing prevalence of *Kingella kingae* in osteoarticular infections in young children. J Pediatr Orthop 18:262–267, 1998.
12. JT Sharp, MD Lidsky, J Duffy, MW Duncan. Infectious arthritis. Arch Intern Med 139:1125–1130, 1979.
13. P Yagupsky, R Dagan, CB Howard, M Einhorn, I Kassis, A Simu. Clinical features and epidemiology of invasive *Kingella kingae* infections in southern Israel. Pediatrics 92:800–804, 1993.
14. R Dagan. Management of acute hematogenous osteomyelitis and septic arthritis in the pediatric patient. Pediatr Infect Dis J 12:88–92, 1993.
15. CW Fink, JD Nelson. Septic arthritis and osteomyelitis in children. Clin Rheum Dis 12:423–435, 1986.
16. CJ Welkon, SS Long, MC Fisher, PD Alburger. Pyogenic arthritis in infants and children: a review of 95 cases. Pediatr Infect Dis 5:669–676, 1986.
17. A Fryden, A Bengtsson, U Foberg, B Svenungsson, B Castor, A Karnell, R Schvarcz, B Lindblom E Kihlstrom. Early antibiotic treatment of reactive arthritis associated with enteric infections: clinical and serological study. Br Med J 301:1299–1302, 1990.
18. A Keat. Sexually transmitted arthritis syndromes. Med Clin North Am 74:1617–1631, 1990.
19. DL Goldenberg. Bacterial Arthritis. In: WN Kelley, ED Harris Jr, S Ruddy, CR Sledge, eds. Textbook of Rheumatology. 5th ed. Philadelphia: WB Saunders, 1997:1435–1449.
20. MA Brancos, P Peris, JM Miro, A Monegal, JM Gatell, J Mallolas, J Mensa, S Garcia, J Munoz-Gomez. Septic arthritis in heroin addicts. Semin Arthritis Rheum 21:81–87, 1991.
21. J Rosenthal, GG Bole, WD Robinson. Acute nongonococcal infectious arthritis: Evaluation of risk factors, therapy, and outcome. Arthritis Rheum 23:889–897, 1980.
22. S Roy, J Bhawan. Ultrastructure of articular cartilage in pyogenic arthritis. Arch Pathol 99:44–47, 1975.

23. JW Smith. Infectious arthritis. Infect Dis Clin North Am 4:523–538, 1990.
24. A Keat. Reactive arthritis. Adv Exp Med Biol 455:201–206, 1999.
25. JLJ Esterhai, I Gelb. Adult septic arthritis. Orthop Clin North Am 22:503–514, 1991.
26. S Andersson, A Krook. Primary meningococcal arthritis. Scand J Infect Dis 19:51–54, 1987.
27. R Mader, R Blake, D Gladman. Isolated septic meningococcal arthritis. Clin Exp Rheumatol 9:411–412, 1991.
28. DL Goldenberg. Septic arthritis. Lancet 351:197–202, 1998.
29. AS Bayer. Gonococcal arthritis syndromes: an update on diagnosis and management. Postgrad Med 67:200–208, 1980.
30. RH Shmerling, TL Delbanco, AN Tosteson, DE Trentham. Synovial fluid tests: What should be ordered? JAMA 264:1009–1014, 1990.
31. PA Baer, J Tenenbaum, AG Fam, H Little. Coexistent septic and crystal arthritis. Report of four cases and literature review. J Rheumatol 13:604–607, 1986.
32. VK Shiv, AK Jain, K Taneja, SK Bhargava. Sonography of hip joint in infective arthritis. Can Assoc Radiol J 41:76–78, 1990.
33. MM Zieger, U Dorr, RD Schulz. Ultrasonography of hip joint effusions. Skeletal Radiol 16:607–611, 1987.
34. P Hilden, K Savolainen, J Tyynela, M Vuento, P Kuusela. Purification and characterization of a plasmin-sensitive surface protein of *Staphylococcus aureus*. Eur J Biochem 236:904–910, 1996.
35. MT Modic, W Pflanze, DH Feiglin, G Belhobek. Magnetic resonance imaging of musculoskeletal infections. Radiol Clin North Am 24:247–258, 1986.
36. J Tehranzadeh, F Wang, M Mesgarzadeh. Magnetic resonance imaging of osteomyelitis. Crit Rev Diagn Imaging 33:495–534, 1992.
37. K Sandrasegaran, A Saifuddin, A Coral, WP Butt. Magnetic resonance imaging of septic sacroiliitis. Skeletal Radiol 23:289–292, 1994.
38. WA Erdman, F Tamburro, HT Jayson, PT Weatherall, KB Ferry, RM Peshock. Osteomyelitis: characteristics and pitfalls of diagnosis with MR imaging. Radiology 180:533–539, 1991.
39. HR Schumacher, R Andrews, G McLaughlin. Arthropathy in sickle-cell disease. Ann Intern Med 78:203–211, 1973.
40. FL Sapico, JA Liquete, RJ Sarma. Bone and joint infections in patients with infective endocarditis: review of a 4-year experience. Clin Infect Dis 22:783–787, 1996.
41. J Black, TL Hunt, PJ Godley, E Matthew. Oral antimicrobial therapy for adults with osteomyelitis or septic arthritis. J Infect Dis 155:968–972, 1987.
42. JD Nelson. Antibiotic concentrations in septic joint effusions. N Engl J Med 284:349–353, 1971.
43. RH Parker, FR Schmid. Antibacterial activity of synovial fluid during therapy of septic arthritis. Arthritis Rheum 14:96–104, 1971.
44. KC Donatto. Orthopedic management of septic arthritis. Rheum Dis Clin North Am 24:275–286, 1998.
45. DL Goldenberg, KD Brandt, AS Cohen, ES Cathcart. Treatment of septic arthritis: comparison of needle aspiration and surgery as initial modes of joint drainage. Arthritis Rheum 18:83–90, 1975.

46. RW Ike. Tidal irrigation in septic arthritis of the knee: a potential alternative to surgical drainage. J Rheumatol 20:2104–2111, 1993.
47. JS Parisien, B Shaffer. Arthroscopic management of pyarthrosis. Clin Orthop 275:243–247, 1992.
48. M Ivey, R Clark. Arthroscopic debridement of the knee for septic arthritis. Clin Orthop 199:201–206, 1985.
49. MJ Smith. Arthroscopic treatment of the septic knee. Arthroscopy. 2:30–34, 1986.
50. RB Salter. The biologic concept of continuous passive motion of synovial joints: the first 18 years of basic research and its clinical application. Clin Orthop 242:12–25, 1989.
51. RB Salter, RS Bell, FW Keeley. The protective effect of continuous passive motion in living articular cartilage in acute septic arthritis: an experimental investigation in the rabbit. Clin Orthop 159:223–247, 1981.
52. KA Anthanasiou, MP Rosenwasser, RL Spilkef, et al. Effects of passive motion on the material properties of healing articular cartilage. 36th Annual Orthopaedic Research Society Meeting 156–156 (abstract), 1990.
53. K Andersen, FN Bennedbaek, BL Hansen. Septic arthritis. Ugeskr Laeger 156:3871–3875, 1994.
54. CJ Kaandorp, HJ Dinant, MA van de Laar, HJ Moens, AP Prins, BA Dijkmans. Incidence and sources of native and prosthetic joint infection: a community based prospective survey. Ann Rheum Dis 56:470–475, 1997.
55. CJ Kaandorp, D Van Schaardenburg, P Krijnen, JD Habbema, MA van de Laar. Risk factors for septic arthritis in patients with joint disease: a prospective study. Arthritis Rheum 38:1819–1825, 1995.
56. RS Klein. Joint infection, with consideration of underlying disease and sources of bacteremia in hematogenous infection. Clin Geriatr Med 4:375–394, 1988.
57. JJ Dubost, I Fis, P Denis, R Lopitaux, M Soubrier, JM Ristori, JL Bussiere, J Sirot, B Sauvezie. Polyarticular septic arthritis. Medicine (Baltimore) 72:296–310, 1993.
58. DL Goldenberg, AS Cohen. Acute infectious arthritis: a review of patients with nongonococcal joint infections (with emphasis on therapy and prognosis). Am J Med 60:369–377, 1976.
59. C Cooper, MI Cawley. Bacterial arthritis in the elderly. Gerontology 32:222–227, 1986.
60. NM McGuire, CA Kauffman. Septic arthritis in the elderly. J Am Geriatr Soc 33:170–174, 1985.
61. EL Schneider. Infectious diseases in the elderly. Ann Intern Med 98:395–400, 1983.
62. JW Smith, JP Sanford. Viral arthritis. Ann Intern Med 67:651–659, 1967.
63. S Berney, M Goldstein, F Bishko. Clinical and diagnostic features of tuberculous arthritis. Am J Med 53:36–42, 1972.
64. G Garrido, JJ Gomez-Reino, P Fernandez-Dapica, E Palenque, S Prieto. A review of peripheral tuberculous arthritis. Semin Arthritis Rheum 18:142–149, 1988.
65. ML Cuellar, LH Silveira, LR Espinoza. Fungal arthritis. Ann Rheum Dis 51:690–697, 1992.
66. ALJ George, JT Hays, BS Graham. Blastomycosis presenting as monoarticular arthritis: the role of synovial fluid cytology. Arthritis Rheum 28:516–521, 1985.

67. BL Hansen, K Andersen. Fungal arthritis: a review. Scand J Rheumatol 24:248–250, 1995.
68. HM Heller, J Fuhrer. Disseminated sporotrichosis in patients with AIDS: case report and review of the literature. AIDS 5:1243–1246, 1991.
69. D Taylor-Robinson, JM Gumpel, A Hill, AJ Swannell. Isolation of *Mycoplasma pneumoniae* from the synovial fluid of a hypogrammaglobulinaemic patient in a survey of patients with inflammatory polyarthritis. Ann Rheum Dis 37:180–182, 1978.
70. BI Asmar, J Andresen, WJ Brown. Ureaplasma urealyticum arthritis and bacteremia in agammaglobulinemia. Pediatr Infect Dis J 17:73–76, 1998.
71. GH Cassell, BC Cole. Mycoplasmas as agents of human disease. N Engl J Med 304:80–89, 1981.
72. LB Vogler, KB Waites, PF Wright, JM Perrin, GH Cassell. Ureaplasma urealyticum polyarthritis in agammaglobulinemia. Pediatr Infect Dis 4:687–691, 1985.
73. D Taylor-Robinson, A Keat. Septic and aseptic arthritis: a continuum? Baillieres Best Pract Res Clin Rheumatol 13:179–192, 1999.
74. EM Ayoub, HA Majeed. Poststreptococcal reactive arthritis. Curr Opin Rheumatol 12:306–310, 2000.
75. A Toivanen. Bacteria-triggered reactive arthritis: implications for antibacterial treatment. Drugs 61:343–351, 2001.
76. S Bengtson, K Knutson. The infected knee arthroplasty: a 6-year follow-up of 357 cases. Acta Orthop Scand 62:301–311, 1991.
77. JM Cuckler, AM Star, A Alavi, RB Noto. Diagnosis and management of the infected total joint arthroplasty. Orthop Clin North Am 22:523–530, 1991.
78. WJ Gillespie. Infection in total joint replacement. Infect Dis Clin North Am 4:465–484, 1990.
79. AC Steere. Diagnosis and treatment of Lyme arthritis. Med Clin North Am 81:179–194, 1997.
80. Centers for Disease Control. Recommendations for test performance and interpretation from the Second National Conference on Serologic Diagnosis of Lyme Disease. MMWR Morb Mortal Wkly Rep 44:590–591, 1995.
81. AC Steere. Lyme disease. N Engl J Med 345:115–125, 2001.
82. JH Epstein, B. Zimmermann, GJ Ho. Polyarticular septic arthritis. J Rheumatol 13:1105–1107, 1986.
83. DL Goldenberg. Infectious arthritis complicating rheumatoid arthritis and other chronic rheumatic disorders. Arthritis Rheum 32:496–502, 1989.
84. DS Morgan, D Fisher, A. Merianos, BJ Currie. An 18 year clinical review of septic arthritis from tropical Australia. Epidemiol Infect 117:423–428, 1996.
85. S Munoz-Fernandez, MA Macia, L Pantoja, A Cardenal, JM Pena, ME Martin, A Balsa, FJ Barbado, JJ Vazquez, BJ Gijon. Osteoarticular infection in intravenous drug abusers: influence of HIV infection and differences with non drug abusers. Ann Rheum Dis 52:570–574, 1993.
86. LH Calabrese. Human immunodeficiency virus (HIV) infection and arthritis. Rheum Dis Clin North Am 19:477–488, 1993.

8
Hand Infections

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I. INTRODUCTION

Although the hand has continual exposure to day-to-day trauma, it seems to suffer the ravages of infection less than other body parts (1). Yet illicit drug use (2), delay in appropriate treatment (3), and open fractures (4) have all demonstrated that infections of the hand and upper extremity are a significant problem. A 30% frequency of both aerobic and anaerobic infections (5) and an increase in the occurrence of mixed infections (those having both gram-positive and gram-negative organisms) (6) require the physician to understand various types of infections thoroughly. A solid understanding of the anatomical characteristics is also necessary.

Establishing a correct diagnosis of an infection is paramount. Many conditions mimic infection, and appropriate evaluation and treatment of these conditions have a major impact on the patient's well-being. For example, pyoderma gangrenosum (Fig. 1) has a characteristic appearance of an ulcer that has central necrosis and surrounding bluish discoloration. It is associated with other systemic diseases, including ulcerative colitis, rheumatoid arthritis, and diabetes, and its treatment is different from that for infection, usually requiring steroids and only local wound care (7). Other diseases that can simulate infection include gout (Fig. 2A,B,C) brown recluse spider bites, metastatic lesions, pseudogout, chemical injuries, and even fascitious injuries (8).

Aerobic and anaerobic cultures should be tested before beginning antibiotic therapy, and if any question regarding the nature of the infection occurs, mycobacterial cultures and biopsy specimens should be sent for laboratory evaluation.

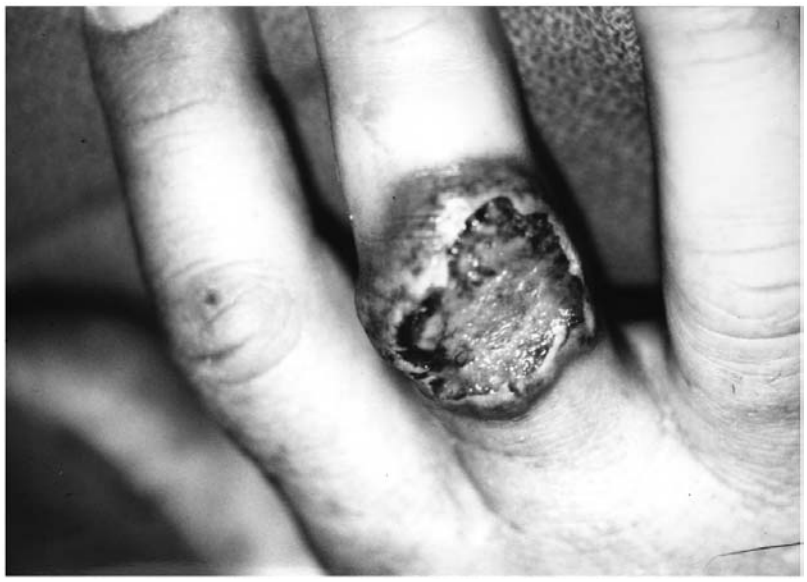
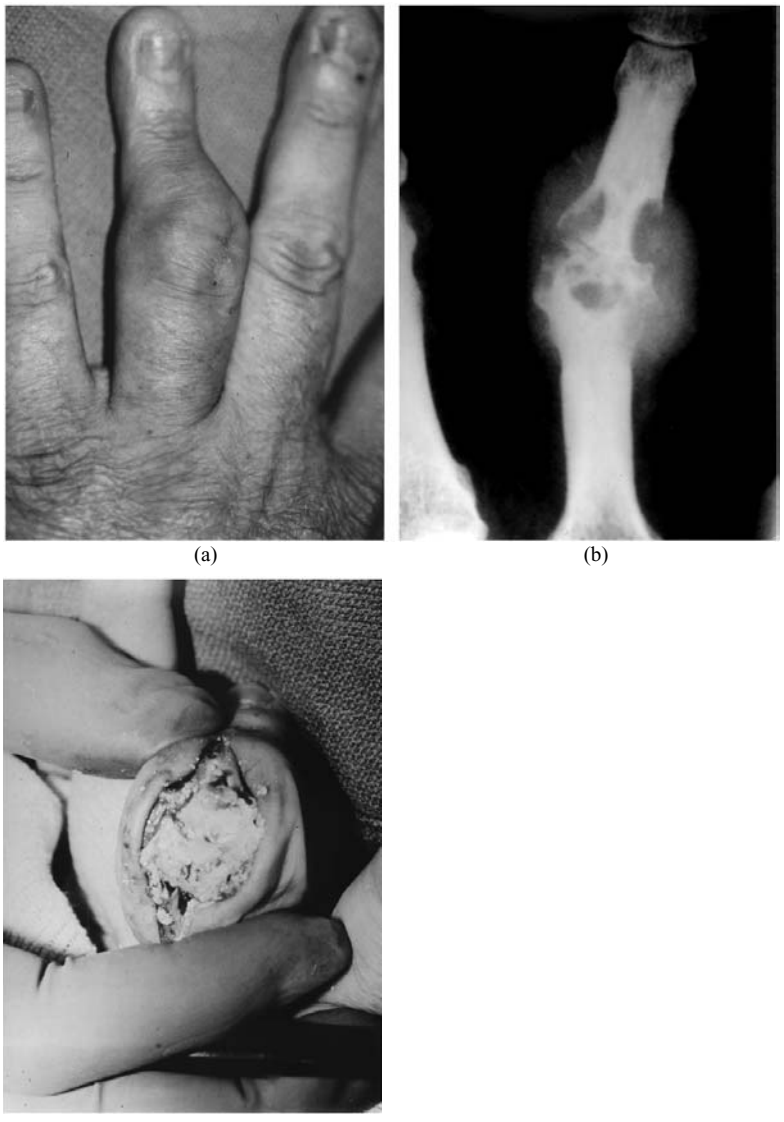


Figure 1 Pyoderma gangrenosum manifested through ulcerating lesions with central necrosis and spreading along peripheral margins.

Awareness of underlying medical problems assists in the diagnosis and treatment of infections of the hand (9–11), and a thorough history and physical examination are necessary. Allergies to medicines, environmental factors, and a history of tetanus prophylaxis should be noted. The evaluation of the affected area should also include radiographs to rule out fractures or foreign materials.

Basic surgical principles must be adhered to when treating these infections. Perhaps no facet of the treatment is more important than adequate débridement. Whether treating acute or chronic infection, insufficient drainage and insufficient removal of infected and/or necrotic tissue severely lessen the chance for successful treatment. Initially, the wounds should be left open or provided with drainage conduits. Although the literature does note that primary closure of infected wounds might be acceptable if one has adequate débridement with excellent skin coverage (12), the safest course is to prevent complete wound closure at the primary débridement. Delayed primary closure and skin grafting of the wound are acceptable (13).

Occupational therapists should be involved early in the treatment of these patients. Stiffness and limited function result if appropriate splinting and range of motion exercises are not initiated at the onset of treatment.



(a) (b)

(c)

Figure 2 Gout: This patient was referred after several incision and drainage procedures for "infection." (a) Note the swelling and previous incision scar. (b) Radiographic changes showing erosion similar to but not due to infection, especially when the soft tissue swelling on the radiographs and the patient's past medical history are considered. (c) Classic "chalky" material consistent with tophus.

The following sections discuss infections as they relate anatomically to the upper extremity. The complex anatomical features of the hand not only allow infections to manifest themselves in a characteristic fashion, but also allow these problems to be discussed in a somewhat systematic manner. After discussion of general concepts, such as osteomyelitis and septic arthritis, we proceed to discuss specific areas of the hand that can become infected in more depth.

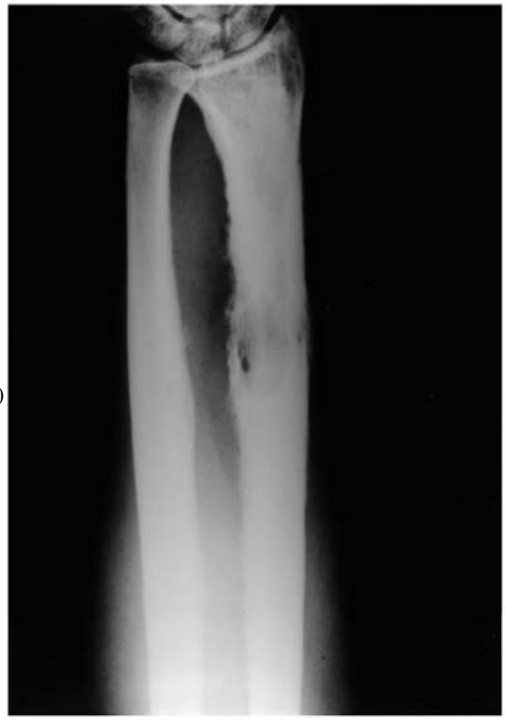
II. OSTEOMYELITIS

Osteomyelitis is not as common in the upper extremity as it is in other areas, representing only approximately 10% of all reported cases of osteomyelitis (14). This is probably due, in part, to the excellent blood supply in the area (15). Despite this, Reily and associates reported nearly a 50% amputation rate for digits of the upper extremity with osteomyelitis (16). Penetrating trauma, vascular and connective tissue diseases, and diabetes are all associated with the development of osteomyelitis. Human bite wounds have also led to osteomyelitis secondary to skin and oral flora (17,18).

The increase in intravenous drug abuse increases the potential for the development of osteomyelitis, particularly in those patients who have been injecting drugs for many years (Fig. 3A,B). Patients who have had prior surgical treatment and have remaining internal fixation devices are at risk for infection with *Staphyloccocus epidermedis*. Otherwise, the most likely organisms are *Staphyloccocus aureus* or a *Streptococcus* species. Mutilating injuries can cause mixed infections of gram-positive and gram-negative bacteria (19). Depending on the extent of bone involvement, débridement may require osseus reconstruction. Usually small defects of the bone heal or cancellous bone grafts can be used (20). If the defect is substantial, corticocancellous grafts and vascularized bone grafts supplemented with skin coverage by grafts or flaps are an alternative. Bone grafting is performed at a later surgery, usually 3 to 8 weeks after the primary débridement, to ensure a clean wound. Larger defects can be initially treated with antibiotic-impregnated cement spacers or beads, or closed irrigation drainage (21,22). Internal fixation is routinely necessary and must achieve the most stable fixation possible so early motion can be initiated. As has been mentioned, amputation is sometimes a necessary option. Stiffness and limited use of the entire hand, which may occur after osteomyelitis of a part of the hand, may make amputation a more functional and useful treatment for the patient.

Since débrided bone takes approximately 4 to 6 weeks to achieve substantial healing for protection by revascularized tissue (23), antibiotics should be given during this time.

(A)



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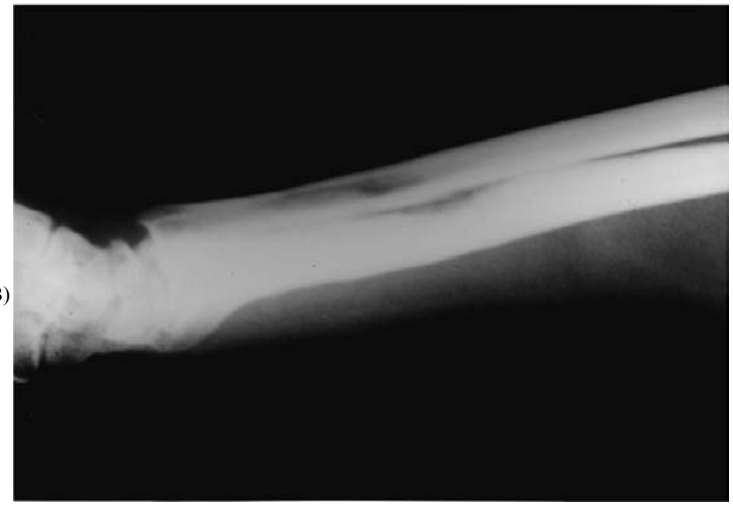

Figure 3 (A) A radiograph demonstrating osteomyelitis in a patient who chronically abuses intravenous drugs. (B) Lateral radiography demonstrating bone erosions in this patient's radius.

III. SEPTIC ARTHRITIS

Several diseases can simulate infection of a joint; therefore, a careful differential diagnosis must be made. Although there are some instances when sepsis of joints seems to occur without antecedent trauma (24), traumatic injury is the most common inciting factor for sepsis of a joint (25). Disease variants such as psoriatic arthritis, Reiter's syndrome, and gout can all cause joint pain, erythema, and warmth. Aspiration can be helpful to search for crystals (in gout, negative needle-shaped birefringent crystals; in pseudogout, rhomboid-shaped positive birefringent crystals); an evaluation of the white blood cell count, which is usually lower than that found in septic joints, can be helpful as well (20).

Surgical treatment is necessary; during incisions particular attention focuses on the joint anatomical features to ensure the maximal return of function. This is particularly important with the proximal interphalangeal joint of the finger. Usually a midlateral incision for the finger is used to prevent disruption of the central slip/lateral bands in an effort to prevent late boutonniere deformity (26). Either primary closure over drains or open management with daily soaks and dressing changes is acceptable for treatment of pyarthrosis, but early range of motion must be instituted.

IV. PARONYCHIAL INFECTIONS

Paronychial infections (Fig. 4) are the most common of all hand infections, and understanding of the anatomical characteristics allows the expeditious treatment of these problems. The paronychia are the areas just radial and ulnar to the nail. The eponychium is the tissue proximal to the nail. Any infection in these areas can adversely affect nail growth and cosmesis of the nail, so the patient should be informed of this possibility. In the early stages, these infections are usually amenable to treatment by warm saline solution soaks and oral antibiotics. The causal organism is usually *Staphlococcus aureus*. If treatment is unsuccessful, or if the infection is severe, surgical methods are indicated. Several variations of incision and drainage of paronychia have been described, including simple elevation of the paronychial fold, removal of a portion of the nail, and direct incision of the paronychia-eponychial junction. The paronychia or eponychia must be excised carefully in order to prevent injury to the germinal and sterile matrices. After drainage, packing is placed and removed in 24 to 48 hours, at which time soaks are begun.

Chronic paronychial infections should alert the physician to a fungal organism (usually *Candida albicans*) (27). The possibility of an underlying disease, such as diabetes, that can cause immunocompromised status in the patient should also be considered (10,27). Surgical treatment is necessary for

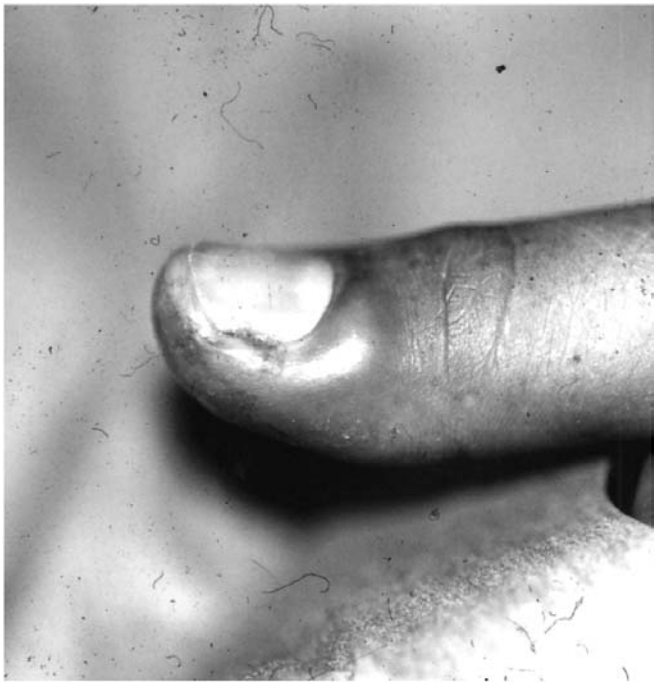

Figure 4 Acute paronychia.

these infections, as topical agents are usually insufficient to cure the problem. Keyser and Eaton (28) described a technique of eponychial marsupialization in which a crescent-shaped portion of skin just proximal to the eponychium is removed and the wound allowed to granulate (Fig. 5A,B). Bednar and Lane (29) recommend also removing the nail as an adjunct to marsupialization to improve results. Dressing changes and topical antifungal ointments are begun 48 hours after surgery.

V. PULP SPACE INFECTIONS

Pulp space infections, so-called felons, are exquisitely painful entities partially due to the anatomical feature of the region. Fibrous septae, which give structural support to the tip and prevent shear of the soft tissues, create subcompartments where an infection can develop, usually after a penetrating trauma. Because of the small closed space, the pain the patient can experience is significant, and tenderness, erythema, and swelling are clues to the diagnosis (30). "Pointing"

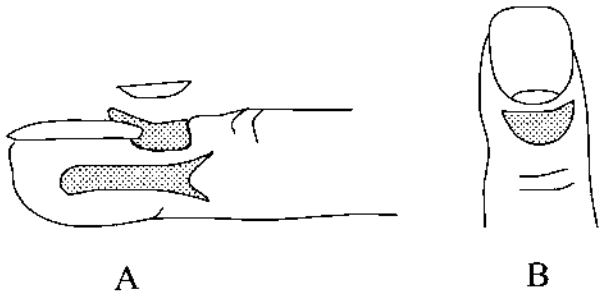

Figure 5 Marsupialization as treatment for chronic paronychia. Notice the crescent of skin removed proximal to the eponychial fold. Care not to injure the germinal matrix in any surgical treatment of paronychia is important. (A) View from side of digit. (B) View from top.

of the infection may develop. Aspiration for diagnosis may be attempted, but a negative aspiration finding may be misleading, as the subcompartment where the pus may reside may not be found. Therefore, the recommended treatment is incision and drainage. Either a longitudinal incision directly over the area of "pointing," carefully avoiding crossing a flexor crease in a perpendicular fashion, or an incision just volar to the nail on the ulnar or radial side (Fig. 6A,B) is made. The lateral incision should not be too volar, because skin slough may occur. Furthermore, the incision should never be continued around the hyponechium (the finger pulp just volar and distal to the nail) to create a "fishmouth" incision;

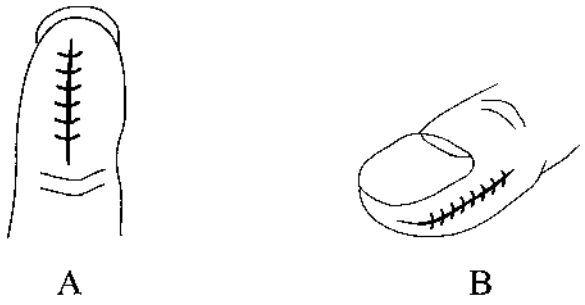

Figure 6 Suggested incisions for treatment of "felons." (A) The volar longitudinal incision can be easily used if there is pointing of the infection. However, the incision should *not* be carried proximal across the distal flexion crease. (B) A "high" midlateral incision can be used. Making the incision too volar risks skin slough of the pulp. This incision should never be continued beyond the midline of the fingertip (the so-called fishmouth incision) as a tender bulbous pulp of the finger may result.

this can lead to a tender bulbous fingertip (31). All septae must be explored, and the bone palpated because osteomyelitis can develop in the distal phalanx.

Acute cases respond well to the incision and drainage with dressing changes and soaks in saline solution begun after 24–48 hours. In severe cases, especially those in which osteomyelitis of the distal phalanx has developed, disarticulation of the distal interphalangeal joint may be necessary.

VI. THENAR, MIDPALMAR, AND HYPOTHENAR SPACE INFECTIONS

There are several potential spaces within the hand that can serve as sites where purulent infections occur. The three spaces most often discussed are the thenar, midpalmar, and hypothenar spaces (Fig. 7).

Thenar space may not be an accurate description since the adductor pollicus muscle acts as the dorsal border, the volar border is the flexor tendons to the thumb and index finger, the radial border is the adductor fascia and proximal phalanx of the thumb, and the ulnar border is a fascial band from the palmar aponeurosis to the third metacarpal. No part of this "space" involves the thenar muscles directly. However, there is a direct confluence with this area and the space dorsal to the adductor and volar to the first dorsal interosseus muscle, which may allow for significant dorsal swelling. Surgical drainage is usually done with an incision along the thenar crease and/or a dorsal incision in the first web space. Because of the anatomical characteristics of the space, a combination of incisions is prudent.

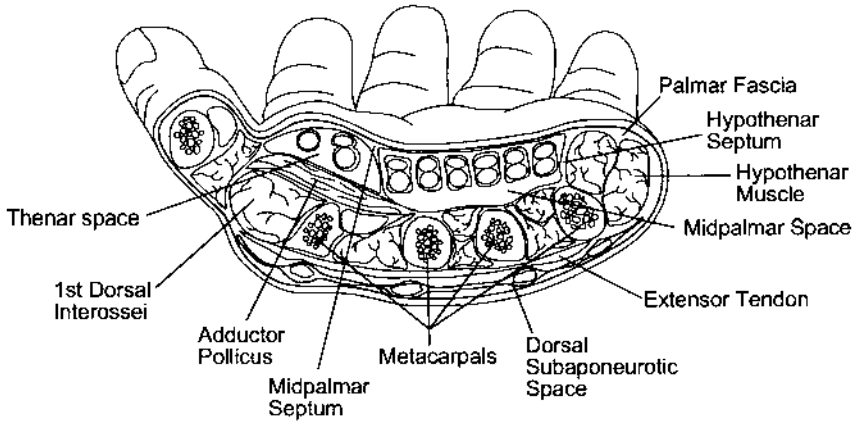

Figure 7 The palmar spaces are identified.

The midpalmar space is defined by the fascia of the hypothenar muscles on the ulnar side, the midpalmar septum radial, and the flexor tendons to the central three digits volar. The dorsal border is the fascia of the second through fourth interosseous muscles and the metacarpals of these digits. Palmar incisions that begin more distal and radial and progress proximal, curving gently to the level of the base of the fifth metacarpal, allow extensive exposure and drainage.

The hypothenar space is essentially the area surrounded by the fascia of the hypothenar muscles. A septum extending from the palmar aponeurosis to the fifth metacarpal may be identified as the radial border in some individuals. Drainage incisions should avoid contact areas of the palm, and the radial aspect of this space is acceptable.

VII. WEB SPACE INFECTIONS

Web space infections, often called "collar button abscesses," are collections of pus in the interdigital spaces. The palmar fascia generally acts as a barrier to purulent material tracking dorsal. However, since this infection is usually due to penetrating trauma, even a tiny defect in the palmar fascia allows the purulent material to loculate dorsal to the fascia in addition to the volar collection. Therefore, the surgeon should consider both dorsal and volar incisions to drain these infections. The volar incisions should be either oblique or zig-zag. Transverse incisions in the web space can lead to contracture and should not be used. On the dorsum of the hand, a straight longitudinal incision can be used to drain the web.

VIII. OTHER DEEP SPACE INFECTIONS

Two other spaces can also be involved as deep space infections of the hand. The dorsal subaponeurotic space, the area below the extensor tendons and superficial to the metacarpals, is one of these spaces. Parona's space, a potential space bounded on its dorsum by the pronator quadratus muscle and volar by the flexor profundus tendons, can also be involved in deep infections of the hand.

IX. FLEXOR TENOSYNOVITIS

Flexor tendons of the fingers function essentially as "ropes" that pull the appropriate digit into grasp. The tendon sheath mechanism provides a gliding surface for these tendons as they traverse the digit, and the thickened pulley system of the sheaths provides stability, making the mechanism function more as

a fishing rod than as a bow and arrow. The vascular supply to the tendons is complex and has been elucidated (32). This complex anatomical feature can lead to increase in tissue pressures of the digit in a patient with suppurative flexor tenosynovitis, and this effect may be of clinical significance (33,34). Although there are many variations, the sheaths of the index, long, and ring fingers generally begin approximately 1 cm proximal to the deep transverse metacarpal ligaments. However, the thumb and little finger frequently have their sheaths confluent to the radial and ulnar bursae, respectively. These bursae allow purulent material readily to track proximal to the wrist and via one bursa and then distal through the other, after traversing Parona's space. This can create the so-called horseshoe abscess. Although hematogenous spread can cause this infection, particularly with gonococcus (35), the usual scenario involves a penetrating injury (36) (Fig. 8A,B).

The clinical signs of slight flexion of the finger, fusiform swelling of the digit, tenderness along the flexor sheath, and exquisite pain with passive extension of the digit were delineated by Kanavel (37). The severity of purulent flexor tenosynovitis has been classified in the following manner (38):

Stage 1: serous exudate and congestion of the sheath
Stage 2: murky or cloudy fluid, purulence, and synovial granulation in the sheath
Stage 3: marked sheath and/or tendon necrosis

Surgical treatment is advocated. Tendon sheath irrigation was described in 1966 by Carter and colleagues (39). Continuous closed tendon sheath irrigation has been a standard method of surgical drainage of these infections since it was popularized by Nevaiser (36). By using a palmar incision to allow access to the sheath at the A1 pulley level and a second incision in the digit distal to the A4 pulley, one can then irrigate the sheath from proximal to distal. A transverse or short longitudinal incision (not crossing distal to the proximal digital crease) in the palm is utilized, and a small Brunner or short midlateral incision is used to allow distal access to the sheath. Irrigation is performed from proximal to distal, using a small angiocatheter, and continued until the effluent is clear. Maintaining the indwelling catheter, the hand is placed in a bulky dressing and irrigation is continued with saline solution at a rate of about 25 cc/h for the next 24–48 hours. The catheter is then removed, and dressing changes and range of motion exercises are begun.

Several variations of this method have been advocated, particularly with attention to the severity of the infection (38,40). In 2000, Lille and colleagues observed that continuous postoperative irrigation with an indwelling catheter for treatment of these infections may not be necessary (41).

We use a midline skin incision the length of the digit to decompress the finger, while exposing and entering the sheath only distal to the A4 pulley. In

(A)

(B)

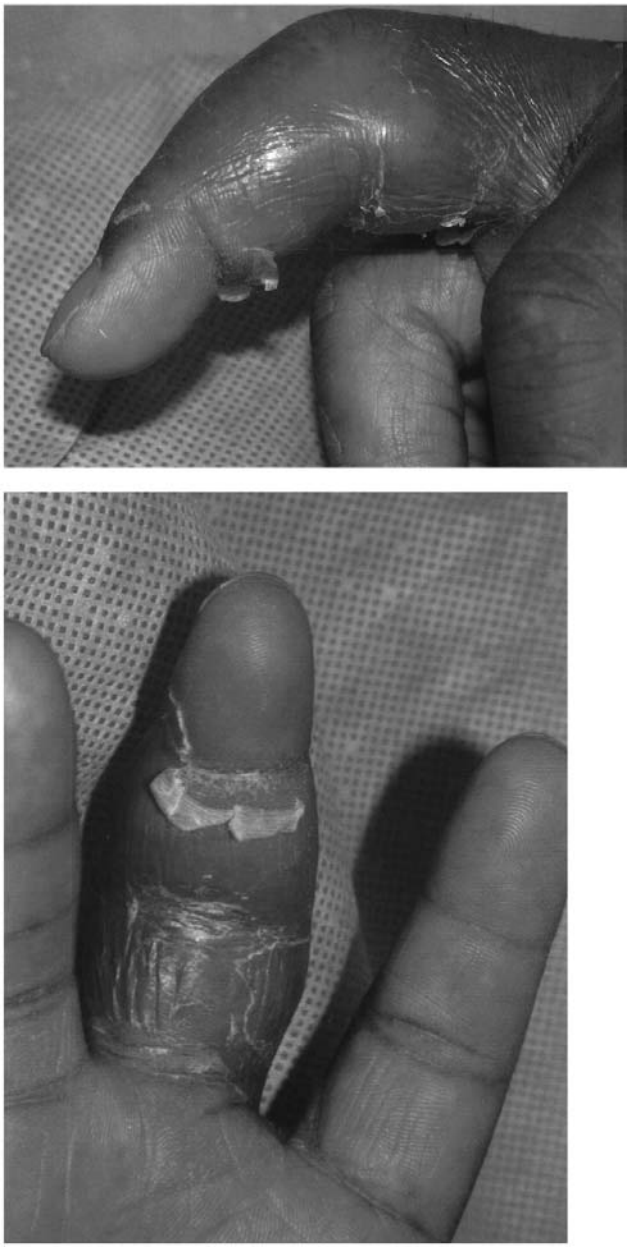

Figure 8 Purulent flexor tenosynovitis in a patient who "got stuck with a splinter" 12 days before admission. (A) Lateral view demonstrating the slight flexion posture. (B) Volar aspect of the digit; note diffuse swelling.

addition, the physician makes a palmar incision during the procedure to allow irrigation of the sheath in much the same fashion advocated by Nevaiser. Tendon sheath exposure other than distal and tendon débridement is prevented unless necrosis is present. We do not leave a catheter in, but begin daily soaks in saline solution and active range of motion exercises on the first postoperative day. This author is convinced that early institution of an aggressive range of motion program under direct physician or therapist supervision is of paramount importance to maximize results.

X. FUNGAL INFECTIONS

Fungal infections are often classified as "atypical hand infections" (42). The importance of a thorough history and physical examination to establish the diagnosis and allow for appropriate treatment cannot be overemphasized. The pathogenesis of fungal infections involves an indolent course, which frequently leads to a delay in diagnosis. Other causes of delay in diagnosis are inadequate cultures and instructions to the laboratory regarding the suspected pathological condition and lack of appropriate biopsy specimens. The various organisms need specific laboratory conditions to ensure the best growth for identification, as discussed later. The immunocompromised host may be particularly susceptible to fungal infections (9,43).

Hand infections due to fungus most often involve the skin, the nail and the areas juxtaposed to the nail (paronychia, eponychium, and hyponechium; see the discussion of paronychial infections). Diagnosis of fungal infections of the nail can be made by using wet potassium hydroxide techniques and subsequent growth on Sabourand's culture medium. *Candida albicans* and *Trichophyton*, *Microsporum*, and *Epidermophyton* spp. are the most common (44).

Tinea (*Trichophyton* spp.) infections can be treated with local care by using antifungal creams such as tolfenate or miconazole. If the infection cannot be controlled with these, systemic agents such as oral griseofulvin or ketocanozole may be needed.

Sporothirx schenkii is a saprophyte found in soil and plant materials, which can exist in virtually any climate. It probably produces the only fungal infection that primarily involves the upper extremity (45). Many plants have sharp thorns; commonly those who garden without protective gloves impale the hand or fingers with sharp thorns from bushes and plants, with resulting inoculation (46). It produces a chronic granulomatous infection beginning with ulcerations and then continuing with lymphatic spread. The lymph nodes and subcutaneous nodules form violet-colored ulcerations that may drain fluid. Cultures should be done with modified Sabaroud's medium and at temperatures below 37°C (preferably 30°C since warm temperatures may prevent or delay growth). Treatment can employ

saturated potassium iodide given orally. However, newer fungal drugs, such as itracanazole, have become the drugs of choice for lymphocutaneous sporotrichosis.

Other fungi such as bastomycosis, coccidiomycosis, histoplasmosis, mucormycosis, aspergellosis, and candidiasis can also be the cause. Some have a discrete geographical distribution. Histoplasmosis is endemic in the Mississippi and Ohio River valleys; coccidiomycosis is most often seen in the southwestern United States, particularly the San Joaquin Valley in California. Although these infections can cause tenosynovitis, bone involvement is also common (47). Synovectomy and débridement usually suffice for the surgical treatment; however, the appropriate pharmacological agents are necessary. For the most part, amphotericin B is the drug of choice. Immunocompromised patients must be considered at risk for systemic fungal infections; fungal infections in these patients may be recalcitrant to routine débridement and drug therapy, and amputation is sometimes necessary (Fig. 9A,B).

XI. MYCOBACTERIUM TUBERCULOSIS

Mycobacterium tuberculosis affects nearly 10 million people, and approximately 20% of newly diagnosed cases have sites other than the pulmonary system involved; 2% show involvement of the elbow, wrist, or hand (48,49). Clinically, the patient may report swelling with only slightly increased warmth (cold abscess) and only mild pain. Radiographic studies do not show severe bone destruction usually associated with bacterial septic joints or osteomyelitis; the minimal periosteal reaction and slight joint space narrowing may be subtle clues to the diagnosis. Aspiration does not yield conclusive findings, and open biopsy is recommended. Aerobic, anaerobic, fungal, and mycobacterial cultures are tested along with a biopsy specimen. Because mycobacterial and fungal cultures take weeks to show growth, the necessity for biopsy specimens should not be underemphasized. It is also important to alert the laboratory to the type of cultures being sent. *Mycobacterium tuberculosis* grows best on Lowenstein Jensen medium at 37°C, a warmer temperature than that for other mycobacteria. Aggressive débridement should be done, but unlike in many other infections, primary wound closure is acceptable. Appropriate antituberculosis medication is of paramount importance in eradicating the infection.

XII. OTHER MYCOBACTERIAL INFECTIONS

Occupational, recreational, and environmental history can direct the treating physician to the diagnosis of atypical mycobacterium or the so-called MOTT

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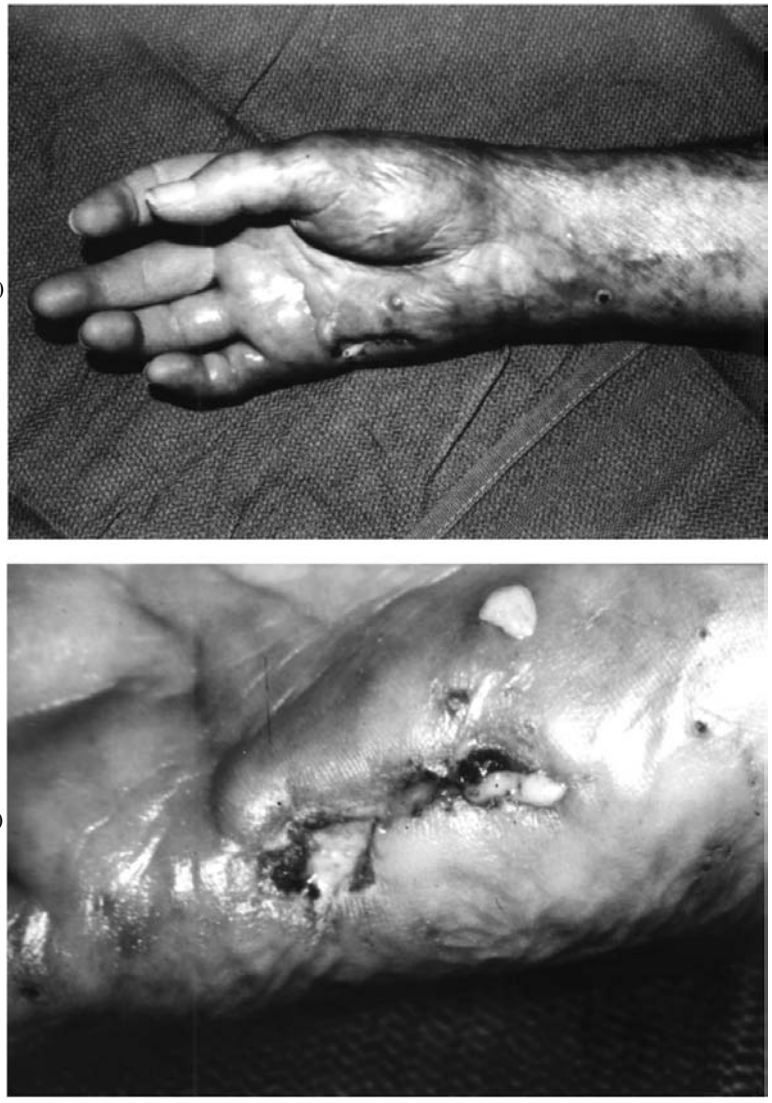


Figure 9 Mucormycosis. This patient has diabetes and the initial site was a foot infection. The subsequent development of mucormycosis of the upper extremity eventually led to amputation of the arm. (A) View of hand and distal forearm. (B) Close up of hand demonstrating induration, skin changes, and drainage.

infections (mycobacterium other than tuberculosis). *Mycobacterium marinum* is associated with exposure to injury in warm water environments, *M. terrae* in rural or farm areas, and *M. avium* in the immunocompromised individual (50,51). Culture of these organisms is at cooler temperatures than are used for *M. tuberculosis*, and the laboratory should be notified of one's presumptive diagnosis so the Lowenstein Jensen medium can be cultured at 30°–32°C.

XIII. VIRAL INFECTIONS

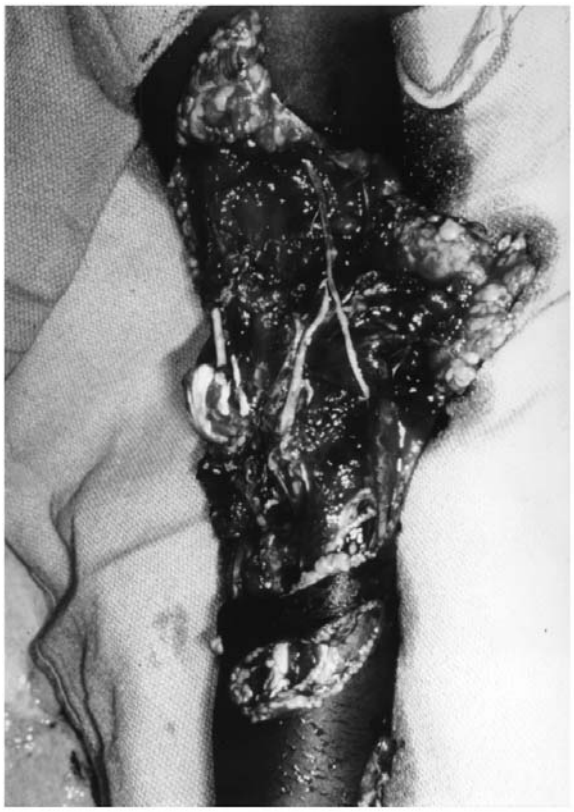
Superficial viral infections of the hand are usually herpetic in origin. These cause vesicular lesions (having clear fluid or turbid fluid, not purulent material). Patients may have lympadenopathy, lympangitis, and fevers. Oral lesions in the infant or child may provide helpful clues to the diagnosis. The erythema and pain may be less severe than in bacterial infections (52). There is an increased risk of these infections to medical and health care personnel. Cross-contamination from patient to staff and vice versa is well recognized, and there is increased risk of this infection in the immunocompromised host (29,52–56).

Observation is the treatment of choice; surgical manipulation can lead to secondary bacterial infection. Resolution of the disease normally takes approximately 2 weeks. Unless the infection is in the immunocompromised host or is extremely extensive, oral antiviral agents are not used; in severe cases, intravenous acyclovir has been administered.

XIV. BITE WOUNDS

Bite wounds are usually discussed as "animal bite wounds" and "human bite wounds." These occur frequently and represent a substantial portion of all visits to emergency rooms (56–58). It is interesting that the nature of the bite wound has an effect on the possibility of infection. Dog bites become infected at a substantially lower rate than domestic cat bites (15–20% versus 50%) (57). This may be related to the difference in wounds that occur with the different animals. Dog bites are secondary to tearing by blunt teeth, with exertion of significant force (up to 450 pounds per square inch) (56) (Fig. 10A,B). Domestic cats have sharp, pointed teeth that essentially cause "injection" injuries with less soft tissue damage, but direct inoculation of bacteria into a wound that is essentially a "closed wound." Although the bacteria for these wounds are a combination of aerobic and anaerobic organisms (56,57,60), *Pasteurella multocida*, which also may be seen in some infections due to dog bites, is isolated in 50% of infections due to cat bites (61). This gram-negative, facultative anaerobe

(A)



(B)

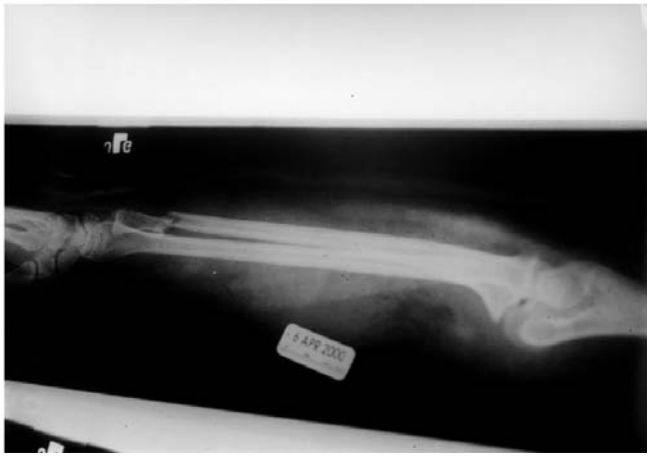


Figure 10 (A) Dog bite showing the extensive wounds and fracture of the ulna attesting to the severity of soft tissue destruction. (B) Radiograph showing the bone injury.

is sensitive to penicillin, and this sensitivity emphasizes the need for both aerobic and anaerobic antibiotic coverage for these infections.

Human bite wounds, whether accidental or the result of altercations, are frequent and have a great potential for subsequent infection. Mann and coworkers (62) categorized the injuries as traumatic amputations and clenched fist injuries, particularly those with skin penetration only. A review of surgical findings of clenched fist injuries noted that these injuries occurred predominantly at the metocarpalphalangeal joint level, violated the joint in nearly 70% of cases, and frequently included bone (17%) or tendon (20%) injury (63). Adequate surgical débridement is essential. One must consider that with the clenched fist, the extensor tendon has a more distal excursion. At surgery the fingers are routinely held in extension, allowing the extensor tendon to "retract" proximal. This obscures the level of injury from visualization; therefore, the treating physician should extend the wound to a more proximal level to ensure that there is a more thorough investigation for tendon injury. The bacteriological features are similar to those of organisms seen in domestic cat and dog bites; however, 46 different organisms have been cultured from a normal human mouth (60,64–66). *Eikenella corrodens*, a gram-negative, facultative anaerobe, is found frequently in the oral flora of humans and appropriate cultures should be requested (65,67). This organism, like *Pastuerella multocida*, is sensitive to penicillin. If these wounds are acute, they may be treated on an outpatient basis (64,68). Primary suture of these wounds is discouraged, and if there are signs of infection, questions regarding the adequacy of débridement, and concerns about patient compliance, surgical exploration in a formal operative theater and hospitalization are recommended.

XV. NECROTIZING SOFT TISSUE INFECTIONS

Necrotizing soft tissue infections include various clinical, microbiological, and pathological syndromes. These infections have recently been prominent in the lay press because of their significant morbidity and mortality rates. Some confusion exists because these infections have been given a variety of names, which can lead to difficulties regarding the specifics of the infection and its treatment. The initial description of this disease is attributed to Jones (69), who, as a surgeon during the Civil War, coined the phrase "hospital gangrene" when he reported it to the United States Sanitary Commission in 1871. Necrotizing ersypiles (70), hemolytic streptococcal gangrene (71), Meleney's gangrene (or postoperative bacterial synergistic gangrene) (72), idiopathic scrotal gangrene (Fournier's gangrene) (73), monomicrobial necrotizing cellulites (74), gram-negative synergistic necrotizing cellulitis (75), and necrotizing fasciitis (76) have all been descriptions used to identify this disease. Necrotizing fasciitis is not the same as

clostridial myonecrosis or "gas gangrene," which causes muscle necrosis. Generally, there is a history of trauma, yet there are reports of necrotizing infections that occurred without a history of trauma (77,78).

Risk factors include diabetes mellitus, intravenous drug abuse, age greater than 50 years, hypertension, and either malnutrition or obesity. Lille and associates reported that 32% of their patients were abusers of intravenous drugs and 62% of the patients in their series had these and other premorbid conditions (79). Francis and associates found that presence of three or more risk factors is predictive of a mortality rate of greater than 50% (80). Holtom and colleagues noted that age above 40 years and positive blood culture results have a statistically significant relationship with mortality rate (P. Holtom and associates, unpublished data). The overall reported mortality rate of necrotizing soft tissue infections is high, ranging from 6% (81) to as great as 76% (82). Norby-Teglund and coworkers (83) found evidence that patients who have high propensity for production of higher amounts of inflammatory cytokines in response to streptococcal superantigens have significantly more severe systemic manifestations than those who produce lower levels of these cytokines. This finding emphasizes the need for a thorough understanding of these infections.

A patient may initially have a localized abscess that is tender, has erythema, and is notable for the absence of lymphangitis and lymphedema. Bluish or blue-gray patches, which are considered pathognomonic (84,85), are not seen until at least 2 to 3 days after the infection begins. An important finding is edema extending beyond the areas of erythema (72,85). The edema can be quite impressive in size, and soon discoloration and bullae may form. The bullae though initially painful become anesthetic within a short time. This anesthesia is an important aspect of necrotizing fasciitis, as noted by Wilson (75) and Janevicus (84). The anesthesia of the bullae and skin is secondary to the cutaneous nerve destruction by the infection, and this sign differentiates it from other entities such as clostridial myonecrosis (discussed later). Very early in the presentation, the patient may not have high elevations of temperature and white blood cell count, although Wall and associates found increases in WBC and blood urea nitrogen (BUN) associated with low serum sodium level common in their series (86). The aggressive nature of this infection causes changes in these parameters to occur rapidly and one should not rely solely on these numbers when considering the gravity of the situation. The "pus" is not typical, in that the fluid is a watery exudate, which has been called "dishwater in nature," and the lack of the gross purulent material found in other infections should alert the treating physician. The infection spreads rapidly along the fascial planes, and the extent of skin involvement usually belies the extent of progression of the disease along the fascial planes (86,87). Wilson (75) emphasized an important diagnostic sign: the ability to probe below the skin just superficial to the fascia distant to any traumatic opening in the skin or via a small incision that the physician makes in

the skin. With cellulitis or erysipelas the probe should not advance, whereas in necrotizing fasciitis due to the progression of the infection along the fascial plane, a probe is easily advanced. So important is this sign that Wilson recommends making a small incision to determine whether undermining exists, so there is no delay in diagnosis, and, if it is present, immediate surgical treatment should be rendered (76). Fine-needle aspiration has been recommended (88), but the recommendations of Stamenkovic (89) may be more accurate. He advises the use of frozen section biopsies to help confirm the diagnosis of necrotizing fasciitis. Radiographic studies have been assessed for their value in the diagnosis of necrotizing infections and differentiation from cellulitis. Routine radiographs may disclose gas in the soft tissue (90); however; gas is seen in necrotizing fasciitis less frequently than in gas gangrene and myonecrosis; therefore, routine radiographs may not be of value. Computed tomography, though perhaps having some use (91) does not yield substantial benefits in diagnosis; however, magnetic resonance imaging does seem to have some potential (92,93). Apparently T_2 images can precisely show the extent of acute cellulitis and identify extension of infection along fascial planes. Enthusiasm for these techniques should be tempered by the need for severely ill patients to lie motionless during the study and the amount of time necessary to perform the studies (93). These factors may make magnetic resonance imaging of limited use in most cases. Ultrasonography has been used as a diagnostic aid in children (94) to assist guided aspiration; however, its usefulness may also be limited by the rapid progression of the disease.

An interesting new development in assisting our ability to diagnose necrotizing fasciitis involves fluorescence in situ hybridization targeted to ribosomal ribonucleic acid (RNA) (95). This method uses probes of radioactively labeled oligonucleotides for the detection of ribosomal RNA in bacterial cells. This test requires only 2 to 3 hours to achieve conclusive results.

Necrotizing fasciitis was originally called *hemolytic streptococcal gangrene* because of the presence of this organism in the original group of patients reported by Meleney (70,71); other authors have noted the presence of various organisms (75,96–99). Giuliano and colleagues (96) described two distinct groups of patients. Type I were those with anaerobic, facultative anaerobic. None of these patients had β-hemolytic group A *Streptococcus* or *Staphylococcus* spp. However, they did have many other organisms, including a variety of non–group A *Streptococcus* spp. Type II patients were those who had group A *Streptococcus* spp. alone or in combination with *Staphylococcus* spp. A recent review of 99 cases of necrotizing fasciitis revealed that in 45% of patients only one organism was cultured, whereas in 53% more than one organism had grown (P. Holtom and coworkers, unpublished data).

Early recognition is essential to successful treatment of necrotizing fasciitis. The common theme in the reviewed literature is that treatment must be aggressive

surgical débridement (71,72,76,85,100–102). The area must be débrided until normal fascia is encountered. Frozen section at the time of surgery can be helpful (90). The wounds should be left open and kept moist. Repeat examination of the wounds should be done no later than 24 hours, sooner if the clinical condition of the patient worsens. Although repeat débridements are frequently necessary, it is the initial débridement that is most important, and the treating physician should not depend on "second and third look débridements" when treating these patients and should be satisfied with no less than an aggressive initial débridement of all infected tissue.

Antibiotics must be given to cover a broad spectrum of anaerobic and aerobic organisms. Cephalosporins, penicillin, aminoglycocides, and quinolones may have all been used in combinations and modified when culture results were available.

Because of the significant infection and extensive surgical débridements of soft tissue, these patients have substantial nutritional needs. They are similar to severely burned patients in the need for nutritional supplements. The physician should consider hyperalimentation for these patients (103). There have been attempts to classify the type of necrotizing fasciitis in an effort to develop treatment protocols (82,102–104). Freischlig and coworkers (82) thought that simplifying these infections into clostridial and nonclostridial types might be useful and concur that radical débridement is the mainstay of treatment.

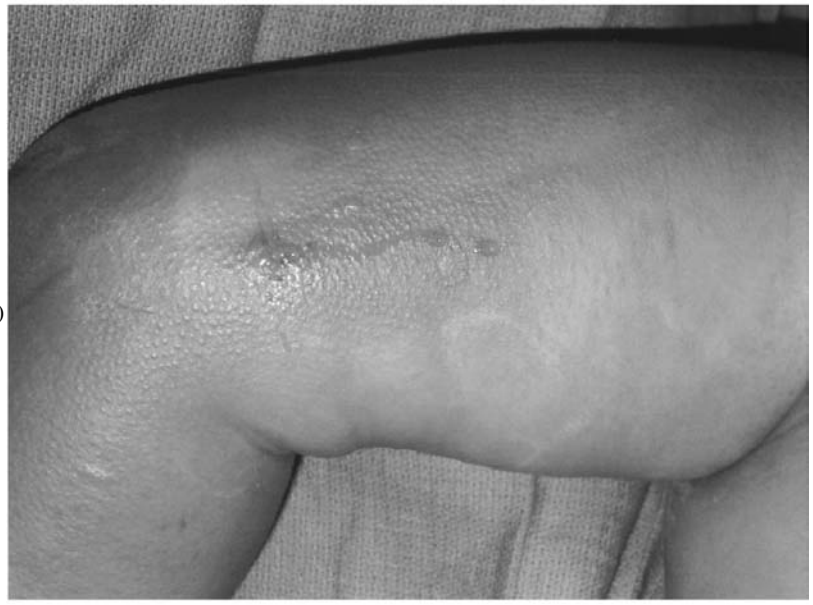
There is documented evidence of the possible use of hyperbaric oxygen therapy as an adjunct in the treatment of necrotizing fasciitis (105–111). It is still controversial but may have efficacy in cases in which anaerobic organisms are found or suspected.

Coverage of the wounds usually requires skin grafts. A 5% mafenide acetate solution has shown promise as an adjunct to skin grafting (112) (Fig. 11A,B,C,D).

XVI. GAS GANGRENE

Gas gangrene is another extremely aggressive infection that has high morbidity and mortality rates. There are generally two major categories noted when discussing these infections: those caused by *Clostridium* species including *C. perfringens*, *C. histolyticum*, *C. septicum*, *C. fallax*, and *C. sporogenes*, and those considered nonclostridial gangrene. The clostridial organisms are found essentially everywhere, including on humans and animals and in soil. These are gram-positive rods, which are anaerobic. Adequate culture requires anaerobic medium supplemented with reducing agents. Nonclostridial gangrene is commonly seen in diabetic patients but has also been described in patients without a history of diabetes. In both patients, the organisms are a mixture of aerobic, anerobic, gram-

(A)



(B)

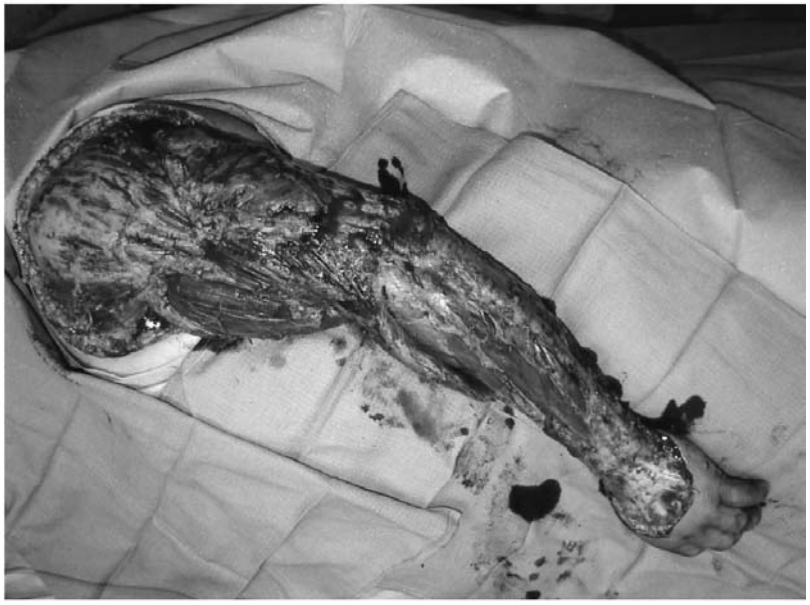


Figure 11 Necrotizing fasciitis. (A) The initial presentation. (B) Primary débridement. (C) Utilization of irrigation catheters for postoperative intermittent irrigation of wounds. (D) Skin grafting for coverage.

(C)

(D)

positive, and gram-negative species. The diversity of organisms that may be present makes aerobic, anerobic, and fungal cultures necessary. We also recommend evaluation of pathological specimens, since fungal and atypical mycobacterial cultures take weeks. The in vivo environment that supports growth of anaerobic organisms can be trauma that causes soft tissue injury that has crushed, devitalized, and contaminated tissue. Diabetics have impaired leukocyte function, neuropathy, and peripheral vascular disease, which create an environment that can contribute to the development of nonclostridial gangrene. Closure of any contaminated wound can create this condition as well. Predisposition to these infections is noted in patients with immunocompromise, vascular injuries or disease, diabetes, and malignancy. The clinical history generally begins a few days after the original tissue violation. Rapid and sometimes massive edema may occur, as well as discoloration of the overlying skin, along with hemorhagic bullae and blebs. The purulence has a foul odor, and the organisms can be seen on Gram stain. Clinically, the patient may have a low-grade fever, but tachycardia and severe pain are noted. The muscles become necrotic and renal failure secondary to acute tubular necrosis can occur. Radiographs may show gas in the soft tissues, but lack of such findings should not dissuade the physician from the diagnosis as rapid progression to septic shock and death can occur if the diagnosis is delayed.

Prevention should be the cornerstone of treatment, and appropriate débridement and incision and drainage of wounds with a potential for development of this disease should be recognized. Closure of any wound that might suggest the possibility for development of a gangrenous infection is not advised. Penicillin is still the drug of choice in treating such infections, but combinations with cephalosporins and aminoglycosides should be used since the contaminated wound and necrotic muscle allow mixed flora to be present. The surgical débridement must be aggressive, and "blind" probing of wounds is not acceptable. Amputation is sometimes necessary, and we recommend that all of the wounds initially be left open. Hyperbaric oxygen as an adjunct to surgical débridement has shown promise (109,110). Certainly adequate supportive medical care must be accomplished, and the aid of infectious disease specialists and medical intensive care specialists is highly recommended for treating these patients.

XVII. SUMMARY

Adequate care of hand infections requires clinical acumen with a thorough knowledge of the anatomical characteristics of the hand. Ruling out pathological conditions other than infection is necessary to begin the proper algorithm for treatment. Identification of underlying conditions that may affect care, obtaining

of appropriate cultures (before initiation of antibiotics), and diagnostic tests, including radiographic modalities, help confirm the diagnosis. Afterward, if the patient's clinical condition allows and reasonable empirical antibiotic therapy based on the type of wound, mechanism of injury, and patient status is initiated, surgical management, when necessary, can be pursued. Knowledge of the anatomical features of the hand is obviously essential to adequately draining and débridement of the infected area, while avoiding "surgical misadventures." However, an understanding of the anatomical characteristics of the hand and proper placement and utilization of appropriate surgical incisions allow rehabilitation to progress more quickly. Postsurgical therapy is of immense importance to complete the treatment program. Hand infections are common and often difficult problems with significant consequences. However, if they are treated with alacrity, physicians and patients can obtain satisfying results when dealing with these problems.

REFERENCES

1. AI Roth, DE Fry, HC Polk Jr. Infectious morbidity in extremity fractures. J Trauma 26:757–761, 1986.
2. SB Schnall, P Holtom, JC Lilley. Abscesses secondary to parenteral abuse of drugs. J Bone Joint Surg 76A(10):1526–1530, 1994.
3. KD Glass. Factors related to resolution of treated hand infections. J Hand Surg (Am) 7(4):388–394, 1982.
4. MJ Patzakis, J Wilkins, RL Basset. Factors influencing infection rate in open fracture wounds. Clin Orthop 243:36–40, 1989.
5. JD Speigel, RM Szabo. A protocol for the treatment of severe infections of the hand. J Hand Surg (Am) 13(2):254–259, 1988.
6. BV Stromberg. Retreatment of previously treated hand infections. J Trauma 25(2):1163–1164, 1985.
7. DC Ferlic. Pyoderma gangrenosum presenting as an acute suppurative hand infection: a case report. J Hand Surg (Am) 8:573–575, 1983.
8. AB Kanavel. Infections of the Hand. 7th ed. Philadelphia: Lea & Febiger, 1939:453–469.
9. TJ Francel, KA Marshall, RC Savage. Hand infections in the diabetic and diabetic renal transplant recipient. Ann Plastic Surg 24(4):304–309, 1990.
10. SZ Glickel. Hand infections in patients with acquired immunodeficiency syndrome. J Hand Surg (Am) 13(5):770–775, 1988.
11. RJ Mann, JM Peacock. Hand infections in patients with diabetes mellitus. J Trauma 17(5):376–380, 1977.
12. JC Scott, BV Jones. Results of treatment of infections of the hand. J Bone Joint Surg 34B(4):581–587, 1952.
13. SB Schnall, V Thommen, P Holtom, T Allari. Delayed primary closure of infections. Clin Orthop 335:286–291, 1997.

14. MR Hausman, SP Lisser. Hand infections. Orthop Clin North Am 23:171–185, 1992.
15. RM Szabo, JD Spiegel. Infected fractures of the hand and wrist. Hand Clin 4(3):477–489, 1988.
16. KE Reily, JC Linz, PJ Stern, E Giza, JD Wyrich. Osteomyelitis of the tubular bones of the hand. J Hand Surg (Am) 22:644–649, 1997.
17. AE Freeland, BS Senter. Septic arthritis and osteomyelitis. Hand Clin 5:533–552, 1989.
18. MH Gonzalez, P Papierski, RF Hall. Osteomyelitis of the hand after a human bite. J Hand Surg (Am) 18(3):520–522, 1993.
19. RH Fitzgerald, WP Cooney III, JA Washington II, RE Van Scoy, RL Linscheid, JH Dobyns. Bacterial colonization of mutilating hand injuries and its treatment. J Hand Surg (Am) 2(2):85–89, 1977.
20. AE Freeland, BS Senter. Septic arthritis and osteomyelitis. Hand Clin 5:533–552, 1989.
21. K Nemoto, M Yanagida, T Nemoto. Closed continuous irrigation as a treatment for infection in the hand. J Hand Surg (Br) 18:783–789, 1993.
22. DA Winniger, RJ Fass. Antibiotic-impregnated cement and beads for orthopedic infections. Antimicrob Agents Chemother 40(12):2675–2679, 1996.
23. JT Mader, GC Landon, J Calhoun. Antimicrobial treatment of osteomyelitis. Clin Orthop 295:87–95, 1993.
24. SB Schnall, E Ziv, P Holtom. Septic joints occurring without prior trauma. (Unpublished data.)
25. ES Rashkoff, WE Burkhalter, RJ Mann. Septic arthritis of the wrist. J Bone Joint Surg 65A:824–828, 1983.
26. NP Wittels, JM Donely, WE Burkhalter. A functional treatment method for interphalangeal pyogenic arthritis. J Hand Surg (Am) 9(6):894–898, 1994.
27. JA McAuliffe, DG Seltzer, J Hornicek. Upper extremity infections in patients seropositive for human immunodeficiency virus. J Hand Surg (Am) 22(6):1084–1090, 1997.
28. JJ Keyser, RG Eaton. Surgical cure of chronic paronychia by eponychial marsupialization. Plast Reconstr Surg 58:66–70, 1976.
29. MS Bednar, LB Lane. Eponychial marsupialization and nail removal for surgical treatment of chronic paronychia. J Hand Surg (Am) 16(2):314–317, 1991.
30. H Bolton, PJ Fowler, J Manchester. Natural history and treatment of pulp space infection and osteomyelitis of the terminal phalanx. Orthop Clin North Am 31B(4):499–504, 1949.
31. FL Canales, WL Newmeyer III, ES Kilgore Jr. The treatment of felons and paronychia. Hand Clin 5(4):515–523, 1984.
32. G Lundborg, R Myrhage, B Rydevik. The vascularization of human flexor tendons within the digital synovial sheath region: structural and functional aspects. J Hand Surg (Am) 2:417–427, 1977.
33. SB Schnall, T Vu-Rose, P Holtom, B Doyle, M Stevanovic. Tissue pressures in pyogenic flexor tenosynovitis of the finger. J Bone Joint Surg 78B:793–795, 1996.

34. WE Floyd III, S Troun, MA Frankle. Acute and chronic sepsis. In: CA Peimer, ed. Surgery of the Hand and Upper Extremity. New York: McGraw-Hill, 1976.
35. RA Schaefer, RJ Enzenauer, A Pruitt, RS Corpe. Acute gonococcal flexor tenosynovitis in an adolescent male with pharyngitis. Clin Orthop 281:212–215, 1992.
36. RJ Nevaiser. Closed sheath irrigation for pyogenic flexor tenosynovitis. J Hand Surg (Am) 3(5):462–466, 1978.
37. AB Kanavel. Infections of the Hand. 7th ed. Philadelphia: Lea & Febiger, 1939:453–469.
38. PJ Juliano, WA Eglseder. Limited open tendon sheath irrigation in the treatment of pyogenic flexor tenosynovitis. Orthop Rev 20(12):1065–1069, 1991.
39. SJ Carter, SO Burman, WL Mersheimer. Treatment of digital tenosynovitis by irrigation with peroxide and oxytetracycline: review of nine cases. Ann Surg 163(4):645–650, 1966.
40. SD Boles, CG Schmidt. Pyogenic flexor tenosynovitis. Hand Clin 14(4):567–578, 1998.
41. S Lille, MW Hayakawa, WM Neumeister, RE Brown, EG Zook, K Murray. Continuous post-operative catheter irrigation in not necessary for the treatment of suppurative flexor tenosynovitis. J Bone Joint Surg 25B(3):304–306, 2000.
42. HA Hoyen, S Lacey, TJ Grahm. Atypical hand infections. Hand Clin 14(4):613–633, 1998.
43. MH Gonzalez, S Bochar, J Novotny, A Brown, N Weinzweig, J Prieto. Upper extremity infections in patients with diabetes mellitus. J Hand Surg 24(4):682–686, 1999.
44. MR Patel. Chronic infections. In: DP Green, RN Hotchkiss, WL Pederson, eds. Green's Operative Hand Surgery. New York: Churchill Livingstone, 1999:1048–1095.
45. JG Rowe, PC Amadio, RS Edson. Sporotrichosis. Orthopedics 12:981, 1989.
46. MM Carr, JC Fielding, G Sibbald, A Freiberg. Sporotrichosis of the hand: an urban experience. J Hand Surg (Am) 20:66–70, 1995.
47. RM Szabo, WI Lanzer, RH Gelberman, et al. Extensor tendon rupture due to *Coccidiomycosis immitis*. Clin Orthop 194:176–180, 1985.
48. DC Busch, LH Schneider. Tuberculosis of the hand and wrist. J Hand Surg (Am) 9(3):391–398, 1984.
49. HG Watts, RM Lifeso. Current concepts review: tuberculosis of bones and joints. J Bone Joint Surg 78A(2):288–299, 1996.
50. SH Kozin, AT Bishop. Atypical *Mycobacterium* infections of the upper extremity. J Hand Surg (Am) 19(3):480–487, 1994.
51. SA Phillips, SKS Marya, MS Dryden, AW Samuel. *Mycobacterium marinum* infection of the finger. J Hand Surg (Br) 20:801–802, 1995.
52. LG Walker, BP Simmons, JL Lovallo. Pediatric herpetic hand infections. J Hand Surg (Am) 15(1):176–180, 1990.
53. JN Bleicher, DL Blinn, D Massop. Hand infections in dental personnel. Plast Reconstr Surg 80(3):420–422, 1987.
54. LC Hurst, R Gluck, SP Sampson, A Dowd. Herpetic whitlow with bacterial abscess. J Hand Surg (Am) 16(2):311–314, 1991.

55. DS Louis, J Silva. Herpetic whitlow: herpetic infections of the digits. J Hand Surg (Am) 4(1):90–93, 1979.
56. H Stern, SD Elek, DM Millar, HF Anderson. Herpetic whitlow: a form of cross infection in hospitals. Lancet 2:871–874, 1959.
57. CR Anderson. Animal bites. Postgrad Med 92(1):134–146, 1992.
58. EJC Goldstein, MF Barones, TA Miller. *Eikenella corrodens* in hand infections. J Hand Surg (Am) 8(5):563–567, 1983.
59. ME Wiggins, E Akelman, APC Weiss. The management of dog bites and dog infections to the hand. Orthopedics 17(7):617–623, 1994.
60. EJC Goldstein, DM Citron. Comparative susceptibilities of 173 aerobic and anaerobic bite wound isolates to sparfloxacin, temafloxacin, clarithromycin, and older agents. Antimicrob Agents Chemother 37(5):1150–1153, 1993.
61. MS Arons, L Fernando, IM Polayes. *Pasteurella multocida*: the major cause of hand infections following domestic animal bites. J Hand Surg (Am) 7(1):47–52, 1982.
62. RJ Mann, TA Hoffeld, CB Farmer. Human bites of the hand: twenty years of experience. J Hand Surg (Am) 2(2):979–1104, 1977.
63. MJ Patzakis, J Wilkens, RL Bassett. Surgical findings in clenched fist injuries. Clin Orthop 220:247–250, 1987.
64. UY Dreyfus, M Singer. Human bites of the hand: a study of one hundred six patients. J Hand Surg (Am) 10(6):884–889, 1985.
65. EJC Goldstein, MF Barones, TA Miller. *Eikenella corrodens* in hand infections. J Hand Surg (Am) 8(5):563–567, 1987.
66. C Shields, MJ Patzakis, MH Myers, JP Harvey Jr. Hand infections secondary to human bites. J Trauma 15(3):235–236, 1976.
67. GM Rayan, JL Putnam, SL Cahill, DJ Flournoy. *Eikenella corrodens* in human mouth flora. J Hand Surg (Am) 13(6):953–956, 1988.
68. S Brooks. Civil War Medicine. Springfield, IL: C.C. Thomas, 1966.
69. H Hammar, L Wanger. Erysipelas and necrotizing fasciitis. Br J Dermatol 96(4):409–419, 1976.
70. FL Meleney. Hemolytic streptococcus gangrene. Arch Surg 9:317–364, 1924.
71. FL Meleney. A differential diagnosis between certain types of infectious gangrene of the skin. Surg Gynecol Obstet 56:847–867, 1933.
72. JA Fournier. Gangrene foudroyante de la verge. Semaine Med 3:345–355, 1883.
73. RT Lewis. Necrotizing soft tissue infections. Infect Dis Clin North Am 6:693–703, 1992.
74. HH Stone, JD Martin Jr. Synergistic necrotizing cellulitis. Ann Surg 175:702–706, 1972.
75. B Wilson. Necrotizing fasciitis. Am Surg 18:416–432, 1952.
76. BW Duncan, SN Adzick, AA de Lorimier, MT Longaker, LD Ferrell, S Zoger, MR Harrison. Necrotizing fasciitis in two children with acute lymphoblastic leukemia. J Pediatr Surg 27(5):668–671, 1992.
77. RS Williams, JAS Carruth, AP Brightwell. Necrotizing fasciitis of the face without significant trauma. Clin Otolaryngol 17(4):344–350, 1992.
78. CR Mchenry, CP Brandt, JJ Piotrowski, DG Jacobs, MA Malangoni. Idiopathic necrotizing fasciitis: recognition, incidence, and outcome of therapy. Am Surg 60(7):490–494, 1994.

79. ST Lille, T Sato, L Engrav, H Foy, GJ Jurkovich. Neerotizing soft tissue infections: obstacles in diagnosis. J Am Coll Surg 182:7–11, 1996.
80. KR Francis, HR Lamaute, JM Davis, WE Pizzi. Implications of risk factors of necrotizing faciitis. Am Surg 59:304–307, 1993.
81. LA Sudarsky, JC Laschinger, GF Coppa. Improved results from a standardized approach in treating patients with necrotizing fasciitis. Ann Surg 206:661–665, 1987.
82. JA Freischlag, G Ajalat, RW Busuittil. Treatment of necrotizing soft tissue infections: the new approach. Am J Surg 149(6):751–755, 1985.
83. A Norby-Telgund, S Chatellier, D Low, A McGeer, K Green, M Kotb. Host variation in cytokine responses to superantigens determine the severity of invasive group A streptoccocal infection. Eur J Immunol 30:3247–3255, 2000.
84. RV Janevicius, SE Hann, MD Batt. Necrotizing fasciitis. Surg Gynecol Obstet 154(1):97–102, 1982.
85. SM Strasberg, MS Silver. Hemolytic streptococcus gangrene: an uncommon but frequently fatal infection in the antibiotic era. Am J Surg 115:763–768, 1968.
86. DB Wall, C de Virgilio, S Black, S Klein. Objective criteria may assist in distinguishing necrotizing fasciitis from nonnecrotizing soft tissue infection. Am J Surg 179:17–21, 2000.
87. MH Gonzalez. Necrotizing fasciitis and gangrene of the upper extremity. Hand Clin 14(4):635–645, 1998.
88. MR Wilkerson, W Paull, FV Coville. Necrotizing fasciitis: review of the literature and case report. Clin Orthop 216:187–192, 1987.
89. I Stamenkovic, PD Lew. Early recognition of potentially fatal necrotizing fasciitis: The use of frozen-section biopsy. N Engl J Med 310(26):1689–1693, 1984.
90. RJ Fisher, MJ Conway, RT Takeshita, MR Sandoval. Necrotizing fasciitis: importance of roentgenographic studies for soft-tissue gas. JAMA 241(8):803–806, 1979.
91. JM Rogers, JV Gibson, WE Farrar, S Schabel. Usefulness of computerized tomography in evaluating necrotizing faciitis. South Med J 77(6):782–783, 1984.
92. A Rahmouni, O Chosidow, D Amthieu, E Gueorguieva, N Jazaerli, C Radier, JM Faivre, JC Roujeau, N Vasile. MR imaging in acute infectious cellulitis. Radiology 192(2):493–496, 1994.
93. P Sarag, C Le Breton, MJ Pavlovi, N Fouchard, G Delzant, JM Bigot. Magnetic resonance imaging in adults presenting with severe acute infections cellulitis. Arch Dermatol 130:1150–1158, 1994.
94. H Chao, M Kong, T Lin. Diagnosis of necrotizing fasciitis in children. J Ultrasound Med 18:277–281, 1999.
95. K Trebesius, L Leitritz, K Adler. Culture independent and rapid identification of bacterial pathogens in necrotizing fasciitis and streptococcal toxic shock syndrome by fluorescence in situ hybridization. Med Microbiol Immunol 188:169–177, 2000.
96. A Giuliano, F Lewis, K Hadley, FW Blaisdell. Bacteriology of fasciitis. Am J Surg 134(1):52–57, 1977.
97. JA Kilborn, LA Manz, MO O'Brien, MC Douglass, HM Horst, W Kupin, EJ Fisher. Necrotizing cellulitis caused by *Legionella micdadei*. Am J Med 92(1):104–106, 1992.
98. LF Ou, FL Yeh, RH Fang, KW Yu. Bacteriology of necrotizing fasciitis: a review of 58 cases. Chin Med J 51(4):271–275, 1993.

99. WM Tang, JWK Wong. Necrotizing fasciitis caused by *Vibrio damsela*. Orthopedics 22(4):443–444, 1999.
100. RE Kaiser, FB Cerra. Progressive necrotizing surgical infections: a unified approach. J Trauma 21(5):349–355, 1981.
101. G Koehn. Necrotizing fasciitis. Arch Dermatol 114:581–583, 1978.
102. KC Wang, C-H Shih. Necrotizing fasciitis of the extremities. J Trauma 32(2):179–182, 1992.
103. JA Majeski, JW Alexander. Early diagnosis, nutritional support, and immediate extensive débridement improve survival in necrotizing fasciitis. Am J Surg 145(6):784–787, 1983.
104. DR Aitken, CT Mackett, LL Smith. The changing pattern of hemolytic streptococcal gangrene. Arch Surg 117(5):561–567, 1982.
105. DR Brown, NC Davis, M Lepawski, J Cunningham, J Kortberk. A multicenter review of the treatment of major truncal necrotizing infections with and without hyperbaric oxygen therapy. Am J Surg 167:485–489, 1994.
106. S Kolo, Y Melamed. Hyperbaric oxygenation for necrotizing fasciitis (letter to the editor). Am J Obstet Gynecol 179:1336, 1998.
107. JH Monestersky, RA Myers. Hyperbaric oxygen treatment of necrotizing fasciitis. Am J Surg 169:187–188, 1995.
108. B Roding, PHA Groeneveld, I Boerema. Ten years of experience in the treatment of gas gangrene with hyperbaric oxygen. Surg Gynecol Obstet 134(4):579–585, 1972.
109. PM Tibbles, JS Edelsberg. Hyperbaric-oxygen therapy. N Engl J Med 334(25):1642–1648, 1996.
110. JH Monestersky, RA Myers. Hyperbaric oxygen treatment of necrotizing fasciitis. Am J Surg 169(1):187–188, 1995.
111. M Hirn. Hyperbaric oxygen in the treatment of gas gangrene and perineal necrotizing fasciitis: a clinical and experimental study. Eur J Surg 570(suppl):1–36, 1993.
112. EC Heinle, WR Dougherty, WL Garner, DA Reilly. The use of 5% mafenide acetate solution in the postgraft treatment of necrotizing faciitis. J Burn Care Rehabil 22(1):35–40, 2001.

9
Total Hip Infections

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I. INTRODUCTION

The low-friction total hip arthroplasty (THA) has revolutionized care of the arthritic hip. The extensive need for this procedure coupled with a high degree of patient satisfaction and excellent longevity made THA one of the most significant contributions in orthopedic surgery in the 20th century. Despite the evolution of knowledge and technology gained over the last 40 years, infection of the periprosthetic environment continues to be a formidable complication of this procedure. Considerable strides have been achieved as the incidence of this complication has declined significantly from the 9% reported in Sir John Charnley's initial experience (1) to the current incidence of 1%–2% (2–4). A variety of prophylactic techniques have been investigated in an effort to decrease this incidence even further. If a periprosthetic infection is suspected, many investigative modalities that aid in confirming the diagnosis are available. With the knowledge of the established indications for the various treatment methods available, the treating surgeon can select the most appropriate course of action and optimize the patient's chance for successful eradication of the infection.

II. EPIDEMIOLOGICAL CHARACTERISTICS

Overall, the deep infection rate after THA currently averages between 1% and 2% (2–4). According to the National Center for Health Statistics, 119,000 primary THA procedures were performed in the United States in 1990 (5). At that time, the cost of treatment for each THA infection approached $50,000 to $60,000 if

the patient had what was, and still is, considered the gold standard of treatment—two-stage reimplantation (6). The overall annual cost for the management of infected THAs in the United States approached $143 million in 1990. It is anticipated that by the year 2030, approximately 248,000 THA procedures will be performed annually (Fig. 1) (5). If the infection rate remains constant, in 2030 nearly 5500 THA infections will occur. Using the 1989 cost figure of $60,000 per THA infection, which is already outdated and, therefore, conservative, the total economic impact in the United States will increase 130% to $330 million in the year 2030.

III. PATHOGENESIS

Infections after THA are the result of pathogenic seeding of the periprosthetic environment by one of two routes: direct or hematogenous. In one series of periprosthetic infections, direct seeding accounted for 51%, hematogenous seeding accounted for 34%, and 14% were of unknown origin (7).

Direct seeding of the prosthetic hip occurs either at the time of surgery or in the early postoperative period. At the time of surgery before the wound has been

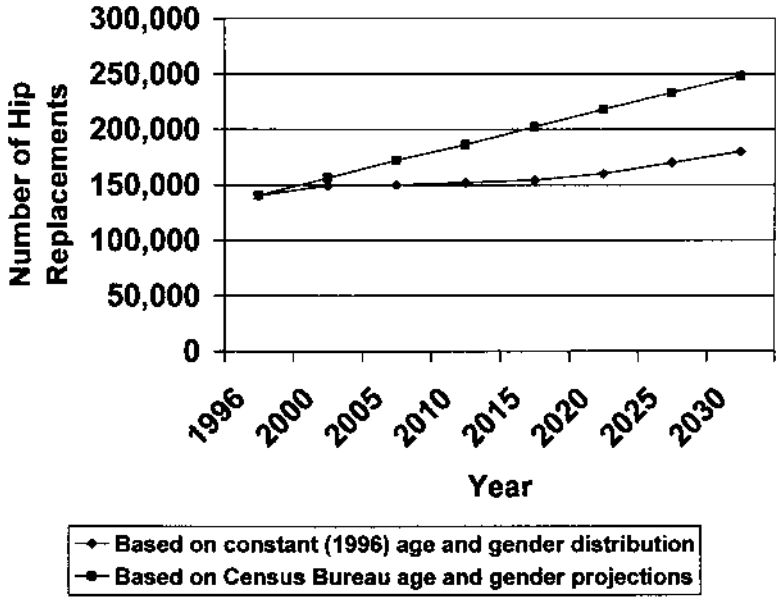

Figure 1 Annual total hip replacements: U.S. population projections through 2030. (From Ref. 5.)

closed, the prosthetic hip is especially vulnerable to pathogenic seeding, as it lies open and exposed to its immediate environment. Bacteria that gain access to the wound can originate from the patient, the operating room environment, or operating room personnel (7,8).

Direct seeding of the joint also can occur in the early postoperative period. In these instances, bacteria gain access to the periprosthetic environment from a contiguous infectious process such as a superficial wound infection or suture abscess. Bacteria may also directly seed the prosthetic joint in the setting of delayed wound healing and its accompanying prolonged wound drainage (9).

Hematogenous seeding refers to the inoculation of the periprosthetic environment by a bacteremic event originating at a remote site. The bacteremia could be secondary to an infection or an invasive procedure of the oral, gastrointestinal, genitourinary, or pulmonary tract (7). Seeding of the prosthetic hip by the hematogenous route can occur at any time during the life of the prosthesis.

Staphylococcal bacteria have been the most commonly isolated pathogens in studies of infected total joint arthroplasty (2,10–13). Streptococci, enterococci, and gram-positive anaerobes are also frequent pathogens; gram-negative bacteria are less common (Table 1). Fungi and mycobacteria have also been encountered in THA infections, but reports are rare (4,7,14).

It has been suggested that the large amount of foreign body used in THA procedures increases the risk of infection of the periprosthetic environment. Elek and Conen demonstrated that fewer bacteria are required to establish an infection in the presence of a foreign body (15). Furthermore, the specific biomaterials

Table 1 Bacteriological Characteristics of Total Hip Infections

	Frequency of isolates (%)			
Pathogen	Garvin[11]	Fitzgerald[2]	Urban[13]	Tsukayama[12]
Gram-positive aerobes	76	64	82	74
Staphylococcus epidermidis	37	29	42	38
Staphylococcus aureus	19	19	17	22
Streptococcus viridans	10	10	8	10
Enterococcus spp.	4	5	—	4
Diphtheroids	4	—	—	—
Micrococcus	—	1	—	—
Unknown	2	—	—	—
Gram-negative aerobes	11	18	9	14
Anaerobes	12	14	9	8
Fungus/miscellaneous	—	5	—	3

employed in THA may also increase the risk of infection by preferentially attracting certain bacterial species. Gristina and associates (16,17), in in vitro and retrieval studies of infected biomaterials, reported the predominance of *Staphylococcus epidermidis* in wounds containing polymers. They also found *Staphylococcus aureus* to be the principal isolate in wounds containing metals. From these findings, Gristina and coworkers proposed the concept of "the race for the surface," which describes the competition between host tissue and bacteria for the colonization of the surface of the implanted foreign materials (16). According to this concept, the surface of prosthetic components is immediately coated with a "conditioning film" at implantation into a biological environment. This film is derived from host tissue and consists of proteins, macromolecules, and cellular elements. It is this "film" that can be colonized by either host tissue cells or bacteria. Therefore, a "race" between host tissue cells and bacteria for the dominance of this conditioning film occurs. Should the host tissue cells colonize the film before bacterial colonization, subsequent bacterial colonizers encounter a living, integrated cell surface with intact host defense mechanisms that is resistant to bacterial colonization (Fig. 2). If bacteria are present in sufficient numbers and can successfully compete for the colonization of the conditioning film, it is unlikely that host tissue cells will be able to displace them, and an infection ensues.

Many bacteria also have the capacity to produce an exopolysaccharide barrier (bioflim or glycocalyx) shortly after colonizing the conditioning film

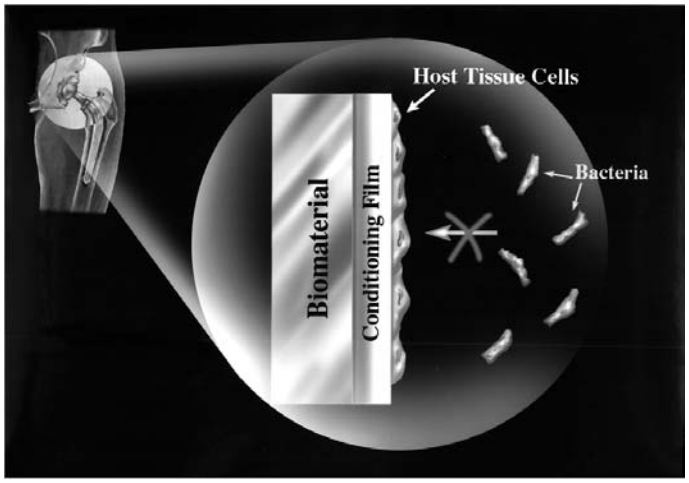

Figure 2 The host tissue cells have colonized the biomaterial and established a surface resistant to bacteria. (Modified from Ref. 16.)

(within 3 to 4 hours). It has been suggested that this glycocalyx acts as an ion exchange resin and produces a microenvironment below its surface that produces an optimal bacterial climate by influencing pH, ion, nutrient, and toxin concentrations (16,18–22). The glycocalyx serves to enhance bacterial nutrition and surface adhesion, confer resistance to host defense mechanisms, and impede the effective penetration of antibiotics (Fig. 3) (16).

Although the "race for the surface" can account for the THA infections that occur at or near the time of surgery, this concept does not explain infections that occur years after the procedure. Gristina and colleagues (16) proposed that in long-standing prosthetic environments, two time-dependent phenomena of total joint replacement, wear and corrosion, promote microenvironmental conditions conducive to the establishment of infection. Wear of the methylmethacrylate releases esters that may be metabolized by *Staphylococcus epidermidis*. Also, ions released from the corrosion of metal may stabilize the glycocalyx, leading to increased adhesion and antagonist resistance (Fig. 4).

Another time-dependent phenomenon that may have a role in the establishment of late THA infections is the immunocompetent fibroinflammatory zone that has been shown to develop at the biomaterial-host interface over time (16). This zone is believed to be the result of the host's attempt to eradicate the implanted biomaterials that it rccognizes as foreign material. Since the implanted components are not eradicated, a chronic inflammatory response that results in

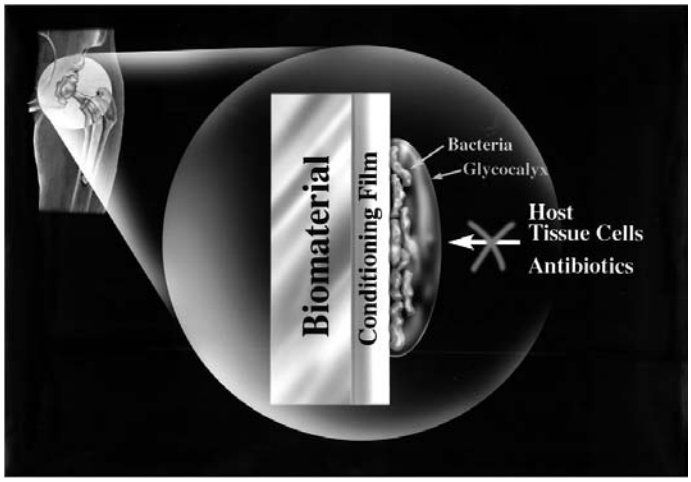

Figure 3 When bacteria are able to colonize the surface of the biomaterial, they produce a biofilm, the glycocalyx, that provides protection against host defense mechanisms and antibiotics. (Modified from Ref. 16.)

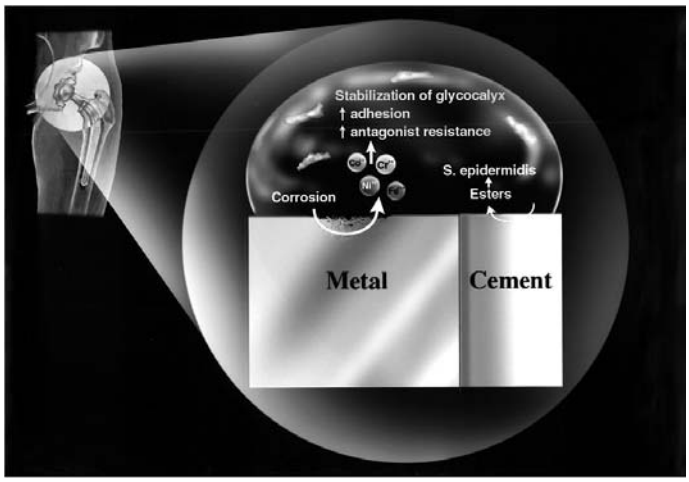

Figure 4 Conditions promoting the establishment of infections. Ions released from metals stabilize the glycocalyx, leading to increased adhesion and antagonist resistance. Esters released from polymethylmethacrylate may be metabolized by *Staphylococcus epidermidis*. (Modified from Ref. 16.)

damage to the adjacent host tissues and a decreased ability of these tissues to fight infection ensues. Particulate debris generated by wear and corrosion accelerate this chronic inflammatory reaction, leading to an expansion of the immunocompetent fibroinflammatory zone and an increased vulnerability to infection should seeding of the periprosthetic environment occur.

IV. SYMPTOMS AND SIGNS

The clinical picture of an infected THA is highly variable as it may be either a fulminating process with obvious local and systemic features of sepsis or an indolent process with few signs and symptoms. The appearance is dependent, to a substantial degree, on the timing of the infection. Infections in the early postoperative period are typically fulminant processes with a combination of local signs such as deep throbbing pain, wound drainage, erythema, and swelling about the hip with the accompanying systemic complaints of fever, chills, and generalized malaise (23–26). These findings are in sharp contrast to the typical postoperative course of an uncomplicated THA and are easily ascribed to a deep infection. Early postoperative infections are the result of seeding of the periprosthetic environment at the time of surgery or shortly after surgery from a contiguous superficial wound infection or prolonged wound drainage.

But not all infections that arise from seeding of the prosthetic joint in the early postoperative period are obvious fulminant infections. Most late chronic infections, infections that appear within 2 years of the index arthroplasty, are also believed to be the result of seeding at the time of surgery and are more subtle, often having mild pain as the only symptom (24,25). Therefore, the clinical picture of an indolent infection is commonly indistinguishable from the typical early postoperative course for an uncomplicated THA and is the chief reason for the delay in diagnosis of these infections. Although the factors that influence the way perioperative seeding of the prosthetic joint manifests itself are not known, some have suggested that the immunocompetence of the patient and virulence of the offending organism likely have a role (27).

Acute hematogenous infections occur in THAs at least 2 years after the index arthroplasty (12). These infections result from seeding of the prosthetic hip from a remote site. Both fulminant and indolent infections can occur in this period, and manifestation of the infection is dependent upon the immunocompetence of the patient and virulence of the offending organism.

Regardless of the presentation, the most common symptom is pain in the groin or thigh, which may vary from mild to severe. As previously mentioned, mild pain in the early postoperative period is difficult to distinguish from the convalescence typically expected of a THA. Pain that does not improve after a reasonable time may be a harbinger of infection. Without a plausible explanation available, a painful arthroplasty should be considered infected until proved otherwise. New-onset pain after several months or years of satisfactory function in the absence of other clinical findings is a diagnostic challenge since differentiating infection from mechanical loosening in this setting can be extremely difficult. Furthermore, these two diagnoses are not mutually exclusive because infection can cause mechanical loosening. In both septic and aseptic failure, the onset of pain can vary from insidious to sudden and severe. Increased pain with weight bearing and activity may be present in both. However, the pain of septic failure is often more persistent and may occur at rest or during activity. Often, pain caused by an infected prosthesis improves with a regimen of antibiotics (26).

V. DIAGNOSIS

The diagnosis of a periprosthetic hip infection can be relatively straightforward if the local and systemic signs suggestive of infection are present. Unfortunately, many THA infections are not obvious and often do not exhibit symptoms and signs of sepsis. Frequently, mild to moderate discomfort in the hip or thigh is the only symptom voiced by patients with an indolent infection. In these cases, radiographic and laboratory investigation can be helpful. Although many diag-

nostic modalities are available to aid in confirming the presence or absence of infection, none has demonstrated 100% reliability. Therefore, the treating physician should enlist the assistance of multiple diagnostic modalities to increase the likelihood of arriving at the correct diagnosis.

The diagnostic studies useful in detecting infection in the periprosthetic hip environment can be divided into two groups based on when they should be used. In the preoperative period, plain radiographs, ultrasonography, radionucleotide imaging, and serum laboratory tests provide useful information for the diagnosis of infection. Hip aspiration may also be done before surgery, and, in contrast to the other preoperative techniques, which provide indirect evidence of infection, aspiration seeks to confirm the presence of infection by identifying the causative organisms. Several intraroperative diagnostic studies, including Gram stain, cultures, frozen sections, and polymerase chain reaction, are also available.

A. Preoperative Diagnostic Studies

1. Plain radiographs

Although plain radiographs are rarely diagnostic for a THA infection, they should be obtained in each suspected case to rule out other causes of pain (fracture, catastrophic component failure, etc.). Most radiographic changes consistent with a periprosthetic infection can also be found in aseptic loosening. Although loosening may coincide with infection, especially chronic infection, it is not a necessary component. Many early postoperative and acute hematogenous infections have been shown to have solidly fixed implants (28).

One finding that may be helpful in distinguishing septic from aseptic loosening is periosteal new bone formation. This radiographic finding has been associated with the presence of deep sepsis in THA and is considered by some to be pathognomonic for this condition (2). Rapidly progressive radiolucent lines and osteolysis as well as early loosening can be suggestive of infection, especially if there is no evidence of severe polyethylene wear, the most common culprit of these phenomena.

2. Ultrasonography

Limited studies have investigated the role of ultrasonography in diagnosing THA infections. Findings that have correlated with an infected hip prosthesis include increased anterior pseudocapsule-to-bone distance, increased intra-articular effusion, and capsular thickening (29,30). The role of this modality, if any, has yet to be defined, and it is not currently recommended for the routine evaluation of an infected THA. Since it incurs no risk to the patient, this test may be used to collect information in difficult to diagnose cases. However, this technique is

highly operator-dependent and is not likely to be as useful in centers that do not commonly perform this test.

3. Radionucleotide imaging

Scintigraphy continues to be investigated as a modality in the diagnosis of THA infections. The various types of scintigraphy that have been studied for this purpose include technetium-99m bone scans, gallium-67 citrate scans, indium-111-labeled white blood cell scans, indium-111-labeled nonspecific polyclonal immunoglobulin G, and technetium-labeled monoclonal antigranulocytic antibody.

Technetium-99m bone scans and gallium-citrate scans have shown high sensitivity in detecting THA infection. Unfortunately, when used alone, each of these tests is nonspecific since both show high uptake in regions of increased bone turnover or inflammation of any cause. False-positive results are associated with aseptic loosening, fractures, neoplastic processes, heterotopic ossification, and inflammatory disorders (28). Also, scan results may remain positive for as long as 1 year after insertion of an uncomplicated THA and more than 2 years after an insertion of uncemented prosthesis (31,32). False-negative findings can occur in infected THAs with subperiosteal pus, soft-tissue swelling, vasospasm, and an inadequate blood supply (28,32). Indium-111-labeled white blood cell scans, on the other hand, have demonstrated low sensitivity (0.38–0.83) but high specificity (0.94–1.00) in diagnosing periprosthetic infections (33,34).

In an effort to improve the accuracy of the scintigraphic techniques mentioned, combinations of these techniques have been investigated. The sequential use of technetium and gallium scans, although more accurate than independent use of each scan, still lacks sufficient accuracy in diagnosing THA infections (34,35). In contrast, the early experience with the combination of technetium and indium scans yielded sensitivities and specificities as high as 0.89 to 1.00 and 0.95 to 0.98, respectively (36,37). Studies in 2000 demonstrated less accuracy of the technetium-indium combination, with sensitivities and specificities ranging from 0.64 to 0.77 and 0.78 to 0.86, respectively (38,39).

Newer nuclear imaging techniques such as indium-labeled immunoglobulin G (^{111}In-IgG) may offer higher degrees of accuracy. Few published reports analyze the use of this new modality exclusively in the evaluation of potentially infected THAs, but preliminary data indicate this may be preferable to the combination study method. The advantage of ^{111}In-IgG over combined technetium and indium scans include need to perform only one test, lower amount of time required to administer the test, lack of need for a phlebotomy before the scan is made, and avoidance of the reinjection of white blood cells. Oyen and associates (40), in a subgroup of patients with failed arthroplasties, reported a sensitivity and specificity of 0.92 (11 of 12) and 0.88 (22 of 25), respectively. In a

study of 87 THA infections, Nijhof and associates (41) reported a sensitivity and specificity of 1.00 and 0.82, respectively. Unfortunately, this scintigraphic modality has the same disadvantage as the other radiopharmaceuticals—detection of inflammation irrespective of cause. As a result, a specificity of 1.00 is difficult to achieve with this technique.

Besides the variable sensitivity and specificity of the scintigraphic tests, other drawbacks include the cost and time required to perform the test. Therefore, many authors reserve the use of these modalities for equivocal cases in which the aforementioned investigative studies have failed to establish the presence or absence of an infection (28). Of the available radionucleotide studies, it is clear that the combination of ^{99m}Tc and ^{111}In- white blood cell (WBC) scans has yielded the most consistent results to date. Further investigation is needed to identify properly the role of ^{111}In-IgG scans in diagnosing THA infection. Until they are proved to be superior to sequential scintigraphy, the combination of technetium-indium scans is currently recommended.

4. Serum laboratory tests

Serum laboratory tests that may aid in the diagnosis of a THA infection include a complete blood count with a differential cell count (CBC with differential), an erythrocyte sedimentation rate (ESR), and a C-reactive protein level (CRP).

In fulminate infections, the CBC with differential may demonstrate the presence of leukocytosis with an increased percentage of immature white blood cells indicating a systemic response to the infection. Unfortunately, this phenomenon rarely occurs in the indolent presentations so the test finding is rarely abnormal in most THA infections (42–44). Using the threshold of 11.0×10^9 white blood cells per liter as an indication of infection in 202 THA revisions, Spangehl and coworkers reported the sensitivity and specificity of this test to be 0.20 and 0.96, respectively (45).

The ESR is an indirect indicator of a systemic response to any inflammatory process. Several studies have shown an association between deep infection and ESR values of greater than 30 to 35 millimeters per hour (46–48). Unfortunately, the ability of the ESR to be influenced by any inflammatory condition decreases its specificity and limits its predictive value when used independently. For example, in uncomplicated THA the ESR may not return to baseline levels until at least 6 months to 1 year after surgery, making this an especially unreliable test in the early postoperative period (46). When the test is used alone, the reported sensitivity and specificity of ESR are 0.82 and 0.86, respectively (45).

C-reactive protein is an acute-phase reactant found in trace amounts in the serum under normal conditions. Similarly to the ESR, CRP is a nonspecific indicator for inflammation, infections, and neoplastic processes. In contrast to the

ESR, CRP levels return to baseline shortly after surgery as normal values have been demonstrated at an average of 3 weeks post surgery (range 1 to 8 weeks) (49–51). Elevated CRP levels of greater than 10 milligrams per liter have been associated with periprosthetic infections. Although the reported sensitivity (0.96) and specificity (0.92) of CRP alone are superior to those reported for ESR alone, its specificity has been shown to increase to 1.00 when it is used concurrently with the ESR (45).

Therefore, it is currently recommended that both the ESR and CRP be used in the initial workup in all THA failures, especially those suspected of being septic. Despite its low sensitivity, we continue to order the CBC with differential in all cases as it may add diagnostic information in a few cases.

5. Hip aspiration

Hip aspiration has been previously used as a routine screening tool to rule out infection in all THA failures (52–54). Current recommendations discourage this practice as its sensitivity and specificity have varied widely when used in this capacity, ranging from 0.50 to 0.93 and 0.82 to 0.97, respectively (28,55,56). Hip aspiration performed under fluoroscopy is now recommended as a second-line diagnostic tool in cases that suggest infection with equivocal ESR and CRP values. Spangehl and coworkers have shown that the addition of a positive preoperative hip aspiration result to elevated ESR and CRP values increases the probability of infection from 0.83 to 0.89 (45). Furthermore, in their review of 202 THA revisions, Spangehl and coworkers (45) found the probability of infection to be zero when the hip aspiration, ESR, and CRP all revealed negative findings (95% confidence interval, 0.00 to 0.04).

Various methods have been recommended to increase the accuracy of a single hip aspiration, including (1) discontinuing any concurrent antibiotic use 2 to 3 weeks before aspiration; (2) limiting the use of local anesthetics during the procedure to just the superficial tissues, as these are bacterostatic; (3) confirming intra-articular position with an arthrogram; (4) obtaining multiple samples during the same aspiration; and (5) obtaining a fine-needle biopsy of synovial tissue during aspiration (44).

B. Intraoperative Diagnostic Studies

1. Gram stain

Several studies have demonstrated the unreliability of a Gram stain of the periprosthetic environment in diagnosing THA infection. In Spangehl's investigation of 202 THAs undergoing revision, the Gram stain showed a sensitivity of 0.19 and specificity of 0.98 (45). Other authors have fared no better, with reported sensitivities ranging from 0 to 0.23 (28,57). This lack of sensitivity has led many

authors to abandon their reliance on the study in favor of use of other diagnostic modalities. The Gram stain is not to be totally abandoned since positive results could provide early information regarding the offending organism and guide initial antibiotic therapy.

2. Cultures

Intraoperative culture remains the standard to which all other diagnostic modalities are compared. However, this test is not foolproof since significant false-positive (2.4% to 31.5%) culture findings have been reported (45). False-negative results may also occur when patients are exposed to antibiotics before the collection of the culture sample. To prevent inaccurate results, precise technique must be used (28): (1) antibiotics should be withheld until specimens have been obtained; (2) instruments used to obtain the cultures should be prevented from touching the skin of the patient; (3) samples should be obtained from the environment close to the prosthesis, and if possible, from inflamed tissue; (4) a minimum of three specimens should be sent fresh to the laboratory for immediate processing; and (5) the specimens should be obtained immediately after the pseudocapsule is opened from an area not previously cauterized, before any irrigation has been used. Using these techniques, Spangehl and coworkers (45) reported a sensitivity and specificity of 0.94 and 0.97, respectively.

Debate exists over what constitutes an infection with respect to the number of culture and/or broth subcultures that demonstrates bacterial growth. It has been contended that late growth of bacteria or growth in the broth subcultures alone likely represents a contaminant. Although in most cases this may be true, the final culture results should be interpreted in the context of all preoperative and intraoperative findings as late growth and growth in liquid medium alone have been found in some cases of THA infection (28).

3. Frozen sections

Intraoperative frozen sections of the periprosthetic environment are used to diagnose THA infections by determining the quantity of inflammatory cells present. This indirect measurement of infection provides additional information that may be especially useful in equivocal cases when the results discussed are inconclusive. Ever since the report by Mirra and associates (58) in 1976, a finding of more than five polymorphonuclear leukocytes per high-power field (5 PMN/hpf) has been thought to be highly suggestive of infection. Using this threshold, most studies have reported sensitivities and specificities of greater than 0.80 and 0.90, respectively (44). When 10 PMN/hpf was used as the index for infection, an increase in specificity occurred (from 0.96 to 0.99) without decreasing sensitivity (0.84) (59). Additional methods that can be used to

ensure more accurate results with the use of this test include taking the samples from areas that appear most inflamed and designating an experienced musculoskeletal pathologist to analyze the samples.

4. Polymerase chain reaction

Polymerase chain reaction (PCR) is a technique that shows promise in diagnosing infected THAs. The PCR technique involves amplifying the nucleic acid extracted from periprosthetic synovial fluid and screening it for the presence of bacterial deoxyribonucleic acid (DNA). This technique has the ability to diagnose periprosthetic infections when only small quantities of bacteria are involved. Indeed, improved sensitivities compared to those of traditional bacteriological studies have been reported with this technique (60,61).

It is this ability to detect minute amounts of nucleic acid that may result in high false-positive rates. Any source of bacterial DNA is a potential source of contamination and may result in a positive PCR result even though the periprosthetic environment is sterile and contains no viable bacteria. Although bacterial species–specific PCR primers have been designed to minimize the false-positive rate, the role of this technique has yet to be perfected.

VI. CLASSIFICATION

A modification of Coventry's original description of periprosthetic infections has been the most widely used classification system to date (2,11,14,62). Periprosthetic infections are divided into three stages based on when the symptoms began after surgery and the route of infection. Stage I infections (acute postoperative) are acute fulminating infections that appear within 3 months after the arthroplasty. These infections are the result of direct seeding of the prosthetic joint during the procedure, early postoperative seeding from an infected wound or hematoma, or hematogenous seeding from a remote site early in the postoperative course. Systemic symptoms are common and the patient usually has an inordinate amount of pain. Persistent wound drainage is often present in these infections. Stage II infections (delayed, deep) are more indolent and appear from 3 months to 2 years after surgery. These patients often have never had a pain-free interval after surgery and can pose a diagnostic dilemma, as mild pain in the absence of fever, chills, and wound drainage can also be suggestive of mechanical loosening. Stage III infections (hematogenous) manifest increasing pain and decreased function in a previously well-functioning hip. A history of a recent, remote infection or procedure involving the skin, oral cavity, urinary tract, respiratory tract, or gastrointestinal tract may precede stage III infections by days to weeks.

A newer classification introduced by Tsukayama annd colleagues (12) in 1996 was designed to guide treatment on the basis of the authors' experience with 106 THA infections. It is an expansion and slight modification of the Coventry system and consists of four categories: (1) Positive intraoperative culture findings: When at least two intraoperative cultures obtained at the time of revision yield positive results, often these results are known only after the revision is performed, as these cases typically had no preoperative signs or symptoms suggesting infection. Recommended treatment consists of 6 weeks of intravenous antibiotics and may not require further operative treatment. (2) Early postoperative infection: Symptoms develop within 1 month after implantation. Treatment of these infections may consist of débridement, exchange of the polyethylene liner, retention of the components, and intravenous antibiotics for at least 4 weeks. (3) Late chronic infection: Symptoms develop insidiously 1 month or more after implantation. Recommended treatment is a two-stage reimplantation. (4) Acute hematogenous infection: Symptoms develop acutely in a previously well-functioning hip. If the prosthesis is well fixed, and the duration of symptoms is short, the infection is treated in the same manner as early postoperative infection. If the prosthesis is loose, it should be treated as a late chronic infection.

Currently, the Tsukayama modification is the preferred classification system at our institution because it is clear and descriptive and serves as an effective guide to treatment.

VII. PROPHYLAXIS

Since the introduction of the low-friction arthroplasty by Sir John Charnley in the 1960s, the reported incidence of infection after THA has steadily decreased (28). Chief among the reasons for this decline are an increased awareness of the problem of deep infection after this surgery and a better understanding of the various factors that predispose to this dreaded complication. Hanssen and coworkers (27) describe an interdependent relationship among the triad of bacteria, host factors, and the wound environment that influences whether or not infection will occur. Using the model proposed by Hanssen and associates, prevention of THA infection is realized by minimizing the number of bacteria in the wound, augmenting the host's ability to fight infection, and optimizing the periprosthetic wound environment. Prophylactic measures that achieve these goals can be applied in both the perioperative and postoperative periods. Perioperative prophylactic measures act either to diminish the degree of bacterial contamination that inevitably occurs at the time of surgery or to lessen the consequences of this contamination. Prophylaxis in the postoperative period aims to decrease the consequences of the transient bacteremias associated with infections or manipulations of remote sites.

A. Perioperative Prophylaxis

The prophylactic modalities available to the treating physician in the perioperative period include antibiotic prophylaxis, clean air technology, optimization of the surgical patient, and meticulous surgical technique.

1. Antibiotic prophylaxis

The administration of systemic antibiotics immediately before surgery is recognized as the most effective prophylactic measure in the prevention of THA infections (27). In a prospective randomized study of 6781 hip arthroplasties and 1274 knee arthroplasties, Lidwell and colleagues (63) reported a reduction in the postoperative infection rate with the use of prophylactic cefazolin of 3.4% (39 of 1161) to 0.8% (24 of 2968). In the same study, the use of clean air technology alone was also effective, but not to the same degree as antibiotic prophylaxis, as rates decreased from 3.4% to 1.2%. Likewise, Marotte and coworkers (64) reported a reduction in infection of 2.8% to 0.5% with the use of several different antibiotic regimens. In that study, the use of laminar vertical flow in the absence of antibiotics did not result in a significant reduction in THA infections compared to use of a conventionally ventilated room without prophylactic antibiotics. Hill and associates (65), in a prospective placebo-controlled study, described a similar reduction in infection rates from 3.3% to 0.9% with the use of prophylactic cefazolin.

Preoperative systemic antibiotics have been shown to be most effective if given shortly before the skin incision. In a large prospective study of 2847 patients who had a variety of clean and clean-contaminated procedures, lower rates of wound infections were demonstrated with prophylactic antibiotics given within 2 hours of the skin incision compared to more than 2 hours before the skin incision (66). Administration of an antibiotic 1 day or more preoperatively provides no additional protection and may alter the patient's natural skin flora (14). Currently, it is recommended that systemic antimicrobial prophylaxis be initiated 15–60 minutes before the skin incision to allow adequate tissue levels to be obtained (8,27,67–69). Arthroplasties that require a tourniquet (e.g., total knee arthroplasty) should receive antibiotic prophylaxis at least 5–10 minutes before inflation.

Although it is agreed by most authors that this prophylactic measure is the most effective at preventing THA infections, controversy continues to exist regarding the optimal antibiotic and duration of prophylaxis. Theoretically, the optimal antibiotic should demonstrate activity against organisms common to periprosthetic infections (*Staphylococcus* and *Streptococcus* spp.), have adequate bone and soft-tissue penetration, have low toxicity, be inexpensive, and have a long half-life to provide coverage throughout the entire surgery. Currently, the first-generation cephalosporin, cefazolin has been the most extensively studied

antibiotic for this role. Cefazolin has been found to meet all the desired criteria mentioned (68) and therefore, is currently the most commonly used antibiotic. Other broad-spectrum antibiotics such as second- and third-generation cephalosporins have also been investigated in this capacity but have not shown better efficacy than cefazolin (27). Cefazolin continues to demonstrate adequate activity against the organisms commonly isolated from THA infections; however, as new patterns of resistance emerge, the optimal choice of antibiotic is expected to evolve as well. Evidence of cefazolin-resistant organisms in total joint arthroplasty has already been reported (70,71). Tanzer and colleagues (71) reported that 7 of 152 patients who had skin swabbing before total knee arthroplasty were found to have *S. epidermidis* resistant to standard doses of cefazolin. Likewise, James and coworkers (70) demonstrated a 25% prevalence of cephalosporin-resistant *S. epidermidis* in patients about to undergo elective THA.

The optimal duration of antibiotic prophylaxis has yet to be determined. Several studies have reported no additional benefit when antibiotic prophylaxis was continued beyond 24 hours (8,72–78). Mauerhan and associates (76) reported no difference in the prevalence of wound infection after total hip or knee arthroplasty between a 1-day regimen of cefuroxime and a 3-day regimen of cefazolin. Similarly, in a study of 466 total joint arthroplasties, no difference in infection rates was seen when 7-day, 3-day, and 24-hour antibiotic regimens were compared (8). Wymenga and colleagues (79) attempted to shorten the prophylactic regimen even further by comparing a single preoperative dose of cefuroxime to a three-dose regimen (preoperative, 6 hours, and 18 hours after surgery). At a mean follow-up of 13 months, the prevalence of infection was 0.83% (11 of 1327) and 0.45% (6 of 1324) in the one-dose and three-dose groups, respectively. Although this difference was not significant, the nearly double infection rate in the one-dose group prompted the authors to recommend the longer three-dose regimen.

As a result of the aforementioned studies, the current consensus on the duration of systemic antibiotic prophylaxis for a routine primary THA is for a single preoperative dose followed by two to three postoperative doses (27,80–82). This shorter regimen is thought to minimize the expense, toxicity, and potential for the development of resistant organisms while still providing adequate antimicrobial activity.

Antibiotics may also be added to the cement of primary THAs as a means of preventing periprosthetic infection. Several series have shown a significant reduction in infection rates after THA using antibiotic-impregnated bone cement in the absence of systemic antibiotics (83–85). However, relatively few randomized, prospective studies have compared antibiotic-impregnated cement with systemic antibiotics (86–89). McQueen and coworkers (86) found no statistical difference in infection rates between the systemic administration of cefuroxime and the addition of cefuroxime to bone cement. In contrast, Josefsson and

associates (87,88), in their experience with 1688 consecutive THAs, found a significantly lower rate of infection at 2-year and 5-year follow-ups with antibiotic-laden cement when it was compared with systemic antibiotics. However, at their 10-year follow-up, additional infections in the antibiotic-laden cement group eliminated the statistically significant difference previously seen (89).

Currently, no standards or clinical guidelines have been established with respect to the routine use of antibiotics in bone cement. Concerns over the potential for the emergence of resistant organsisms, toxic reactions to the antibiotics, additional protective effect of use in combination with systemic antibiotics, and mechanical effects of adding antibiotics have tempered its use; less than 20% of primary THAs and less than 50% of revision THAs are performed with this technique (90). As is done in other centers (91), we reserve prophylactic antibiotic-impregnated cement for THA revisions as there seems to be an additional benefit to their use in preventing infection.

2. Clean air technology

Clean air technology refers to the various techniques used to minimize the number of airborne bacteria in the operating suite during surgery. The majority of airborne bacteria are derived from the skin and hair of individuals present in the operating room at the time of surgery including the patient, surgeons, nurses, anesthesiologists, and circulating personnel. As a result, the bacteria are almost always gram-positive (92). When airborne, bacteria are rarely found individually. Instead, they usually reside on droplets, dust, and shed epithelial cells ranging in size from 8 to 14 micrometers (93). Individually, bacteria range in size from 0.3 to 10 micrometers. The number of bacteria that can be shed by individuals is highly variable and ranges from 5000 to 55,000 particles per minute (8). Individuals who shed substantially more bacteria than their counterparts, known as *dispersers*, have been associated with an increased risk of wound infection (94,95).

One form of clean air technology is the use of laminar airflow within the operating room suite. Conventional operating rooms contain atmospheric air that is filtered (removing approximately 97% of particles 0.5 μm in size or larger) and exchanged (28–32 room air exchanges per hour) (96). Clean air rooms decrease the number of airborne bacteria by more frequent exchange (up to 300 air changes per hour), a higher degree of filtration (1–2 μm), and laminar flow of the operating room air. Filtration to the level of 1–2 μm has been reported to result in sterilized air (1). Laminar flow involves air moving at a uniform velocity along parallel lines in a confined space. Clean air rooms have been shown to decrease the average count of viable airborne bacteria per cubic foot from 5.4 to 0.45 in clean air rooms and to 0.1 when body exhaust suits were used in addition to clean air rooms (97).

Two types of laminar flow have been investigated, horizontal and vertical. Vertical laminar airflow is generally considered more effective and practical than horizontal airflow in reducing airborne contamination, especially in the absence of body exhaust suits (1,27,92,96). This effectiveness is thought to be due to the increased turbulence at the operative field seen with the use of horizontal airflow compared to vertical airflow. In the absence of body exhaust suits, members of the surgical team continue to emit airborne organisms, which increase the likelihood of infection in the presence of turbulent airflow at the operative site. When personnel isolator body suits are used, members of the surgical team no longer emit airborne organisms, and turbulence at the operative site can be tolerated (1,27). In some studies (98), the use of horizontal airflow has actually been associated with an increased prevalence of infection, which is believed to be due to this increased air turbulence at the surgical site as a result of improper positioning of personnel between the airflow unit and patient.

Despite the theoretical benefits of laminar airflow, this prophylactic modality has not been universally embraced. In 1969, Charnley and Eftekhar were the first authors to report their experience with clean air technology and the use of laminar airflow and concluded that this technique was the most important factor in the reduction of their infection rate from 9% to 1% (73). Other authors have also demonstrated a dramatic reduction in infection rates to 0.5% and 0.8% (63,65). The controversy surrounding this technique emerged from the shortcomings that none of these studies was prospective or randomized and that confounding variables, especially the concomitant use of prophylactic antibiotics, were not controlled. For example, in 1982 the Medical Research Council of Great Britain published the findings of their large multicenter trial evaluating the effect of clean-air operating rooms in 8055 total joint arthroplasties (Table 2) (63). The prevalence of infection was 1.5% in the conventional rooms and 0.6% in the

Table 2 The Independent and Combined Effects of Clean-Air and Prophylactic Antibodies on the Rate of Infection after Total Joint Arthroplasty

Prophylactic antibiotics	Laminar air flow		
	No	Yes	
No	39 of 1161 (3.4%)	13 of 1060 (1.2%)	($p < 0.01$)
Yes	24 of 2968 (0.8%) ($p < 0.001$)	10 of 2863 (0.3%) ($p < 0.01$)	($p < 0.1$)

Source: From Ref. 63.

clean air rooms ($p < 0.001$). When the use of antibiotic prophylaxis was accounted for, clean air rooms were still shown to have significant independent effect without the use of antibiotics as the rate of infection decreased from 3.4% in conventional rooms to 1.2% in clean air rooms ($p < 0.01$). When antibiotics were used independently of clear air rooms, the infection rate dropped even more, from 3.4% to 0.8%. When the combination of clean air rooms and antibiotic prophylaxis was used, the prevalence of infection decreased further, from 0.8% to 0.3%, but this effect was not significant ($p < 0.1$). Fitzgerald's study of 7305 arthroplasties supports the lack of a statistically significant difference between the two operating room environments (conventional versus clean air) when prophylactic antibiotics are used (3). However, it should be noted that in Fitzgerald's study, the clean-air environment consisted of horizontal laminar airflow without the concomitant use of isolator body exhaust suits.

At this time, the role of laminar airflow in the prophylaxis of total joint arthroplasty is controversial if prophylactic antibiotics are also used. Proponents point to the trend of lower infection rates seen in Lidwell's study (63) and the need to provide additional prophylaxis in an era of increasing antibiotic resistance (99,100). Critics point to the lack of significant differences in the setting of concomitant prophylactic antibiotics and the increased expense of installing and maintaining laminar airflow systems (3,27,97).

Ultraviolet light has also been used intraoperatively to sterilize bacteria present on airborne particles (8). In investigations since 1935, several studies have shown a decrease in postoperative wound infection rates with the use of this modality (101–104). Although it is a relatively inexpensive alternative to laminar airflow systems, the lack of definitive studies and concerns about the exposure of the operating room personnel have thus far prevented its widespread acceptance (27,102).

Other measures have been recommended in an effort to decrease the potential for airborne bacterial contamination during surgery. Fitzgerald has shown increased levels of airborne bacteria within the operating suite during times of increased activity (Fig. 5) (96). In that report, high airborne bacterial counts were encountered before surgery just after the patient entered the room, while the anesthesia team was active, and during patient positioning times when instrument packs are often already open and uncovered. Similarly, Brown and coworkers (105) encountered a 4.4-fold increase in airborne bacterial counts with preincision activity during preparation and draping of the patient. Even with a scrubbed and gowned leg holder, the bacterial air counts were still 2.4-fold higher than counts during the surgery itself. On the basis of these findings, it has been recommended that instrument packs be either covered before incision or opened only after skin preparation and draping have been completed (96,105). It is also recommended that operating room traffic be limited before and during the procedure. Ritter and colleagues (106) demonstrated a significant increase in

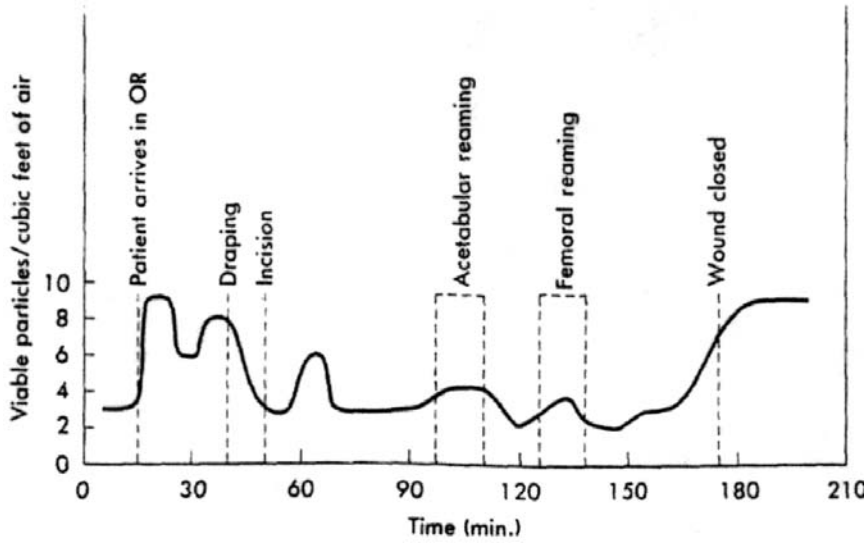

Figure 5 Airborne contamination during total hip arthroplasty. (From Ref. 96.)

microbiological counts in an unoccupied operating room when the door was left open to the hallway, and a sixfold increase with the addition of five operating room personnel. Wearing surgical facemasks under an overlapping hood and minimizing conversation during the procedure have also been associated with decreased levels of airborne contamination in the absence of full-body isolation suits (107).

3. Optimization of the total hip arthroplasty patient

Several patient-dependent risk factors have been known to increase the likelihood of development of infection after surgical procedures. Although a relative few of these risk factors have been directly correlated with an increased risk of infection after THA, they have been associated with conditions that increase the risk of development of infection (delayed wound healing, etc.). The relative vulnerability to infection of THA in comparison to other surgical procedures warrants an appreciation of these risk factors. Patients considered to be at high risk are those who are of advanced age, malnourished, or obese; have diabetes mellitus or rheumatoid arthritis; or are using immunosuppressive medication. Each of these conditions has been associated with impairment of the immune system. Unfortunately, many of these conditions are common THA patients. Therefore, it is recommended that patients with these risk factors who are to have THA would

benefit from the optimization of these risk factors, if possible, or might require more intensive prophylactic techniques to minimize their risk of sepsis.

Advanced age, in the absence of disease, has been associated with a diminished humoral (B cell) and cell-mediated (T cell) immune response resulting in a decrease in antibody formation, depressed delayed-type hypersensitivity (DTH) responses, decreased proliferative response, and altered helper-to-suppressor activity ratio (108). Decreased thymic activity and constant antigenic pressure throughout life have been suggested as factors for this impaired immunity.

Both extremes of nutrition, malnutrition and obesity, have been found to be directly related to an increased incidence of postoperative wound complications. Although no direct correlation has been made between these nutritional abnormalities and THA infections per se, the causal relationship of wound complications and THA infection is well recognized (9,96,109). In one study, persistent wound drainage was associated with a 3.2 times higher risk of deep infection (9). Malnutrition, which may be present in as many as 48% of all surgical patients (110), results in impairment of many host defense mechanisms including humoral and cell-mediated immunity, phagocyte function, physical barriers (skin and mucous membranes), and other nonspecific defenses (interferon, lysozymes, and complement). At present, no universally accepted definition of malnutrition of patients undergoing total joint arthroplasty has been established. However, several nutritional parameters have been associated with increased risk of postoperative wound complications. Greene and coworkers (111), in a review of 217 consecutive total hip or knee arthroplasties, found that a preoperative lymphocyte count of less than 1500 cells/mm^3 was associated with a five times greater frequency of development of major wound complication, and an albumin level of less than 3.5 g/dl had a seven times greater frequency. Low preoperative serum transferrin levels have also been associated with an increased risk of wound complications after THA (112). The nutritional index of Rainey-McDonald (Table 3) which relies on serum albumin and transferrin levels, may aid in determining which patients are at increased risk for postoperative infection (113). The elective nature of THA provides opportunity for the treating physician to reverse these nutritional deficiencies; such reversal has been shown to improve immune system function and reduce the rate of infection-related complications (114).

Table 3 The Nutritional Index of Rainey-McDonald[a]

$= [(1.2 \times \text{serum albumin}) + (0.0013 \times \text{serum transferrin})] - 6.43$

[a] Values less than or equal to 0 are consistent with nutritional depletion.
Source: From Ref. 113.

Obesity has also been identified as a risk factor for poor wound healing after a variety of surgical procedures (115,116). The effect of obesity on wound healing after total joint arthroplasty, in particular, is less clear as several reports support (76,117–119) and several refute (120–122) its association with impaired wound healing. In addition to the possibility of a negative effect of obesity on the postoperative wound, clinical and epidemiological data indicate that obese patients have a greater susceptibility to infectious illnesses than lean patients (115,116,123,124). It has been suggested that hyperglycemia, hyperinsulinemia, and hyperlipidemia may have a negative effect on the function of certain immune cells (124,125), but the exact effect is unknown at this time. Several alterations in various measures of immune function have been noted in obese subjects, including impairment of phagocytosis (124,126). Whether or not obesity can be "optimized" before surgery is uncertain at this time because the effects of its reversal, by either diet or bariatric surgery, on wound healing and infection have not been sufficiently studied. It has been noted, however, that large weight loss in obese patients was actually found to result in immune system impairment long after the diet had ended (124).

Chronic diseases not uncommonly encountered in THA patients, especially rheumatoid arthritis and diabetes mellitus, have also been associated with an increased risk of periprosthetic infection. The increased risk of these two illnesses can be at least partially attributed to an acquired reduction of immunoresponsiveness with abnormal neutrophil chemostaxis and phagocytosis (14). Patients with rheumatoid arthritis have up to a 2.6 times greater risk of development of a THA infection when compared to osteoarthritics (1,52,73,117,127–129). This increased risk is believed to be present not only in the immediate postoperative period, but throughout the lifetime of the prosthesis (129). Efforts to optimize the rheumatoid patient before surgery have centered on the cessation of the immunosuppressant methotrexate, which is frequently used in the treatment of this disease. Several authors have advocated the temporary cessation of methotrexate around the time of surgery to decrease the incidence of postoperative wound infection (130–132). Alternatively, others advocate continued methotrexate use through the perioperative period to prevent a flare-up of rheumatoid arthritis (133–135). The most reasonable approach in this patient population may be to withhold methotrexate for a short time during the perioperative period. A period of 2 weeks before and after the surgery seems to minimize the flare-ups while preventing any increased chance of development of infection (131). More definitive studies are needed to confirm whether or not this approach is effective.

Diabetic patients are also considered at higher risk for development of deep infection after total joint arthroplasty than nondiabetic patients (79,136–140). This increased risk of infection is thought to be due not only to an impaired immune system, but also to microvascular disease (14,141). Efforts to minimize the infection risk in diabetics have used additional prophylactic measures and

normalizing blood sugar counts. Maintaining serum glucose levels below 220 mg/dL has been associated with a decreased risk of postoperative wound infection after major cardiovascular and abdominal surgery (142). No reports of the effect of "normalizing" serum glucose levels in the setting of THA have been published. Additional prophylactic measures that have been attempted include the combination of antibiotic-impregnated cement with preoperative systemic antibiotics. In a study of 78 total knee arthroplasties, Chiu and associates (143) reported a significantly lower infection rate ($p = 0.02$) in diabetics with the addition of cefuroxime-impregnated cement (0 of 41 knees, 0%) compared to diabetics whose knees were implanted without antibiotic-impregnated cement (5 of 37, 13.5%). Although it is unknown why the infection rate in this study was so high in the control group, the effective additional prophylaxis used in diabetics is duly noted and may be indicated in this patient population of increased infectious risk.

The transfusion of allogenic blood in the perioperative period has also been associated with an increased infection risk in THA (144–146). In a multicenter study of blood management in 9482 total hip or knee arthroplasties, Bierbaum and colleagues (144) found a significantly higher rate of infection ($p \leq 0.001$) in patients who had received allogenic blood versus autologous blood. The possible mechanism for this phenomenon is an impairment of cellular immunity resulting in a deficient immune response (145,147). Since the need for any kind of blood transfusion after THA can be as high as 57% (144), a rational approach to this problem is necessary. Identification of the patient likely to need blood after THA should be made in the preoperative period well before the date of surgery to allow time for alternative techniques to be used. Transfusion practices that can reduce, if not eliminate, the need for allogenic blood include autologous blood donation, hemodilution, and perioperative blood salvage.

4. Meticulous surgical technique

The adherence to meticulous surgical technique is essential in reducing the incidence of infection after THA. Proper technique actually begins in the preoperative period with the preparation of the operative site. Shaving of the operative site inevitably inflicts small superficial lacerations in the skin ("nicks") that can become colonized over time and lead to wound infections (148,149). Therefore, the surgical site should be shaved as close to surgery as possible, and not the night or day before.

The operative site should be prepared with an antiseptic agent and covered with an antiseptic-impregnated adhesive drape before incision. After skin preparation, recolonization of the skin can occur within 30 minutes by bacteria sequestered in hair follicles and sebaceous glands located within the structure of the skin. If the process is left unchecked, normal levels of skin colonization may

be achieved within 3 hours (150). A plastic drape impregnated with slow-release iodophor inhibits this skin recolonization and prevents lateral migration of bacteria from exposed areas of the skin that were scrubbed but do not involve the incision. It has also been recommended that at the end of longer procedures, as the edges of this plastic adhesive drape are peeled away from the incision before wound closure, it is reasonable to scrub the exposed skin and incision with a povidone-iodine solution to reduce any bacterial colonization that may have occurred (27). This technique must be weighed against the possibility of damage to the exposed tissue that the direct application of povidone-iodine might cause. If this practice is to be employed, a less concentrated solution should be used to clean the exposed tissue. Once the surgery is under way, efforts should be made to expedite the procedure as much as possible as prolonged surgical times have been associated with an increase in the rate of periprosthetic infection (96,112).

The method of gloving during THA is controversial as one study has shown that there are no difference in wound contamination of single- and double-gloving regimens and that contamination results from sources other than glove puncture (106). Nevertheless, double gloving is still recommended over single gloving (27). If latex gloves are to be used on the outside, they should be exchanged frequently, as Sanders and associates (151) have shown that the number of punctures after use of double latex gloves correlated directly with the duration of wear. In that study, all gloves were found to have punctures after 180 minutes. If the constraints of cost, convenience, and comfort allow, a cloth outer glove may be used as it has been associated with a significantly lower rate of puncture ($p \leq 0.0001$) than a latex outer glove (151).

The remainder of the surgeon's attire has also been investigated for its ability to prevent the spread of airborne bacteria or direct contamination. Facemasks donned beneath an overlapping hood, instead of over the hood, and minimization of airborne contamination have been shown to decrease airborne contamination (107). In addition, Gore-Tex gowns (W. L. Gore and Associates, Flagstaff, Arizona) are reported to prevent the dispersion of bacteria 1000 times more effectively than ordinary cotton gowns (152).

Several standard operative instruments have been reported to accumulate bacterial contaminants. The suction tip has been recognized as a source of intraoperative contamination (153–155). This is likely due to the large volume of air that passes through it during the procedure. Therefore, the suction tip should not be placed into the medullary canal for prolonged periods to prevent drawing airborne contaminants into the wound. Also, the frequent exchanging of the suction tip at 30-minute intervals and use of a clean suction tip at the time of the preparation of the femoral canal help minimize this source of bacterial contamination (27). The splash basin has also been shown to be prone to contamination. In one study, 74% of splash basins were culture-positive at the end of the

orthopedic procedure (156). Therefore, instruments that have been placed in the splash basin should not be reintroduced into the wound.

Delicate handling of the tissue and prevention of extensive dissection from the underlying fascia serve to reduce the quantity of devitalized tissue within the wound. Copious irrigation is also encouraged not only to prevent tissue desiccation, but also to provide an additional method of wound decontamination. At closure of the wound, dead space is to be avoided and strict hemostasis is to be achieved as a tense hematoma can compromise the surrounding tissue and impede antibiotic access (157). The use of surgical drains to facilitate hematoma evacuation is controversial, and if they are to be used, removal should be accomplished within 24 to 48 hours to prevent retrograde contamination of the wound (158–161).

B. Postoperative Prophylaxis

From the moment of its insertion, the prosthetic hip is susceptible to infection during episodes of transient bacteremia. Any bacteremia can cause infection of a total joint replacement by the hematogenous route (7). This risk of hematogenous seeding lasts throughout the lifetime of the prosthesis and may result from infections or manipulations of remote body sites. Some of the more common origins of hematogenous infection are the oral cavity, skin, genitourinary tract, and gastrointestinal tract (7).

Postoperative prophylaxis, in the form of antibiotics, aims to protect the prosthetic hip from this seeding. Despite this ever-present risk of hematogenous infection in THA, this method of prophylaxis remains a controversial subject. Whereas the rate of bacteremia after dental and other diagnostic or therapeutic procedures has been well documented (162), the rate of actual seeding of the prosthetic joint from these hematogenous events remains unknown. At issue is whether the prevalence of hematogenous seeding from these transient bacteremic events is sufficiently high to outweigh the risk and cost of antibiotic prophylaxis. This answer remains unknown.

Currently, there are relatively few generally accepted indications for postoperative prophylaxis. One of the few consensus statements on this topic was released in 1997 as a joint effort by the American Dental Association and the American Academy of Orthopaedic Surgeons (163). In this joint advisory statement, the appropriate use of antibiotic prophylaxis in dental patients with total joint replacements was outlined (Table 4). Also defined were procedures associated with significant degrees of bacteremia (Table 5), and patients at risk for hematogenous infection (Table 6). This advisory statement followed studies that demonstrated the frequency and intensity of bacteremia to be highest after oral procedures, lower after genitourinary procedures, and lowest in gastrointestinal procedures (162). Furthermore, Osmon and coworkers (164) demonstrated that

Table 4 Suggested Antibiotic Prophylaxis Regimens in Patients with Total Joint Replacements Undergoing Dental Procedures[a]

1. Patients not allergic to penicillin: cephalexin, cephradine, or amoxicillin 2 g PO 1 h before dental procedure
2. Patients not allergic to penicillin but unable to take oral medications: cefazolin 1 g or ampicillin 2 g IM/IV 1 h before procedure
3. Patients allergic to penicillin: clindamycin 600 mg PO 1 h before dental procedure
4. Patients allergic to penicillin and unable to take oral medications: clindamycin 600 mg IM/IV 1 h before procedure

[a] No second doses are recommended for any of these dosage regimens.
Source: From Ref. 163.

Table 5 Incidence Stratification of Bacteremic Dental Procedures

Higher incidence[a]
- Dental extractions
- Periodontal procedures including surgery, subgingival placement of antibiotic fibers/strips, scaling and root planning, probing, recall maintenance
- Dental implant placement and reimplantation of avulsed teeth
- Endodontic (root canal) instrumentation or surgery only beyond the apex
- Initial placement of orthodontic bands but not brackets
- Intraligamentary local anesthetic injections
- Prophylactic cleaning of teeth or implants where bleeding is anticipated

Lower incidence[b]
- Restorative dentistry[c] (operative and prosthodontic) with/without retraction cord[d]
- Local anesthetic injections (nonintraligamentary)
- Intracanal endodontic treatment; postplacement and buildup
- Placement of rubber dam
- Postoperative suture removal
- Placement of removable prosthodontic/orthodontic applicances
- Taking of oral impressions
- Fluoride treatments
- Taking of oral radiographs
- Orthodontic appliance adjustment

[a] Prophylaxis should be considered for patients with total joint replacement who meet the criteria in Figure 10. No other patients with orthopedic implants should be considered for antibiotic prophylaxis before dental treatment/procedures.
[b] Prophylaxis not indicated.
[c] This includes restoration of carious (decayed) or missing teeth.
[d] Clinical judgment may indicate antibiotic use in selected circumstances that may create significant bleeding.
Source: From Ref. 163.

Table 6 American Dental Association–American Academy of Orthopaedic Surgeons Advisory Statement: Antibiotic Prophylaxis in Dental Patients with Total Joint Arthroplasty

Patients at potential increased risk of hematogenous total joint infection
Immunocompromised patients
Inflammatory arthopathies; rheumatoid arthritis, systemic lupus erythematosus
Disease-, drug-, or radiation-induced immunosuppression
Other patients
Insulin-dependent (type I) diabetes
First 2 years after joint replacement
Previous prosthetic joint infections
Malnourishment
Hemophilia

Source: From Ref. 163.

the rate of deep periprosthetic infection linked to an oral source was greatest in the first 2 years after an arthroplasty, occurring at a frequency of 0.14 case per 1000 joint-years, whereas the annual rate after the first 2 years was only 0.03 case per 1000 joint-years.

The use of prophylactic antibiotics in patients with THA who are having iatrogenic manipulation of the genitourinary tract (cystoscopy, etc.) or the gastrointestinal tract (endoscopy, etc.) remains controversial. The incidence of hematogenous seeding after these procedures and the efficacy of prophylactic antibiotics in preventing this seeding are unknown. Until a consensus is reached, prophylaxis for these procedures must be addressed on an individual basis and should be influenced by the number of risk factors present.

VIII. TREATMENT

The primary goals in the treatment of THA infections are the relief of pain, a functional lower extremity, and the eradication of infection. The mainstays of treatment are a prolonged course of antibiotics and surgery. Whereas both antibiotics and surgery, when used alone, have been able to suppress infections involving the prosthetic hip temporarily, consistent eradication usually requires both of these interventions.

Parenteral antibiotics should be initiated immediately after cultures of the periprosthetic environment are obtained. The initial antibiotic should be a broad-spectrum agent that is likely to be active against the organisms common to periprosthetic infections. Often a first-generation ephalosporin (cefazolin) or a penicillinase-resistant penicillin (methicillin or oxacillin) suffices. Once the

Table 7 Treatment Methods and Indications in Treating Periprosthetic Hip Infections

Treatment	Success rate	Indications	Comments
Two-staged reimplantation	92%	Most periprosthetic infections Adequate bone stock Medical fitness for multiple surgeries	Consistent superior success rates Gold standard
One-staged reimplantation	82%–92%	Sensitive bacteria Non-glycocalyx-producing bacteria Few or no risk factors for infection Adequate bone stock Medical nonfitness for multiple surgeries	Higher success rates with antibiotic cement
Resection arthroplasty	98%	Highly resistant organism Multiple risk factors for infection Poor bone or soft tissue quality Medical nonfitness for multiple surgeries	Suboptimal functional result
Hip arthodesis	100%	Adequate bone stock Young, functionally demanding patient	Improved functional results vs. resection Few studies

Débridement with retention	0%–80%	Less than 3 to 4 weeks of symptoms Sensitive organism Few or no risk factors for infection Well-fixed prosthesis	Key concern: duration of infection
Chronic suppressive therapy	47%–67%	Sensitive organism Treatable with oral antibiotics Medical nonfitness for surgery Patient refusal of further surgery No systemic sepsis	Requirement of long-term antibiotic course
Arthroscopic débridement with retention	100%	Less than 2 to 4 weeks of symptoms Sensitive organism Few or no risk factors for infection Well-fixed prosthesis Medical nonfitness for multiple surgeries	One study, small number of patients Requirement of long-term antibiotic course Role yet to be defined
Hip disarticulation		Life-threatening or refractory infections Severe loss of bone or soft tissue	Salvage procedure

organism, or organisms, has been identified, antibiotic treatment is modified in favor of a more specific agent to which the pathogens are sensitive. Consultation with an infectious disease specialist is advised to aid in selecting the appropriate antibiotic.

It has been recommended that the dosage of the selected antibiotic should be determined by performing postpeak serum bactericidal titers (SBTs). Lieberman and associates (165) established a SBT threshold of 1 : 8 as 27 of 28 (96%) THA infections were successfully treated when this titer was attained. In contrast, in two of four (50%) hips that did not achieve this threshold, a recurrent infection developed. The technique of determining serum bactericidal titers begins with obtaining specimens of serum 1, 1.5, 2, 3, or 6 hours after the fifth dose of antibiotics, depending on whether the dose is administered every 4, 6, 8, 12, or 24 hours, respectively. These serum samples are then diluted from 1 : 2 to 1 : 2048. The offending bacteria are added to each dilution and cultures are performed. The SBT is defined as the highest dilution of serum that kills 99% of the infecting bacteria.

In the past, recommendations for the duration of antibiotic treatment have varied from weeks to indefinitely. However, in the recent literature, most authors favor an antibiotic course lasting from 4 to 6 weeks (4). McDonald and associates (166), in a retrospective study of reimplantation after THA infection, reported the recurrence of infection in three of seven (43%) hips that had less than 4 weeks of parenteral antibiotics. In contrast, recurrence developed in only 1 of 13 (8%) hips that received parenteral antibiotics for more than 4 weeks.

Surgery, on the other hand, cannot completely eliminate the offending organism from the periprosthetic environment, but resection of infected tissue does serve to reduce the pathogenic load, allowing more effective eradication by the antibiotic. Indeed, the natural history of an infected THA without both antibiotics and surgery has been associated with increased morbidity and mortality rates (52,167,168).

The treatment options available to the orthopaedic surgeon include (1) two-stage reimplantation, (2) one-stage reimplantation, (3) resection arthroplasty, (4) débridement with retention of the prosthesis, (5) chronic suppressive antibiotics only, (6) arthroscopic débridement with retention of the prosthesis, (7) hip arthrodesis, and (8) hip disarticulation. The optimal treatment method for a particular case depends on several factors (Table 7).

The duration of the infection is an important factor in determining the optimal treatment for a THA infection. This factor chiefly influences whether the original prostheses may be retained or removed. It has been shown that a high rate of success can be achieved with component retention in infections of less than 1 month in duration (12). Component retention is preferable as it is a less extensive procedure and bone stock is preserved. This 1-month threshold is believed to be directly related to the amount of glycocalyx bacteria are able to produce. In

bacterial infections of less than 1 month, it has been postulated that insufficient amounts of glycocalyx are present, enabling local débridement, antibiotics, and prosthetic retention to be effective. Correspondingly, in infections of more than 1 month's duration, it has been proposed that increased amounts of glycocalyx are present, making prosthetic retention less reliable than resection (12).

The virulence of the offending pathogen must also be considered. *Virulence* has been traditionally defined as the inherent aggressiveness of the pathogen. For instance, *Staphylococcus aureus* is considerably more virulent than *Staphylococcus epidermidis* as it is more proactive in establishing infection, whereas *S. epidermidis* is more a pathogen of opportunity (10). Tn this age of continuing antibiotic ineffectiveness, an organism's resistance to antibiotics is also considered evidence of virulence. Organisms of high virulence should be treated more aggressively than their low-virulence counterparts.

Other factors to consider in determining the appropriate treatment are the quality of remaining bone in the periprosthetic environment, stability of the implant, patient's overrall medical condition, and patient's willingness to undergo additional procedures (Table 8).

A. Two-Stage Reimplantation

The two-stage reimplantation technique involves removal of the prostheses and resection of all infected tissue, followed by reimplantation of a new prosthesis at another surgical setting. The interval between surgeries is at least 6 weeks and consists of intravenous antibiotics. Once the antibiotic interval is completed, if results of diagnostic studies indicate the eradication of the infection, new components are then implanted. Confirmation of successful treatment is imperative before reimplantation and, like the diagnosis of infection itself, may be challenging. Experience with total knee infections suggests that a waiting period of 1 month off antibiotics followed by an aspirate and culture of the previously infected joint may identify the few patients (3%–20%) who remain infected even after prosthetic removal and prolonged antibiotics (169).

Table 8 Factors Considered in Determining Optimal Treatment for Periprosthetic Hip Infections

Duration of the infection
Virulence of the offending organism
Quality of bone
Quality of the surrounding soft tissue
Stability of the implant
Patient's overall medical condition
Patient's willingness to undergo additional procedures

Two-stage reimplantation is considered the standard in the treatment of periprosthetic hip infections because the highest success rates (average 92%) have been reported with this technique (4,170). The prerequisites for this method of treatment include adequate bone stock or a bone stock deficiency amenable to reconstruction, minimal serious medical comorbidities, and patient willingness to undergo two additional procedures (Table 7).

Controversy exists regarding the optimal fixation of the femoral component at the time of reimplantation. Traditionally, the high success rate enjoyed by the two-stage reimplantation technique involved the use of antibiotic-impregnated cement fixation of the femoral component (171). Desire to preserve bone stock and concern about the potential adverse effects of cement on the immune system led to trials of cementless femoral fixation. The initial experience with cementless femoral fixation at the time of reimplantation after infection was substandard, resulting in both high rates of loosening (18%) and high rates of recurrent infection (18%–30%) (172–174). However, studies in 1999 and 2000 contradicted these initial results (175,176). Ferring and associates (175), using cementless femoral fixation at the time of reimplantation, reported successful eradication of periprosthetic hip infections in 23 of 25 patients (92%). They also reported radiographic evidence of bone ingrowth at the femoral component in 24 of 25 patients (96%) at 4.8 years of follow-up. Similarly, Haddad and colleagues (176), in the largest review of two-stage cementless revision for infection, reported successful treatment in 46 of 50 (92%). In this study, antibiotic-impregnated cement beads were implanted at the time of resection and left in place during the 3-week interval between stages, and antibiotics were continued for at least 3 months after the reimplantation. These two studies suggest that equal short- to intermediate-term results can be achieved with cementless and cemented femoral fixation. Currently unanswered is which technique offers better fixation in the long-term.

B. One-Stage Reimplantation (Direct-Exchange Arthroplasty

The one-stage reimplantation technique involves the excision of all prosthetic components and infected tissue and the implantation of new components during the same surgical procedure. After surgery, a parenteral antibiotic regimen of at least 4 to 6 weeks is administered. The advantages of this technique over a two-staged procedure include the lower cost and morbidity rate associated with the need for one less procedure.

The overall experience with one-stage reimplantation has demonstrated inferior success rates in comparison with the two-stage technique (Table 9) (4,170,171,177,178). In a literature review of 12 reports, Jackson and Schmalzried (178) found a cumulative success rate of 83% at an average follow-up of 4.8

Table 9 Success Rates of One-Stage and Two-Stage Reimplantation: With and Without Antibiotic-Laden Cement

	One-stage		Two-stage	
Author	Number of hips	Success (%)	Number of hips	Success (%)
Cement with antibiotics				
Bucholz et al.[179]	667	77	x	x
Carlsson et al.[180]	59	90	18	78
Murray[181]	13	38.5	22	95.5
Wroblewski[182]	102	91	x	x
Hope et al.[183]	72	87.5	19	100
Elson[184]	235	87.5	61	96.5
Garvin et al.[185]	21	90.5	55	92.7
Duncan and Masri[186]	x	x	46	93
Sanzen et al.[187]	72	76	30	74.6
Raut et al.[188]	57	86	x	x
Miley et al.[189]	47	87	x	x
Ure et al.[190]	20	100	x	x
Callaghan et al.[171]	24	91.7	x	x
	Total = 1389	Average = 82%	Total = 251	Average = 92%
Cement without antibiotics				
Hunter[177]	55	18	10	60
Hughes et al.[191]	13	92.3	13	84.6
Tablott et al.[192]	x	x	25	80
Cherney and Amstutz[193]	5	80	28	64
Fitzgerald[2]	x	x	111	90
Jupiter et al.[194]	18	78.1	x	x
Salvati et al.[195]	31	91	28	89
Callaghan et al.[196]	14	86	18	94.5
McDonald et al.[166]	x	x	82	86.6
Lieberman et al.[165]	x	x	32	91
	Total = 136	Average = 59%	Total = 347	Average = 84%

Source: Modified from Ref. 171.

years. However, studies that followed more stringent indications have demonstrated success comparable to that of the two-stage technique. Ure and coworkers (190), at an average of 10 years after a one-stage reimplantation for THA infection, reported no recurrences of infection (100% success) in 20 patients. Likewise, Callaghan and associates (171) reported successful eradication of THA infections in 22 of 24 (91.7%) hips treated with a one-stage protocol. It is clear

from the literature to date that the high success rate of one-stage reimplantation can only be consistently achieved with proper patient selection. Generally accepted criteria for one-stage reimplantation include (1) a pathogen sensitive to antibiotics, (2) non–glycocalyx-producing bacteria, (3) a patient with few or no risk factors for infection (rheumatoid arthritis, diabetes mellitus, etc.), (4) a wound in which there is adequate bone and soft tissue to support reconstruction of the hip, and (5) comorbid medical conditions that place the patient at increased risk with a second major procedure (190). Without strict adherence to these indications, the patient is at an increased risk of recurrence and its potential adverse sequelae. Unfortunately, only a limited number of THA infections meet the indications for one-stage reimplantation.

No controversy regarding the femoral fixation method in one-stage reimplantation exists because most authors recommend the use of cement fixation for this technique (4). In fact, there is little experience with the use of cementless one-stage reimplantation for the treatment of periprosthetic hip infections. In Jackson and Schmalzried's review of the one-stage reimplantation literature (178), 1282 of the 1299 (99%) procedures were performed with antibiotic-impregnated cement. In the remaining 17 procedures, it was unclear as to whether antibiotics were mixed in the cement. One reason for this endorsement of cement fixation is the ability to introduce an additional antibiotic load in the wound by adding antibiotics to the cement. This local depot results in higher concentrations of antibiotics within the wound compared to those in intravenous administration. In order to achieve the same local concentrations via the intravenous route, increased doses that could potentiate systemic complications would be required. Although the reported elution characteristics of antibiotics in cement have varied, it appears that the higher local concentrations attained by antibiotic-impregnated cement last for at least several days, and in some studies, several weeks (186). The antibiotic should be effective against the infecting organism and stable when exposed to heat so that its efficacy is maintained during polymerization of the cement.

C. Resection Arthroplasty

The resection arthroplasty technique involves the removal of all components and involved tissue with no subsequent reimplantation. After the resection, a parenteral antibiotic regimen similar to that used for the reimplantation techniques is begun. This is essentially a salvage operation for the patient who is not a candidate for one of the reimplantation techniques. The accepted indications for this technique include (1) the presence of a highly resistant organism, (2) poor quality of bone and soft tissues, (3) patient risk factors predisposing to recurrent infections (chronic immunosuppression, intravenous drug use, etc.), (4) inability or unwillingness of the patient to comply with the postoperative regimens of the reimplantation techniques, and (5) a medically unfit patient (4,197).

This technique has demonstrated acceptable success with respect to pain relief and eradication of infection (198–204). However, the functional results are inferior to those of the reimplantation techniques as an inevitable leg length discrepancy results in a prominent lurching gait and a corresponding increase in energy expenditure during ambulation (205). Furthermore, the functional results after resection arthroplasty for infection tend to be inferior to those of resection arthroplasty for other diagnoses. Other factors associated with a worse functional prognosis include extensive proximal femoral resection, advanced age, poor medical condition, and arthritis of the contralateral hip (203). Nevertheless, some patients are able to function satisfactorily but require ambulatory aids and shoe lifts (199).

D. Hip Arthrodesis

Although limited experience exists with the use of the hip arthrodesis technique in the setting of THA infections, hip arthrodesis has been shown to be effective, especially in young and active patients. Kostuik and Alexander (206) reported successful eradication of infection in seven THA infections treated with hip arthrodesis. Four of the infections were treated with a one-stage revision. The remaining three THA infections were noted to have gross purulence at the time of surgery and subsequently underwent a staged fusion 6 weeks later. The age of the patients ranged between 23 and 67; five patients were between the ages of 23 and 33 years. A return to preoperative function and occupation was possible in five of the seven patients.

Hip arthrodesis demonstrates superior postoperative functional results when compared to resection arthroplasty (206). In contrast to resection arthroplasty patients, arthrodesis patients can stand unaided, do not have difficulties performing household duties, do not require significant external support (canes at most), and are more able to conduct heavy occupational activities (202,206). These improved functional results must be weighed against the potential risk of recurrent infection associated with the retained hardware implanted at the time of fusion.

E. Débridement with Retention of Components

The débridement with retention of components technique involves the debridement of the involved soft tissues, exchange of the polyethylene insert, and retention of the remaining components combined with a postoperative course of parenteral antibiotics. As with the one-stage reimplantation technique, the presence of specific criteria has been shown to be necessary to optimize the results when using débridement and retention. The advantage of débridement with retention is the preservation of bone stock, which is considerably reduced by any technique involving prosthetic removal. The results of this technique have

been variable, with success rates anywhere between 0% and 80% reported (207). Generally accepted criteria for the use of this technique are (1) duration of infection less than 1 month, (2) pathogen sensitive to antibiotics, (3) absence of extensive scar tissue, (4) minimal or no risk factors for infection, and (5) well-fixed prosthesis (4,12).

Chief among the criteria mentioned is the duration of infection of less than 1 month. Using débridement with retention combined with a postoperative antibiotic regimen, Tsukayama and coworkers (12) were successful in treating 25 of 35 (71%) early postoperative infections (duration less than 1 month). In the six acute hematogenous infections, only three (50%) were successfully eradicated. According to Tsukayama and colleagues less successful results were produced in infections present for longer than 1 month. The findings of Crockarell and colleagues (207) support the importance of early treatment when using débridement with retention. In their relatively unsuccessful experience (14% overall success), débridement with retention was only successful in early postoperative and acute hematogenous infections with less than 14 days of symptoms and was unsuccessful for each of their 18 late chronic infections.

The difficulty for the treating surgeon when contemplating using this technique lies in determining the onset of infection. The onset of infection in the early postoperative period (less than 1 month from the index arthroplasty) is relatively straightforward as these infections are presumed to be the result of seeding of the periprosthetic environment at, or shortly after, the time of surgery. Likewise, it is usually not difficult to determine that the onset of infection in chronic infections is greater than 1 month as these are usually characterized by several months of gradually increasing symptoms The difficulty occurs in attempting to determine accurately the onset of infection in acute hematogenous infections. In the acute hematogenous infections, the treating surgeon is dependent on the duration of symptoms as an indicator of the duration of infection. Unfortunately, it can be difficult to determine whether the development of symptoms is from an acute infection that has just begun, or from a subacute indolent infection that has just become symptomatic despite being present for several weeks or months. Some patients may have an obvious bacteremic event immediately before the development of symptoms, which may aid in distinguishing between an acute and a subacute/chronic process. Those patients for whom this distinction cannot be made should be managed as if they have a chronic infection.

F. Chronic Suppressive Therapy

The chronic suppressive therapy method of treatment entails long-term antibiotic therapy without any adjunctive surgical intervention. The goal of chronic suppressive therapy is to control the infection by inhibiting the growth and proliferation of the offending bacteria. This form of therapy should not be

considered as a first-line modality and is only indicated for patients who are not surgical candidates, patients with serious comorbid medical conditions associated with an unacceptable surgical risk, and patients who refuse surgery. Additional necessary criteria include identification of the infecting organism, which must be sensitive to an oral antibiotic. The oral antibiotic should have the potential for minimal side effects when given long-term.

Chronic suppressive therapy has demonstrated inferior success rates to those of the other techniques. Goulet and coworkers (208) in a study of 19 THA infections at an average follow-up of 4.1 years, reported no deterioration in only nine hips (47%). Although these authors included surgical débridement in some of their cases, this had no influence on the outcome. Drancourt and associates (209) reported successful treatment in 8 of 12 (67%) THA infections at a follow-up of 12 to 57 months. In this study, the combination of rifampin and ofloxacin (a fluoroquinolone) was used, and sensitivity to both antibiotics was a requirement for inclusion in the study. The addition of rifampin to antibiotic regimens for orthopedic implant infections has been shown to be beneficial by other authors as well, as it is believed that a combination regimen is more effective in preventing failures of treatment secondary to the emergence of resistant organisms (210,211). Unfortunately, the use of ofloxacin and other fluoroquinolones in chronic suppressive therapy may be limited in the future as quinolone resistance continues to increase among staphylococcal isolates. During the 1990s, staphylococcal resistance to fluoroquinolones increased to the point where 90% of staphylococci that are resistant to oxacillin are also resistant to fluoroquinolones (212). As a result, other oral antibiotic agents have been investigated but have only shown marginal success. High doses of oral co-trimoxazole (trimethoprim-sulfamethoxazole) led to a successful outcome in only four of eight (50%) THA infections; three of the four failures occurred because of intolerance to the drug (213). Likewise, in another study by Drancourt and coworkers, only 7 of 17 (41%) THA infections were cured with a regimen of fusidic acid and rifampin, and the emergence of resistant organisms accounted for a significant proportion of the failures (214).

The question with long-term antibiotic suppressive therapy is one of duration. Although Drancourt and colleagues (209) demonstrated considerable success with a 6-month regimen of oral antibiotics, other authors recommend lifelong antibiotics if suppressive therapy is to be the primary treatment for a THA infection (215). Unfortunately, prolonged suppressive antibiotic therapy does risk the emergence of resistant organisms (209,214), which may necessitate one of the salvage procedures discussed previously.

G. Arthroscopic Débridement with Component Retention

To our knowledge, currently only one study has reported the use of arthroscopic débridement with component retention. Hyman and coworkers (215) described

their experience with eight THA infections in which each patient had arthroscopic drainage, lavage, and débridement of the infected prosthetic hip followed by a 2- to 6-week course of intravenous antibiotics and then lifelong oral antibiotics. At a mean of 70 months, there were no recurrences of infection (100% success) and no evidence of progressive radiolucent loosening. The greater success achieved with this technique compared to the use of chronic suppressive therapy alone may be due to the promptness of the débridement since each patient experienced 37 or fewer days of symptoms before treatment. As previously mentioned, prompt débridement is essential to eradicating infection as it acts to decrease the bacterial load before significant pathogen adherence to the prosthetic components and the establishment of the glycocalyx, which sequesters them from host defense mechanisms and antibiotics. However, one of the concerns about arthroscopic débridement is the ability to débride the entire joint adequately.

The minimally invasive nature of this procedure provides an attractive alternative to open débridement, which may be beneficial to patients whose medical condition precludes extensive surgery. It must be emphasized that this technique is a form of chronic suppressive therapy and should only be used when the criteria for chronic suppressive therapy apply. Despite the findings of Drancourt and associates (209), it is still widely believed that chronic suppressive therapy does just that—it only suppresses the infection, and if the antibiotics were to be discontinued, recurrence of the infection would be likely (215). In contrast, open débridement combined with a short-term antibiotic regimen is a legitimate treatment method that has a reasonable chance of eradicating the infection.

H. Hip Disarticulation

The hip disarticulation technique is a salvage procedure and is to be considered only as a measure of last resort. Fenelon and colleagues (216) successfully treated 10 of 11 patients with chronically infected hip arthroplasties using this technique. In their study, multiple failed revisions for infection was found to be a risk factor for progression to hip disarticulation. The indications for hip disarticulation include life-threatening infections, severe loss of soft tissue and bone stock, and vascular injury to the external iliac vessels (216).

IX. SUMMARY

Total hip arthroplasty provides a fertile environment for infection because of the combined effect of an extensive dissection, prolonged operative time, and implantation of a large amount of foreign body. The staphylococcal species of bacteria continue to be the most common offending pathogens in THA infections and typically originate from the skin of the patient or operating room personnel. Despite extensive perioperative and postoperative prophylactic measures, the rate

of these infections continues to average 1%–2%. The diagnosis of THA infections may be challenging in all but the most fulminant infections because the signs and symptoms of an indolent infection (the most common presentation) can be minimal. Furthermore, no one diagnostic test has demonstrated 100% reliability; therefore, a combination of investigative modalities is recommended in these often difficult to diagnose infections. Once the presence of infection has been confirmed, two-stage reimplantation is the treatment method of choice in all but a minority of cases. Depending on the timing of the infection, virulence of the offending pathogen, and condition of the patient, some cases may benefit from less extensive procedures such as débridement with retention of components or one-stage reimplantation. Several salvage treatment options also exist for the rare cases that are not amenable to the first-line treatment options.

REFERENCES

1. J Charnley. Postoperative infection after total hip total replacement with special reference to air contamination in the operating room. Clin Orthop 87:167–187, 1972.
2. RH Fitzgerald Jr. Infected total hip arthroplasty: diagnosis and treatment. J Am Acad Orthop Surg 3(5):249–262, 1995.
3. RH Fitzgerald Jr. Total hip arthroplasty sepsis: prevention and diagnosis. Orthop Clin North Am 23(2):259–264, 1992.
4. KL Garvin, AD Hanssen. Current concepts review: infection after total hip arthroplasty. J Bone Joint Surg 77A(10):1576–1588, 1995.
5. A Praemer, S Furner, DP Rice. Musculoskeletal Conditions in the United States. 2d ed. Park Ridge, IL: American Academy of Orthopaedic Surgeons, 1999:119–138.
6. TP Sculco. The economic impact of infected total joint arthroplasty. Instr Course Lect 42:349–351, 1992.
7. BD Brause. Sepsis: the rational use of antimicrobials. In: JJ Callaghan, AG Rosenberg, HE Rubash, eds. The Adult Hip. Philadelphia: Lippencott-Raven, 1998:1343–1349.
8. CL Nelson. Prevention of Infection. In: MC Evans, ed. Surgery of the Musculoskeletal System. New York: Churchill Livingston, 1990:4313–4321.
9. VV Surin, K Sundhold, L Bäckman. Infection after total hip replacement. J Bone Joint Surg 65B:412–418, 1983.
10. KL Garvin, SH Hinrichs, JA Urban. Emerging antibiotic-resistant bacteria: their treatment in total joint arthroplasty. Clin Orthop 369:110–123, 1999.
11. KL Garvin, RH Fitzgerald Jr, EA Salvati, BD Brause, OA Nercessian, SL Wallrichs, DM Ilstrup. Reconstruction of the infected total hip and knee arthroplasty with gentamicin-impregnated Palacos bone cement. Instr Course Lect 42:293–302, 1993.
12. DT Tsukayama, R Estrada, RB Gustilo. Infection after total hip arthroplasty: a study of the treatment of one hundred and six infections. J Bone Joint Surg 78A:512–523, 1996.

13. JA Urban, S Hinrichs, H Dong, BP Hasley, KL Garvin. Skin bacterial counts in patients with a history of an infected total joint arthroplasty. 68th Annual Meeting of the American Academy of Orthopaedic Surgeons. San Francisco, February 28–March 4, 2001.
14. JP McAuley, G Moreau. Sepsis: etiology, prophylaxis and diagnosis. In: JJ Calaghan, AG Rosenberg, HE Rubash, eds. The Adult Hip. Philadelphia: Lippincott-Raven, 1998:1295–1306.
15. SD Elek, PE Conen. The virulence of staphylococcus pyogenes for man: a study of the problems of wound infection. Br J Exp Pathol 38:573–586, 1957.
16. AG Gristina, E Barth, LX Webb. Microbial adhesion and the pathogenesis of biomaterial centered infections. In: R Gustillo, ed. Orthopaedic Infection, Diagnosis and Treatment. Philadelphia: WB Saunders, 1989:26–36.
17. AG Gristina, CD Hobgood, E Barth. Biomaterial specificity, molecular mechanisms and clinical relevance of S. epidermidis and S. aureus infections in surgery. In: G Pulverer, PG Quie, G Peters, eds. Pathogenicity and Clinical Significance of Coagulase-Negative Staphylococci. Stuttgart: Gustav Fischer-Verlag, 1987:143–157.
18. AG Gristina, JW Costerton. Bacterial adherence and the glycocalyx and their role in musculoskeletal infection. Orthop Clin North Am 15:517–535, 1984.
19. AG Gristina, M Oga, LX Webb, CD Hobgood. Adherent bacterial colonization in the pathogenesis of osteomyelitis. Science 228:990–993, 1985.
20. AG Gristina, CD Hobgood, E Barth. Biomaterial specificity, molecular mechanisms and clinical relevance of S. epidermidis and S. aureus infections in surgery. In: G Pulverer, PG Quie, G Peters, eds. Pathogenicity and Clinical Significance of Coagulase-Negative Staphylococci. Stuggart: Gustav Fischer-Verlag, 1987:143–157.
21. HW Paerls. Influence of attachment on microbial metabolism and growth in aquatic ecosystems. In: DC Savage, M Fletcher, eds. Bacterial Adhesion. New York: Plenum Press, 1985:363–400.
22. MRW Brown, P Williams. The influence of environment on envelope properties affecting survival of bacteria in infections. Ann Rev Microbiol 39:527–556, 1985.
23. NS Eftekhar. The infected total hip. Instr Course Lect 26:66–74, 1977.
24. JM Cuckler, AM Star, A Alavi, RB Noto. Diagnosis and management of the infected total joint arthroplasty. Orthop Clin North Am 22(3):523–530, 1991.
25. AG Gristina, J Kolkin. Current concepts review: total joint replacement and sepsis. J Bone Joint Surg 65A:128–134, 1983.
26. DL Hamblen. Diagnosis of infection and the role of permanent excision arthroplasty. Orthop Clin North Am 24(4):743–749, 1993.
27. Hanssen AD, Osmon DR, Nelson CL. Prevention of deep periprosthetic joint infection. J Bone Joint Surg 78A(3):458–471, 1996.
28. MJ Spangehl, ASE Younger, BA Masri, CP Duncan. Diagnosis of infection following total hip arthroplasty. Instr Course Lect 47:285–295, 1998.
29. M Graif, E Schwartz, S Strauss, M Mouallem, M Schecter, B Morag. Occult infection of hip prosthesis: sonographic evaluation. J Am Geriatr Soc 39(2):203–204, 1991.

30. MT van Holsbeeck, WR Eyler, LS Sherman, TJ Lombardi, E Mezger, JJ Verner, JR Schurman, K Jonsson. Detection of infection in loosened hip prostheses: efficacy of sonography. Am J Roentgenol 163(2):381–384, 1994.
31. SG Oswald, D van Nostrand, CG Savory, JJ Callaghan. Three-phase bone and indium white blood cell scintigraphy following porous-coated hip arthroplasty. J Nucl Med 30:274–280, 1990.
32. WA Wegener, A Alavi. Diagnostic imaging of musculoskeletal infection: Roentgenography; gallium, indium-labeled white blood cell, gammaglobulin, bone scintigraphy, and MRI. Orthop Clin North Am 22:401–418, 1991.
33. PR Glithero, P Grigoris, LK Harding, SR Hesslewood, DJ McMinn. White cell scans and infected joint replacements: failure to detect chronic infection. J Bone Joint Surg 75B:371–374, 1993.
34. KD Merkel, ML Brown, MK Dewanjee, RH Fitzgerald Jr. Comparison of indium-labeled-leukocyte imaging with sequential technetium-gallium scanning in the diagnosis of low-grade musculoskeletal sepsis: a prospective study. J Bone Joint Surg 67A:465–476, 1985.
35. AWJ Kraemer, R Saplys, JP Waddell, J Morton. Bone scan, gallium scan, and hip aspiration in the diagnosis of infected total hip arthroplasty. J Arthroplasty 8(6):611–613, 1993.
36. JA Johnson, MJ Christie, MP Sandler, PF Parks Jr, L Homra, JJ Kaye. Detection of occult infection following total joint arthroplasty using sequential technetium-99m HDP bone scintigraphy and indium-111-WBC imaging. J Nucl Med 29:1347–1353, 1988.
37. CJ Palestro, CK Kim, AJ Swyer, JD Capozzi, RW Solomon, SJ Goldsmith. Total hip arthroplasty: periprosthetic indium-111-labelled leukocyte activity and complementary technetium 99-m-sulfur colloid imaging in suspected imaging. J Nucl Med 31:1950–1955, 1990.
38. DM Scher, K Pak, JH Lonner, JE Finkel, JD Zuckerman, PE Di Cesare. The predictive value of indium-111 leukocyte scans in the diagnosis of infected total hip, knee, or resection arthroplasties. J Arthroplasty 15:295–300, 2000.
39. RE Teller, MJ Christie, W Martin, EP Nance, DW Haas. Sequential indium-labeled leukocyte and bone scans to diagnose prosthetic joint infections. Clin Orthop 373:241–247, 2000.
40. WJ Oyen, RA Claessens, JW van der Meer, FH Corstens. Detection of subacute infectious foci with indium-111-labeled autologous leukocytes and indium-111-labeled human nonspecific immunoglobulin G: a prospective comparative study. J Nucl Med 32:1854–1860, 1991.
41. MW Nijhof, WG Oyen, A van Kampen, RA Claessens, JW van der Meer, FH Corstens. Evaluation of infections of the locomotor system with indium-111-labelled human IgG scintigraphy. J Nucl Med 38(8):1300–1305, 1997.
42. GC Canner, ME Steinberg, RB Heppenstall, R Balderston. The infected hip after total hip arthroplasty. J Bone Joint Surg 66A:1393–1399, 1984.
43. NS Eftekhar. Diagnosis of infection in joint replacement surgery. In: NS Eftekhar, ed. Infection in Joint Replacement Surgery: Prevention and Management. St. Louis: CV Mosby, 1984:115–130.

44. MJ Spangehl, CP Duncan, JX O'Connell, BA Masri. Prospective analysis of preoperative and intraoperative studies for the diagnosis of infection in 210 consecutive revision total hip arthroplasties. The Annual Meeting of The American Academy of Orthopaedic Surgeons. San Francisco, Feb 15, 1997.
45. MJ Spangehl, BA Masri, JX O'Connell, CP Duncan. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. J Bone Joint Surg 81A:672–683, 1999.
46. IW Forster, R Crawford. Sedimentation rate in infected and uninfected total hip arthroplasty. Clin Orthop 168:48–52, 1982.
47. B Thoren, A Wigren. Erythrocyte sedimentation rate in infection of total hip replacements. Orthopedics 14:495–497, 1991.
48. L Sanzén, AS Carlsson. The diagnostic value of c-reactive protein in infected total hip arthroplasties. J Bone Joint Surg 71B:638–641, 1989.
49. K Aalto, K Österman, H Peltola, J Räsänen. Changes in erythrocyte sedimentation rate and c-reactive protein after total hip arthroplasty. Clin Orthop 184:118–122, 1984.
50. RR Choudhry, RP Rice, PD Triffitt, WM Harper, PJ Gregg. Plasma viscosity and c-reactive protein after total hip and knee arthroplasty. J Bone Joint Surg 74B:523–524, 1992.
51. K Laiho, H Maenpaa, H Kautiainen, M Kauppi, K Kaarela, M Lehto, E Belt. Rise in serum C reactive protein after hip and knee arthroplasties in patients with rheumatoid arthritis. Ann Rheum Dis 60(3):275–277, 2001.
52. RH Fitzgerald Jr, DR Nolan, DM Ilstrup, RE Van Scoy, JA Washington II, MB Coventry. Deep wound sepsis allowing total hip arthroplasty. J Bone Joint Surg 59A:847–855, 1977.
53. DA O'Neill, WH Harris. Failed total hip replacement: assessment by plain radiographs, arthrograms, and aspiration of the hip joint. J Bone Joint Surg 66A:540–546, 1984.
54. P Roberts, AJ Walters, DJ McMinn. Diagnosing infection in hip replacements: the use of fine-needle aspiration and radiometric culture. J Bone Joint Surg 74B(2):265–269, 1992.
55. TK Fehring, B Cohen. Aspiration as a guide to sepsis in revision total hip arthroplasty. J Arthroplasty 11(5):543–547, 1996.
56. PF Lachiewicz, GD Rogers, HC Thomason. Aspiration of the hip joint before revision total hip arthroplasty: clinical and laboratory factors influencing attainment of a positive culture. J Bone Joint Surg 78A:749–754, 1996.
57. CJ Della Valle, DM Scher, YH Kim, CM Oxley, P Desai, JD Zuckerman, PE Di Cesare. The role of intraoperative gram stain in revision total joint arthroplasty. J Arthroplasty 14(4):500–504, 1999.
58. JM Mirra, HC Amstutz, M Matos, R Gold. The pathology of the joint tissues and its clinical relevance in prosthesis failure. Clin Orthop 117:221–240, 1976.
59. JH Lonner, P Desai, PE DiCesare, G Steiner, JD Zuckerman. The reliability of analysis of intraoperative frozen sections for identifying active infection during revision hip or knee arthroplasty. J Bone Joint Surg 78A:1553–1558, 1996.

60. DP Hoeffel, SH Hinrichs, KL Garvin. Molecular diagnosis of infection. Semin Arthroplasty 9(4):281–291, 1998.
61. BD Mariana, DS Martin, MJ Levine, RE Booth Jr, RS Tuan. Polymerase chain reaction detection of bacterial infection in total knee arthroplasty. Clin Orthop 331:11–22, 1996.
62. MB Coventry. Treatment of infections occurring in total hip surgery. Orthop Clin North Am 6(4):991–1003, 1975.
63. OM Lidwell, EJ Lowbury, W Whyte, R Blowers, SJ Stanley, D Lowe. Effect of ultraclean air in operating rooms on deep sepsis in the joint after total hip or knee replacement: a randomised study. Br Med J 285:10–14, 1982.
64. JH Marotte, GA Lord, JP Blanchard, JL Guillamon, P Samuel, JP Servant, PH Mercier. Infection rate in total hip arthroplasty as a function of air cleanliness and antibiotic prophylaxis: 10-year experience with 2384 cementless Lord Madreporic prostheses. J Arthroplasty 2(1):77–82, 1987.
65. C Hill, R Flamant, F Mazas, J Evrard. Prophylactic cefazolin versus placebo in total hip replacement: report of a multicentre double-blind randomized trial. Lancet 1:795–796, 1981.
66. DC Classen, RS Evans, SL Pestotnik, SD Horn, RL Menlove, JP Burke. The timing of prophylactic administration of antibiotics and the risk of surgical-wound infection. N Engl J Med 326:281–286, 1992.
67. S Nasser. Prevention and treatment of sepsis in total hip replacement surgery. Orthop Clin North Am 23(2):265–277, 1992.
68. CE Wiggins, CL Nelson, R Clarke, CH Thompson. Concentration of antibiotics in normal bone after intravenous injection. J Bone Joint Surg 60A:93–96, 1978.
69. E Salvati. Infected total hip replacement. In: MC Evarts, ed. Surgery of the Musculoskeletal System. New York: Churchill Livingston, 1990:4475–4493.
70. James PJ, Butcher IA, Gardner ER, Hamblin DL. Methicillin resistant Staphylococcus epidermidis in infection of total hip arthroplasties. J Bone Joint Surg 76B(5):725–727, 1994.
71. M Tanzer, J Miller, GK Richards. Preoperative assessment of skin colonization and antibiotic effectiveness in total knee arthroplasty. Clin Orthop 299:163–168, 1994.
72. WJ Brown. Microbiology of the infected total joint arthroplasty. Semin Arthroplasty 5:107–113, 1994.
73. J Charnley, N Eftekhar. Postoperative infection in total prosthetic replacement arthroplasty of the hip joint: with special reference to the bacterial content of the air of the operating room. Br J Surg 56:641–649, 1969.
74. AJ Davies, RM Lockley, A Jones, M el-Safty, JC Clothier. Comparative pharmacokinetics of cefamandole, cefuroxime, and cephradine during total hip replacement. J Antimicrob Chemother 17:637–640, 1986.
75. F Doyon, J Evrard, F Mazas. An assessment of published trials on antibiotic prophylaxis in orthopaedie surgery. French J Orthop Surg 3:49–53, 1989.
76. DR Mauerhan, CL Nelson, DL Smith, RH Fitzgerald Jr, TG Slama, RW Petty, RE Jones, RP Evans. Prophylaxis against infection in total joint arthroplasty: one day of efuroxime compared with three days of cefazolin. J Bone Joint Surg 76A(1):39–45, 1994.

77. CL Nelson, TG Green, RA Porter, RD Warren. One day versus seven days of preventive antibiotic therapy in orthopaedic surgery. Clin Orthop 176:258–263, 1983.
78. HH Stone, RB Haney, LD Kolb, CE Geheber, CA Hooper. Prophylactic and preventive antibiotic therapy: timing, duration, and economics. Ann Surg 189:691–699, 1979.
79. AB Wymenga, JR van Horn, A Theeuwes, HL Muytjens, TJ Slooff. Perioperative factors associated with septic arthritis after arthroplasty: prospective multicenter study of 362 knee and 2651 hip operations. Acta Orthop Scand 63(6):665–671, 1992.
80. PA Gross, TL Barrett, EP Dellinger, PJ Krause, WJ Martone, JE McGowan Jr, RL Sweet, RP Wenzel: purpose of quality standards for infectious diseases. Infectious Diseases Society of America. Clin Infect Dis 18(3):421, 1994.
81. AF Heath. Antimicrobial prophylaxis for arthroplasty and total joint replacement: discussion and review of published clinical trials. Pharmacotherapy 11:157–163, 1991.
82. CW Norden. Antibiotic prophylaxis in orthopedic surgery. Rev Infect Dis 13(suppl 10):S842–846, 1991.
83. B Espehaug, LB Engesaeter, SE Vollset, LI Havelin, N Langeland. Antibiotic prophylaxis in total hip arthroplasty: Review of 10,905 primary cemented total hip replacements reported to the Norwegian arthroplasty register, 1987 to 1995. J Bone Joint Surg 79B:590–595, 1997.
84. M Lynch, MP Esser, P Shelley, BM Wroblewski. Deep infection in Charnley low-friction arthroplasty: comparison of plain and gentamicin-loaded cement. J Bone Joint Surg 69B:355–360, 1987.
85. WR Murray. Use of antibiotic-containing bone cement. Clin Orthop 190:89–95, 1984.
86. M McQueen, A Littlejohn, SP Hughes. A comparison of systemic cefuroxime and cefuroxime loaded bone cement in the prevention of early infection after total joint replacement. Int Orthop 11:241–243, 1987.
87. G Josefsson, L Lindberg, B Wiklander. Systemic antibiotics and gentamicin-containing bone cement in the prophylaxis of postoperative infections in total hip arthroplasty. Clin Orthop 159:194–200, 1981.
88. G Josefsson, G Gudmundsson, L Kolmert, S Wilkstrom. Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty: a five-year survey of 1688 hips. Clin Orthop 253:173–178, 1990.
89. G Josefsson, L Kolmert. Prophylaxis with systemic antibiotics versus gentamicin bone cement in total hip arthroplasty: ten-year survey of 1688 hips. Clin Orthop 292:210–214, 1993.
90. D Heck, A Rosenberg, M Schink-Ascani, S Garbus, T Kiewitt. Use of antibiotic-impregnated cement during hip and knee arthroplasty in the United States. J Arthroplasty 10(4):470–475, 1995.
91. AD Hanssen, DR Osmon. The use of prophylactic antimicrobial agents during and after hip arthroplasty. Clin Orthop 369:124–138, 1999.

92. JP Nelson. Operating room clean rooms and personnel isolator systems. Instr Course Lect 27:52–57, 1977.
93. WE Anspach Jr. Barrier materials and special air-handling systems for bacteriologic control in the operating room. Instr Course Lect 27:47–51, 1977.
94. RR Davies, WC Noble. Dispersal of bacteria on desquamated skin. Lancet 2:1295–1297, 1962.
95. CW Walter, RB Kundsin. The airborne component of wound contamination and infection. Arch Surg 107:588–595, 1973.
96. RH Fitzgerald Jr. Contamination of the surgical wound in the operating room. Instr Course Lect 27:41–46, 1977.
97. JP Nelson. Prevention of postoperative infection by airborne bacteria. In: RB Gustillo, ed. Orthopaedic infection: diagnosis and treatment. Philadelphia: WB Saunders, 1989:75–80.
98. EA Salvati, RP Robinson, SM Zeno, BL Koslin, BD Brause, PD Wilson Jr. Infection rates after 3175 total hip and total knee replacements performed with and without a horizontal unidirectional filtered airflow system. J Bone Joint Surg 64A:525–535, 1982.
99. SP Hughes. The role of antibiotics in preventing infections following total hip replacement. J Hosp Infect 11(suppl C):41–47, 1988.
100. L Klenerman, D Seal, K Sullens. Combined prophylactic effect of ultraclean air and cefuroxime for reducing infection in prosthetic surgery. Acta Orthop Belg 57(1):19–24, 1991.
101. D Hart. Operating room infections: control of air-borne pathogenic organisms, with particular reference to the use of special bactericidal radiant energy: preliminary report. Arch Surg 34:874, 1937.
102. JD Lowell, RB Kundsin. Ultraviolet radiation: its beneficial effect on the operating room environment and the incidence of deep wound infection after total hip and total knee arthroplasty. Instr Course Lect 27:58–65, 1977.
103. RH Overholt, RH Betts. A comparative report on infection of thoracoplasty wounds: experiences with ultraviolet irradiation of operating room air. J Thorac Cardiovasc Surg 9:520, 1940.
104. RL Wright, JF Burke. Effect of ultraviolet radiation on post-operative neurosurgical sepsis. J Neurosurg 31:533–537, 1969.
105. AR Brown, GJ Taylor, PJ Gregg. Air contamination during skin preparation and draping in joint replacement surgery. J Bone Joint Surg 78B:92–94, 1996.
106. MA Ritter, H Eitzen, MLV French, JB Hart. The operating room environment as affected by people and the surgical face mask. Clin Orthop 111:147–150, 1975.
107. RM Letts, E Doermer. Conversation in the operating theater as a cause of airborne bacterial contamination. J Bone Joint Surg 65A:357–362, 1983.
108. JC Marshall, JL Meakins. Immune responses and musculoskeletal disease. In: MC Evarts, ed. Surgery of the Musculoskeletal System. New York: Churchill Livingston, 1990:4381–4397.
109. AP Weiss, KA Krackow. Persistent wound drainage after primary total knee arthroplasty. J Arthroplasty 8:285–289, 1993.

110. BR Bistrian, GL Blackburn, E Hallowell, R Heddle. Protein status of general surgical patients. JAMA 230:858–860, 1974.
111. KA Greene, AH Wilde, BN Stulberg. Preoperative nutritional status of total joint patients. J Arthroplasty 6(4):321–325, 1991.
112. S Gherini, BK Vaughn, AV Lombardi, TH Mallory. Delayed wound healing and nutritional deficiencies after total hip arthroplasty. Clin Orthop 293:188–195, 1993.
113. CL Puskarich, CL Nelson, FR Nusbickel, HF Stroope. The use of two nutritional indicators in identifying long bone fracture patients who do and do not develop infections. J Orthop Res 8(6):799–803, 1990.
114. RK Chandra. Nutrition and the immune system: an introduction. Am J Clin Nutr 66:460S–463S, 1997.
115. R Fasol, M Schindler, B Schumacher, K Schlaudraff, W Hannes, R Seitelberger, V Schlosser. The influence of obesity on perioperative morbidity: retrospective study of 502 aortocoronary bypass operations. Thorac Cardiovasc Surg 40:126–129, 1992.
116. MJ Moulton, LL Creswell, ME Mackey, JL Cox, MR Rosenbloom. Obesity is not a risk factor for significant adverse outcomes after cardiac surgery. Circulation 94:87–92, 1996.
117. MG Wilson, K Kelley, TS Thornhill. Infection as a complication of total knee arthroplasty. J Bone Joint Surg 72A:878–883, 1990.
118. R Winiarski, P Barth, P Lotke. Total knee arthroplasty in morbidly obese patients. J Bone Joint Surg 80A:1770–1774, 1998.
119. RY Wong, PA Lotke, ML Ecker. Factors influencing wound healing after total knee arthroplasty. Orthopaedic Transactions 10:497, 1986.
120. JJ Jiganti, WM Goldstein, CS Williams. A comparison of the perioperative morbidity in total joint arthroplasty in the obese and nonobese patient. Clin Orthop 289:175, 1993.
121. K Soballe, F Christensen, T Luxhoj. Hip replacement in obese patients. Acta Orthop Scand 58:223, 1987.
122. SH Stern, JN Insall. Total knee arthroplasty in obese patients. J Bone Joint Surg 72A:1400–1404, 1990.
123. MM Gottschlich, T Mayes, JC Khoury, GD Warden. Significance of obesity on nutritional, immunologic, hormonal, and clinical outcome parameters in burns. J Am Diet Assoc 93:1261–1268, 1993.
124. DD Stallone. The influence of obesity and its treatment on the immune system. Nutr Rev 52:37–50, 1994.
125. S Moriguchi, M Kato, K Sakai, S Yamamoto, E Shimizu. Exercise training restores decreased cellular immune functions in obese Zucker rats. J Appl Physiol 84:311–317, 1998.
126. DC Nieman, DA Henson, SL Nehlsen-Cannarella, M Ekkens, AC Utter, DE Butterworth, OR Fagoaga. Influence of obesity on immune function. J Am Diet Assoc 99:294–299, 1999.
127. GP Arden, AR Taylor, BM Ansell. Total hip replacement using the McKee-Farrar prosthesis in rheumatoid arthritis: Still's disease and ankylosing spondylitis. Ann Rheum Dis 29(1):1–5, 1970.

128. PA Freeman, P Lee, TW Bryson. Total hip joint replacement in osteoarthritis and polyarthritis: a statistical study of the results. Clin Orthop 95:224, 1973.
129. R Poss, TS Thornhill, FC Ewald, WH Thomas, NJ Batte, CB Sledge. Factors influencing the incidence and outcome of infection following total joint arthroplasty. Clin Orthop 182:117–126, 1984.
130. SL Bridges Jr, A Lopez-Mendez, KH Han, IC Tracy, GS Alarcon. Should methotrexate be discontinued before elective orthopedic surgery in patients with rheumatoid arthritis? J Rheumatol 18(7):984–988, 1991.
131. SL Bridges Jr, LW Moreland. Perioperative use of methotrexate in patients with rheumatoid arthritis undergoing orthopedic surgery. Rheum Dis Clin North Am 23(4):981–993, 1997.
132. MT Carpenter, SG West, SA Vogelgesang, DE Casey-Jones. Postoperative joint infections in rheumatoid arthritis patients on methotrexate therapy. Orthopedics 19(3):207–210, 1996.
133. A Escalante, TD Beardmore. Risk factors for early wound complications after orthopedic surgery for rheumatoid arthritis. J Rheumatol 22(10):1844–1851, 1995.
134. RS Perhala, WS Wilke, JD Clough, AM Segal. Local infectious complications following large joint replacement in rheumatoid arthritis patients treated with methotrexate versus those not treated with methotrexate. Arthritis Rheum 34(2):146–152, 1991.
135. J Sany, JM Anaya, F Canovas, B Combe, C Jorgensen, S Saker, MN Thaury, JP Gavroy. Influence of methotrexate on the frequency of postoperative infectious complications in patients with rheumatoid arthritis. J Rheumatol 20(7):1129–1132, 1993.
136. SP England, SH Stern, JN Insall, RE Windsor. Total knee arthroplasty in diabetes mellitus. Clin Orthop 260:130–134, 1990.
137. TJ Menon, D Thjellesen, BM Wroblewski. Charnley low-friction arthroplasty in diabetic patients. J Bone Joint Surg 65B:580–581, 1983.
138. B Moeckel, MH Huo, EA Salvati, PM Pellicci. Total hip arthroplasty in patients with diabetes mellitus. J Arthroplasty 8(3):279–284, 1993.
139. PJ Papagelopoulos, OB Idusuyi, SI Wallrichs, BF Morrey. Long term outcome and survivorship analysis of primary total knee arthroplasty in patients with diabetes mellitus. Clin Orthop 330:124–132, 1996.
140. K Yang, SJ Yeo, BP Lee, NN Lo. Total knee arthroplasty in diabetic patients: a study of 109 consecutive cases. J Arthroplasty 16(1):102–106, 2001.
141. JM Olefsky. Diabetes Mellitus. In: JB Wyngaarden, LH Smith Jr, JC Bennett, eds. Cecil's Textbook of Medicine. 19th ed. Philadelphia: WB Saunders, 1991:1291.
142. JJ Pomposelli, JK Baxter III, TJ Babineau, EA Pomfret, DF Driscoll, RA Forse, BR Bistrian. Early postoperative glucose control predicts nosocomial infection rate in diabetic patients. J Parenter Enteral Nutr 22(2):77–81, 1998.
143. FY Chiu, CF Lin, CM Chen, WH Lo, TY Chang. Cefuroxime-impregnated cement at primary total knee arthroplasty in diabetes mellitus: a prospective, randomized study. J Bone Joint Surg 83B:691–695, 2001.
144. BE Bierbaum, JJ Callaghan, JO Galante, HE Rubash, RE Tooms, RB Welch. An analysis of blood management in patients having a total hip or knee arthroplasty. J Bone Joint Surg 81A:2–10, 1999.

145. N Blumberg, JM Heal. Immunomodulation by blood transfusion: an evolving scientific and clinical challenge. Am J Med 101:299–308, 1996.
146. P Innerhofer, C Walleczek, G Luz, P Hobisch-Hagen, A Benzer, B Stockl, G. Hessenberger, W Nussbaumer, W Schobersberger. Transfusion of buffy coat-depleted blood components and risk of postoperative infection in orthopedic patients. Transfusion 39(6):625–632, 1999.
147. SJ Kendall, J Weir, R Aspinall, D Henderson, J Rosson. Erythrocyte transfusion causes immunosuppression after total hip replacement. Clin Orthop 381:145–155, 2000.
148. SF Mishriki, DJW Law, PJ Jeffrey. Factors affecting the incidence of postoperative wound infection. J Hosp Infect 16:223–230, 1990.
149. R Seropian, BM Reynolds. Wound infection after preoperative depilatory versus razor preparation. Am J Surg 121:251–254, 1971.
150. DH Johnston, JA Fairclough, EM Brown, R Morris. Rate of bacterial recolonization of the skin after preparation: four methods compared. Br J Surg 74:64, 1987.
151. R Sanders, P Fortin, E Ross, D Helfet. Outer gloves in orthopaedic procedures: cloth compared with latex. J Bone Joint Surg 72A:914–917, 1990.
152. J Wilkins, MJ Patzakis. Peripheral Teflon catheters: potential source for bacterial contamination of orthopedic implants? Clin Orthop 254:251–254, 1990.
153. CG Greenough. An investigation into contamination of operative suction. J Bone Joint Surg 68B:151–153, 1986.
154. RA Meals, L Knoke. The surgical suction tip: a contaminated instrument. J Bone Joint Surg 60A:409–410, 1978.
155. HH Strange-Vognsen, B Klareskov. Bacteriologic contamination of suction tips during hip arthroplasty. Acta Orthop Scand 59:410–411, 1998.
156. RA Baird, FR Nickel, LD Thrupp, S Rucker, B Hawkins. Splash basin contamination in orthopaedic surgery. Clin Orthop 187:129–133, 1984.
157. CL Nelson, JA Bergfield, J Schwartz, M Kolczun. Antibiotics in human hematoma and wound fluid. Clin Orthop 108:138–144, 1975.
158. RW Acus III, JM Clark, IA Gradisar Jr, MW Kovacik. The use of post-operative suction drainage in total hip arthroplasty. Orthopedics 15(11):1325–1328, 1992.
159. CJ Drinkwater, MJ Neil. Optimal timing of wound drain removal following total joint arthroplasty. J Arthroplasty 10(2):185–189, 1995.
160. S Overgaard, NO Thomsen, B Kulinski, NB Mossing. Closed suction drainage after hip arthroplasty: prospective study of bacteria cases. Acta Orthop Scand 64(4):417–420, 1993.
161. D Willemen, J Paul, SH White, DW Crook. Closed suction drainage following knee arthroplasty: effectiveness and risk. Clin Orthop 264:232–234, 1991.
162. DT Durack. Prevention of infective endocarditis. N Engl J Med 332:38–44, 1995.
163. AAOS and ADA Expert Panel. Advisory statement: antibiotic, prophylaxis for dental patients with total joint replacements. AAOS Bull 45:911, 1997.
164. DR Osmon, JM Steckelberg, AD Hanssen. Incidence of prosthetic joint infection due to viridans streptococci. The annual meeting of the Musculoskeletal Infection Society. Snowmass CO, August 20, 1993.

165. JR Lieberman, GH Callaway, EA Salvati, PM Pellicci, BD Brause. Treatment of the infected total hip arthroplasty with a two-stage reimplantation protocol. Clin Orthop 301:205–212, 1994.
166. DJ McDonald, RH Fitzgerald Jr, DM Ilstrup. Two-stage reconstruction of a total hip arthroplasty because of infection. J Bone Joint Surg 71A:828–834, 1989.
167. CL Nelson, MC Evarts, J Andrish, K Marks. Results of infected total hip replacement arthroplasty. Clin Orthop 147:258–261, 1980.
168. JP Nelson. Deep infection following total hip arthroplasty. J Bone Joint Surg 59A:1042–1044, 1977.
169. MA Mont, BJ Waldman, DS Hungerford. Evaluation of preoperative cultures before second-stage reimplantation of a total knee prosthesis complicated by infection. J Bone Joint Surg 82A:1552–1557, 2000.
170. BA Masri, EA Salvati. Sepsis: two-stage exchange. In: JJ Callaghan, AG Rosenberg, HE Rubash, eds. The Adult Hip. Philadelphia: Lippincott-Raven, 1998:1317–1330.
171. JJ Callaghan, RP Katz, RC Johnston. One-stage revision surgery of the infected hip: a minimum 10-year follow-up study. Clin Orthop 369:139–143, 1999.
172. DJ Berry, HP Chandler, DT Reilly. The use of bone allografts in two-stage reconstruction after failure of hip replacements due to infection. J Bone Joint Surg 73A:1460–1468, 1991.
173. E Morscher, R Babst, H Jenny. Treatment of infected joint arthroplasty. In: Orthop 14:161–165, 1990.
174. BJ Nestor, AD Hanssen, R Ferrer-Gonzales, RH Fitzgerald Jr. The use of porous prostheses in delayed reconstruction of total hip replacements that have failed because of infection. J Bone Joint Surg Am 76A:349–359, 1994.
175. TK Ferring, TF Calton, WL Griffin. Cementless fixation in 2-stage reimplantation for periprosthetic sepsis. J Arthroplasty 14:175–181, 1999.
176. FS Haddad, SK Muirhead-Allwood, ARJ Manktelow, I Bacarese-Hamilton. Two-stage uncemented revision hip arthroplasty for infection. J Bone Joint Surg 82B:689–694, 2000.
177. GA Hunter. The results of reinsertion of a total hip prosthesis after sepsis. J Bone Joint Surg 61B:422–423, 1979.
178. WO Jackson, TP Schmalzried. Limited role of direct exchange arthroplasty in the treatment of infected total hip replacements. Clin Orthop 381:101–105, 2000.
179. HW Buchholz, RA Elson, E Engelbrecht, H Lodenkamper, J Rottger, A Siegel. Management of deep infection of total hip replacement. J Bone Joint Surg 63B:342–353, 1981.
180. AS Carlsson, G Josefsson, L Lindberg. Revision with gentamicin-impregnated cement for deep infection in total hip arthroplasties. J Bone Joint Surg 60A:1059–1064, 1978.
181. WR Murray. Treatment of established deep wound infection after hip arthroplasty: a report of 65 cases. In: RE Leach, FT Hoaglund, EJ Riseborough, eds. Controversies in Orthopaedic Surgery. Philadelphia: WB Saunders, 1982:382–398.
182. BM Wroblewski. One-stage revision of infected cemented total hip arthroplasty. Clin Orthop 211:103–107, 1986.

183. PG Hope, KG Kristinsson, P Norman, RA Elson. Deep infection of cemented total hip arthroplasties caused by coagulase-negative staphylococci. J Bone Joint Surg 71B:851–855, 1989.
184. R Elson. Sepsis: one-stage exchange. In: JJ Callaghan, AG Rosenberg, HE Rubash, eds. The Adult Hip. Philadelphia: Lippencott-Raven, 1998:1307–1316.
185. KL Garvin, BG Evans, EA Salvati, BD Brause. Palacos gentamicin for the treatment of deep periprosthetic hip infections. Clin Orthop 298:97–105, 1994.
186. CP Duncan, BA Masri. The role of antibiotic-loaded cement in the treatment of an infection after a hip replacement. Instr Course Lect 44:305–313, 1995.
187. L Sanzen, AS Carlsson, G Josefsson, LT Lindberg. Revision operations on infected total hip arthroplasties: two-to-nine-year follow-up study. Clin Orthop 229:165–172, 1988.
188. VV Raut, PD Sidney, BM Wroblewski. One-stage revision of infected total hip replacements with discharging sinuses. J Bone Joint Surg 76B:721–724, 1994.
189. GB Miley, AD Scheller Jr, RH Turner. Medical and surgical treatment of the septic hip with one-stage revision arthroplasty. Clin Orthop 170:76–82, 1982.
190. KJ Ure, HC Amstutz, S Nasser, TP Schmalzried. Direct-exchange arthroplasty for treatment of infection after total hip replacement: an average ten-year follow-up. J Bone Joint Surg 80A:961–968, 1998.
191. PW Hughes, EA Salvati, PD Wilson Jr, EL Blumenfeld. Treatment of subacute sepsis of the hip by antibiotics and joint replacement criteria for diagnosis with evaluation of twenty-six cases. Clin Orthop 141:143–157, 1979.
192. RD Talbott, AR Glassburn, JP Nelson, JP McElhinney, RL Greenberg. Implantation of total hip arthroplasty after known deep infection. Orthop Trans 4:97, 1980.
193. DJ Cherney, HC Amstutz. Total hip replacement in the previously septic hip. J Bone Joint Surg 65A:1256–1265, 1983.
194. JB Jupiter, AW Karchmer, JD Lowell, WH Harris. Total hip arthroplasty in the treatment of adult hips with current or quiescent sepsis. J Bone Joint Surg 63A:194–200, 1981.
195. EA Salvati, KM Chekofsky, BD Brause, PD Wilson Jr. Reimplantation in infection: a 12-year experience. Clin Orthop 170:62–75, 1982.
196. JJ Callaghan, EA Salvati, BD Brause, CM Rimnac, TM Wright. Reimplantation for salvage of the infected hip: rationale for the use of gentamicin-impregnated cement. Frank Stinchfield Award. In: RH Fitzgerald Jr, ed. Thirteenth Open Scientific Meeting of the Hip Society, St Louis, CV Mosby 65-94, 1985.
197. EL Masterson, BA Masri, CP Duncan. Treatment of infection at the site of total hip replacement. Instr Course Lect 47:297–306, 1998.
198. SA Ahlgren, G Gudmundsson, E Bartholdsson. Function after removal of a septic total hip prosthesis: a survey of 27 girdlestone hips. Acta Orthop Scand 51:541–545, 1980.
199. WT Ballard, DA Lowry, RA Brand. Resection arthroplasty of the hip. J Arthroplasty 10:772–779, 1995.
200. ES Bittar, W Petty. Girdlestone arthroplasty for infected total hip arthroplasty. Clin Orthop 170:83–87, 1982.

201. RB Bourne, GA Hunter, CH Rorabeck, JJ Macnab. A six-year follow-up of infected total hip replacements managed by girdlestone arthroplasty. J Bone Joint Surg 66B:340–343, 1984.
202. J Clegg. The results of the pseudocapsule after removal of an infected total hip prosthesis. J Bone Joint Surg 59B:298–301, 1977.
203. JD Grauer, HC Amstutz, PF O'Carroll, FJ Dorey. Resection arthroplasty of the hip. J Bone Joint Surg 71A:669–678, 1989.
204. JP McElwaine, J Colville. Excision arthroplasty for infected total hip replacements. J Bone Joint Surg 66B:168–171, 1984.
205. RL Waters, J Perry, P Conaty, B Lunsford, P O'Meara. The energy cost of walking with arthritis of the hip and knee. Clin Orthop 214:278–284, 1987.
206. J Kostuik, D Alexander. Arthrodesis for failed arthroplasty of the hip. Clin Orthop 188:173–182, 1984.
207. JR Crockarell, AD Hanssen, DR Osmon, BF Morrey. Treatment of infection with debridement and retention of the components following hip arthroplasty. J Bone Joint Surg 80A:1306–1313, 1998.
208. JA Goulet, PM Pellicci, BD Brause, EM Salvati. Prolonged suppression of infection in total hip arthroplasty. J Arthroplasty 3(2):109–116, 1988.
209. M Drancourt, A Stein, JN Argenson, A Zannier, G Curvale, D Raoult. Oral rifampin plus ofloxacin for treatment of staphylococcus-infected orthopaedic implants. Antimicrob Agents Chemother 37:1214–1218, 1993.
210. CW Norden, J Fierer, RE Bryant, and the Chronic Staphylococcal Osteomyelitis Study Group. Chronic staphylococcal osteomyelitis: treatment with regimens containing rifampin. Rev Infect Dis 5(S3):S495–S501, 1983.
211. AF Widmer, A Gaechter, PE Ochsner, W Zimmerli. Antimicrobial treatment of orthopedic implant-related infections with rifampin combinations. Clin Infect Dis 14(6):1251–1253, 1992.
212. I Shalit, SA Berger, A Gorea, H Frimerman. Widespread quinolone resistance among methicillin-resistant Staphylococcus aureus isolates in a general hospital. Antimicrob Agents Chemother 33:593–594, 1989.
213. A Stein, JF Bataille, M Drancourt, G Curvale, JN Argenson, P Groulier, D Raoult. Ambulatory treatment of multidrug-resistant staphylococcus-infected orthopedic implants with high-dose oral Co-trimoxazole (Trimethoprim-Sulfamethoxazole). Antimicrob Agents Chemother 42:3086–3091, 1998.
214. M Drancourt, A Stein, JN Argenson, R Roiron, P Groulier, D Raoult. Oral treatment of Staphylococcus spp. infected orthopaedic implants with fusidic acid or ofloxacin in combination with rifampin. J Antimicrob Chemother 39:235–240, 1997.
215. JL Hyman, EA Salvati, CT Laurencin, DE Rogers, M Maynard, DB Brause. The arthroscopic drainage, irrigation, and debridement of late, acute total hip arthroplasty infections: average 6-year follow-up. J Arthroplasty 14(8):903–910, 1999.
216. GCC Fenelon, G von Foerster, E Engelbrecht. Disarticulation of the hip as a result of failed arthroplasty: a series of 11 cases. J Bone Joint Surg 62B:441–446, 1980.

10
Periprosthetic Total Knee Infection

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I. INTRODUCTION

The treatment of the infected total knee represents one of the most challenging problems encountered in adult reconstructive surgery. Treating patients with periprosthetic knee infection is often an intense, but rewarding, experience. After successful treatment, patients, aware that their leg could have been amputated, are grateful for salvage.

The treatment of prosthetic knee infection requires an understanding of several key elements: the infection process itself, the host in which the infectious organism lives, and the treatment modalities to combat the problem. This overview is written with the experience of treating over 350 periprosthetic infections. This chapter reviews what are considered the primary elements in treating periprosthetic knee infections. Research over the last 10 years has given us an updated paradigm in evaluating and treating prosthetic knee infections. The main concepts of the paradigm are the following:

1. A staging system for prosthetic joint infection that can help direct treatment
2. An understanding of the bacterial "biofilm state" to allow development and employment of logical treatment regimens
3. Treatment regimens that focus more on the host (i.e., patient) than the infecting organism
4. The use of radical wound débridement techniques, including medullary canal débridement

5. Judicious use of muscle flaps for compromised wounds of the soft tissue envelope
6. Dead space management with high-dose antibiotic–loaded acrylic spacers

II. EPIDEMIOLOGICAL CHARACTERISTICS AND ECONOMIC IMPACT

The incidence of periprosthetic knee infection is variable but is generally low. However, the clinical and economic impact of treating these infections is great. At large medical centers where there are dedicated surgical joint replacement teams and uniform postsurgical care services, the incidence of periprosthetic knee infection is reported to be between 0.5% and 2% (1–8). In community-based hospitals or centers where there are no dedicated joint arthroplasty services, the incidence of periprosthetic infection may be higher; the incidence of periprosthetic knee infection can be as high as 5%. Periprosthetic infection rates are higher for revision knee surgery than for primary knee replacement surgery (1,4,6–9).

In the year 2000, 525,000 primary knee replacements were performed worldwide. Three hundred thirty-five thousand primary total knee replacements were performed in the United States alone (10). At the author's center, the average cost of treating a chronic periprosthetic knee infection is $75,000. Translating this to the U.S. population, the estimated annual impact of periprosthetic knee infection is approximately $450 million to 500 million.

III. CLASSIFICATION

In centers where a large number of periprosthetic knee infections are seen, most surgeons would agree that infection about the knee presents with varying levels, or degrees, of infection. Among treating physicians, there is the empirical determination that there are some infections that "look curable," whereas there are other infections that "should be amputated." Although there are presently some guidelines for the appropriate treatment of patients with acute and chronic prosthetic knee infections, there is little common ground in terms of appropriate patient selection for various treatment modalities. For all of the treatment options that have been proposed for periprosthetic knee infection, there has been no common grading of the patient's medical status or the status of the patient's local wound.

Systemic factors that regulate the host immune system play a critical role in the patient's ability to combat an infection. Treatment regimens, logically, should be modified on the basis of the patient's inherent ability to combat the infection.

In addition, the ability to fight a prosthetic joint infection at the local site emphasizes the importance of local tissue health. Competent local soft tissues provide a vascular supply to deliver oxygen and immune cells to the area of infection. In addition, a healthy soft tissue envelope protects the infected joint from further environmental exposure. Alternatively, if the local soft tissues are compromised, an infection may linger.

A staging system for evaluating prosthetic joint infections has been developed at the author's institution. It is a system that incorporates the acuteness of the infection, the overall immune/medical status of the patient, and the local factors at the site of infection that may alter treatment. The staging system was developed and studied over a 5-year period with more than 220 prosthetic joint infections (4,11–14). The staging system is currently being modified in collaboration with members of the Musculoskeletal Infection Society (MSIS), who will soon be adopting the staging system. It will then be used to compare treatments among surgeons and will allow more uniform selection of patients for multicenter trials.

The staging system for prosthetic joint infection incorporates three major categories to describe the infection and the patient, objectively in a progressive system indicating worsening severity. The staging system is outlined in Tables 1 and 2. The three main categories are infection type, systemic host grade, and local extremity grade. The infection type describes the acuteness of the infection. Infections are basically divided into acute infections (<3 weeks duration) or chronic infections (>3 weeks duration). The systemic host grade describes the ability of the patient to combat the infection. The objective factors defining this category focus on the competency of the patient's immune system or related medical factors that support proper functioning of the immune system. Finally, the local extremity grade rates the extent of soft-tissue damage in the area around the affected joint. Objective factors in this category take into consideration local factors that would impair local wound healing. The staging system incorporates all three categories in the following fashion: stage equals infection type plus systemic host grade plus local extremity grade. Examples of the nomenclature include I-A-1, II-B-2, or III-C-1.

This staging system for prosthetic joint infection has proved effective when examining outcomes. In a large series of 70 periprosthetic knee infections at the author's institution, many outcome parameters correlated with worsening medical grade and local wound grade (13). Recurrent infection and permanent knee resection were associated with a worsening medical host grade. Amputation was closely related to a worsening local wound grade. Complications in treatment were directly related to worsening medical host grade and worsening local wound grade. With future studies that enroll a larger number of patients in multicenter trials, we will eventually be able to identify and recommend targeted treatment modalities for specific levels of medical compromise and local wound compromise.

Table 1 Proposed Staging System[a] for Periprosthetic Joint Infection Musculoskeletal Infection Society

Category	Grading	Description
Infection type	I	Early postoperative infection (<4 weeks' post operative)
	II	Hematogenous infection (<4 weeks' duration)
	III	Late chronic infection (>4 weeks' duration)
Systemic host grade (medical/immune status)	A	Uncompromised (no compromising factors)
	B	Compromised (one or two compromising factors)
	C	Significant compromise (more than two compromising factors) or one of the following: Absolute neutrophil count <1000 CD4 T cell count <100 Intravenous drug abuse Chronic active infection at other site Dysplasia/neoplasm of immune system (e.g., myelodysplasia, CLL)
Local extremity grade	1	Uncompromised (no compromising factors)
	2	Compromised (one or two compromising factors)
	3	Significant compromise (>two compromising factors) or one of the following: Soft tissue loss requiring muscle transposition or free flap transfer Bone loss requiring structural allograft or substituting megaprosthesis Local wound irradiation $\geq$ 4000 rads

[a] Stage, infection type + systemic host grade + local extremity grade (e.g., I-A-1, III-B-2). CLL.
Source: Ref. 36.

IV. CLINICAL PRESENTATION AND DIAGNOSIS

The clinical presentation of periprosthetic knee infection differs in an acute infection and a chronic infection. For an acute infection (early postoperative or acute hematogenous infection), the main presenting symptoms are acute progressive pain, swelling, stiffness, and developing redness. Typically, the patient clinically feels fine, but over a short period of 6 to 12 hours, the knee becomes progressively symptomatic. If the infection is aggressive, the patient shortly thereafter becomes systemically ill with malaise, fever, and chills. The clinical signs of an acute periprosthetic knee infection include the abrupt onset of an antalgic gait, increasing knee warmth, and progressively limited knee range. The

Table 2 Proposed Staging System for Periprosthetic Joint Infection Compromising Factors[a]

Systemic host (medical/immune)
Age ≥80
Alcoholism
Chronic active dermatitis/cellulitis
Chronic indwelling catheter
Chronic malnutrition (albumin <3.0 g/dL)
Current nicotine use (inhalational or oral)
Diabetes (requiring oral agents and/or insulin)
Hepatic insufficiency (cirrhosis)
Immunosuppressive drugs (e.g., methotrexate, prednisone, cyclosporin)
Malignancy (history or active)
Renal failure requiring dialysis
Systemic inflammatory disease (e.g., RA, SLE)
Systemic immune compromise from infection or disease (e.g., HIV, acquired immunodeficiency)
Local extremity grade (wound)
Infection of a revision arthroplasty
Recurrent infection after joint débridement with prosthesis retention
Recurrent infection after prosthetic exchange protocol
Recurrent open foot sores (neuropathic or structural)
Multiple incisions (creation of skin bridges)
Sinus tract
Vascular insufficiency to extremity: absent extremity pulses, calcific arterial disease, venous insufficiency with skin plaques or intermittent sores

SLE, systemic lupus erythematosus; HIV, human immunodeficiency virus; ABG, arterial blood gas; RA, rheumatoid arthritis.

knee shows global erythema and the skin later becomes hot and shiny. A large effusion is typical. Attempts at passive range of motion testing frequently cause an intense pain response. The knee is usually kept in a flexed position of 20 to 30 degrees, and patients do not allow the knee to flex more than 80 to 90 degrees. An arthrocentesis of the joint typically shows turbid yellow fluid or frank pus.

The diagnosis of an acute periprosthetic knee infection is best achieved by a comprehensive medical history and physical exam. Serum blood tests should include complete blood count with differential, Westergren sedimentation rate, and C-reactive protein. The serum white blood cell count and Westergren sedimentation rate can be normal during early infection presentation, but the C-reactive protein is always elevated. An arthrocentesis of the knee is mandatory whenever there is a suspicion of infection. An elevated white blood cell count above 10,000 with a differential showing predominantly acute inflammatory cells

indicates a high likelihood of infection. With an acute infection there rarely is the need for radioisotope studies. Additionally, if the clinical presentation and other test results are abnormal, the surgeon should never wait for culture results from the knee aspiration to proceed with surgical débridement. The decision for surgery should be made clinically.

In contrast, a chronic periprosthetic infection has a slower presentation. The patient who has a developing chronic prosthetic knee infection usually describes a short pain-free interval after the knee arthroplasty. Usually, the patient makes consistent progress in physical therapy and postoperative pain has subsided. However, during the third or fourth month after surgery, the patient begins to complain of pain in the knee and starts to limp. The pain slowly progresses in intensity and frequency. The patient then begins to lose range of motion. The knee starts to feel warm but is not hot. As the infection progresses, the sentinel signs of rest pain and night pain, which may require narcotics, develop. The knee usually does not show much erythema, but the soft tissues feel indurated and tight. Passive range of motion by the examiner elicits pain throughout the range, but the pain is worse at the ends of the range. Later, as more swelling develops, the knee shows a developing boil, which later turns into a draining sinus. An arthrocentesis result is usually unimpressive, revealing yellow, slightly cloudy to cloudy fluid. The string sign finding is negative.

The diagnosis of a chronic periprosthetic knee infection may be straightforward or more difficult. If a patient shows a developing boil or draining sinus around the knee, the diagnostic work-up is complete. However, this type of presentation does not always occur. Frequently, the patient has a painful knee with mild to moderate swelling. As in an acute infection, a comprehensive medical history and physical examination are most important. Increasing pain and gradual loss of knee range raise suspicion of infection. Diagnostic tests should include a complete blood count with differential, Westergren sedimentation rate, and C-reactive protein. With chronic periprosthetic knee infections, the C-reactive protein is almost always positive. The only circumstance in which a C-reactive protein result may be negative occurs when the patient is taking intravenous or oral antibiotics. In a chronic periprosthetic knee infection, it is not unusual to have a normal serum white blood cell (WBC) result. In addition, patients who are malnourished or are anemic may have a normal Westergren sedimentation rate (WSR). Knee arthrocentesis rarely shows frank pus. Usually, the fluid is yellow or amber and is slightly cloudy. Cultures of the knee fluid can yield negative findings in a low-grade infection. Since surgery for a chronic periprosthetic knee infection is not an emergency, there is time for radioisotope scanning if the physician is not certain of the diagnosis. A 24-hour indium^{III}-labeled white cell study is the most useful test. A triple-phase technetium 99m Tc-MDP bone scan has a positive result in infection but does not differentiate among mechanical loosening, osteolysis, and infection. In contrast, an indium scan with labeled

white cells primarily has a positive result only in areas of infection. Rarely, an indium scan yields a positive finding in an area of recent bleeding.

V. PATHOGENESIS

A. Bacteria Biofilm

A major defining element in the treatment of periprosthetic knee infection is learning a thoroughly different paradigm of bacterial interaction with the human host in chronic disease. This requires an understanding of bacterial biofilms. Bacterial biofilms are produced by bacteria and can form on foreign objects implanted within the body. Just as important, biofilms can also form on any devitalized native tissue. The archetypal model for this is cystic fibrosis pneumonia whereby the biofilm from *Pseudomonas aeruginosa* forms on devitalized lung parenchyma, perpetuating an everlasting disease state. Although the model of germ theory of disease was validated in the late 19th century by Robert Koch, it has only been in the last decade that the biofilm model has really been introduced and understood.

A summary of the salient issues of bacterial biofilms as they relate to the clinical treatment of prosthetic joint infection can be helpful. A bacterial biofilm comprises bacterial cells and an extracellular matrix made of a polysaccharide coating. The extracellular matrix holds the bacterial cells together, forming a microcolony, which in its mature form has a defined structure (Fig. 1) (5,16,17).

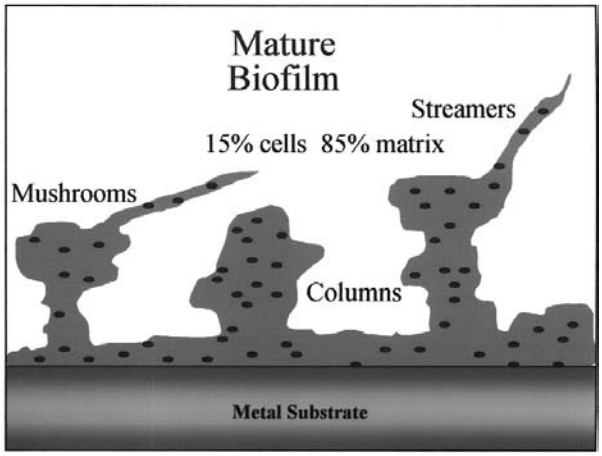


Figure 1 Diagram of mature biofilm state. The biofilm forms a base layer from which outer growths occur. The outer layer can form streamers of biofilm that can break off to infect other nearby areas or enter the blood system to seed distant sites hematogenously.

The volume of the microcolony filled by bacterial cells is approximately 30% or less. The rest of the microcolony is filled by the extracellular matrix, or slime layer, and periodic holes or "channels" for nutrient flow. In the mature form, a complete microecology exists. The outer cells of the biofilm are more metabolically active and allow more rapid cell division because of their greater access to nutrient channels. In contrast, the inner areas may essentially be in a metabolic dormant state, subject to low oxygen tensions (16). Not infrequently, different bacterial species (with different biofilm consistencies) may coexist in a symbiotic relationship. Cells within the biofilm can communicate. Bacteria communicate via signaling molecules, which have been found to be lactone derivatives (16). When bacteria attach to a medical implant (or to devitalized tissue), a biofilm does not form unless there is a specific "quorum" of cells present. This is communicated via quorum sensing molecules (lactone derivatives). However, once a quorum of cells is present, a biofilm can be formed within hours. The clinical relevance of bacterial biofilms in the treatment of periprosthetic knee infection is summarized as follows:

1. Almost all bacteria are capable of forming a biofilm. Those bacteria implicated most often with chronic infection in medical devices all form biofilms.
2. Once in a bacteria biofilm state, bacterial cells become up to 1000 times more resistant to antibiotic therapy. Bacterial cells in the biofilm state turn on and express numerous genes that make them more resistant to antibiotics. There are multiple defences used. The traditional method of quantifying bacterial killing concentrations for antibiotics describes killing doses for cells in their individualized form (planktonized cells). Clinically, administrating bacterial killing concentrations does not affect bacteria in a biofilm state. Only cells floating in their individual planktonized state are killed. This is why antibiotics alone are insufficient for treating chronic periprosthetic knee infection. In the future, a more apt description for antibiotic therapy may be "biofilm killing levels," once chemotherapeutic agents capable of killing cells in the biofilm state are found.
3. The biofilm is very resistant to the cellular and humeral immune system. Antibodies can attack and destroy localized areas of the biofilm. However, the area of attack is limited to the outer boundaries, so the inner core of cells is protected. The same is true of cellular immune response. Actually, immune attack of the biofilm, paradoxically, can be detrimental. Localized attack can break bacteria into individual cells, allowing them to spread systemically or to adjacent local regions.

4. Currently, there are no germ-fighting cleansers that can dissolve a biofilm safely without sustaining acceptable damage to surrounding host tissue. Even chlorine bleach in its full strength has difficulty penetrating the deepest layers of certain biofilms (bleach at this strength could never be used clinically). Furthermore, the biofilm cannot be effectively removed completely with mechanical scrubbing. Research is currently under way to find agents that can signal a biofilm to dissolve. This research involves agents that mimic signaling molecules of the biofilm or agents that block them.

In conclusion, if a periprosthetic knee infection has attained a chronic state whereby a biofilm has enveloped the knee prosthesis (and adjacent devitalized tissue), the only way to treat the infection effectively is surgical extirpation of the implant and all devitalized tissue. Radical débridement of adjacent soft tissue and bone is emphasized, as biofilms can persist on these tissues as well. Sometimes, this can mean loss of vital support structures, including ligaments and cortical bone. However, this is a more favorable choice than having a recurrent infection after reimplanation. As a corollary, an acute infection, defined now as any infection that has not formed a biofilm, should be treated aggressively, without delay. Acute prosthetic knee infection should be categorized as an acute orthopedic emergency.

VI. TREATMENT

Treatment of periprosthetic knee infection takes into account the factors involved in infection staging, along with an understanding of the bacterial biofilm state. The treatment algorithms for periprosthetic knee infection are shown in Fig. 2. The determination as to whether the knee infection has developed into a chronic biofilm state directs the initial treatment. In a chronic periprosthetic knee infection, resection arthroplasty is the initial treatment unless the patient is too medically ill or the knee is too damaged, when an amputation is advocated. On the other hand, with an acute infection, there is potential for implant salvage. Initial treatment is focused on a radical débridement of the knee with retention of implant components. It must be emphasized that treatment of periprosthetic knee infection, whether classified as acute or chronic, is surgical. Systemic antibiotic therapy is a supplement to surgical treatment and is not considered an alternative to surgery. The only real exception to this edict is the rare case when chronic oral antibiotic suppression is chosen. This is discussed at the end of this section.

For an acute periprosthetic knee infection, radical débridement and lavage of the knee are needed. This is discussed further in Section VI. Intravenous antibiotics are tailored toward the infecting bacteria and their sensitivities. Intravenous antibiotics are administered for 6 weeks. After this period, the patient

is monitored with serial laboratory tests, measuring the Westergren sedimentation rate and C-reactive protein at 3 and 6 months after surgery. If the lab results remain normal, the infection is likely eradicated. If the results show progressive elevation, then the infection has not been eradicated and is now considered chronic. Any clinical sign of recurrent infection means the knee infection should then be treated as a chronic periprosthetic knee infection.

For treatment of chronic periprosthetic knee infection, algorithms are modified according to the severity of medical compromise and local wound damage. If knee salvage is the goal, then resection arthroplasty is the initial treatment. Primary amputation is strongly considered for grade C medical host or a grade 3 local knee wound. After resection arthroplasty, intravenous antibiotics are administered.

The duration of antibiotic chemotherapy and total prosthetic explanation time for periprosthetic knee infection are not exactly defined. The duration of antibiotic therapy in most centers ranges from 2 to 8 weeks (4 to 6 weeks is most common). The preferred duration of antibiotic therapy is 6 weeks. This allows the soft tissues adequate time to heal and edema to abate. However, most experts agree that a period off antibiotics (10–14 days) is important to determine whether the knee will flare again with infection. After completing this rest period off antibiotics, the knee is tested to determine whether the infection has been controlled. Evaluation should include knee fluid for cell count and differential, knee fluid for culture studies, serum quantitative C-reactive protein, and Westergren sedimentation rate. Reimplantation is predicated on having sterile aspiration culture findings, a normal cell count analysis result, and normal serum laboratory findings. If the initial evaluation is indeterminate (i.e., persistently elevated serum levels or false-positive culture result), the studies are repeated in 2 to 3 weeks. If the study results are worse and/or culture findings remain positive, another débridement procedure is required. If the study results are again indeterminate or there is no established trend, an indium^{III}–labeled WBC test should be ordered. If the result is negative, reconstruction can begin. However, if the result is positive in the knee area, another débridement procedure is indicated.

There are exceptions to having a normal C-reactive protein and Westergren sedimentation rate. These lab findings may be persistently elevated in patients with inflammatory arthritis or other inflammatory conditions. Also, in some cases with articulated antibiotic-loaded cement spacers, excessive wear of the articulated spacer can elicit a reactive methylmethacrylate synovitis. In the author's experience, a cement particulate debris synovitis can independently elevate the C-reactive protein. In this scenario, a second aspiration should be done to confirm an aseptic joint. Concomitantly, the patient should be instructed to minimize excessive wear to the cement spacer to show that the C-reactive protein is declining on follow-up testing. Indium^{III}–labeled white blood cell testing in this scenario can be deceiving. The cement debris synovitis can elicit an acute

inflammatory response, which can cause a false-positive indium test result. Patients with articulating antibiotic-loaded cement spacers should be advised not to bend their knees excessively (even if they feel well), except for brief exercise periods.

If infection recurs during the treatment period, repeat débridement is performed and intravenous antibiotics are reinstituted. If the infection cannot be successfully eradicated after several attempts of surgical débridement, then one should reassess treatment options. Failure after aggressive débridements usually means the medical host status is too weak to treat the infection. If this is the case, then one should consider amputating the knee or leaving it permanently resected.

Distinguishing acute infection from chronic infection is sometimes very difficult. At this point, there is no specific test that can be performed to detect a biofilm state. Medical judgment incorporating a comprehensive history and physical examination, combined with other diagnostic tests, is best. Most experts would agree that 3 to 4 weeks of clinical infection, likely indicates chronic infection. Some experts would consider an even shorter period such as 7 to 14 days. As a rule, however, any documented infection of more than 3 weeks in duration can be considered chronic. If there is discrepancy in the medical history, it is best to err toward identifying the infection as acute and treat it as such. The morbidity caused by declaring an acute infection as chronic is great. It implies that prosthetic implants must be removed—a formidable challenge when implant components are well fixed. Conversely, declaring a chronic infection as acute implies that the implants are to be retained. If this initial treatment algorithm fails, then there has not been excessive loss. The patient will have been subjected to one additional surgical débridement, but for the most part, salvage from the infection is still possible.

Determining how long an infection has actually been present is also difficult. Patients may not be able to give accurate histories defining when the knee actually became painful and swollen. Also, with acute infections in the postoperative period, it is hard to distinguish between postsurgical pain and pain from infection. Usually, postsurgical pain is declining in intensity and frequency, whereas patients with an acute infection experience rather rapid and progressive pain. In addition, the increased pain is accompanied by more swelling, erythema, and warmth. This is the condition in which diagnostic arthrocentesis is most valuable. If there is any doubt whatsoever that an infection may be present, an arthrocentesis is mandatory.

Finally, chronic oral antibiotic suppression is a possible treatment option in limited circumstances, when certain criteria are met. It should be understood that chronic oral suppression should be a decision made by the surgeon in the best interests of the patient. It should not be a treatment option solely because the job of surgical treatment is too daunting or adequate ancillary care is not available to the surgeon. If this is the case, then referral to a tertiary center is advisable.

Employing a trial of chronic oral suppression to "buy some time" or "see whether conditions settle down" does nothing except create further soft tissue destruction and bone destruction. If salvage of the infected total knee is the goal, then chronic oral suppression is not an option. Of course, there are always going to be exemplary cases in which delay in treatment is required, but the concept of early and aggressive surgical management should not change.

Patients considered for chronic oral suppression fit into limited groups: patients with a limited projected life span for whom the infection is not causing significant pain and suffering and those to whom a two-stage protocol for chronic infection would likely cause further harm.

Patients who have a limited life span are those who suffer from terminal cancer or are very elderly (although many salvage procedures have been performed on patients above 90 years old). These patients would rather spend their remaining days with family and friends than in a hospital setting. Other patients may be so medically ill with other disease processes (e.g., heart failure, severe chronic obstructive pulmonary disease) that the risks of surgery are greater than the expected benefits.

There are several criteria that must be met for chronic oral suppressive treatment. First, the antibiotic chosen has to have documented specificity to the infecting organism. With the understanding that a biofilm will never be cured with antibiotics alone, chronic suppression mitigates the localized inflammatory response by planktonized cells. This allows, ideally, a "peaceful coexistence" between host and bacteria. Clinical experience at the author's institution suggests that chronic antibiotic suppression, more often than not, fails in less than 1 year. At that point, the infection process with its continued slowly smoldering course causes mechanical loosening, pain, and disability. The result is that surgical débridement or amputation is required. However, there are a few cases in which chronic suppression has worked long term and patients remain relatively comfortable.

The second criterion is that the patient, during the course of treatment of chronic suppression, remains comfortable and is not allowed to become systemically ill as a result of disseminated infection. If pain increases in the local area, it indicates failure of treatment, and alternative options should be explored. Similarly, if a patient becomes systemically toxic, chronic suppressive therapy should be discontinued.

VI. SURGICAL DÉBRIDEMENT OF THE INFECTED TOTAL KNEE

The approach to débridement of the infected knee is analogous to resection of a tumor: that is, all abnormal areas must be resected to effect a cure. In the case of infection, all soft tissue and bony areas that look infected must be resected. If they

are not, in areas where nonviable tissue persists, bacteria in the biofilm state will continue to live and multiply. From a knee function standpoint, this is a hard concept to accept. Débridement of vital ligaments, tendons, and bone can require drastic salvage techniques to restore knee function. However, by not emphatically following this principle, the surgeon encounters recurrent infection. In the compromised host, recurrent infection often leads to amputation.

In the case of acute periprosthetic knee infection, in which prosthetic components are to be maintained, débridement principles include the following: (1) an extensile incision for complete exposure of the knee, (2) synovectomy of inflamed synovium to debulk bacterial load, (3) complete circumferential exposure and débridement of prosthetic-bone interfaces, (4) exchange of modular polyethylene parts, and (5) copious lavage (minimum of 9 L) employing a mechanical irrigating device.

An extensile approach allows inspection of all areas of the knee. Abscess pockets may be missed by so-called miniarthrotomies and even by moderately sized arthrotomies. Arthroscopic lavage techniques are to be avoided, as they do not allow for adequate débridement of the knee. A radical débridement of synovium and other infected tissue is paramount. A debulking of bacterial load to the greatest extent possible reduces the chance that residual bacteria will grow to develop a biofilm.

It is important to débride the prosthetic bone interface circumferentially. This interface is the area where the infection will attack and grow into the inaccessible regions between prosthesis and bone. Exposing this interface for the lavage process is key. Débridement of this interface can be complicated when implants have been in place a long time and there is osteolysis. In this situation, débridement may destabilize remaining fixation, but failure to débride the region risks recurrence of infection. Débridement of prosthetic bone interfaces takes precedence. If the implant becomes loose, then one should proceed with a two-stage protocol. Patients who have implants that radiographically show significant osteolysis should be apprised preoperatively of the possibility of implant resection. Exchange of modular polyethylene parts should be performed when possible. Between the modular interfaces there is always a thin fibrin layer where bacteria can persist. If not opened, this area may not be adequately flushed with the lavage process. Finally, after mechanical débridement, the entire knee must be lavaged copiously. Irrigation with pulsatile mechanical irrigation penetrates all surfaces to flush all suppurative material. A minimum of 9 L is preferred. However, the lavage process should continue until all areas look clean. This may require 18 to 21 L of irrigation solution in some cases. Within the irrigation, triple antibiotics are used. In each 3 L bag of saline irrigation solution, 100,000 units of bacitracin, 1 million units of polymixin, and 80 mg of gentamycin are added.

Débridement of the chronically infected knee must be approached with a "no prisoners" approach. That is, all dysvascular/necrotic areas must be

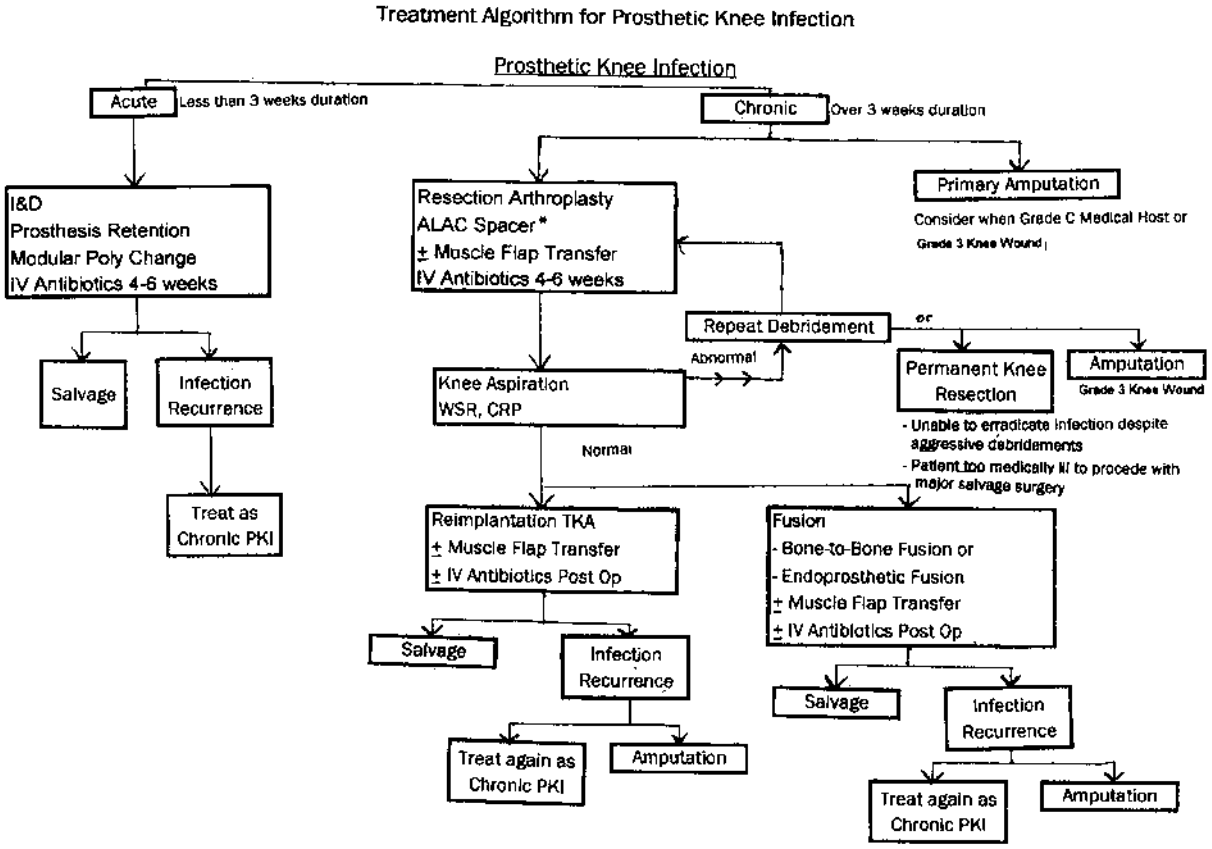
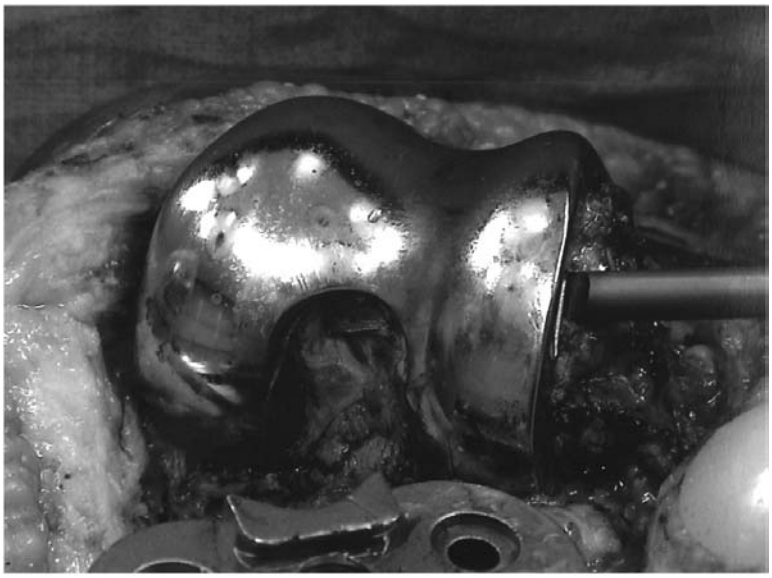


Figure 2 Treatment algorithm for prosthetic knee infection. *ALAC – Antibiotic-loaded acrylic cement

(a)



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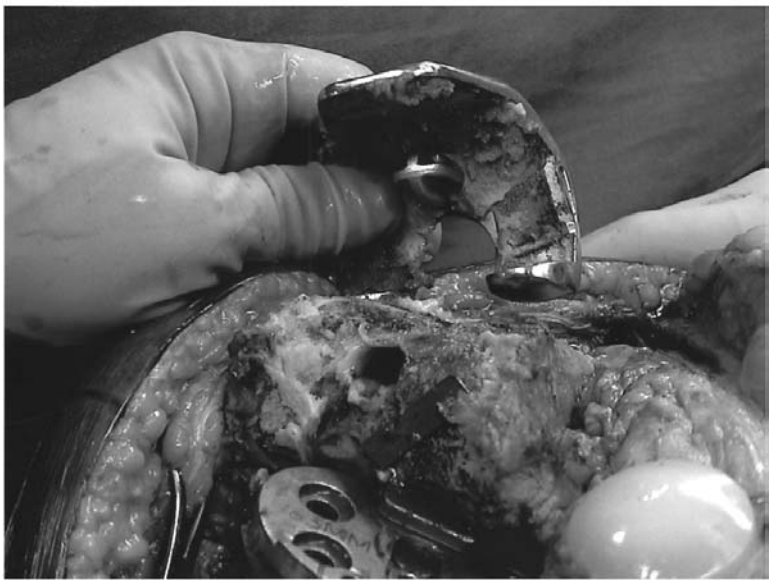


Figure 3 Intraoperative photographs showing the use of an ultrasonically driven tool blade to remove a well-fixed knee implant. (a) Photograph showing dissection of ultrasonically driven tool blade between porous ingrowth femoral component and host bone. (b) Photograph showing broken tool blade in bone. This demonstrates ability of ultrasonically driven blade to dissect into bone easily.

surgically extirpated to effect a cure. For chronic infections, a complete radical débridement is required. This includes resection of all implant components, removal of all other remaining foreign material, and opening of the medullary canals of the femur and tibia for débridement and lavage.

The surgical exposure must be extensile to allow broad visual inspection. In the tibia area, the incision should be curved toward the medial ankle, in case a medial gastrocnemius flap is required at a later time. All draining sinus tracts are surgically ellipsed all the way down into the joint. If the sinus tracts pass through vital ligaments, these areas must unfortunately be thoroughly débrided, even if this means loss of structural integrity. A radical synovectomy, including the posterior knee, is always required. Posterior synovial débridement is best achieved with the knee at 90 degrees of flexion after prosthetic components have been resected. Lamina spreaders are placed between the femur and tibia to allow full exposure of the posterior recesses.

Resection of prosthetic components first requires exposure of the prosthesis-bone interface. Complete circumferential exposure is needed. Specialized prosthetic removal instruments should be available to minimize bone loss and facilitate removal. Presently, there are prosthetic removal instrument sets designed for this purpose. The use of ultrasonically driven tool blades (Ultradrive Device, Biomet, Inc., Warsaw, IN) is recommended. These ultrasonically driven tool blades can be used to disrupt cement-bone interfaces easily. In addition, these tools can disrupt well-fixed porous ingrowth knee devices with equal ease (Fig. 3). These tools have significantly reduced operative time for component removal and lessen the amount of bone loss during prosthetic removal. Large extraction devices (e.g., slap hammers) should not be used, as they tend to remove excessive bone during mechanical disruption of prosthetic parts. Rather, sequential disruption of prosthetic interfaces along with axial disimpaction along the periphery allows a more controlled removal of parts.

After component removal, all bony areas are inspected to identify any remaining foreign debris (i.e., cement, metal, sutures, wires, or screws) and devitalized tissue (including allografts). Recurrent infection is often associated with retained cement or retained metallic pieces. These pieces can harbor bacteria in a biofilm state. All allograft material that is not alive must be removed. A test to determine bone viability is the "paprika sign." With a small osteotome, the allograft bone surface is chiseled. Punctate bleeding from bone indicates living, viable bone. If the bone does not bleed, it is dead and should be removed. Remember also that bone substitute materials that fill cavitary bone voids are nonviable materials that must be removed. Similarly, particulate allograft material if dead must be removed. Particulate allograft material that has not incorporated is usually easily removed with a curette. Viable allograft pieces are incorporated to the host bone and usually stay in place with curettage.

An important aspect of successful knee débridement is the opening of the medullary canals; this cannot be emphasized enough. Studies in 1999 clearly demonstrated the presence of bacteria in adjacent medullary canals in chronic infections (18). Canals must be opened widely, scraped of fibrous tissue, brushed, and lavaged. Power reaming should be avoided because this process causes endosteal necrosis, which can allow bacteria to adhere and thereby perpetuate the infection.

VII. DEAD SPACE MANAGEMENT

A. Historical Perspective of Acrylic Spacers and the Use of Muscle Flaps

In the last decade, management for periprosthetic knee infection has evolved significantly with the use of interpositional cement spacers and muscle flap transfers. Historically, chronic periprosthetic knee infection, if not amputated, was treated with resection arthroplasty without using concomitant acrylic (methylmethacrylate) antibiotic spacers (12,19). The reason cited was that methylmethacrylate would serve as a foreign body surface where bacteria would linger. Early studies concluded that the most likely sources of recurrent infection in periprosthetic knee infection were inadequate débridement and retained foreign debris. In addition, early studies of antibiotic elution from polymethylmethacrylate (PMMA) indicated a rapid elution of antibiotics. This meant that these spacers served more as foreign bodies and were more likely to cause harm than good. As a result, resected knees were left without spacers and the joint tissues contracted. Once this occurred, restoration of normal joint function with reimplantation was nearly impossible. An alternative treatment modality using the medial gastrocnemius rotational flap evolved. The medial gastrocnemius flap could be used either as an interpositioned spacer at resection or later at the time of reimplantation to cover deficient soft tissue areas that were stretched out during the reimplantation. These techniques, although successful, still did not restore soft tissue pliability and were not associated with the best functional results (12). The contracted/scarred soft tissue envelope never really could achieve its previous pliability and restore good functional knee range.

The major change in the use of acrylic antibiotic-loaded interpositional spacers in periprosthetic knee infection has been the use of high-dose multiple antibiotics. Bench studies have confirmed effective antibiotic elutions for as long as 6 to 8 weeks with high-dose antibiotic regimens. This turns the acrylic cement spacer into a useful treatment tool. If the dead space in the knee can be treated at initial resection with an antibiotic-loaded acrylic cement (ALAC) spacer, soft tissues around the knee can be maintained at appropriate tension. This may

Table 3 Muscle Flap Applications for Periprosthetic Knee Infection

Type of flap	Description	Indications
Interposition flap	Flap placed into resected knee joint	Permanent knee resection Placed in lieu of acrylic antibiotic spacer Medical gastrocnemius flap best choice for this use
Coverage flap at resection arthroplasty	Flap placed in areas of soft tissue deficiency	Poor wound healing with knee drainage Soft tissue necrosis Open wounds after resection of large abscess
Coverage flap of reimplantation TKA	Flap placed in areas of soft tissue deficiency	Placed when soft tissues stretched from reimplantation that do not close or tension too great to allow knee range of motion
Coverage flap during débridement for acute PKI	Flap placed in areas of soft tissue deficiency	Poor wound healing with persistent knee drainage Soft tissue necrosis
Prophylatic flap at primary or revision TKA (wound not yet infected)	Flap placed in areas of soft tissue damage	Prior soft tissue irradiation Prior traumatic wounds with extensive soft tissue scar and contraction Severe angular deformities that pose wound closing problems

PKI, periprosthetic knee infection; TKA, total knee arthroplasty.

obviate the need of a rotational muscle flap. The muscle flap instead can be reserved for use at the reimplantation, if needed.

B. Current Use of Muscle Flap Transfer in Periprosthetic Knee Infection

Muscle flap coverage for periprosthetic knee infection is a valuable treatment method when required. Muscle flap transfer can be used in several applications. These applications are summarized in Table 3. The transferred muscle serves several valuable purposes. The main reason for a muscle flap transfer in periprosthetic knee infection is that the muscle covers and protects an attenuated or deficient soft tissue envelope. With infected knee wounds, excessively tight closures almost always open and drain, leading to more misery and surgery. A wound left open to fill by secondary intention can become reinfected with other bacteria. Instead, a muscle transfer introduces healthy tissue with a rich vascular supply into the wound. This promotes wound healing and allows the remaining soft tissue envelope to be repaired in its more natural relaxed position (12,13,19–23).

Table 4 Muscle Flap Options for Periprosthetic Knee Infection

Sources	Comments[a]
Medial gastrocnemius rotation	Most common; long excursion, can add half of Achilles tendon to reconstruct deficient patellar tendon; attention to location of MCL during harvest and prevention of cutting of MCL required
Lateral gastrocnemius rotation	Muscle usually small; limited excursion; reserved for lateral knee soft tissue deficits only; peroneal nerve at risk during dissection
Rectus abdominus myocutaneous free flap	Proximal anastomosis preferred; better predictable flow; use of saphenous vein AV loop tied into groin; if good distal circulation, can tie into tibial artery; cutaneous portion of flap can use to obviate need for large STSG
Latissimus dorsi free flap	Same recommendations for proximal tie-in; only muscle able to be harvested, tends to be wider than rectus and have shorter excursion; best for wide anterior soft tissue deficits

[a] MCL, Medial Collateral ligament. AV, Arterial-venous. STSG, split thickness skin graft.

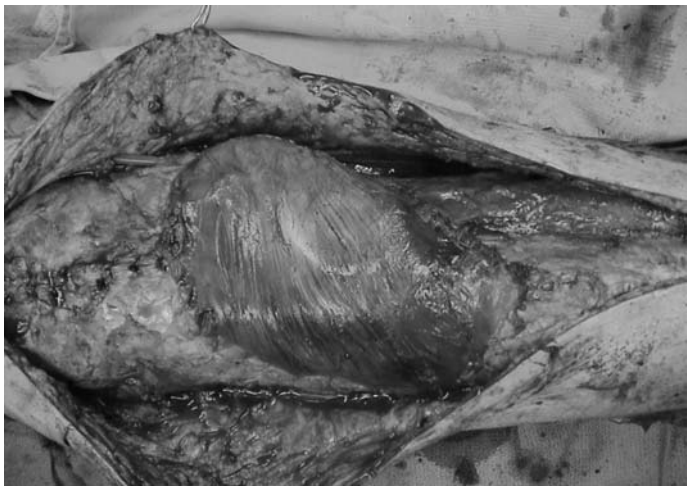


Figure 4 Intraoperative photograph of medial gastrocnemius rotational flap, used during the closure of a knee with a resection arthroplasty. The knee has an acrylic antibiotic-loaded cement spacer in place. This shows the significant excursion that can be obtained by this muscle if properly harvested.

The other benefit of muscle flap transfer is its ability to deliver antibiotics to the compromised area of infection (12,19,22,23). When the muscle flap transfer is applied as an interpositional spacer or as covering of a wound at the time of prosthetic resection, the rich vascular supply of the muscle allows delivery of antibiotics to a relatively hypovascular area. This is especially pertinent to the knee wound with multiple incisions, where the relative lack of blood supply to the wound limits the effective antibiotic delivery to the area. The muscle flap, once placed on (or into) the damaged area, attaches and heals to its surrounding area. A vascular neogenesis occurs at this interface (19,20,23). Over time, the damaged tissues become better perfused and, thus, healthier. After muscle flap transfer, the knee wound looks healthier over time and the soft tissue envelope becomes more supple.

There are multiple muscle flap transfers that can be used for the knee. The major muscle transfers commonly used in periprosthetic knee infection are listed in Table 4. Muscle flap transfers are grouped as rotational muscle flap transfers or free muscle flap transfers. In a free muscle transfer, the vascular pedicle to the muscle is cut and reanastamosed microsurgically near the knee region.

The medial gastrocnemius rotational flap is considered the main workhorse for muscle flap transfer around the knee. The medial gastrocnemius muscle is relatively "hearty" and can be rotated at 90-degree angles (Fig. 4). It is much larger than the lateral gastrocnemius flap. The medial gastrocnemius muscle is

used to cover medial and anterior soft tissue deficits. If the muscle is well developed, it can even be used to fill anterolateral deficiencies.

When using a medial gastrocnemius flap, the soft tissue incision heals better when the incision is curved gently toward the medial malleolus, rather than making a sharp right angle incision to the posterior midline. The entire muscle should be harvested every time, as it is not unusual to underestimate the amount of muscle needed to rotate across the front of the knee. Dissection of the muscle all the way into the popliteal fossa enhances proximal mobilization and rotation. Be careful not to cut the medial colateral ligament during the gastrocnemius harvest. The medial colateral ligament can only be cut when a constrained hinged knee prosthesis is used. Sometimes cutting the medial colateral ligament is required to gain the needed muscle excursion to cover the required soft tissue deficits.

The lateral gastrodnemius flap is reserved for pure lateral deficiencies. The muscle is generally much smaller than the medial side. Furthermore, its excursion is limited by the peroneal nerve. Pulling the muscle too tightly over the peroneal nerve can result in permanent nerve injury.

A free muscle flap transfer is a difficult technical procedure. It should only be used in salvage situations in which a medial gastrocnemius flap is inadequate to cover the defect. An experienced microvascular surgeon is needed to transfer this muscle. Free muscle transfer for periprosthetic knee infection has been used at the author's institution on 11 occasions. Some muscle flap transfers have failed. Our experience suggests that the vascular reanastomosis be placed proximal to the knee. Successful reanastomosis of a free flap transfer distal to the knee is less predictable. Associated distal arterial occlusive disease seen in older patients can make the reanastomosis difficult. Furthermore, arterial plaques can break off and shower into the muscle pedicle, compromising the viability of the free flap. For these reasons, all free muscle transfers are now reanastomosed proximal to the knee. To take the tension off the vascular pedicle and allow earlier joint motion a reverse saphenous vein loop that is tied into the proximal femoral vessels in the thigh is often used. This assures generous vascular flow to the muscle pedicle.

C. Antibiotic-Loaded Acrylic Spacers

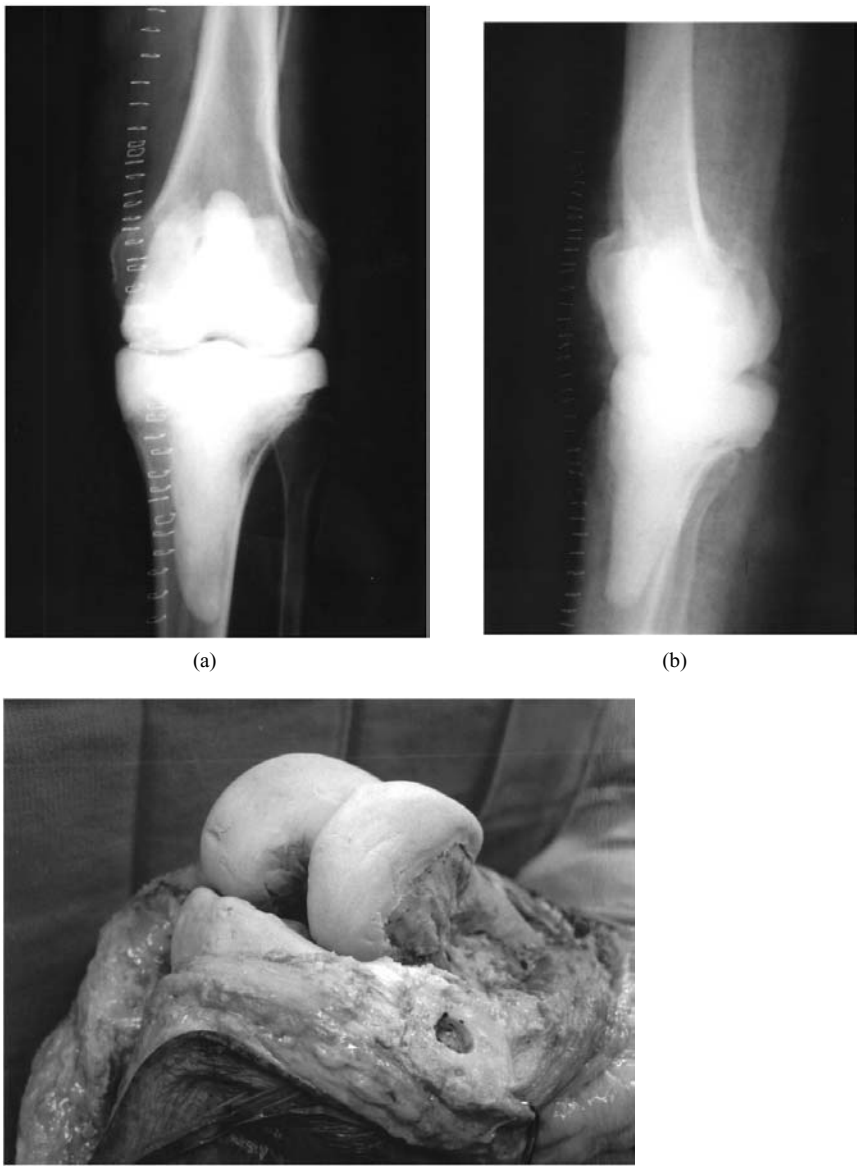
In the two-stage resection protocol for chronic periprosthetic knee infection, all efforts should be made to fill the knee dead space (the large area of the joint remaining after prosthetic removal) with an ALAC spacer. Rarely is a knee left without some type of ALAC spacer. The type of ALAC spacer used is controversial. The majority of surgeons working with periprosthetic infections advocate only the use of antibiotic-loaded cement, as this provides consistent long-term antibiotic delivery. The high doses of antibiotic within the cement inhibit bacterial growth onto and within the spacer during the resection period.

Some surgeons use sterilized prosthetic components that are placed back into the knee and are loosely cemented with antibiotic-loaded cement (24,25). This technique has been named a *prostalic spacer*. The disadvantage of a prostalic implant is that the exposed metallic surfaces may serve as an adherent area for remaining bacteria. These bacteria then can again form a biofilm, even in the presence of the surrounding antibiotic-loaded cement. A hybrid technique employs molding antibiotic-loaded cement, called an *articulating ALAC* spacer, into femoral and tibial articulating components (Fig. 5) (26–29). This technique is tedious and more technically demanding. However, if properly constructed, the articulating ALAC spacer can function as well as the prostalic spacer (29).

For reasons of biofilm prevention and consistent antibiotic delivery, the use of antibiotic-loaded cement only, for knee spacers is preferred. If there is adequate bone stock and surrounding soft tissue support, the cement can be molded into articulating components. If there is significant bone and/or soft tissue deficiency, a nonarticulating spacer block and rod is used (Fig. 6) (30). In either construct, antibiotic-loaded cement must be placed within the medullary canals to deliver antibiotic to this "at risk" area where bacteria frequently persist. When using an antibiotic spacer rod and block construct, a small metallic rod within the core of cement can be used to form a cement-coated rod. This rod is placed within the medullary canals of the femur and tibia; then the leg is distracted open. Additional antibiotic-loaded cement is placed in between the femur and tibia to form a block. The block of cement incorporates the rod, creating a stable construct. This provides support and comfort. The cement block is built up with enough cement anteriorly to keep the extensor mechanism stretched out and prevent the gutters from contracting. With the articulating ALAC spacer, a long leg brace is used. During ambulation, the brace is locked in extension and the patient is instructed to use only touch-weight bearing on the leg. The brace is unlocked three times daily for bending exercises up to 90 degrees. With the ALAC spacer block and rod, the leg is casted or placed in a long leg brace. Again, the patient is instructed to use only touch-weight bearing on the leg.

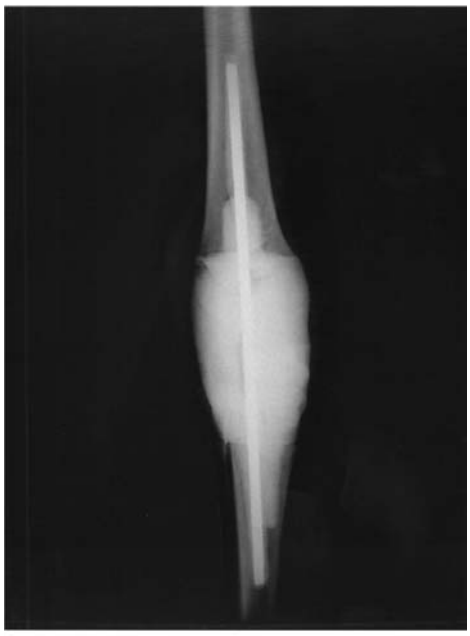
Antibiotic elution from ALAC spacers has been studied. Effective antibiotic elution from PMMA is dependent on several factors (31). These include the type of cement used, porosity of cement (after antibiotics are added), surface area of exposed cement, and antibiotic concentration. Studies comparing presently used PMMA products show that Palacos bone cement has the overall best elution properties (31). Additionally, Palacos is impregnated with chlorophyll to give it a distinct light green coloration, which makes it easier to distinguish from bone during removal.

There are several formulas for the amount of antibiotics placed into cement (12,27,31). The antibiotics used must be heat-stable during the cement curing process. Cement-antibiotic formulas currently used include the following:

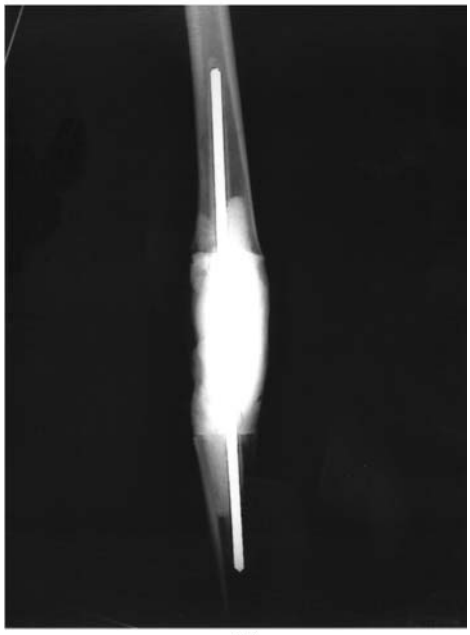


(a) (b) (c)

Figure 5 AP radiograph (a) and lateral radiograph (b) demonstrating an articulating ALAC spacer. Spacer components are molded by hand. They are made to resemble total knee components. With postoperative bracing, these articulating spacers can achieve 90 degrees of flexion. (c) Intraoperative picture of the articulated ALAC spacer. AP, anteroposterior; ALAC, antibiotic-loaded acrylic cement.



(a)



(b)

Figure 6 (a) AP radiograph (b) and lateral radiograph of an ALAC spacer block and rod. The metallic core is completely covered with antibiotic-loaded cement. It prevents the spacer rod and block from breaking with bending loads. AP, anteroposterior; ALAC, antibiotic-loaded acrylic cement.

Formula 1: 4 g vancomycin, 3.6 g tobramycin, 6 g cefoxitin per 50 g bag of cement
Formula 2: 4 g vancomycin, 3.6 g tobramycin per 50 g bag of cement
Formula 3: 2 g vancomycin, 2.4 g tobramycin per 50 g bag of cement

The formula used most often by the author is Formula 1. The usual amount of cement used for an ALAC spacer for the knee is 3 bags of cement. However, large bony resections may require the use of up to six or seven bags. With the high doses of antibiotics used in the cement, serum levels of vancomycin and tobramycin are seen for up to 3 to 5 days. It is important that all medical staff caring for the patient understand this effect. Dosage of intravenous vancomycin and tobramycin must be carefully tailored during this period. In cases of impaired renal function, Formula 3 is recommended. If the patient is dialysis-dependent, the standard formula is used; then serum trough levels of vancomycin and tobramycin are followed. Intravenous antibiotics are then tailored to the infecting organism(s).

VIII. RECONSTRUCTION PRINCIPLES

The reconstruction principles for reimplantation total knee arthroplasty after infection generally follow the same guidelines established for revision total knee arthroplasty. The basic principles of reconstruction are, in order of use, the following:

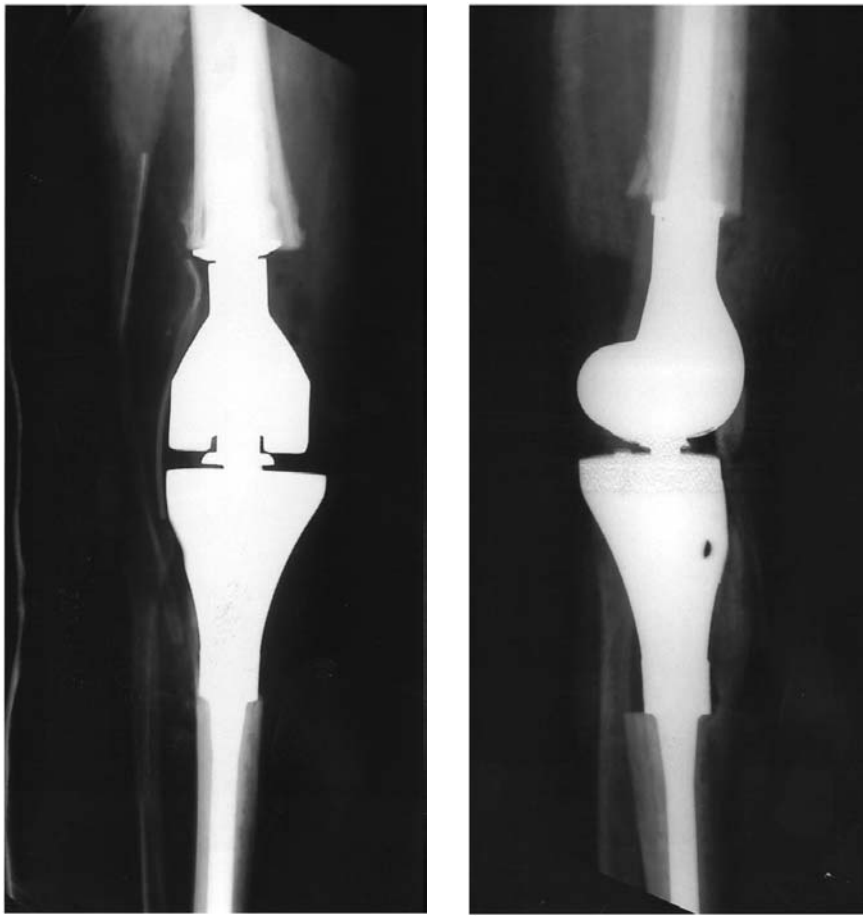
1. Reestablish a stable tibial platform. This re-creates the original joint line. For large tibial deficiencies, the fibular head can be used as a guide to determine the original joint line.
2. Reconstruct the femoral component. Metallic and/or bony augmentations may be required.
3. Adjust flexion and extension gaps of the knee with modularity of femoral component design. The flexion gap can be adjusted by changing the size of the femoral component. Posterior metallic augmentations may be required to fill bone gaps. The extension gap can be adjusted with distal femoral metallic augmentations.
4. Assess the level of constraint. Ligament deficiency may require more progressive constraint built into the prosthetic system. The three levels of constraint are unconstrained (posterior cruciate ligament retaining and posterior stabilized) knee systems, constrained nonhinged knee systems, and hinged rotating tibial platform knee systems.

5. Assess extensor mechanism and balance. Resurfacing of the patella requires a minimum 13 mm thickness and adequate bone stock to hold patellar pegs in place. Adjust the patellar mechanism to allow central patellar tracking.

Reconstruction of the knee after resection arthroplasty for infection poses some unique issues that differ from revision for aseptic loosening or mechanical dysfunction. First, ligament deficiency is more commonly encountered with the aggressive knee débridements required to eradicate infection. Constrained implant designs, both nonhinged and hinged, should be readily available in case less constrained options do not provide the stability needed. The use of medullary stem support for both femoral and tibial components in all reconstructions is advocated. In most cases, metaphyseal bone about the knee is weak from infection and prior débridement of well-fixed implants. Furthermore, mechanical abrasion by ALAC spacers can weaken bone if patient compliance is poor (32). Long medullary stems provide graduated load transfer from metaphysis to diaphysis, which diminishes concentrated forces at the prosthesis-bone interface about the knee joint.

Second, for segmental deficiencies of bone about the knee, the trend for reconstruction after infection is to avoid bulk allografts and instead use a bone substituting megaprosthesis (Fig. 7). There are several reasons for this. First, a structural allograft, which is immunogenic itself, is an independent risk variable for reinfection. Second, an allograft is a three-dimensional porous structure that can potentially harbor bacteria deep inside its core. If there are any remaining bacteria at the time of reimplantation, these bacteria can hide and multiply within the dead allograft. In contrast, a bone substituting megaprosthesis is solid and only its surface is vulnerable. If an early infection develops, there is a much better chance of salvage with incision and drainage than with an allograft that cannot be washed out deep inside its core. Third, healing of an allograft after prior infection is less predictable. The reasons are the presence of less vascular supply, which is due to prior damage from infection, and damaged host bone that may not support the allograft. Furthermore, allograft placement requires more extensile exposure and fixation techniques.

Finally, not infrequently after reconstruction of the infected total knee, ligaments about the knee can stretch out, causing laxity and potential instability. At reimplantation it is hard to assess the overall integrity of the ligament-capsular complex of the knee. What is initially felt as “tight” and/or “intact” may only be scar tissue that will later stretch out and provide less support. At reimplantation, a paradox occurs. If the soft tissue is not fully débrided of excess scar tissue at the time of reconstruction, the knee soft tissues do not generally stretch out. Knee motion remains limited. On the other hand, by fully débriding scar tissues at reimplantation, soft tissues are allowed to stretch during the rehabilitation phase.



(a) (b)

Figure 7 (a) AP radiograph (b) and lateral radiograph of salvage knee prosthesis. These prosthetic components substitute for deficient femoral and tibial bone that would otherwise require allograft bone for reconstruction. In this construct, there are no remaining collateral ligament attachments. Therefore, the femoral and tibial components are linked mechanically with a hinge. AP, anteroposterior.

Unfortunately, this may allow more stretching than the prosthetic system can tolerate. The knee becomes mechanically unstable. At reimplantation, the use of a constrained femoral component design is advocated. A femoral component design that allows either a posterior stabilized tibial insert or a constrained tibial insert to be used is recommended. Not all knee systems incorporate this

design feature. If the posterior stabilized tibial insert cannot support the increased laxity from ligament stretch, a constrained tibial insert can be exchanged later to provide the needed ligament support.

IX. PREVENTION

Periprosthetic infections tend to occur in patients who have a compromised medical/host immune system (13,33–35). At the present time, this fact cannot be changed. However, the treating physician is capable of employing many techniques to minimize the occurrence of periprosthetic knee infection. In general, the strategies revolve around the concept of minimizing bacterial exposure to the prosthetic implants (33–35).

Preoperatively, patients should be carefully examined to determine areas of potential bacterial penetration. Patients who have dental disrepair must have their teeth repaired or extracted. Periodontal disease absolutely must be addressed and must be quiescent before knee replacement surgery. Patients who have a history of recurrent open foot sores should be evaluated by a foot specialist. Treatment should focus on preventing recurrence of these sores. Patients with recurrent rashes or lower extremity stasis sores must have a dermatologist available for quick, appropriate treatment. Additionally, patients must be educated preoperatively on proper hygiene techniques. For example, diabetics must be taught not to draw blood during toenail trimming. Rheumatoid patients who cannot inspect their feet must have a health care provider inspect their feet and web spaces for any breakdown.

During knee replacement surgery, methods to minimize infection include the use of perioperative antibiotics and efficient surgical technique. Perioperative prophylatic antibiotic therapy with a first-generation cephalosporin is still the recommended treatment. Prophylatic antibiotic administration has shown best efficacy when given immediately before surgery. The recommended length of treatment should be 24 hours.

Prolonged surgery time has been implicated as an independent factor for development of periprosthetic knee infection (7,34). Employing a surgical team for knee replacement surgery standardizes all aspects of the procedure including surgical site preparation, intraoperative equipment organization, and equipment sterilization. Personnel familiar with joint replacement equipment provide efficient surgical technique and minimize surgical time.

The use of operative laminar flow rooms and covered surgeon hood systems in reducing the rate of periprosthetic knee infection is debatable. At most major centers, one or both of these systems are used (1,14,33–35). If laminar flow rooms are to be used, studies do show that vertical laminar flow is better than horizontal laminar flow. Horizontal laminar flow systems create turbulent flow

when operating room personnel stand in front of the oncoming flow. This effect is mitigated with vertical laminar flow systems.

Postoperatively, there are several methods to reduce the risk of periprosthetic infection. First, all health care providers should follow standard universal infection precautions. Washing hands between patient visits and using gloves for dressing changes are simple, but very effective, techniques to minimize cross-contamination of surgical wounds. Postoperative wound drainage is a major factor that must not be ignored. A draining knee wound is a direct avenue for bacterial inoculation to the deep tissues. Several studies confirm the higher rate of infection in total knees when drainage is seen more than 4 to 5 days (7,34). If wound drainage occurs, anticoagulation treatment must be modified, and the knee must be immobilized. Persistent drainage beyond 5 days must be treated with open surgical débridement. Antibiotics used alone do not suffice.

X. SUMMARY

Understanding the basic edicts of management of periprosthetic knee infection provides a logical, stepwise approach to treatment. First, treatment should focus on the affected "host" (i.e., patient) and not the "bug" (i.e., bacteria). Surgery and antibiotic chemotherapy cannot succeed in eradicating the infection unless the patient's immune system is adequately competent. Employing a staging system to evaluate patients before treatment provides a framework around which treatment is to be directed. Patients who are more immune-compromised often require more radical surgical treatment. Some may never be rid of infection unless the leg is amputated. In contrast, patients with fully competent immune/medical systems are more likely to respond to surgical débridement and adjuvant antibiotic therapy. Prognosis for salvage in this group tends to be better. Using a staging system provides the information needed to direct treatment.

Second, an understanding of the bacterial biofilm state is key to logical treatment. Bacteria in a biofilm state allow for persistent infection. At present, there are no medically safe methods to "wash off" or eradicate bacterial biofilms. The only way to eradicate the infection is through surgical extirpation. A chronic infection by definition indicates that the bacteria are in a biofilm state. Therefore, treatment of chronic infection always requires removal of prosthetic components. Just as importantly, biofilms form on dead bone and dysvascular soft tissue. These tissues must also be removed to eliminate the infection.

Third, local wound management of periprosthetic knee infection must be incorporated into the management plan. A radical débridement of the knee, whether in an acute or chronic infection, is a vital part of treatment. A simple lavage does not suffice. For acute infections, a full arthrotomy with synovectomy and débridement gives the best chance for cure. For chronic infections, implant

removal and débridement are not enough. Débridement of the medullary canals is also required, as they are very often the source of lingering chronic infection. Acrylic antibiotic-loaded spacers provide the local wound area with concentrated antibiotics. Furthermore, the antibiotic-loaded acrylic spacer maintains the soft tissue envelope. This makes reimplantation easier and often reduces the need for a rotational muscle coverage flap. If local soft tissues are attenuated, closure must not be left under tension. Wounds closed in this manner dehisce and drain, promoting further bacterial contamination. Instead, a muscle flap to cover the affected area takes care of this problem. A muscle flap provides a new vascular supply to the area, allowing the wound to heal. Also, because of its rich vascular supply, the flap acts as an endogenous antibiotic delivery system to the infected area.

Finally, in the reconstruction phase of periprosthetic knee infection, the bone and surrounding soft tissue envelope are often damaged by the infection. Implants should provide additional support to bone and ligaments with revision-style implants. If a patient has a compromised immune system, one should not use bulk support allografts if at all possible. A structural allograft is dead bone with an internal structure where bacteria may hide. If any bacterial colonies are left over from initial débridement, they can be disseminated into and thrive within this dead bone. In this situation, a metallic replacing endoprosthesis is a better choice. If bacterial contamination is present, this can later be washed if there are clinical signs of drainage or infection.

Management of periprosthetic knee infection is demanding. Treatment requires patience and mental fortitude. However, the rewards of successful treatment are satisfying. Patients, knowing that their limb and life are at jeopardy, are grateful for preservation of their limb and leg function.

REFERENCES

1. LS Borden, PF Gearen. Infected total knee arthroplasty. J Arthroplasty 2:27–36, 1987.
2. TS David, MS Vrahas. Perioperative lower urinary tract infections and deep sepsis in patients undergoing total joint arthroplasty. J Am Acad Orthop Surg 8:66–74, 2000.
3. GA Engh, DJ Ammeen. Clinical manifestations of a sometimes silent disease. Orthopedics 22:799–801, 1999.
4. AD Hanssen, JA Rand. Evaluation and treatment of infection at the site of a total hip or knee arthroplasty. Instr Course Lect 48:111–122, 1999.
5. AD Hanssen, JA Rand, DR Osmon. Treatment of the infected total knee arthroplasty with insertation of another prosthesis: the effect of antibiotic-impregnated bone cement. Clin Orthop 309:44–55, 1994.
6. K Hirakawa, BN Stulberg, AH Wilde, TW Bauer, M Secic. Results of 2-stage reimplantation for infected total knee arthroplasty. J Arthroplasty 13(1):22–28, 1998.

7. MJ Spangehl, BA Masri, JX O'Connell, CP Duncan. Prospective analysis of preoperative and intraoperative investigations for the diagnosis of infection at the sites of two hundred and two revision total hip arthroplasties. J Bone Joint Surg Am 81A(5):672–683, 1999.
8. RE Windsor, JN Insall, WK Urs, DV Miller, BD Brause. Two-stage reimplantation for the salvage of total knee arthroplasty complicated by infection. J Bone Joint Surg Am 72A:272–278, 1990.
9. JN Insall, FM Thompson, BD Brause. Two-stage reimplantation for infected total knee arthroplasty. J Bone Joint Surg Am 65A:1087–1098, 1983.
10. KA Martinelli, DT Lemaitre. American Academy of Orthopaedic Surgeons Preview Meeting. Merrill Lynch, Dallas, February 11, 2002.
11. G Cierny, JT Mader, JJ Pennick. A clinical staging system for adult osteomyelitis. Contemp Orthop 10:17–37, 1985.
12. EJ McPherson, MJ Patzakis, JE Gross, PD Holtom, M Song, LD Dorr. Infected total knee arthroplasty: two-stage reirnplantation with a gastrocnemius rotational flap. Clin Orthop 341:73–81, 1997.
13. EJ McPherson, W Tontz Jr, M Patzakis, C Woodsome, P Holtom, L Norris, C Shufelt. Outcome of infected total knee utilizing a staging system for prosthetic joint infection. Am J Orthop 28(3):161–165, 1999.
14. DT Tsukayama, R Estrada, RB Gustilo. Infection after total hip arthroplasty: a study of the treatment of one hundred and six infections. J Bone Joint Surg Am 78A:512–523, 1996.
15. JW Costerton, PS Stewart. Battling biofilms. Sci Am 75–81, 2001.
16. JW Costerton, PS Stewart, EP Greenberg. Bacterial biofilms: a common cause of persistent infections. Science 284:1318–1322, 1999.
17. AG Gristina, JW Costerton. Bacterial adherence to biomaterials and tissue: the significance of its role in clinical sepsis. J Bone Joint Surg Am 67A:264–273, 1985.
18. EJ McPherson, P Holtom, M Patzakis. Location of positive intraoperative cultures in infected total knee arthroplasty. Musculoskeletal Infection Society Annual Meeting. Snowmass and Aspen, CO, 1999.
19. EZ Brown, BN Stulberg, R Sood. The use of muscle flaps for salvage of failed total knee arthroplasty. Br J Plast Surg 47:42–45, 1994.
20. W Calderon, N Chang, SJ Mathes. Comparison of the effects of bacterial inoculation in musculocutaneous and fasciocutaneous flaps. Plast Reconstr Surg 77:785–792, 1986.
21. I Eishima, SJ Mathes, P Paty. Comparison of the intracellular bacterial killing activity of leukocytes in rnusculocutaneous and random-pattern flaps. Plast Reconstr Surg 86:541–547, 1990.
22. M Gerwin, KG Rothaus, RE Windsor, BD Brause, JN Insall. Gastrocnemius muscle flap coverage of exposed or infected knee prostheses. Clin Orthop 286:64–70, 1993.
23. GB Irons, J Fisher, EH Schmitt III. Vascularized muscular myocutaneous flaps for management of osteomyelitis. Orthop Clin North Am 15:473–480, 1984.
24. AA Hofmann, KR Kane, TK Tkach, RL Plaster, MP Camargo. Treatment of infected total knee arthroplasty using an articular spacer. Clin Orthop 321:45–54, 1995.
25. EL Masterson, BA Masri, CP Duncan. Treatment of infection at the site of total hip replacement. Instr Course Lect 47:297–306, 1998.

26. R Emerson, W Head, L Higgins. Comparison of functional knee spacer with a block spacer in the treatment of infected total knee prostheses. American Academy of Orthopaedic Surgeons Annual Meeting. Orlando, FL, 2000.
27. RE Jones, A Cadambi, GE Maale. Antibiotic cement implant composites: a protocol for staged revision of infected total hip and knee arthroplasties. Orthopedics 3:133–143, 1995.
28. EJ McPherson, K Lewonowski, L Dorr. Use of articulated PMMA spacer in the infected total knee arthroplasty. J Arthroplasty 10:87–89, 1995.
29. W Tontz, EJ McPherson. Articulated vs. non-articulated spacers in infected total knee arthroplasty. American Academy of Orthopaedic Surgeons Annual Meeting. San Francisco, 2001.
30. MH Henderson Jr, RE Booth Jr. The use of an antibiotic-impregnated spacer block for revision of the septic total knee arthroplasty. Semin Arthroplasty 2(1):34–39, 1991.
31. N Greene, PD Holtom, CA Warren, RL Ressler, L Shepherd, EJ McPherson, MJ Patzakis. In vitro elution of tobramycin and vancomycin polymethylmethacrylate beads and spacers from Simplex and Palacos. Am J Orthop 27:201–205, 1998.
32. TF Calton, K Fehring, WL Griffin. Bone loss associated with the use of spacer blocks in infected total knee arthroplasty. Clin Orthop 345:148–154, 1997.
33. RH Fitzgerald Jr. Total hip arthroplasty sepsis: prevention and diagnosis. Orthop Clin North Am 23:259–264, 1992.
34. G Peersman, R Laskin, J Davis, M Peterson. Infection in total knee replacement: a retrospective review of 6489 total knee replacements. Clin Orthop 392:15–23, 2001.
35. H Segawa, DT Tsukayama, RF Kyle, DA Becker, RB Gustilo. Infection after total knee arthroplasty: a retrospective study of the treatment of eighty-one infections. J Bone Joint Surg 81A(10): 1434–1445, 1999.
36. EJ McPherson, AD Hanssen, GE Maele, PD Holton, DR Osman. MSIS staging system for periprosthetic infection staging. Musculoskeletal Infection Society 12th Annual Open Scientific Meeting. Snowmass, CO, Aug 1–3, 2002.

11
Diabetic Foot Infection

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I. INTRODUCTION

Approximately 6% of the population of the United States, or over 10 million people, have been diagnosed with diabetes mellitus. The incidence of new cases is close to 800,000 per year (1). Diabetic foot infection utilizes the greatest number of hospital days for the diabetic population. It has been estimated that there are between 50,000 and 80,000 lower extremity amputations per year performed on patients with diabetes mellitus. Foot ulcerations and subsequent infection are the precursors for the vast majority of these amputations. Diabetic ulcers and infections are well known to be complicated and difficult to treat. The pathogenesis of diabetic foot ulcers, and subsequent infections, is complex and involves three active processes: angiopathy, neuropathy, and immunopathy. An understanding of these processes is essential for both treatment and prevention of diabetic foot ulcers. Wound care techniques, antimicrobial and surgical therapy, and adjunctive therapy all contribute to the management of this difficult to treat condition.

II. PATHOGENESIS AND PATHOPHYSIOLOGICAL CHARACTERISTICS

More than 90% of diabetic foot osteomyelitis is caused by a contiguous focus of infection. Angiopathy, neuropathy, and immunopathy frequently lead to decreased defenses of the host and subsequent infection in the diabetic foot (2).

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Peripheral vascular disease is a common finding in the diabetic patient, involving both the large and small vessels, often collaterally (3). Large vessel damage causes changes in the skin, which predispose the diabetic foot to injury. Vascular impairment, as evaluated by measurement of ankle pressure, has been found to correlate with the development of diabetic foot ulcer (4). Microangiopathy is a debated topic. Tooke and colleagues have discussed the "hemodynamic hypothesis" of the pathogenesis of diabetic microangiopathy (5). This hypothesis states that in the early stages, vessel capillaries of diabetic patients have increased microvascular pressure and flow. The increased capillary pressure results in an injury response within the microvascular endothelium. Injury causes release of extravascular matrix proteins that results in microvascular sclerosis. Sclerosis is manifested in the arteriole as hyalinosis and in the capillary as basement membrane thickening, the ultrastructural hallmark of diabetic microangiopathy (6,7). With increasing duration of diabetes, the sclerotic process results in the limitation of vasodilatation with reduced maximal hyperemia and loss of autoregulatory capacity. It has been observed that nailfold capillary pressure is elevated in the early stages of insulin-dependent diabetes, and this elevation is positively correlated with glycemic control, as judged by the glycosilated hemoglobin value at the time of pressure measurement. Tooke and coworkers have suggested a role for intrinsic capillary fragility leading to microhemorrhage and hypothesize that this may explain the potential for rapid advancement of infection through tissue planes (5). Raskin and associates observed a significant reduction in the width of skeletal muscle capillary basement membrane with improved control of blood glucose levels in type I diabetic patients (8).

The importance of restoration of perfusion in the management of diabetic foot problems has been observed. LoGerfo noted that several studies have excluded the existence of an arteriolar or microcirculatory occlusive process (9). Moreover, microvascular disease is not associated with reduction in luminal diameters. If an occlusive lesion existed in the microcirculation, it would be a contraindication for arterial reconstruction. As a consequence of these findings, arterial reconstruction must be considered in every case of arterial occlusion. Wyss and associates showed that arteriopathy does not cause an impairment of oxygen diffusion; peripheral vascular disease is more often related to ulcers in nondiabetic patients, whereas in diabetic patients, neuropathy is usually the underlying cause of foot ulceration (10).

Neuropathy occurs early in the pathogenesis of diabetic foot problems and is the most prominent risk factor for diabetic foot ulcers. All components of nerve function are compromised. The progress of this polyneuropathy is variable, but, in general, the longest, finest fibers are affected first. This includes the motor fibers to the intrinsic muscle of the foot. With the loss of lumbrical function, the toes become drawn up into the "claw" position. As a result, there are points of increased susceptibility to pressure or friction beneath the metatarsophalangeal

joints, over the dorsum of the toes, or at the tips of the toes. In some patients, this process leads to Charcot foot (11,12). Autonomic dysfunction also occurs early in the course of neuropathy. In the foot, autonomic dysfunction results in shunting of blood through direct arteriole-venule communications, diminishing the effectiveness of perfusion (13). The result is loss of hair, sweat, and oil gland function, leading to dry, scaly skin that cracks and fissures easily. Vibration, pain, and temperature sensations are affected more than touch or proprioception. This sensory loss results in a decreased awareness of pressure injury or trauma. The decreased sensation in combination with the motor-nerve-induced deformity sets the stage for ulcerations (14,15).

The contribution of immunopathy to the development of infection in diabetic patients is still controversial. Humoral immunity in the patient with diabetes mellitus appears to be normal (16). Levels of circulating immunoglobulins and number of B lymphocytes have been found to be in the normal range. Also, complement fixation appears to he normal in a mouse model. The impaired defense mechanism appears to be in the cellular immunity; impaired leukocyte function and impaired intracellular killing have been observed. A defect in chemotaxis of polymorphonuclear leukocytes has been described by Mowat and Baum (17). Hyperglycemia appears to be the major determinant of these defects, since they are partially or completely reversed by improved glycemic control. MacCuish and colleagues demonstrated a decrease in phytohemagglutinin-induced lymphocyte transformation in poorly controlled diabetes but not in well-controlled diabetes (18). It has also been displayed that an altered response to some bacterial antigens is present in diabetic patients, regardless of glycemic control (19).

III. CLINICAL PRESENTATION

The patient usually has foot ulceration surrounded by inflammatory signs (erythema, edema, pain, heat, and loss of function), along with the presence of purulent discharge from the wound. The ulceration is typically a round, punched-out, painless area on the plantar surface of the foot under points of bony prominence or pressure. Dorsal lesions can occur with deformities such as hammertoes or result from tight shoes. The ulcerations may have a ring of hyperkeratosis around the periphery. Patients are usually afebrile (20).

IV. DIAGNOSIS

A. Clinical Evaluation

The diagnosis of infection in a patient with a diabetic foot ulceration should be made primarily on clinical findings around the wound. The presence of signs of

inflammation is very common, but in some cases it can be suppressed by the altered immune response and by the angiopathy.

The presence of purulent discharge permits differentiation between infection and a noninfectious cause of inflammation such as Charcot's joint, inappropriate footwear, or excessive weight bearing. The size of the wound and presence of tracts to deep tissues are important findings and should be recorded. Any sinus tract should be explored with a sterile instrument to determine whether bone can be probed.

Constitutional symptoms, such as fever and malaise, are not consistently present. On the basis of clinical findings, several classifications of the diabetic foot wound have been developed. Most of the currently used classification systems are based on the appearance and the depth of the wound. One of the more useful and most commonly used is the Wagner classification (21,22) (Table 1). A similar, expanded classification has been developed by Armstrong and Lavery (23) (Table 2). This classification applies a stage for each grade of foot ulcer. According to a 2001 study, the stage is a better predictor of outcome than the grade of the ulcer (24). Lipsky has suggested a system for classifying infected wounds that is based on the concept of severity of the infection (25) (Table 3). We have used a simplified version of the Wagner classification, the Common Classification System. The four stages in this classification system are cellulitis, ulcer, abscess/osteomyelitis, and gangrene. These categories are based on physicians' common descriptions of diabetic foot abnormality and treatment. We reviewed 8 years of experience with this system in 1998 (26).

Clinical examination of a diabetic patient who has a foot disorder also includes evaluation for neuropathy and vascular insufficiency. A Semmes-Weinstein monofilament can be used to determine the extent of neuropathy by testing and mapping the sensation of the sole of the foot (27). Neuropathy can also be measured by proprioception and vibration by using a 128-Hz tuning fork (28). Determination of the vascular status has implications for the prognosis and the choice of surgical management. The most frequently used techniques are the measurement of ankle brachial blood pressure index (ABI) and transcutaneous

Table 1 Wagner Classification of Diabetic Foot Ulcers

Grade 0	Preulcerative area with no open lesions
Grade 1	Superficial ulceration
Grade 2	Full thickness ulceration to a tendon or capsule; no abscess or osteomyelitis
Grade 3	Deep ulcer with or without bone involvement, with abscess, osteomyelitis, or joint sepsis
Grade 4	Gangrene of part of the foot; foot is salvageable
Grade 5	Gangrene of a majority of the foot; salvage unlikely

Table 2 Armstrong's Wound Classification

Grade 0:	Pre- or postulcerative lesion, completely epithelialized
Grade 1:	Superficial wound not involving tendon, capsule, or bone
Grade 2:	Wound penetrating to tendon or capsule
Grade 3:	Wound penetrating to bone or joint

For each grade, as appropriate
B: infected
C: ischemic
D: infected and ischemic

oxygen tension measurements (29,30). An ABI greater than 0.90 suggests normal circulation; an ABI greater than 0.50 but less than 0.90 suggests mild to moderate vascular disease, and a possible delay in wound healing; and an ABI less than 0.50 suggests severe vascular disease and markedly impaired wound healing (31). Cutaneous oxygen tensions are measured by a modified Clark electrode applied to the skin surface. Measurement of transcutaneous partial pressure of oxygen is easy to perform, but the equipment is not available in all centers (32,33).

B. Laboratory Evaluation

A complete blood count, liver function tests, and electrolytes, serum iron, serum protein, and albumin levels are usually obtained to define the nutritional status and healing capabilities of the diabetic patient. Laboratory values are usually of poor value for the diagnosis of osteomyelitis in the immunocompromised host (34). The white blood cell count, sedimentation rate, and glycosylated hemoglobin level are often elevated in acute osteomyelitis, but normal in chronic bone infection.

C. Imaging Studies

Imaging techniques are of great value for the diagnosis of diabetic foot osteomyelitis. Conventional radiology is still the test of choice for the diagnosis

Table 3 Lipsky Classification of Diabetic Foot Infected Wound

	Superficial ulcer/ cellulitis	Deep soft tissue/ bone involvement	Tissue necrosis/ gangrene	Systemic toxicity
Mild	+	−	−	−
Moderate	+	+/−	+/−	−
Severe	+	+/−	+/−	+

of neuroarthopathy and osteomyelitis. The plain radiographs show bone reabsorption related to osteomyelitis 10 to 14 days after the bone infection has occurred, when 30% to 50% of the bone has been absorbed (35). These bone changes may occur more rapidly in diabetic patients than in nondiabetic patients with osteomyelitis, because of the inability to contain the bone infection in the diabetic patient. The radiographs initially show osteopenia and soft tissue swelling. Early bone changes include thinning of the cortical bone and loss of trabeculae in the cancellous bone. These are followed by cystic changes as the infection evolves. Progressive bone and joint destruction is followed by complete bone and joint loss (36).

Specificity of plain radiographs has been calculated to be no more than 69% when vascular insufficiency is present. Bone radiographic changes may represent neuroarthropathy or healing fractures. Cortical scalloping indicates periosteal ischemia and not necessarily infection. In the diagnosis of diabetic foot osteomyelitis, a baseline radiograph is obtained and then another radiograph is obtained after 10 to 21 days to determine whether progressive bone changes have occurred. Abnormal radiography findings combined with clinical evidence of a contiguous focus of infection are highly predictive of osteomyelitis (37).

When the diagnosis of osteomyelitis is unclear, other imaging studies may be obtained. These studies include radionuclide scans, computerized tomography (CT) scans, and magnetic resonance imaging (MRI). The radionuclide scans are highly sensitive but poorly specific for the diagnosis of osteomyelitis. The technetium-99m scan demonstrates increased isotope accumulation in areas of osteoblastic activity and increased vascularity. False-negative scan results are possible when patients have severe ischemia. False-positive findings are common because of the overlying soft tissue inflammation. Gallium-67 citrate bone scans are very sensitive for the diagnosis of osteomyelitis but have poor spatial discrimination, making it difficult to distinguish between bone and soft tissue inflammation. Thus, investigators often prefer to perform the gallium scan after the technetium-99 three-phase bone scan. The labeled leukocyte scan (usually performed with indium-111) is the most sensitive tool for the diagnosis of acute infection. A negative isotope-labeled leukocyte scan result rules out osteomyelitis in patients with neuroarthropathy (38–40).

Computed axial tomography may be useful in the diagnosis of osteomyelitis to identify areas of devitalized bone and assess the involvement of surrounding soft tissues. This imaging technique may assist in planning the surgical approach. However, in comparison with long bone osteomyelitis, CT scan is less useful in diabetic foot infection, because of the small size of the anatomical structures (41).

MRI is the most sensitive and specific tool in the diagnosis of osteomelitis. MRI is useful in distinguishing areas of neuroarthropathy, which are identified as a low signal on all pulse sequences within bony structures and soft tissues. With

osteomyelitis, high marrow signals on all pulse sequences are seen, except the T_1-weighed images. Because of the high cost of the test, MRI may only be cost-effective for patients who have a questionable diagnosis of osteomyelitis or in planning a difficult surgical approach (42).

D. Soft Tissue and Bone Culture

Swab cultures of ulcers or draining sinuses are not very accurate but are a helpful first step. Swab cultures typically identify only about 66% of the pathogenic bacteria. Blood cultures rarely yield positive findings in osteomyelitis patients since the infection is "walled off" from the rest of the tissues.

Cellulitis and osteomyelitis in the diabetic foot are usually polymicrobial infections (43,44). The most common bacteria are *Staphylococcus aureus*, *Streptococcus* spp., coagulase-negative staphylococci, and enterococci. Gram-negative aerobic organisms including *Proteus mirabilis* and *Pseudomonas aeruginosa* are frequently isolated. Anaerobic bacteria are cultured in approximately 20% of patients. Bone cultures obtained at surgical débridement are of great value for the diagnosis of osteomyelitis. Antibiotic administration must be discontinued 48–72 hours before surgery so residual antibiotics will not retard bacterial growth. A bone sample should have pathological analysis for historical confirmation of the diagnosis (45).

V. TREATMENT AND MANAGEMENT

Diabetic foot infection is very difficult to cure, and osteomyelitis is very challenging to treat and requires a multidisciplinary approach. Consistent and frequent wound care is crucial to the healing process, as well as appropriate antibiotic therapy, good nutrition, and glycemic control.

A. Current Wound Care Techniques

Wound care has an important place in the treatment of a diabetic foot ulcer (46). Wound characteristics must first be accurately evaluated and documented. The color of the wound bed, size, periwound skin appearance, amount of drainage, color, adherence, odor, and location of the wound, must all be assessed. Wound treatment is dynamic, and the products used should reflect the changing stages of the wound. Usually, wound care consists of the use of topical agents (disinfectants, topical antibiotics, products for chemical débridement) and wound dressings. The primary function of a wound dressing is to promote a moist healing environment for tissue repair. Different dressings have different properties, such as exudate absorptive capacity, moisture promotion, ability to débride

nonviable tissue and reduce bacterial colonization, and potential use as an antibiotic delivery system to the wound bed (47). In 2000, tissue engineered skin substitutes (Apligraft and Dermagraft) were used to treat nonhealing wounds (48). A topical gel containing becaplermin (Regranex), a recombinant human platelet–derived growth factor, seems to be promising in enhancing the healing process (49). These new treatments are expensive and may be helpful for selected patients with ulcers that are unresponsive to standard therapy.

B. Off-loading

Pressure reduction, or off-loading, is a critical element in the management of diabetic foot ulcers. The excessive pressure that occurs in a neuropathic diabetic foot must be alleviated in order to facilitate wound healing (50). Several methods have been used for off-loading, such as bed rest, non–weight bearing, crutches, walkers, and myriad orthotic devices. The goal of off-loading is to reduce the pressure at the site of the lesion while maintaining ambulation. Total contact casts are plaster casts that distribute pressure across the plantar foot surface. Since the patient cannot remove the cast, compliance is forced. These devices have been shown to be effective (51). The use of removable devices implies the need for education of the patient about compliance.

C. Antimicrobial Therapy

Several trials of the antibiotic treatment of diabetic foot infections have been published. However, since different study designs, definitions, and endpoints have been used, their results are almost impossible to compare. The overall outcome of those studies is similar; a clinical response can be expected in 80%–90% of patients who have mild to moderate infection (25,52). No regimen emerges as superior to another. Antibiotic treatment usually starts with an empirical regimen. Even if the most important and more common pathogens are covered, the severity of infection is another criterion to guide the choice of antibiotics. In the treatment of severe infections, the margin for error is smaller; therefore, a broader-spectrum agent and intravenous administration are usually needed. All regimens must be active against staphylococci and streptococci. For patients who have severe infections or were previously treated, adequate coverage against gram-negative bacilli and enterococci is given. Gangrenous and foul-smelling wounds are treated with antianaerobic regimens. Initial treatment of a previously untreated patient with a non-limbthreatening infection is focused primarily on staphylococci and streptococci. Initial treatment of limb-threatening infections requires broad-spectrum antibiotics because these infections are frequently polymicrobial (*Stapylococcus aureus*, group B streptococci, other streptococci, Enterobacter-

iaceae, anaerobic gram-positive cocci, and *Bacteroides* spp., including *B. fragilis*) (53,54).

Parenteral drugs effective against staphylococci are nafcillin and clindamycin. Methicillin-resistant staphylococci require glycopeptides (vancomycin, teicoplanin) or newer agents such as oxazolidinones (linezolid). It has been suggested that combination therapy with rifampin can enhance activity against staphylococci.

Oral fluoroquinolones are commonly used with an antistaphylococcal drug in the treatment of these infections. Because of their excellent bioavailability and favorable bone penetration, oral administration of these antibiotics usually replaces parenteral therapy (55). Their spectrum includes aerobic gram-negative bacteria and some gram-positive pathogen. Since their coverage against gram-positive bacteria is sometimes poor and resistance may emerge among *Staphylococcus aureus* strains, their use as single agents is inappropriate.

Other useful antimicrobial agents include ampicillin-sulbactam, amoxicillin-clavulanic acid, trimethoprim-sulfamethoxazole, metronidazole, and minocycline (56).

When cultures and sensitivity tests are available, the regimen may be changed and the antimicrobial spectrum narrowed. However, the response to the empirical regimen is also of great importance: the patient may respond to a treatment ineffective in vitro and, conversely, infection may worsen despite adequate coverage for all the isolated organisms.

The optimal duration of antibiotic therapy has not been extensively studied. Treatment is given for 2 weeks for infections that involve only soft tissues (25). The treatment is started by the intravenous route and continued orally since clinical improvement is noticed. Bone infection requires a longer course of antibiotics, lasting 4 to 6 weeks. The antibiotic treatment can be shorter if the infected bone is surgically removed. When an amputation is performed proximal to the bone and soft tissue infection, antibiotic therapy is given for 1 to 3 days. If surgical treatment is not possible or acceptable to the patient, a long-term suppressive treatment is given (57).

D. Surgical Treatment of Diabetic Foot Osteomyelitis

When a definitive surgical procedure would lead to unacceptable patient morbidity or disability, or in cases in which the patient refuses surgical treatment, a long-term suppressive antibiotic therapy is generally offered. However, most of these patients require a definitive surgical procedure (58). Local débridement surgery may be performed for a patient who has osteomyelitis in a bone amenable to débridement. Débridement is performed on viable hard and soft tissues, where good bleeding is present. Bleeding in and around diabetic bone may be limited by ischemia. Unless good tissue oxygen tension is present or provided, the wound does not heal and

ultimately requires an ablative procedure. The patient who has extensive osteomyelitis and marginal or poor tissue oxygen perfusion usually requires some type of ablative surgery (22,59). Digital and ray resections, transmetatarsal amputations, midfoot disarticulation, and Chopart's, Lisfranc's, and Syme's amputations (amputation of the foot with retention of the heel pad) permit the patient to ambulate without a prosthesis. The amputation level is determined by the vascularity and potential viability of the tissues proximal to the site of infection and the requirement of thorough débridement. The amputation site must also be stable and not prone to early breakdown after surgery. It is important to assess the vascularity of the tissue at the amputation site to determine the potential for successful wound healing. As a result of performing early distal vascular bypass surgery, angioplasty or angioplasty plus stenting is often possible to provide enough blood flow to allow healing in the area to be débrided or ablated (60).

E. Adjunctive Therapy of Diabetic Foot Osteomyelitis

Despite advances in antimicrobial treatment and in the management of diabetic foot osteomyelitis, the need for radical surgical treatment (amputation) is still high. Therefore, some approaches have been studied to increase the cure rate and avoid amputation. Hyperbaric oxygen has been used for many years as an adjunctive treatment. Oxygen plays an important role in the physiological mechanisms of wound healing (61). Hyperbaric oxygen (HBO) therapy may raise tissue oxygen tensions to levels at which wound healing can be expected. Moreover, phagocitic activity requires optimal oxygen tensions. HBO increases the killing ability of leukocytes, is lethal for certain anaerobic bacteria, and has been associated with anti-inflammatory activity (62). Several studies have shown the beneficial activity of HBO in the therapy of diabetic foot ulcers. In one comparative study, Zamboni and associates showed a greater reduction of the wound surface area in the HBO-treated group than in a group treated with antibiotics alone (63). Also, Faglia and colleagues demonstrated a reduction in the amputation rate in the HBO-treated group when compared with a group treated only with antibiotics (64). In this study, diabetic patients primarily had ischemic ulcers.

In 1997 recently, human recombinant granulocyte colony-stimulating factor (G-CSF) was studied as an adjunctive therapy for the treatment of diabetic foot infection. This agent increases the release of neutrophils from bone marrow, improves neutrophile function, and has been used in the treatment of infection in nonneutropenic patients. Gough and associates administered G-CSF for 7 days in a randomized trial. G-CSF-treated patients displayed faster eradication of pathogens, quicker resolution of cellulitis, shorter hospital stay, shorter duration of antibiotic treatment, and no need for surgery, when compared with an antibiotic-only treatment group (65). In a randomized trial, de Lalla and colleagues treated

diabetic patients who had limb-threatening infections with G-CSF plus standard antimicrobial therapy for 21 days. This administration was associated only with a lower rate of amputation, without any significant difference in cure or improvement (66). In a more recent trial, Yonem and colleagues confirmed the improvement in neutrophil function, but without any clinically significant effect (67). Further studies are needed to support recommendations about the use of G-CSF in diabetic foot infections.

VI. PREVENTION

Education, orthotics, nonprescription self-care, and common sense can prevent or heal early diabetic foot ulcers. Education must emphasize standard foot care. There should be emphasis on the daily inspection of the toes and the feet. Foot washing and moisturizing with creams are mandatory to prevent skin openings. Patients should avoid activities, such as walking barefoot or wearing improperly fitted shoes, that might cause unnecessary trauma to neuropathic or angiopathic feet.

VII. SUMMARY

Infections in the diabetic foot require complex care. Although not all foot infections can be prevented, a dramatic reduction in their frequency has been achieved through a multidisciplinary approach to patient management involving orthopedic and vascular surgeons, infectious disease specialists, primary care physicians, nurse educators, and orthotic technicians. Neuropathy, angiopathy, and immunopathy are predisposing factors for the development of the diabetic foot infection. Infections have differing severity, ranging from cellulitis and ulcers to osteomyelitis and gangrene. Antimicrobial treatment is usually performed with combinations of different antibiotics. Antibiotics are administered initially by the intravenous route and, when an improvement is seen, continued by the oral route. Surgical treatment includes débridement and various levels of amputation. Poor blood glucose control, poor patient compliance with treatment regimens, as well as smoking, obesity, and concomitant medical problems hinder the healing process. Prevention of diabetic foot problems is based on patient education, good blood glucose control, and proper foot care.

REFERENCES

1. Center for Disease Control. Prevalence and Incidence of Diabetes. Morbid Mort Wkly Rep 139:809–812, 1998.

2. WS Joseph, JL LeFrock. The pathogenesis of diabetic foot infections—immunopathy, angiopathy, and neuropathy. J Foot Surg 26:S7–S11, 1987.
3. C Dinerstein, R Mason, F Giron. Lower extremity complications of diabetes mellitus. Surg Rounds 7:26–41, 1984.
4. L Delbridge, M Appleberg, TS Reeve. Factors associated with development of foot lesions in the diabetic. Surgery 93:78–82, 1983.
5. JE Tooke, PD Brash. Microvascular aspects of diabetic foot disease. Diabet Med 13:S26–S29, 1996.
6. SG Goldemberg, M Alex, RA Joshi, HT Blumenthal. Nonatheromatous peripheral vascular disease of the lower extremity in diabetes mellitus. Diabetes 8:26l–273, 1959.
7. O Aagenaes, H Moe. Light- and electron-microscope study of skin capillaries of diabetics. Diabetes 10:253–258, 1961.
8. P Raskin, AO Pietri, R Unger, WA Shannon Jr. The effect of diabetic control on the width of skeletal muscle capillary basement membrane in patients with type I diabetes mellitus. N Engl J Med 309:1546–1550, 1983.
9. FW LoGerfo, JD Coffman. Vascular and microvascular disease in the diabetic foot: implication for foot care. N Engl J Med 311:1615–1619, 1984.
10. CR Wyss, FA Matsen, CW Simmons, EM Burgess. Transcutaneous oxygen tension measurements on limbs of diabetics and non diabetics with peripheral vascular disease. Surgery 95: 339–346, 1984.
11. L Klenerman. The Charcot joint in diabetes. Diabet Med 13:S52–S54, 1995.
12. H Partsh. Neuropathies of the ulcero-mutilating types: clinical aspects, classification, circulation measurements. Vasa 6:1–48, 1977.
13. AJM Boulton, JHB Scarpello, JD Ward. Venous oxygenation in the diabetic neuropathic foot: evidence for arteriovenous shunting? Diabetologia 22:6–8, 1982.
14. JE Deanfield, PR Daggett, MJG Harrison. The role of autonomic neuropathy in diabetic foot ulceration. J Neurol Sci 43 :203–210, 1980.
15. ME Edmonds, KH Nicolaides, PJ Watkins. Autonomic neuropathy and diabetic foot ulcerations. Diabet Med 3:56–59, 1986.
16. RE Dolkart, B Halpern, J Perlman. Comparison of antibody response in normal and alloxan diabetic mice. Diabetes 20:162–167, 1971.
17. AG Mowat, J Baum. Chemotaxis of polymorphonuclear leukocytes from patients with diabetes mellitus. N Engl J Med 284:621–627, 1971.
18. AC MacCuish, SJ Urbaniak, CJ Campbell, LJ Duncan, WJ Irvine. Phytohaemoagglutinin transformation and circulating lymphocyte subpopulation in insulin-dependent diabetic patients. Diabetes 23:708–712, 1974.
19. JI Casey, BJ Heeter, KA Klyshevich. Impaired responses of lymphocytes of diabetic subjects to antigen of Staphylococcus aureus. J Infect Dis 136:495–501, 1983.
20. RT Laughlin, JH Calhoun, JT Mader. The diabetic foot. J Am Acad Orthop Surg 3:218–225, 1995.
21. FW Wagner Jr. The diabetic foot. Orthopedics 10:163–172, 1987.
22. JH Calhoun, J Cantrell, J Cobos, J Lacy, RR Valdez, J Hokanson, JT Mader. Treatment of diabetic foot infection: Wagner classification and outcome. Foot Ankle 9:101–106, 1988.

23. DG Armstrong, LA Lavery. Diabetic foot ulcers: prevention, diagnosis and classification. Am Fam Physician 15:1325–1332, 1998.
24. SO Oyibo, EB Jude, I Tarawneh, HC Nguyen, DG Armstrong, LB Harkless, AJ Boulton. The effects of ulcer size and site, patient's age, sex and type and duration of diabetes on the outcome of diabetic foot ulcers. Diabetic Med 18:133–138, 2001.
25. BA Lipsky. Evidence-based antibiotic therapy of diabetic foot infections. FEMS Immunol Med Microbiol 26:267–276, 1999.
26. JH Calhoun, P Keogh, S Koen, JT Mader. Diabetic foot infections: 902 cases: a prospective study of protocol versus non-protocol treatment. American Orthopaedic Foot and Ankle Society Meeting. New Orleans, March 22, 1998.
27. JM Sosenko, M Kato, R Soto, DE Build. Comparison of quantitative sensory-threshold measures for their association with foot ulceration in diabetic patients. Diabet Care 13:1057–1061, 1990.
28. L Klenerman, C McCabe, D Cogley, S Crerand, P Laing, M White. Screening for patients at risk of diabetic foot ulceration in a general diabetic outpatient clinic. Diabet Med 13:561–563, 1996.
29. J Apelquist, J Castenfors, J Larsson, A Stensom, CD Agardh. Prognostic value of systolic ankle and toe blood pressure levels in outcome of diabetic foot ulcer. Diabet Care 12:373–378, 1989.
30. SA Carter. Clinical measurement of systolic pressures in limbs with arterial occlusive disease. JAMA 207:1869–1874, 1969.
31. M Kalani, K Brismar, B Fagrell, J Ostergren, G Jorneskog. Transcutaneous oxygen tensions and toe blood pressure as predictors of outcome of diabetic foot ulcers. Diabet Care 22:147–151, 1999.
32. KS Christensen, M Klark. Transcutaneous oxygen measurements in peripheral occlusive disease. An indicator of wound healing in leg amputation. J Bone Joint Surg 68:423–426, 1986.
33. PJ Sheffield. Measuring tissue oxygen tension: a review. Undersea Hyperb Med 25:179–188, 1998.
34. DG Armstrong, LA Lavery, M Sariaya, H Ashry. Leucocytosis is a poor indicator of acute osteomyelitis of the foot in diabetes mellitus. J Foot Ankle Surg 35:280–283, 1996.
35. F Di Gregorio, A Bray, A Pedicelli, C Settecasi, F Priolo. Diagnostic imaging of the diabetic foot. Rays 22:550–561, 1997.
36. RD Boutin, J Bossmann, DJ Santgoris, D Reilly, D Resnick. Update on imaging of orthopaedic infection. Orthop Clin North Am 29:41–66, 1998.
37. DW Shults, GC Hunter, KE McIntyre, FN Parent, JJ Piotrowski, VM Bernhard. Value of radiographs and bone scans determining the need for therapy in diabetic patients with foot ulcers. Am J Surg 158:595–530, 1989.
38. W Becker. Imaging osteomyelitis and the diabetic foot. Q J Nucl Med 43:9–20, 1999.
39. JE Johnson, EJ Kennedy, MJ Shereff, NC Patel, BD Collier. Prospective study of bone, indium-111-labeled white blood cell, and gallium-67 scanning for the evaluation of osteomyelitis in the diabetic foot. Foot Ankle Int 17:10–16, 1996.
40. J Harvey, MM Cohen. Technetium-99-labeled leukocytes in diagnosing diabetic osteomyelitis in the foot. J Foot Ankle Surg 36:209–214, 1997.

41. BR Williamson, DC Teates, CD Phillips, BY Croft. Computed tomography as a diagnostic aid in diabetic and other problem feet. Clin Imaging 13:159–163, 1989.
42. D Weinstein, A Wang, R Chambers, CA Stewart, HA Motz. Evaluation of magnetic resonance imaging in the diagnosis of osteomyelitis in diabetic foot infections. Foot Ankle 14:18–22, 1993.
43. LA Lavery, M Sariaya, H Ashry, LB Harkless. Microbiology of osteomyelitis in diabetic foot infections. J Foot Ankle Surg 34:61–64, 1995.
44. AT El-Tahawy. Bacteriology of diabetic foot. Saudi Med J 21:344–347, 2000.
45. J Wheat. Diagnostic strategies in osteomyelitis. Am J Med 78(suppl 6B):218–224, 1985.
46. JM Dunn. Local wound care in the diabetic. Clin Podiatr Med Surg 4:413–418, 1987.
47. MR Day, SE Fish, RD Day. The use and abuse of wound care materials in the treatment of diabetic ulcerations. Clin Podiatr Med Surg 15:139–149, 1998.
48. VJ Falanga. Tissue engineering in wound repair. Adv Skin Wound Care 13:15–19 2000.
49. TJ Wieman, JM Smiell, Y Su. Efficacy and safety of a topical gel formulation of recombinant human platelet-derived growth factor-BB (becaplermin) in patients with chronic neuropathic diabetic ulcers. Diabet Care 21:822–827, 1998.
50. JH Bauman, JP Girling, PW Brand. Plantar pressures and trophic ulceration. J Bone Joint Surg 45:652–673, 1963.
51. DR Sinacore. Total contact casting for diabetic neurotrophic ulcers. Phys Ther 76:296–301, 1996.
52. D Pittet, B Wyssa, C Herter-Clavel, K Kursteiner, J Vaucher, PD Lew. Outcome of diabetic foot infections treated conservatively: a retrospective cohort study with long-term follow-up. Arch Intern Med 159:851–856, 1999.
53. BA Cunha. Antibiotic selection for diabetic foot infections: a review. J Foot Ankle Surg 39:253–257, 2000.
54. DN Gerding. Foot infections in diabetic patients: the role of anaerobes. Clin Infect Dis 20(suppl 2):S283–S288, 1995.
55. LO Gentry, GG Rodriques. Oral ciprofloxacin compared with parenteral antibiotics in the treatment of osteomyelitis. Antimicrob Agents Chemother 34:40–43, 1990.
56. P Venkatesan, S Lawn, RM MacFarlane, EM Fletcher, RG Finch, WJ Jeffcoate. Conservative management of osteomyelitis in the feet of diabetic patients. Diabet Med 14:487–490, 1997.
57. BA Lipsky, AR Berendt. Principle and practice of antibiotic therapy of diabetic foot infections. Diabet Metab Res Rev 16(suppl 1):S42–S46, 2000.
58. VG Ha, H Siney, JP Danan, C Sachon, A Grimaldi. Treatment of osteomyelitis in the diabetic foot: contribution of conservative surgery. Diabet Care 19:1257–1260, 1996.
59. MD Kerstein, V Welter, V Gahtan, AB Roberts. Toe amputation in the diabetic patient. Surgery 122:546–547, 1997.
60. FW LoGerfo, GW Gibbons, FB Pomposelli Jr, DR Campbell, A Miller, DV Freeman, WC Quist. Trends in the care of the diabetic foot: expanded role of arterial reconstruction. Arch Surg 127:617–621, 1992.
61. DR Knighton, IA Silver, TK Hunt. Regulation of wound-healing angiogenesis: effect of oxygen gradients and inspired oxygen concentration. Surgery 90:262–269, 1981.

62. G Sumen, M Cimsit, L Eroglu. Hyperbaric oxygen treatment reduces carrageenan-induced acute inflammation in rats. Eur J Pharmacol 431:265–268, 2001.
63. WA Zamboni, HP Wong, LL Stephenson, MA Pfeifer. Evaluation of hyperbaric oxygen for diabetic wounds: a prospective study. Undersea Hyperb Med 24:175–179, 1997.
64. E Faglia, F Favales, A Aldenghi, P Calia, A Quarantiello, G Oriani, M Michael, P Campagnoli, A Morabito. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer. Diabet Care 19:1338–1343, 1996.
65. A Gough, M Clapperton, N Rolando, AVCM Foster, JP Howard, ME Edmonds. Randomised placebo-controlled trial of granulocyte-colony-stimulating factor in diabetic foot infection. Lancet 35:855–859, 1997.
66. F de Lalla, G Pellizzer, M Strazzabosco, Z Martini, G Du Jardin, L Lora, P Fabris, P Benedefti, G Erie. Randomized prospective controlled trial of recombinant granulocyte colony-stimulating factor as adjunctive therapy for limb-threatening diabetic foot infection. Antimicrob Agents Chemother 45:1094–1098, 2001.
67. A Yonem, B Cakir, S Guler, OO Azal, A Corakci. Effects of granulocyte-colony stimulating factor in the treatment of diabetic foot infection. Diabetes Obes Metab 3:332–337, 2001.

12
Hematogenous Pyogenic Infection of the Spine

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I. CLASSIFICATION

Hematogenous spinal infection is a category of disease that encompasses several entities with characteristic presentations and clinical courses. It can be pyogenic (bacterial), granulomatous (tuberculosis or fungal), or parasitic (echinococossis). In general, pyogenic infection of the spine has been reported as either spondylodiscitis or pyogenic osteomyelitis (1). Isolated diskitis, or infection limited solely to the disk space, has been identified as a complication of surgery or discography (2). Diskitis can also affect children (3); however, in 1996 magnetic resonance imaging (MRI) findings depicted cases of diskitis in children as actually being spondylodiskitis (4). These findings have been corroborated in adults by other findings of concurrent disk and vertebral body involvement (5). However, granulomatous infection, especially tuberculosis, may be a spondylitis in the initial stages (6), and brucella infection, as is manifested radiologically, very often remains as spondylitis. Pure pyogenic spondylitis and diskitis have also been reported with certainty (7) (Figs. 1 and 2). The concept of spondylitis (denoting osteomyelitis of the vertebral body) originates from the theory that, in adults, infection starts in the subchondral bone as an osteomyelitic lesion and then spreads into the adjacent intervertebral disk (1,8). Table 1 shows the incidence of the

different manifestations of pyogenic spinal infections. Our findings (95% in a series of 101 cases) (7) show that spondylodiskitis represents the vast majority of pyogenic spinal infections. This supports the hypothesis expressed by Ghormley and associates (9), who stated that intervertebral disk space infection and vertebral osteomyelitis were probably different stages of the same disease process.

Epidural abscess can complicate pyogenic infection of the spine in 33% of cases and is referred to as *secondary epidural abscess*. When it is found as an isolated entity, independently of spondylodiskitis, it is referred to as *primary epidural abscess*, which constitutes 2% of all spinal infections. Six percent of all

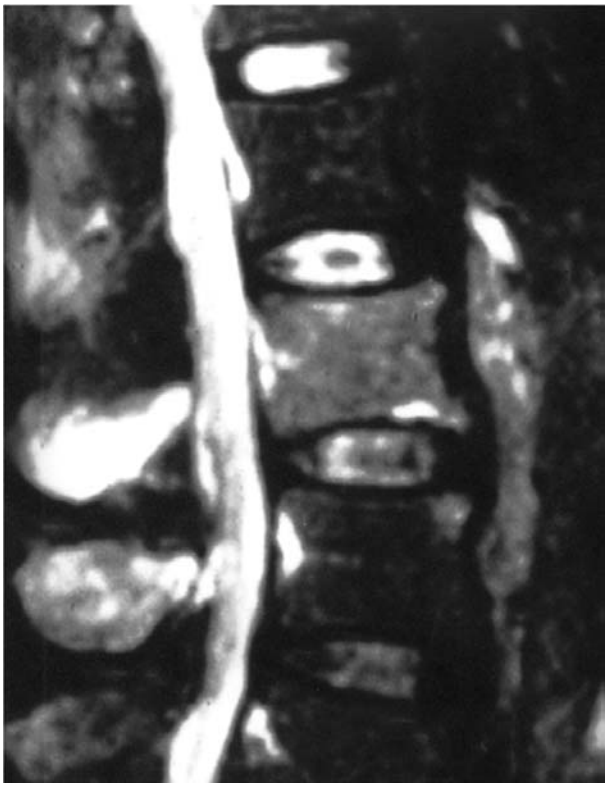


Figure 1 Sagittal T_2-weighted MRI image demonstrating homogenous high-intensity signal of the L3 vertebral body suggesting spondylitis. The infection process was confirmed by percutaneous transpedicular biopsy. MRI, magnetic resonance imaging (From Ref. 7.)

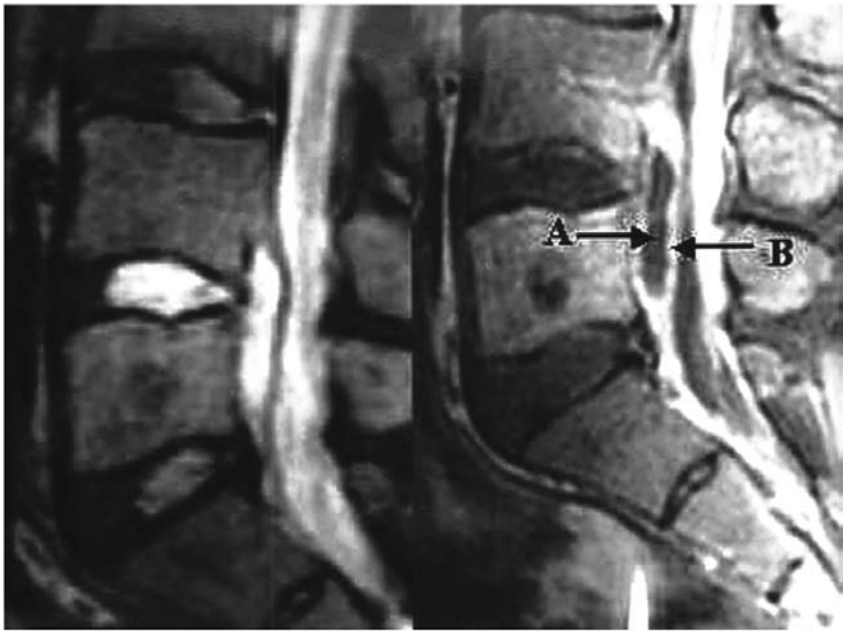


Figure 2 A rare case of hematogenous pyogenic diskitis. Left, T_2-weighted MRI-sagittal image showing high-intensity signal in the L4-L5 disk space and a high-intensity signal posteriorly in the corresponding epidural space suggestive of purulent material. Right, gadolinium-enhanced T_1-weighted MRI image demonstrating a low-intensity signal in the anterior epidural space at the L4-L5 level suggesting pus. Note: The pus is surrounded by a ring of hyperintense signals, suggesting vascular inflammatory granulation tissue (see arrow B). MRI, magnetic resonance imaging.

Table 1 Nomenclature and Incidence of Manifestations of Pyogenic Spinal Infection

Pyogenic infection of the spine	Different stages of spondylodiskitis	Diskitis	1%	Pyogenic vertebral osteomyelitis
		Spondylitis	1%	
		Spondylodiskitis	95%	
	Secondary epidural abscess		33%	
	Primary pyogenic epidural abscess		2%	
	Pyogenic facet arthropathy		1–6%	

epidural abscesses are primary in nature and 94% are secondary; the secondary are far the most common (7). Secondary epidural abscesses usually occupy the anterior epidural space and may spread posteriorly, whereas primary epidural abscesses are usually confined to the posterior epidural space. The anatomical location of an epidural abscess dictates the most appropriate surgical approach.

A 1999 report (10) stated that the annual frequency of spinal epidural abscess is on the rise. This increase is due, in part, to sophisticated spinal imaging techniques with more sensitive diagnostic accuracy, on one hand, as well as several other factors, such as intravenous drug abuse, invasive spinal studies (11) (epidural catheter, discography, etc.), and the growing number of spine surgical procedures, on the other. The overall frequency is quoted to range between 0.2% and 1.2% of hospital admissions, or 0.1% of all hospital admissions during the decade 1983–1993.

Hematogenous pyogenic facet joint infection is a rarely diagnosed condition, representing approximately 6% of all pyogenic spinal infection in one series

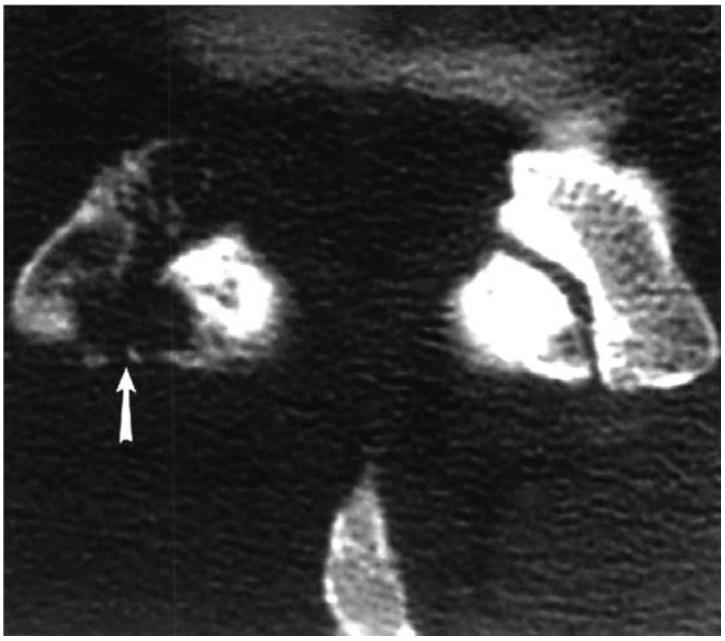


Figure 3 Axial computed tomographic scan through the lumbar facet joints. Notice the erosive bony changes (arrow) of the involved right facet joint. (From Ref. 12.)

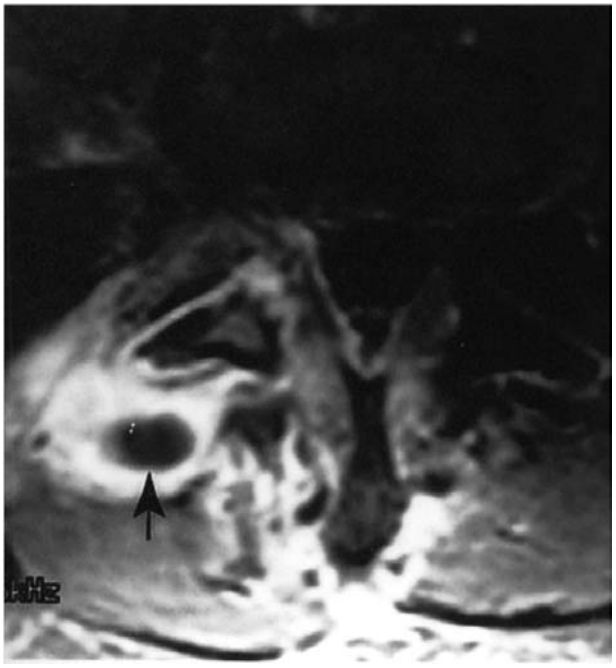


Figure 4 Axial, contrast-enhanced T_1-weighted MRI demonstrating infected right facet joint with adjacent paraspinal muscle enhancement and abscess formation (arrow). MRI, magnetic resonance imaging (From Ref. 12.)

(12). Thirty cases have been reported in the literature (Figs. 3 and 4). Twenty-seven of these were located in the lumbar spine and three were located in the subaxial cervical spine (13). Pyogenic infection involving the C1-C2 facet joint (13–16) has been associated with osteomyelitis of the occipitoatlantoaxial complex and/or the odontoid process, suggesting that it may be a separate pathological entity from isolated hematogenous facet joint infection. Approximately 25% of lumbar facet joint infections are associated with epidural abscess formation (17–22) and nearly 30% of these are accompanied by a severe neurological deficit (12). In the cervical spine, two of the three reported cases were associated with epidural abscess formation, and all three patients demonstrated a neurological deficit ranging in severity from hemiparesis to unilateral upper extremity weakness. This suggests that cervical facet joint infections are associated with a greater rate of morbidity than those of the lumbar spine (12).

Table 2 Bacteriological Characteristics of Spinal Infection

Overall results		
No organism	24.4%	(24/98)
Isolated bacteria	75.5%	(74/98)
One bacterium	51.0%	(50/98)
Two bacteria	16.3%	(16/96)
Polybacteria	8.1%	(8/98)
Gram-positive bacteria[a]		
Staphyloccus species	62.7%	(64/98)
MSSA	36.2%	(37/98)
MSSE	14.7%	(15/98)
MRSA	6.8%	(7/98)
MRSE	4.9%	(5/98)
Streptococcus species	19.6%	(20/98)
Enterococcus Gr D	3.9%	(4/98)
Diphtheroids	1.9%	(2/98)
Citobacter	0.9%	(1/98)
Gram-negative bacteria		
Pseudomonas aeruginosa	3.9%	(4/98)
Escherichia coli	2.9%	(3/98)
Enterobacter spp.	0.9%	(1/98)
Providencia spp.	0.9%	(1/98)
Proteus mirabilis	0.9%	(1/98)
Stento Malo	1.9%	(2/98)
Anaerobes	2.9%	(3/98)

[a] MSSA, methicillin-sensitive *Staphyloccus aureus*; MSSE, methicillin-sensitive *Staphyloccus epidermidis*; MRSA, methicillin-resistent *S.* aureus; MRSE, methicillin-resistant *S. epidermis.*

II. BACTERIOLOGICAL AND RISK FACTORS

A. Bacteriological Factors

Tissue culture data are listed in Table 2. The most commonly isolated organism in our series was *Staphylococcus aureus* (62.7%) (23). This accords with most of the reported literature, as *Staphylococcus aureus* accounts for 42% to 84% of isolated organisms (2,3,23–32), followed in frequency by *Streptococcus* species and gram-negative bacilli (3,8,24,26,27,32–34). *Staphylococcus epidermidis* (coagulase-negative *Staphylococcus* sp.) is not an unusual organism; it occurred in 14.7% of a reported series (23) and can occur spontaneously in non-compromised

hosts, in contrast to conclusions of previous publications (11,35–39). Multiple organisms have been present in 24.4% of our cases (23) and have been shown to occur at approximately the same rate by others (1,3,40). Polymicrobial infections do not alter patient outcome (7,23).

Negative culture results were obtained 24.4% of the time in our series, a rate consistent with that of other investigators (27,41,42).

B. Risk Factors

Risk factors for spinal infections are listed in Table 3. Many spinal infections are preceded by infections elsewhere (genitourinary tract, soft tissues, upper respiratory, or gastrointestinal tract), as observed in our series (2,3,7,8,31,43–48). Risk factors that compromise the immune system, such as diabetes mellitus, rheumatoid arthritis, or chronic steroid use (8,26,29,40,44,45,48–51), render the host more susceptible to spinal infections. It also should be noted that approximately one-fourth of our patients had a history of intravenous drug abuse. The incidence of ankylosing spondylitis as a predisposing factor in our series was 1% (7), reflecting the findings of Kabasakal and colleagues (52), who reported that 8% of ankylosing spondylitis cases are complicated by spondylodiskitis.

Trauma may also play a role in spondylodiskitis and epidural abscess (37,53,54) it occurred in 1% of our cases (23).

III. PATHOLOGICAL AND HISTOPATHOLOGICAL CHARACTERISTICS

Initial hematogenous spread of infection in the spine, in most cases, affects the anterior subchondral bone in the vertebral body adjacent intervertebral disk and

Table 3 Risk Factors for Pyogenic Spinal Infection[a]

Liver diseases	9.9%	(10/101)
Diabetes	13.8%	(14/101)
End-stage renal disease	7.9%	(8/101)
Intravenous drug abuse	24.8%	(25/101)
Tobacco use	24.8%	(25/101)
Malignancy and HIV	7.9%	(8/101)
Infection elsewhere	29.7%	(30/101)
Ankylosis spondylodiskitis	1.0%	(1/101)
Trauma	1.0%	(1/101)

[a] HIV, human immunodeficiency virus.

then involves the disk space. However, in adults, disk infection can also be caused by spinal invasive procedures or by hematogenous spread of microorganisms directly to the periphery of the intervertebral disk (55,56).

Acute inflammation mostly commonly produces histological changes in the disk tissue; it was found in 75% of surgical specimens with disk tissue (57). Histopathological features include vascular proliferation, myxoid degeneration, and necrosis of the disk tissue. The adjacent bone shows evidence of chronic osteomyelitis with marrow fibrosis and a variable amount of plasma cell infiltration mixed with lymphocytes in 33% of cases. Evidence of acute osteomyelitis can also be present. The diagnostic yield for detecting the pathogenic organism in tissue sections with the use of histochemical stains is rather low (15%); usually the organism is detected in severe cases with florid acute inflammation and abscess formation (44%). Although histopathological evaluation has high diagnostic accuracy at biopsy, tissue should be submitted for culture, which has higher sensitivity and specificity for detecting the etiological organism.

IV. CLINICAL MANIFESTATION AND DIAGNOSTIC CHALLENGES

Male patients predominated in our series, constituting 75.2% (7). Other studies found male patient distributions of 51% (58) to 81% (5), and even 91% (28); in several reports predominance was approximately 60% (25,29,44,59).

Historically, the greatest challenge in treating infections of the vertebral column has been properly diagnosing the condition in a timely fashion. Patients typically report insidious onset of back or neck pain that is often misdiagnosed as a strain or attributed to degenerative changes (29,30). Proper diagnosis can even be delayed for months (46).

Laboratory studies such as leukocyte count and erythrocyte sedimentation rate (ESR) can be construed as diagnostic challenges since they are not sensitive and are nonspecific (7). According to reports in the literature, elevated leukocyte counts range from 13% to 60% (3,26,28,29,31,40,44,60) of cases. Levels of ESR are elevated more commonly, ranging from 73% to 100% (8,26–29,31,32,40,44) of cases. In our series, leukocyte count and ESR rate values were elevated only 42% and 81% of the time, respectively, in cases of pure spondylodiskitis (23), However, there was a statistically significant ($p < 0.001$) tendency toward association of elevated leukocyte counts and erythrocyte sedimentation rates with epidural abscess, suggesting that these tests are more sensitive in the presence of epidural abscess (leukocyte count, 89.6%; ESR, 100%) (23). This implies that these parameters, when elevated, represent “red flags” for a more serious condition.

Plain radiographs may take not show any signs of infectious changes for 2 to 12 weeks (28,44). However, the clinician equipped with a knowledge of risk factors for spinal infection (such as preexisting infection of the genitourinary, gastrointestinal, or upper respiratory tracts, or immunosuppression), a high level of suspicion, and sensitive imaging modalities (i.e., magnetic resonance imaging and bone and gallium scans) can make an accurate diagnosis, even for indolent infections, in as little as 2 weeks from initial presentation (7,61).

Complications of spondylodiskitis are deformities and epidural abscesses predisposing to mechanical (spinal pain and deformity) and neurological compromise, respectively (7). The most dreaded complication is paralysis. Thecal sac compression can be caused by either frank epidural abscess (29%) (23) or epidural inflammatory granulation tissue of spondylodiskitis (6%) (23). The condition of spinal epidural abscess still carries significant morbidity (11%–30%) and mortality (3%–30%) rates (62) when paraplegia is present; the prognosis for recovery is very poor (24). In our series, 37% of patients who had epidural abscess had paraplegia (23), only 23% recovered completely, and 7.7% had a partial recovery; the mortality rate was 7.7%.

The most frequent anatomical location of spondylodiskitis was the lumbar spine (56.1%), followed by the thoracic (33.7%) and the cervical spine (10.2%) (23). As has been reported in the literature (43), we encountered secondary epidural abscess most commonly in the lumbar spine (39.3%), followed by the thoracic spine (33.3%) and cervical spine (27.2%) (23). In contrast, the most frequent anatomical site for thecal sac encroachment, either by epidural abscess or by epidural granulation tissue, was the cervical spine (90%), followed by the thoracic (33%) and the lumbar spine (23.6%) (23). However, dreadful neurological complications (paraparesis or paraplegia) as a result of thecal sac compression occurred more frequently in the thoracic (81.8%) and cervical (55.6%) regions, as opposed to the lumbar (7.7%) spine (23). These findings are in agreement with a previous report (50) that more cephalad levels of involvement are more prone to development of neurological changes, although this report (50) showed a higher incidence of paraplegia in the cervical spine, in contrast to the thoracic spine in our series (23). The poor prognosis of the thoracic epidural abscess can be attributed to the small subarachnoid space in the thoracic spine and its tenuous vascularity. These two factors can predispose to readier mechanical compromise and thrombosis of the nutrient vessels, respectively. Therefore, in cases of cervical or thoracic infection, more caution should be exercised to assess possible secondary epidural abscess formation and prevent its neurological sequelae. There are also other factors, apart from anatomical location of infection (more cephalad location), that predispose to paralysis, such as increases in age, steroid use, diabetes, and rheumatoid arthritis (50).

Secondary epidural abscess resulting from spondylodiskitis occurred in 33% of our patients, compared with a report of 38% (24) and a review citing rates of 4% to 11% (63).

Purulent epidural abscess had a poorer prognosis than inflammatory epidural granulation tissue (18% versus 100% complete or partial recovery), as did paralysis in comparison to paraparesis (31% versus 100% recovery) (7).

Primary epidural abscess, in contrast, was rare in our series, constituting only 2% of all spinal infections, but carried a grave prognosis (23). Both patients in our series with this condition had severe neurological deficits and neither recovered after surgical decompression. Previous reports in the literature showed higher rates of primary epidural abscess formation, but several of these studies were conducted without the use of sophisticated imaging. More recent studies, which included MRI, showed primary abscess rates of 12% (54), 14% (34), and 29% (48). Studies conducted without MRI reported primary abscess rates of 36% (49), 63% (64), and 80% (24).

V. IMAGING MODALITIES FOR IDENTIFICATION OF VERTEBRAL OSTEOMYELITIS

Radiographic findings (65) typically lag 2 to 3 weeks behind clinical symptoms. The earliest signs include blurring of the endplates and decrease in the disk space height; they are followed by bone destruction of the adjacent vertebrae. When bone sclerosis supervenes signifies repetitive process. Chronic spondylodiskitis at times can be indistinguishable from diskogenic degenerative end plate changes or infection superimposed on chronic degenerative disk disease (65).

Computed tomography (CT) and MRI provide more accurate anatomical details than radionuclide imaging techniques. However, the morphological abnormalities seen on MRI and CT do not always distinguish between a "burnt out" infection and an ongoing one, since the abnormal changes of the infectious process tend to be somehow permanent. CT and MRI assess only regional changes of infection that, in fact, may be widespread (66). Gallium-67 (^{67}Ga) used sequentially after 99 Technician Methyldiphosphinate (^{99}Tc MDP) bone scan increases the specificity of the diagnosis. ^{67}Ga can also highlight distant septic foci in the soft tissue or skeleton, which may be more amenable to biopsy or culture than the spine (66,67).

Radionuclide ^{67}Ga has excellent intrarater and interrater reliability and reproducibility; it is more accurate than haematological investigation (ESR, white blood cell [WBC] count, blood cultures) and almost equal in sensitivity MRI in the diagnosis of vertebral osteomyelitis (68). Sequential ^{67}Ga scanning is a reliable and sensitive tool to evaluate the infectious process, response to antibiotic therapy (68), and evolution of the disease activity, and it is more sensitive than

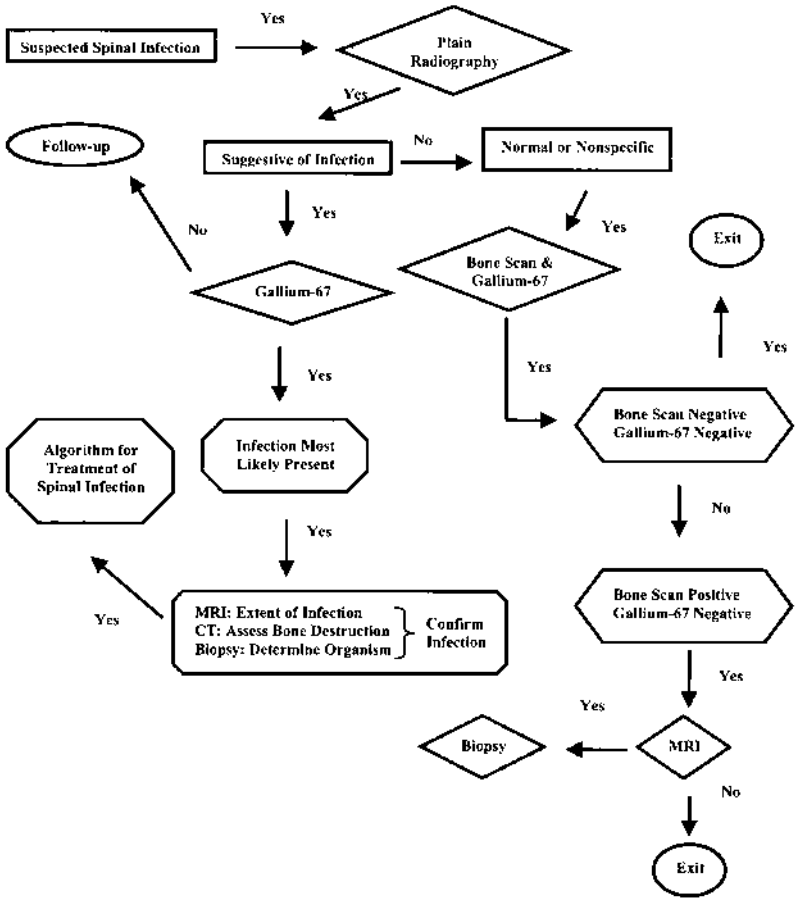


Figure 5 Imaging diagnostic algorithm for spinal infections. (From Ref. 66.)

MRI in assessing the progress of the infection. In the majority of cases, ^{67}Ga findings usually become negative within 3 months (68). As an instrument for assessing the evolution of infection, subsequent gallium scans do not require combination with bone scans. In this context ^{67}Ga radionuclide imaging is a cost-effective imaging resource, as well as an accurate method for assessing and managing spinal infection (68) (Fig. 5).

CT scan (65) may show a small hypodense area within the disk in the early stages of spondylodiskitis. CT scan allows better definition of the destructive inflammatory process of the endplate and adjacent trabecular bone and also may demonstrate paravertebral or intraspinal involvement. Intravenous contrast injection may show ring enhancement of an epidural abscess displacing the thecal sac posteriorly.

Table 4 Imaging Investigation

Tests[a]	Sensitivity	Specificity	Accuracy
Radiography	82%	57%	73%
MRI	96%	92%	94%
^{111}In-WBC	61%	98%	66%
Gallium and bone scan	90%–100%	78%–100%	86%–100%

[a] MRI, magnetic resonance imaging; ^{111}In, indium-111; WBC, white blood cell.
Source: Refs. 27,58,66,88, and 89.

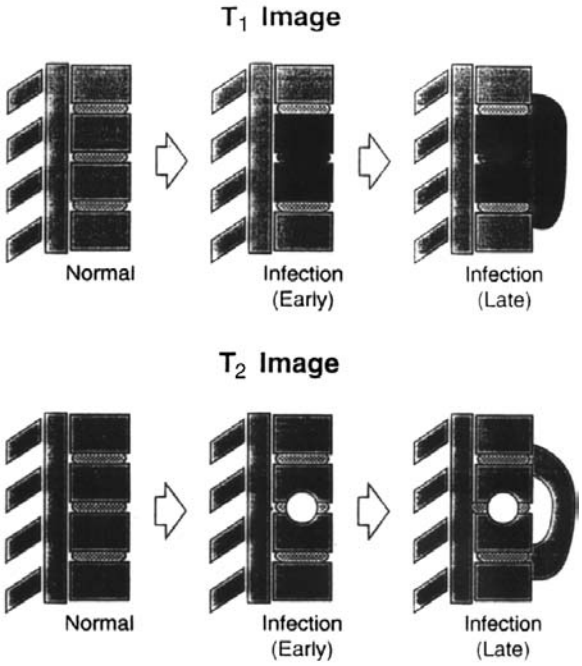


Figure 6 Early and late stages of MRI depiction of pyogenic spondylodiskitis as described by Ring and coworkers. MRI, magnetic resonance imaging. (Scoliosis Research Society. J Bone Joint Surg 18:97, 1994. (Used with permission.)

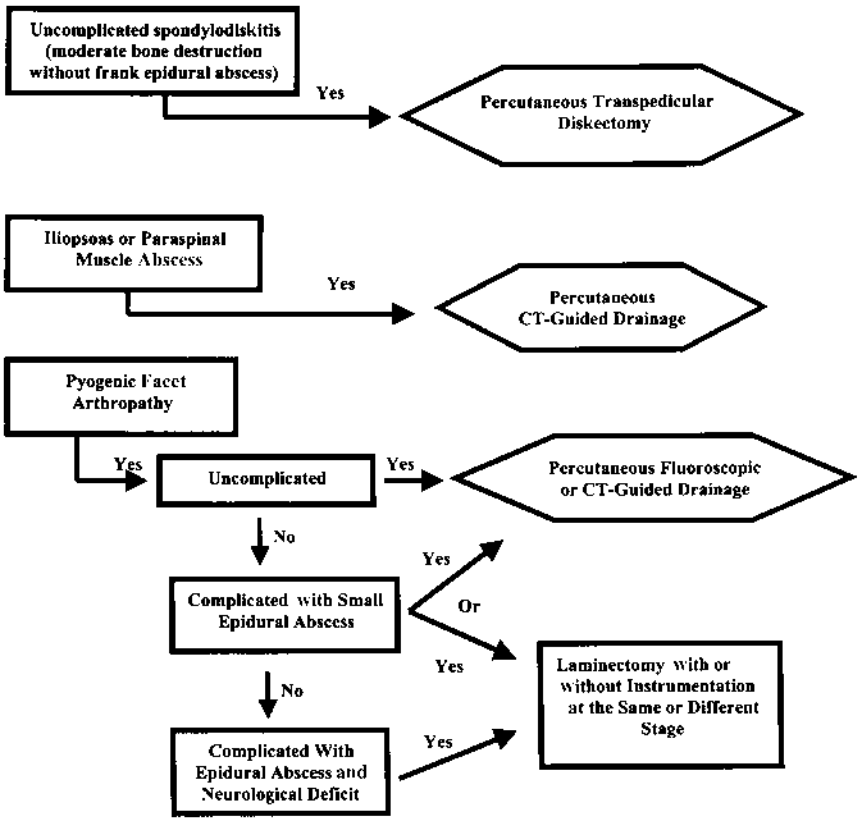


Figure 7 Imaging diagnostic algorithm for minimally invasive surgery.

MRI is more sensitive than CT scan, which, in turn, is more sensitive than conventional radiography in showing spondylodiskitis. MRI is as sensitive as bone scans in detecting spondylodiskitis, but definitely more specific (58) (Table 4).

Infection of inververtebra1 disk space and adjacent vertebral bodies is usually visualized as a region of low signal intensity (hypointense) on T_1-weighed images and of high signal intensity (hyperintense) on T_2-weighed images. The disk space is narrow and the vertebral body endplates are indistinct (61,69) (Fig. 6).

Sagittal images are useful for demonstrating prevertebral soft tissue extension of the inflammatory process; coronal images display paraspinal soft tissue spread; axial images show the extent of epidural involvement and the degree of neurocompression (70).

Some investigators have recommended short T_1 inversion recovery (STIR) images for the evaluation of spinal osteomyelitis. With this technique, by suppression of the signal from the fat, the normal bone marrow appears dark, and, in contrast, pathological processes of high water content, such as inflammation, appear very bright. This approach provides images with high contrast between pathological and normal tissue (70,71).

Epidural abscess can be demonstrated on SET_1-weighted images as low or intermediate signal intensity. On proton-density and T_2-weighted images they have high signal intensity, and, on gradient echo images, they appear as hyperintense or isointense lesions. The delineation of the abscess is variable on T_2-weighted images (43,70). The purulent fluid in the inflammatory portion of the abscess shows a markedly increased signal (T_2-weighted images), whereas the surrounding edema of the inflammatory process and the granulation tissue has inhomogeneous areas of mildly increased signal intensity. Some researchers have found no correlation between the signal on MRI (T_2-weighted images) and the stage of epidural abscess (61,70). However, the epidural abscess can be well delineated on the gadolinium-enhanced T_1-weighted images (72). Gadopentetate dimeglumine–enhanced T_1-weighted MRI (gadolinium-enhanced) is also helpful in delineating the extent of the abscess in the presence of granulation tissue and in defining the activity of the infectious process and determining the response to antibiotic therapy. However, in acute epidural abscess (mainly pus) with minimal or no granulation tissue, gadolinium intravenous (IV) injection with MRI shows either no enhancement or minimal peripheral enhancement (72).

When hemorrhage complicates spondylodiskitis it can be seen as a heterogeneous high signal on T_1- and T_2-weighted images (appearing as epidural hematoma) (73).

Hyperintense signal on T_2-weighted images from the cord is suggestive of myelitis caused by spinal cord compromise (vascular or mechanical effects). This is usually expected to regress after appropriate and emergent treatment consisting of epidural abscess evacuation and/or antibiotic therapy (61,70,73).

VI. PRINCIPLES OF THERAPEUTIC MANAGEMENT AND LABORATORY GUIDANCE

Once a diagnosis is obtained, the treatment for vertebral osteomyelitis is intravenous antibiotics, followed by oral antibiotics and immobilization (8). Tissue cultures should be obtained as soon as possible before initiating antibiotic treatment. Tissue samples should be tested for aerobic, anaerobic, acid-fast, and fungal organisms. At this point, broad-spectrum antibiotics should be started, including an antistaphylococcal agent, since *Staphylococcus* species is identified as the infecting organism in more than 50% of all cases (23,40). Gram-negative

organisms and streptococcal species are also common infecting organisms and should be considered when choosing the initial antibiotic regimen (8,26,27,32,74). As culture results and sensitivities become available, appropriate changes to therapy should be made. There is a 25% to 50% chance that negative culture results will be obtained (6,44,63). This result can be due to pretreatment with antibiotics, use of a small-bore biopsy needle, or natural evolution of disk infection (75). If negative culture findings are obtained, a repeat biopsy by the percutaneous transpedicular route (76) can be performed (after IV therapy is suspended for at least 2 full days) or, in lieu of this, broad-spectrum antibiotic treatment is continued. Treatment includes at least 6 weeks of IV antibiotics followed by appropriate oral antibiotics (8,23,63) for 4 to 6 weeks. Administration of less than 4 weeks of IV antibiotics has been associated with a high recurrence rate (40,50).

Clinical response to treatment should be monitored by weekly ESR values; typically these should decrease to less than 50% of pretreatment values before antibiotics are discontinued (8,63,77). If the sedimentation rate remains high after a full course of antibiotics, then either the spinal infection has not resolved or the ESR remains elevated because of other causes. ESR may be elevated in healthy elderly people (78), patients taking certain medications (5,79), and pregnant women (74). In children, C-reactive protein levels respond more rapidly to treatment than does the ESR and its decrease is a sensitive indicator that the patient is responding to the treatment regimen (80,81). A gallium radionuclide scan, which is both sensitive and specific for spinal infection, should be obtained at 6 weeks. A negative result signals that the infection has resolved (68), regardless of the sedimentation rate value. Beware when a patient, who despite treatment, has signs of sepsis or neurological deficit, since they may indicate that a secondary epidural abscess has formed (22). Given this situation, appropriate investigation includes an emergent MRI scan (61) with gadolinium contrast enhancement and, if an abscess is found, immediate surgical decompression.

Our preference in biopsy method is the transpedicular approach (23,27,76,82,83), which is a minimally invasive surgical procedure, useful not only for diagnostic purposes, but also as an effective therapeutic modality (see Section XI). Two objectives can be accomplished through this approach. By debulking and draining the infected tissues, early and effective control of the infection can be accomplished, thereby preventing it from spreading into epidural space. Second. it is highly feasible, by opening channels between the vertebral body and the adjacent intervertebral disk space, to allow granulation tissue from the vertebral body (75) to invade, absorb, and control the disk space infection and potentially accomplish spontaneous fusion at a much earlier stage. As a corollary, it is reasonable to advocate the use of transpedicular diskectomy in early stage of spondylodiskitis in an attempt to control the infection, expedite the healing process in good alignment, and prevent the progression of bone destruction that

may lead to painful kyphotic deformity and instability (17,27). Seventy-five percent of unselected patients treated by this method experienced a decrease in pain within 24 hours (27) with progressive resolution of neurological deficit. It can also be undertaken in patients with secondary epidural abscess with minimal neurological deficit. However, when treating an epidural abscess in this manner, and if the neurological status deteriorates, the treating physician should not postpone an appropriate surgical decompression (45).

In general, the presence of an epidural abscess, whether primary or secondary, is a surgical emergency because of the high incidence of paraplegia (8,12,23,24,29,37,49,50,54,60), especially in the thoracic spine (23,50). Even in the presence of complete paraplegia, surgical decompression is not contraindicated because significant recovery from neurological deficit is attainable (7). The rate of recovery from complete paraplegia has been reported to range from 23% to 67% (23,28,50,84). Surgical decompression should be carried out immediately since the chances for recovery decrease significantly in the presence of complete motor paraplegia for more than 48–72 hours (7,47,48). In cases of severe paraparesis or paraplegia attributed to secondary epidural abscess and/or kyphotic deformity, surgical intervention, including anterior decompression and reconstruction with bone graft (preferably autogenous rather than allograft), and instrumented posterior stabilization, are highly recommended as the treatment of choice (23,29,85). It has been shown that bone grafts can be incorporated in the presence of infection (85) with radiographic evidence of fusion in an average of 6 to 8 months (3–15 months). Laminectomy alone in spondylodiskitis is contraindicated because it may render the spine more unstable (40,50,84).

In the presence of primary epidural abscess, posterior decompression with or without instrumented stabilization suffices in the majority of cases.

Surgery is also not contraindicated for patients who are moribund with sepsis (50). Four of five of our patients who were septic as a result of epidural abscess recovered completely after surgery and one died (7).

Small epidural abscess with mild neurological deficit can be successfully managed with conservative treatment and close monitoring. However, the treating physician must keep in mind that when an epidural abscess is managed in this manner, a patient's status may deteriorate suddenly and rapidly despite weeks of antibiotic treatment (45).

Late surgical reconstruction is indicated in cases of disabling lower back pain secondary to deformity, pseudoarthrosis, or instability (7).

VII. PYOGENIC FACET JOINT ARTHROPATHY

Uncomplicated cases involving the lumbar spine can be treated successfully with fluoroscopically guided percutaneous drainage followed by 2 weeks of

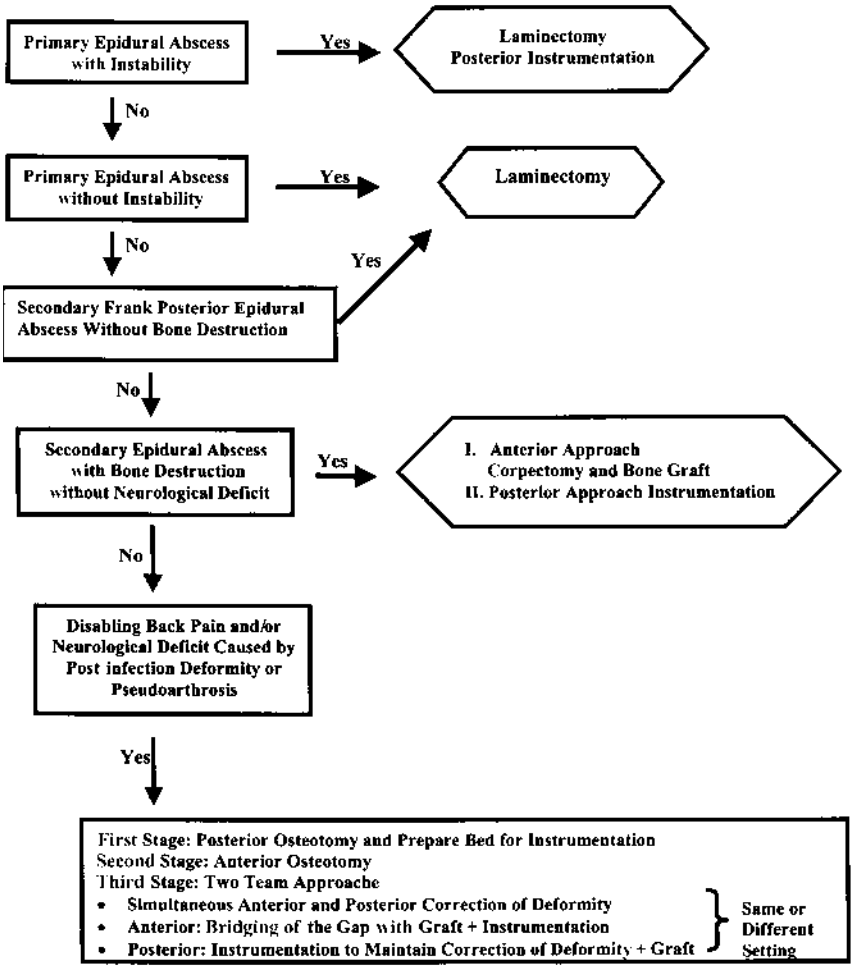


Figure 8 Imaging diagnostic algorithm of conventional surgical procedures.

appropriate intravenous antibiotics and 6 weeks of oral antibiotics (12,17,19,86). Percutaneous drainage in the cervical spine has not yet been attempted because of the serious nature of cervical spinal infection. This method of treatment should only be considered in cases not associated with epidural abscess formation, neurological deficit, or sepsis. Otherwise, emergent open decompression is indicated (8,12,23,24,29,37,49,50,54,60). Figures 7, 8 and 9 depict algorithmic approaches to the treatment of pyogenic spinal infection.

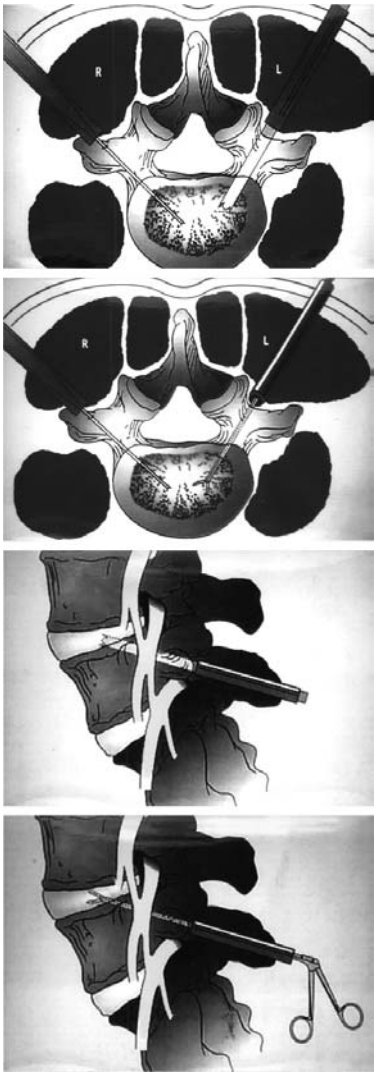


Figure 9 Percutaneous transpedicular diskectomy. (a,b). Axial views. Right side (R), diagrammatic demonstration of the guide pin and the entry point into the disk space; at the entry of the pedicle is the position of the dilator and biopsy sleeve. (a) Left side (L), depicits the toothed biopsy tool cutting a core of a bone from the pedicle and vertebral body to allow the easy passage of the diskectomy forceps as seen in (b), left side. (c) Lateral view: cephaled angulation through pedicle and subchondral plate of the toothed biopsy tool. (d) The position of the biopsy tool external sleeve for the easy percutaneous passage of the diskectomy instrumentation. (From Ref. 7.)

VIII. ORTHOSIS

Immobilization is best achieved with a thoracolumbar sacral orthosis (TLSO). Its purposes are to ensure patient comfort and to help maintain stability and minimize deformity while the infection is resolving, over approximately 3 months (8). Subsidence of pain heralds the formation of a solid fibrous union. With this conservative approach, ankylosis may take up to 2 years (15,25) and occurs in only approximately 35% of cases. Several studies have shown that mechanical back pain is frequently associated with conservative treatment (5,87). Eighty-seven percent of the patients in our series had severe, disabling back pain. Those who were treated surgically had a better clinical outcome than those treated with antibiotics alone (26% residual back pain versus 64% residual back pain) (23). This suggests that patients treated surgically fare better than those treated by conservative means (7).

IX. DIET AND LIFE-STYLE

Diet and life-style have no bearing in the early stages of the disease process. Diet should be tailored to allow maximal recovery rate of patients who are debilitated by sepsis.

X. PHARMACOLOGICAL TREATMENT

After tissue biopsy is obtained, begin broad-spectrum antibiotics with a combination of clindamycin and levofloxacin until culture sensitivities are obtained. In the presence of purulent epidural abscess (when the blood-brain barrier has been breached), we recommend beginning with vancomycin and ceftazidime and then switching to culture-specific antibiotics when sensitivities are available. Maintain IV antibiotics for 4 to 6 weeks followed by oral antibiotics for up to 6 weeks, if necessary. Continue until the ESR is less than 50% of the pretreatment value or until the gallium radionuclide scan result is negative.

A. Clindamycin Hydrochloride (Cleocin)

1. Standard Dosage

A dosage of 900 mg IV is administered every 8 hours for 6 weeks in adult patients. Dosage modification may be required for patients with severe renal or hepatic impairment. Modification of dosage is not necessary in mild to moderate renal or hepatic dysfunction.

2. Contraindications

Previous hypersensitivity to clindamycin is a contraindication to its use. Clindamycin should be used cautiously when patients have a history of gastrointestinal (GI) disease, particularly colitis.

3. Main drug interactions

Clindamycin has been noted to have neuromuscular blocking properties that may increase effects observed with concomitant neuromuscular blocker therapy (e.g., tubocurarine, pancuronium).

4. Main side effects

GI side effects include nausea, vomiting, diarrhea, and abdominal pain, as well as antibiotic-associated pseuodomembranous colitis. Morbilliform rash is the most frequently reported adverse reaction. Phlebitis at the IV injection site has been noted. Transient rises in liver function test levels have been observed during therapy.

5. Special points

Onset of diarrhea should be investigated promptly. If antibiotic-associated diarrhea is confirmed by appropriate tests (e.g., stool for *Clostridium difficile* toxin), clindamycin should be discontinued and appropriate anti-infective therapy (oral metronidazole or oral vancomycin) should be administered.

6. Cost-effectiveness

Drug acquisition cost for the recommended dosage and duration of therapy is approximately $270; the total may vary slightly because of a number of factors.

B. Levofloxacin (Levaquin)

1. Standard dosage

Standard dosage is 500 mg IV every 24 hours. The dosage may be switched to oral therapy to obtain the same antibiotic serum level. The timing of this switch must be individualized on the basis of the clinical status of the patient. Dosage should be modified in the presence of renal impairment. Total duration of therapy for IV, oral (PO) or IV/PO combined therapy is 6 weeks.

2. Contraindications

Previous hypersensitivity to levofloxacin and/or other quinolone antibiotics is a contraindication to use of lexofloxacin.

3. Main drug interactions

Antacids, sucralfate, calcium, magnesium, and iron-containing products significantly reduce the oral absorption of levofloxacin. The oral drug should be given at least 2 hours before or after these interfering agents. Levofloxacin generally possesses a much lower liability for drug interaction when compared to older quinolones such as ciprofloxacin.

4. Main side effects

Diarrhea, nausea, headache, and constipation are the most frequently observed side effects in clinical trials. Insomnia, dizziness, vomiting, and rash are also reported in 1%–3% of patients. Hypotension may result from too rapid IV administration. The IV dosage should be given over at least 60 minutes. Tendinitis and tendon ruptures have been reported.

5. Special points

Serum levels obtained with oral therapy are virtually identical to those achieved with IV therapy at equal dosages. Therefore, the feasibility of switching to PO therapy should be considered if the patient's clinical status permits.

6. Cost effectiveness

At the recommended dosage and duration, the medication cost from IV therapy is approximately $900; the cost of oral medication is approximately $240 and varies as a result of a number of factors. Substantial saving can be realized with oral therapy if it is appropriate for the individual patient.

C. Ceftazidime (Fortaz, Fazidime)

1. Standard dosage

Standard dosage is $\sim$2 g IV every 8 hours for 6 weeks for adult patients with normal renal function. The dosage must be modified in the presence of renal dysfunction or creatine clearance below 50 mL/min.

2. Contraindications

Previous hypersensitivity to cephalosporins and penicillins contraindicates its use. Use with caution when patients have a previous history of type I hypersensitivity reactions to penicillins.

3. Main drug interactions

Aminoglycoside may result in additive or synergistic antibacterial activity against a number of gram-negative organisms when used in combination.

4. Main side effects

Diarrhea, nausea, vomiting, and antibiotic-associated pseuodomembranous colitis may be observed. Hypersensitivity reactions have been reported in 1%–3% of patients. Transient elevations of liver function test levels have been reported in less than 2% of patients. Local reactions such as phlebitis and/or pain at the injection site have been noted.

5. Special points

Ceftazidime may cause overgrowth of nonsusceptible organisms such as *Candida* spp., *S. aureus*, *Enterococcus*, spp., *Enterobacter* spp., or *Pseudomonas* spp. Therefore, careful observation is required for evidence of suprainfection.

6. Cost-effectiveness

At the recommended dosage and duration, the medication cost is approximately $1960; it varies as a result of a number of factors.

D. Vancomycin (Various Products)

1. Standard dosage

Dosage is 1 g IV every 12 hours for 6 weeks in adult patients with normal renal function. In the elderly and in patients with impaired renal function, the appropriate dosage and interval should be determined by vancomycin serum levels. A dose of 1 g or less should be administered over 60 minutes; a dose greater than 1 g should be administered over at least 90 minutes.

2. Contraindications

Known hypersensitivity to vancomycin contraindicates use. Use with caution in the presence of renal dysfunction or history of previous hearing loss and for elderly adults. Results of appropriate tests of renal function, auditory function, and vancomycin serum levels should be monitored as appropriate throughout the course of therapy.

3. Main drug interactions

Because of its potential for additive nephrotoxicity and/or ototoxicity, vancomycin should be used with caution in combination with other known nephrotoxic or ototoxic drugs (aminoglycosides, amphotericin B, cisplatin, loop diuretics).

4. Main side effects

Ototoxicity and nephrotoxicity are the chief side effects. Pain and thrombophlebitis occur with IV administration. If a prolonged course of therapy is anticipated, placement of a central line (a peripherally inserted central catheter [PICC] or midline) should be considered for vancomycin administration. Various rashes including urticaria, macular rashes, and exfoliative dermatitis have been reported. "Red man syndrome," consisting of a decrease in blood pressure accompanied by flushing or rash on the face, neck, and upper extremities, can occur with rapid IV infusion (see earlier discussion), leukopenia, and, rarely, thrombocytopenia. Antibiotic-associated pseudomembranous colitis has been reported.

5. Special points

Prolonged therapy with vancomycin requires careful patient monitoring. It is important that renal and/or auditory function be monitored on a scheduled basis. Vancomycin serum levels should be used to monitor and modify dosage as required.

6. Cost-effectiveness

Drug acquisition cost for the recommended dosage and duration of therapy is approximately $485 and may vary.

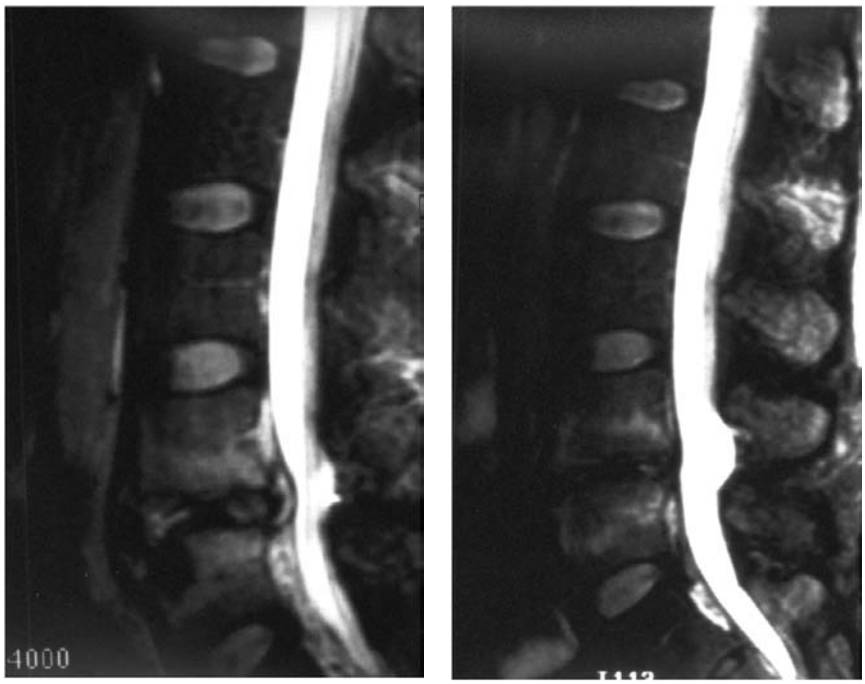
XI. SURGICAL TREATMENT

Minimally Invasive Surgery

Uncomplicated spondylodiskitis

Percutaneous Transpedicular Diskectomy

Standard procedure. A modified Kambin-Craig large-bore trephine is inserted, under fluoroscopic guidance, through the pedicles and superior endplate of the lower infected vertebra into the infected intervertebral disk. Through the cannulated sleeve of the biopsy tool, extraction of infected disk tissue is performed by using a diskectomy forceps. These tissue samples are sent for histopathological and bacterial studies. Then, an automated nucleotome is used to evacuate the infected disk tissue (39). Antibiotic lavage is then carried out for a



(a) (b)

Figure 10 (a) Sagittal T_2-weighted magnetic resonance (MR) image of the lumbar spine in a 38-year-old woman that demonstrates changes typical of spondylodiskitis with a small epidural component. (b) Sagittal T_2-weighted MR image of the lumbar spine, 2 months postoperatively, showing resolution of the infection without kyphosis. The diskectomy accelerated the natural process of healing and prevented kyphotic deformity.

period of 48 hours through drains inserted into the pedicle holes (Figs. 9a,b,c,d and 10a,b).

Complications. The usual surgical risks prevail.

Contraindications. Severe neurological deficit such as paraplegia or paraparesis due to epidural abscess contraindicates the procedure, which is also contraindicated in the presence of deformity secondary to bony loss. In these cases, open surgical decompression and realignment are indicated.

Special points. Spondylodiskitis normally heals itself, but it can cause epidural abscess and bone destruction leading to paraplegia, deformities, and often pain. Débridement of these infections at an early stage can accelerate natural healing and prevent progression to bone destruction and neurological

complications. The large tissue sample increases the chance of positive culture findings. The majority of patients treated in this manner experience a decrease in symptoms and stabilization or resolution of neurological deficits within 24 hours. It can be used for patients who are high-risk surgical candidates because of either systematic effects of the spinal infection or preexisting medical problems.

Cost-effectiveness. The procedure is less costly than open surgical procedures and can be done in the radiology suite as well as the operating room. It is more expensive than computed tomography (CT)-guided biopsy but yields more positive culture results. In contrast to CT-guide biopsy, it is therapeutic as well as diagnostic.

Iliopsoas abscess

Percutaneous computed tomography–guided drainage

Standard procedure. A large-bore spinal needle is percutaneously inserted, under CT guidance, into the abscess. The abscess is then aspirated and sent for culture analysis. Next, an obturator, through which a drain is inserted, is placed, allowing continued drainage of the abscess for 5 to 7 days. This procedure can be performed with percutaneous transpedicular diskectomy.

Complications. Complications have not been encountered in our experience; potentially complications are minimal.

Contraindications. Severe neurological deficit such as paraplegia, paraparesis, or canal compromise due to epidural abscess contraindicates its use, as does the presence of the deformity secondary to bony loss. In these cases, open surgical decompression and realignment are indicated.

Special points. The procedure is minimally invasive. It is useful as treatment modality, as an adjunct to medical conservative treatment, when iliopsoas abscess is present. It is effective as open drainage, but with far less associated morbidity.

Cost-effectiveness. It is less costly than open drainage.

Pyogenic facet arthropathy

Percutaneous fluoroscopically guided drainage

Standard procedure. A modified Kambin-Craig large-bore trephine is percutaneously inserted under fluoroscopic guidance into the facet capsule. The abscess is then aspirated and sent for culture testing. A drain may be inserted through the trephine for continuous drainage.

Complications. The usual surgical risks prevail.

Contraindications. Neurological deficit secondary to epidural abscess is a contraindication to use. We do not recommend this procedure for pyogenic facet joint infection of the cervical spine.

Special points. Minimally invasive and effective, it is associated with less morbidity than open drainage.

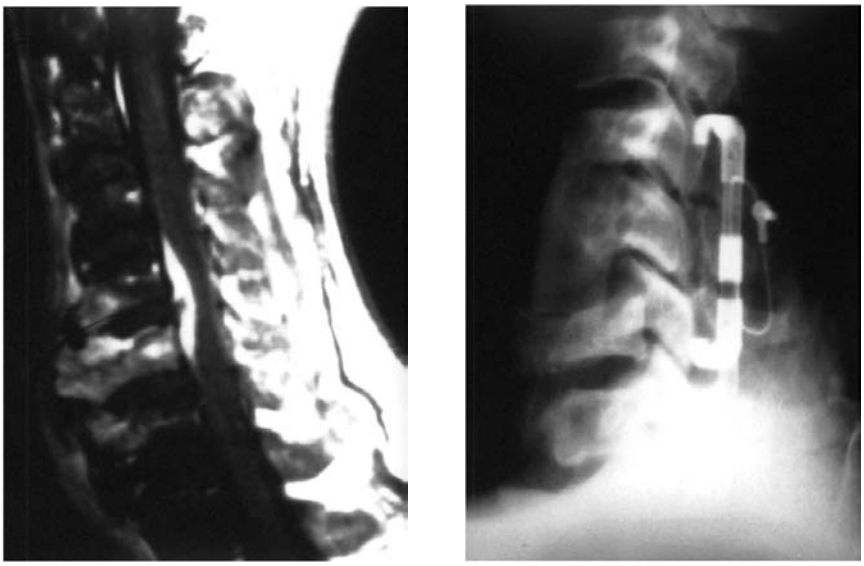
Cost-effectiveness. It is less costly than open surgical drainage.

Conventional Surgical Procedures

Primary epidural abscess

Posterior decompression-laminectomy

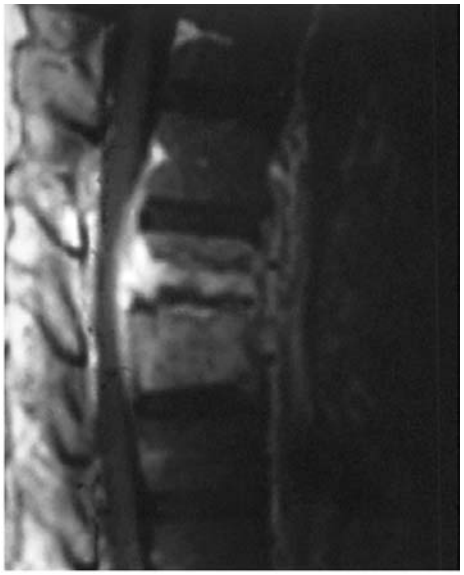
Standard procedure. Through a posterior approach, perform a midline laminectomy including all levels harboring epidural abscess. If decompression is judged to be destabilizing, then augment with posterior fusion and instrumentation.



(a) (b)

Figure 11 (a) Spondylodiskitis complicated by an anterior epidural abscess that resulted in complete motor paraplegia. (b) The patient was treated within 6 hours of the onset of paraplegia by means of anterior decompression reconstruction with autologous iliac bone graft strut, posterior stabilization, and autologous bone graft. The patient recovered completely from paraplegia.

(a)



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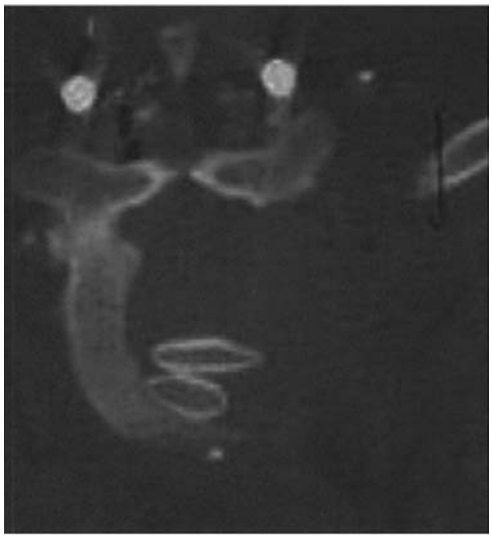


Figure 12 (a) T_1-weighted contrast-enhanced MRI-sagittal view demonstrating an epidural abscess secondary to spondylodiskitis at the T5–T6 level producing a severe neurological deficit. (b) The spine was decompressed through an anterior approach; an autogenous rib graft was used. (c) Posteriorly, the spine was stabilized by means of Varigrip Instrumentation that maintained the correction until consolidation was completed. MRI, magnetic resonance.

(c)

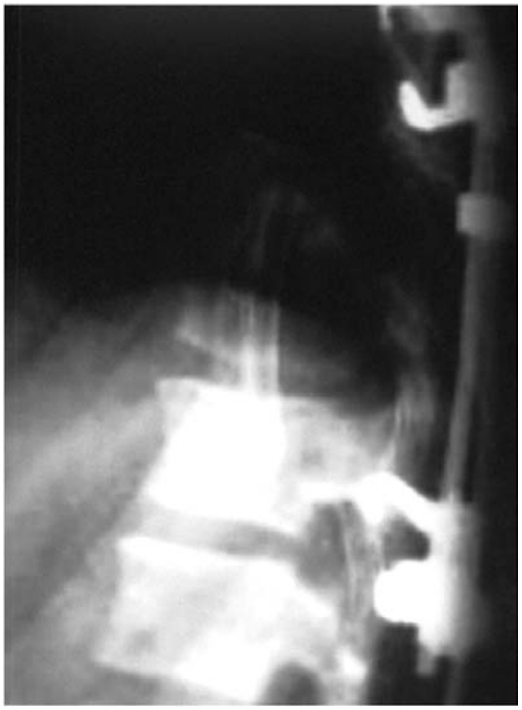


Figure 12 *continued*

Complications. The usual surgical risks prevail.

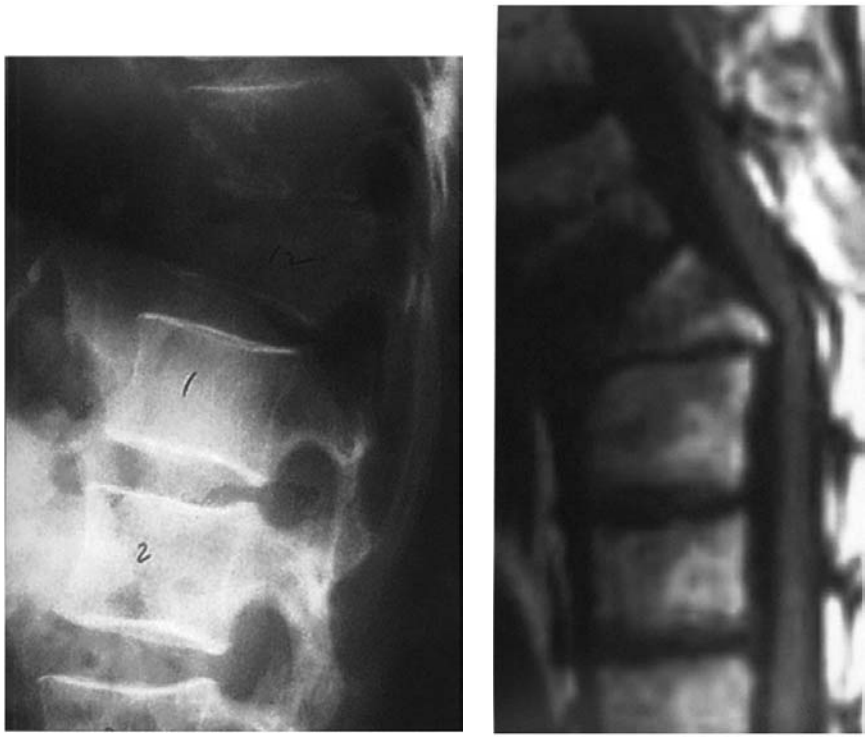
Contraindications. There are no contraindications; in the presence of neurological deficit, surgery is indicated, even for a morbid patient.

Special points. It is effective for treatment of a primary epidural abscess, which is usually located in posterior epidural space. Sepsis, paraplegia, or severe paraparesis is an indication for immediate surgical intervention. Surgical delay may lead to irreversible paraplegia.

2. Secondary epidural abscess with deformity, with or without neurological deficit

a.) Anterior débridement and neural decompression with posterior instrumentation for stabilization and/or deformity correction

Standard procedure. Through an anterior approach (retroperitoneal, transthoracic, or anterior cervical), débride devitalized disk and bone, decompress neural elements, and place an autogenous graft. The second stage of the

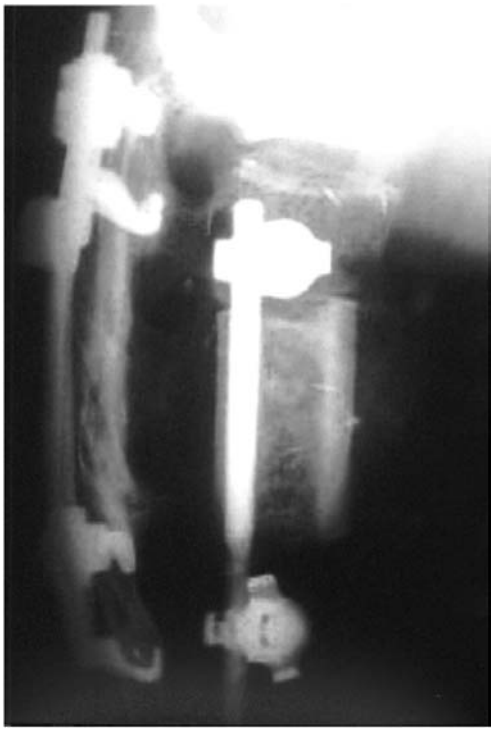


(a) (b)

Figure 13 (a,b,c) spondylodiskitis (T11–T12). (a) Lateral radiography demonstrating a severe post spondylodiskitis (T11–T12) symptomatic kyphotic deformity that complicated a successful eradication of the infection with intravenous antibiotics. (b) Sagittal T_1-weighted magnetic resonance image shows the kyphotic deformity compromising the thecal sac. (c) Lateral radiograph showing correction of the deformity by means of anterior corpectomy, reconstruction with femoral allograft, and anterior and posterior stabilization.

procedure includes a posterior approach and instrumentation for deformity correction. The second stage can be done in the same setting after the anterior procedure or at later date, if conditions warrant (Fig. 12a,b).

Contraindications. No definite contraindications prevail. The procedure may be contraindicated if a patient has serious comorbidity, or if he or she has complete paraplegia for more than 72 hours. In this situation, medical management along with minimally invasive surgery is an alternative, but less desirable, option.



(c)

Figure 13 (*continued*)

Complications. The usual surgical risks prevail.

Special points. It is indicated for patients with secondary epidural abscess causing compression. There are no contraindications due to sepsis. Patients with severe bone destruction fare better with surgery than those with medical treatment alone. Results are rewarding, even in cases of complete paraplegia, if treatment is instituted early. If secondary frank epidural abscess involves the posterior epidural space, laminectomy alone may be indicated in the absence of anterior bone destruction.

3. Disabling back pain or neural compression caused by post-infectious deformity or pseudoarthrosis

a.) Anterior osteotomy, deformity correction, bone graft, instrumentation staged with posterior instrumentation for stabilization and maintenance of correction

Standard procedure. This procedure has three stages. First, with the patient prone, osteotomize ankylosed bone through a posterior approach at the level of kyphosis and prepare for instrumentation. The wound is loosely closed. Then, a second-stage procedure is performed at the same or at a different time within a week, depending on the patient's condition. This second-stage procedure involves osteotomization or excision of the ankylosed spine through an anterior approach with the patient in the lateral decubitus position. Next the third-stage procedure is performed. With the help of another surgical team, the posterior wound is reentered and a correction of deformity is performed simultaneously through the anterior and posterior approaches. An allograft or autograft is placed anteriorly to bridge the gap of the excised kyphus, and posterior spinal instrumentation is placed to maintain the corrected deformity (Figs. 13a,b,c).

Contraindications. High-risk surgical patients should not have this procedure, which is a major surgical reconstruction.

Complications. Neurological injury, pseudoarthrosis, and failure of instrumentation may occur.

Special points. It is indicated for patients who have disabling back pain secondary to pseudoarthrosis or instability and for patients who have a neurological deficit due to increased kyphotic deformity.

XII. SUMMARY

Hematogenous pyogenic infection of the spine has been labeled *spondylitis, diskitis*, *spondylodiskitis*, *vertebral pyogenic osteomyelitis*, *pyogenic spinal infection*, and *vertebral osteomyelitis associated with disk space infection*, creating confusion in nomenclature. All of these are different entities with a wide spectrum of infection. Some of these, such as diskitis, may also represent different stages of the same disease process, called *spondylodiskitis*. In our series, infection limited to the disk space (diskitis) or the vertebral body (spondylitis) occurred only at a rate of 1% of all spinal infections; most (95%) cases were spondylodiskitis, suggesting that spondylodiskitis is the major part of a spectrum of spinal infections. Pyogenic facet arthropathy infection rates range from 1% to 6%. Epidural abscess associated with spondylodiskitis, known as *secondary epidural abscess*, occurred at a rate of 33% of all spinal infections in our series. When found independently of spondylodiskitis, it is called *primary epidural abscess* and was present in only 2% of all spinal infections. The most common organism is *Staphylococcus aureus*; rates range from 42% to 84%. Culture findings are expected to be negative in 24.4% of cases. Many spinal infections are

preceded by infection elsewhere or intravenous drug abuse; they are more likely among immunocompromised hosts. Leukocyte count and sedimentation rates are not sensitive diagnostic tests, but when levels are elevated they may serve as red flags suggesting a more serious infection, such as an epidural abscess. Involvement of the cervical spine has a high tendency for epidural abscess formation (90%), whereas epidural abscess in the thoracic spine has an 82% rate of dreadful neurological complications (paraplegia/paraparesis). Twenty-three percent of patients with epidural abscess recovered completely, 7.7% partially; the mortality rate was 7.7%. Both MRI and radionuclide imaging (gallium scan) are very sensitive tools for the diagnosis of spinal infections. MRI provides more accurate anatomical details, and gallium scan is cost-effective for assessing the progress of the infectious process. The cornerstone of therapy for uncomplicated spondylodiskitis is intravenous followed by oral antibiotics, along with bracing. However, patients treated surgically (26% residual pain) had better pain relief than those treated conservatively (64% residual pain). Surgeries include the following: (1) minimally invasive surgery (percutaneous transpedicular diskectomy) for uncomplicated spondylodiskitis (i.e., no deformity or neurological deficit), (2) percutaneous CT-guided drainage for uncomplicated facet pyogenic arthropathy and iliopsoas abscess, (3) laminectomy for primary epidural abscess, (4) anterior decompression and fusion with posterior instrumentation for spondylodiskitis complicated by deformity and/or neurological deficit, and (5) late reconstruction for back pain and deformity caused by a remote spinal infection.

REFERENCES

1. R Calderone, J Larsen. Overview and classification of spinal infections. Ortho Clin North Am 27:1–8, 1996.
2. D Musher, S Thorsteinsson, J Minuth, R Luchi. Vertebral osteomyelitis. Arch Intern Med 136:105–110, 1976.
3. AM Borowski, WN Crow, AG Hadjipavlou, G Chaljub, J Mader, F Cesani, E vanSonnenberg. Interventional radiology case conference: the University of Texas Medical Branch: Percutaneous management of spondylodiskitis. Am J Roentgenol 170:1587–1592, 1998.
4. D Ring, D Wenger. Pyogenic infectious spondylitis in children: the evolution to current thought. Am J Orthop 25:342–348, 1996.
5. M Patzakis, S Rao, J Wilkins, TM Moore, PJ Harvey. Analysis of 61 cases of vertebral osteomyelitis. Clin Orthop 264:178–183, 1991.
6. G Gorse, M Pais, J Kusske, T Cesario. Tuberculous spondylodiskitis: a report of six cases and a review of the literature. Medicine (Baltimore) 62:178–193, 1983.
7. A Hadjipavlou, S Berguist, J Chen, J Necessary, A Muffoletto. Vertebral osteomyelitis. Cur Treat Options 2:226–237, 2000.

8. R Osenback, P Hitchon, A Menezes. Diagnosis and management of pyogenic vertebral osteomyelitis in adults. Surg Neurol 33:266–275, 1990.
9. R Ghormley, W Bickel, D Dickson. A study of acute infectious lesions of the intervertebral disks. South Med J 33:347–352, 1940.
10. P Sampath, D Rigamonti. Spinal epidural abscess: a review of epidemiology, diagnosis, and treatment. J Spinal Disord 12:89–93, 1999.
11. D Loaire, H Fairley. Epidural abscess following spinal anesthesia. Anesth Analg 57:351–353, 1978.
12. A Muffoletto, L Ketonen, J Mader, W Crow, A Hadjipavlou. Hematogenous pyogenic facet joint infection. Spine 26:1570–1576, 2001.
13. A Muffoletto, R Nander, R Westmark, H Nauta, K Garges, A Hadjipavlou. Hematogenous pyogenic facet joint infection of the subaxial cervical spine: a report of two cases and review of the literature. J Neurosurg 9(1 suppl):153–158, 2001.
14. S Ahlback, S Collert. Destruction of the odontoid process due to atlantoaxial pyogenic spondylodiskitis. Acta Radiol Diagn 10:394–400, 1970.
15. B Frederickson, H Yuan, R Olans. Management and outcome of pyogenic vertebral osteomyelitis. Clin Orthop 131:160–167, 1978.
16. A Sullivan. Subluxation of the atlantoaxial joint: sequel to inflammatory process of the neck. J Pediatr 35:451–464, 1949.
17. M Ben Hamouda, H Rajhi, M Golli, N Bergaouni, A Chaouch, H Hasine, A Ganouni. Arthrite septique interapophysaire posterieure lombaire. J Radiol 78:373–376, 1997.
18. F Douvrin, F Callonnec, F Proust, A Janvresse, J Simonet, J Thiebot. Arthrite septique interapophysaire lombaire. Apropos de 3 cas. J Neuroradiol 23:234–240, 1996.
19. M Ergan, M Macro, CL Benhamou, P Vandermarcq, T Colin, JL L'Hirondel, C Marcelli. Septic arthritis of lumbar facet joints: A review of six cases. Rev Rheum (English edition) 64:386–395, 1997.
20. D Farrokh. Isolated septic arthritis of the articular surface of the lumbar spine—the contribution of MRI. J Belge Radiol 80:289–291, 1997.
21. J Halla, J Blinak, J Hardin, S Finn S. Septic arthritis of the C1–C2 lateral facet joint and torticollis: pseudo-Grisel's syndrome. Arthritis Rheum 34:84–88, 1991.
22. S Hennan, J Briton. Septic arthritis in a lumbar facet joint: a rare cause of an epidural abscess. Neuroradiology 37:462–464, 1995.
23. A Hadjipavlou, J Mader, J Necessary, A Muffoletto. Hematogenous pyogenic spinal infection and their surgical management. Spine 25:1668–1679, 2000.
24. AS Baker, R Ojemann, MN Swartz, EP Richardson Jr. Spinal epidural abscess. N Engl J Med 293:463–468, 1975.
25. S Collert. Osteomyelitis of the spine. Acta Orthop Scand 48:283–290, 1977.
26. SE Emery, DP Chan, HR Woodward. Treatment of hematogenous pyogenic vertebral osteomyelitis with anterior débridement bone grafting. Spine 14:284–291, 1989.
27. A Hadjipavlou, W Crow, A Borowski. Percutaneous transpedicular discectomy and drainage in pyogenic spondylodiscitis. Am J Orthop 27:188–197, 1998.

28. HB Kemp, J Jackson, J Jeremiah, A Halla. Pyogenic infections occurring primarily in intervertebral discs. J Bone Joint Surg 55B:698–714, 1973.
29. S Rath, U Neff, O Schneider, H Richter. Neurosurgical management of thoracic and lumbar vertebral osteomyelitis and discitis in adults: a review of 43 consecutive surgically treated patients. Neurosurgery 38:926–933, 1996.
30. F Sapico, J Montgomerie. Vertebral osteomyelitis. Infec Dis Clin North Am 4:539–550, 1990.
31. A Torda, T Gottlieb, R Bradbury. Pyogenic vertebra osteomyelitis: analysis of 20 cases and review. Clin Infect Dis 20:320–328, 1995.
32. F Waldvogel, PS Papageorgiou. Osteomyelitis: the past decade. N Engl J Med 303:360–370, 1980.
33. D Leys, F Lesoin, C Viaud, F Pasquier, M Rousseaux, M Jomin, H Petit. Decreased morbidity from acute bacterial spinal epidural abscess using computed tomography and non-surgical treatment in selected patient. Ann Neurol 17: 350–355, 1985.
34. Case records of the massachusetts general hospital: weekly clinicopathologica1 exercises. Case l2-1982: low back pain and fever in a 71-year old man. N Engl J Med 306:729–737, 1982.
35. J Brian Jr, G Westerman, W Chadduck. Septic complications of chemonucleolysis. Neurosurgery 15:730–734, 1984.
36. E Carragee. Pyogenic vertebral osteomyelitis. J Bone Joint Surg Am 79A:874–880, 1997.
37. R Darouiche, B. Hamill, S Greenberg, S Weathers, D Musher. Bacterial spinal epidural abscess: review of 43 cases and literary survey. Medicine (Baltimore) 71:369–385, 1992.
38. D De Wit, R Mulla, MR Cowie, JC Mason, KA Davies. Vertebral osteomyelitis due to Staphylococcus epidermidis. Br J Rheum 32:339–341, 1993.
39. J Ferguson, W Kirsch W. Epidural ampyema following thoracic extradural block: case report. J Neurosurg 41:762–764, 1974.
40. FL Sapico, JZ Montgomerie. Pyogenic vertebral osteomyelitis: report of nine cases and review of the literature. Rev Infect Dis 1:754–776, 1979.
41. T Taylor, B Dooley. Antibiotics in the management of postoperative disc space infections. Aust N Z J Surg 48:74–77, 1978.
42. WY Yu, C Siu, PC Wing, JF Schweigel, N Jetha. Percutaneous suction aspiration for osteomyelitis. Spine 16:198–202, 1991.
43. EJ Angtuaco, JR McConnell, WM Chadduck, S Flanigan. MR imaging of spinal epidural sepsis. Am J Roentgenol 149(6): 1249–1253, 1987.
44. J Digby, J Kersley. Pyogenic non-tuberculous spinal infection: an analysis of thirty cases. J Bone Joint Surg Br 61B:47–55, 1979.
45. ML Hlavin, HJ Kaminski, JS Ross, E Ganz. Spinal epidural abscess: a ten-year perspective. Neurosurgery 27:177–184, 1990.
46. M Liebergall, G Chaimsky, J Lowe, G Robin, Y Floman. Pyogenic vertebral osteomyelitis with paralysis: prognosis and treatment. Clin Orthop 269:142–150, 1991.

47. R Martin, H Yuan. Neurosurgical care of spinal epidural, subdural and intramedullary abscesses and arachnoiditis. Orthop Clin North Am 27:125–136, 1996.
48. G Redekop, R Del Maestro. Diagnosis and management of spinal epidural abscess. Can J Neurol Sci 19:180–187, 1992.
49. O De Curling, D Gower, J McWhorter. Changing concepts in spinal epidural abscess: a report of 29 cases. Neurosurgery 27:185–192, 1990.
50. FJ Eismont, HH Bohlman, PL Soni, VM Goldberg, AA Freehafer. Pyogenic fungal vertebral osteomyelitis with paralysis. J Bone Joint Surg Am 65A:19–29, 1983.
51. GL Rea, JM McGregor, CA Miller, ME Miner. Surgical treatment of spontaneous spinal epidural abscess. Surg Neurol 19:180–187, 1992.
52. Y Kabasakal, SL Garret, A Calin. The epidemiology of spondylodiscitis in ankylosing spondylitis—a controlled study. Br J Rheum 35:660–663, 1996.
53. P Korovesis, P Sidiropoulos, G Piperos, A Kerogiannis. Spinal epidural abscess complicating closed vertebral fracture. Spine 5:761–764, 1993.
54. D Rigamonti, L Liem, AL Wolf, MS Fiandaca, Y Numaguchi, FP Hsu, ES Nussbaum. Epidural abscess in the cervical spine. Mt Sinai J Med 61:357–362, 1994.
55. A Garcia Jr, SA Gratham. Hemotogenous pyogenic vertebral osteomyelitis. J Bone Joint Surg Am 42A:429–435, 1960.
56. RM Ozuma, RB Delamarter. Pyogenic vertebral osteomyelitis and postsurgical disc space infectious. Orthop Clin North Am 27:87–94, 1996.
57. E Lucio, A Adesokan, A Hadjipavlou, W Crow, PA Adegbonega. Pyogenic spondylodiscitis RA radiologic/pathologic and culture correlation study. Arch Path Lab Med 14:712–716, 2000.
58. MT Modic, DH Feiglin, DW Piraino, F Boumphrey, MA Weinstein, PM Duchesneau, S Rehm. Vertebral osteomyelitis: assessment using MRI. Radiology 157:157–166, 1985.
59. D Stoker, C Kissin. Percutaneous vertebral biopsy: a review of 135 cases. Clin Radiol 36:569–577, 1985.
60. E Verner, D Musher. Spinal epidural abscess. Med Clin North Am 69:375–385, 1985.
61. M Post, R Quencer, B Montalvo, B Katz, FJ Eismont, BA Green. Spinal infection evaluation with MR imaging and intraoperative US. Radiology 169: 765–771, 1998.
62. D Kaufman, J Kaplan, N Litman. Infectious agents in spinal epidural abscesses. Neurology 30:844–850, 1980.
63. F Sapico. Microbiology and antimicrobial therapy of spinal infections. Orthop Clin North Am 27:9–13, 1996.
64. R Danner, B Hartman. Update of spinal epidural abscess: 35 cases and review of the literature. Rev Infect Dis 9:265–274, 1987.
65. R Varma, P Lander, A Ajjaf. Imaging of pyogenic infectious spondylodiskitis. Radiol Clin North Am 39:203–213, 2001.
66. R Lisbona, V Derbakyan, J Novales-diaz, A Veksler. A Gallium-67 scintigraphy in tuberculous and notuberculous infection spondylodiscitis. J Nucl Med 34:853–859, 1993.

67. S Norris., M Ehrlich, D Keim, H Guiterman, K McKusick. Early diagnosis of disc-space infection using Gallium-67. J Nucl Med 19:384–386, 1978.
68. A Hadjipavlou, F Cesani-Vazquez, J Villaneuva-Meyer, JT Mader, JT Necessary, W Crow, RE Jensen, G Chaljub. The effectiveness of gallium citrate Ga 67 radionuclide imaging in vertebral osteomyelitis revisited. Am I Orthop 27: 179–183, 1998.
69. A Thrush, D Enzmann. MRI of infectious spondylitis. Am J Neurol Radiol 11:1171–1780, 1990.
70. R Kricum, E Shoemaker, G Chovanes, H Stephens. Epidural abscess of the cervical spine: MRI findings in five cases. Am J Roentgenol 158:1145–1149, 1992.
71. R Bertino, B Porter, G Stimac, S Tepper. Imaging spinal osteomyelitis and epidural abscess with short T_1 inversion recovery (STIR). Am J Neurol Radiol 9:563–564, 1988.
72. M Post, G Sze, R Quencer, FJ Eismont, BA Green, H Gahbauer. Gadolinium-enhanced MRI in spinal infection. J Comput Assist Tomogr 14:721–729, 1990.
73. D Enzmann. Infection and inflammation. In: D Enzmann, R DeLaPaz, J Rubin, eds. Magnetic Resonance of the Spine. St. Louis: Mosby, 1990.
74. T Casey, B Main. Factors influencing the normal erythrocyte sedimentation rate, including pregnancy. N Z Med 1 69:155–156, 1969.
75. R Fraser, O Osti, B Vernon-Roberts. Discitis after discography. J Bone Joint Surg Br 68B: 26–35, 1987.
76. WN Crow, AM Borowski, AG Hadjipavlou, EM Walser, S Arya, MB Calme, J Amps, R Jensen, S Somisetty, B Alford, A Adesokan. Percutaneous transpedicular automated nucleotomy for débridement of infected disc. J Vasc Interv Radiol 9:161–165, 1998.
77. D Covey, J Albbright. Cinical significance of the erythrocyte sedimentation rate in orthopaedic surgery. J Bone Joint Surg Am 69A:148–151, 1987.
78. RA Griffiths, WR Good, NP Watson, HF O'Donnell, PJ Fell, JM Shakespeare. Normal erytbrocyte sedimentation rate in elderly. Br Med J 289:724–725, 1984.
79. J Burton. Effect of oral contraceptives on erythrocyte sedimentation rate in healthy young women. Br Med J 3:214–215, 1967.
80. S Penches, Z Stern, D Bar-Or. Heparin and the ESR (letter). Arch Intern Med 138:1864–1865, 1978.
81. I Roine, I Faingezicht, A Arguedas, JF Herrera, F Rodriguez. Serial C-reactive protein to monitor recovery from acute hematogenous osteomyelitis in children. Pediatr Infect Dis J 14:40–44, 1995.
82. C Ottolenghhi. Aspiration biopsy of the spine: technique for the thoracic spine and results of twenty-eight biopsies in this region and over-all results of 1050 biopsies of other spinal segments. J Bone Joint Surg Am 51A:1531–1544, 1969.
83. D Stringham, A Hadjipavlou, R Dzioba, P Lander. Percutaneous transpedicular biopsy of the spine. Spine 19:1985–1991, 1994.
84. A Hadjipavlou. Percutaneous transpedicular management of spondylodiscitis of the lumbar spine. Presented to Canadian Orthopaedic Association. Ottawa, June 1998.

85. D Fang, KM Cheung, ID Dos Remedios, YK Lee, JC Leong. Pyogenic vertebral osteomyelitis: treatment by anterior spinal debridenient and fusion. J Spinal Disord 7:173–180, 1994.
86. W Roberts. Pyogenic vertebral osteomyelitis of a lumbar facet joint with associated epidural abscess: A case report with review of the literature. Spine 13:948–952, 1988.
87. GB Ambrose, M Albert, CS Neer. Vertebral osteomyelitis: a diagnostic problem. JAMA 197(8):619–622, 1996.
88. CJ Palestro, CK Kim, AJ Swyer, S Vallabhajosula, SJ Goldsmith. Radionuclide diagnosis of vertebral osteomyelitis: indium-111-leukocyte and technetium-99m-methylene diphosphonate bone scintigraphy. J Nucl Med 32(10):1861–1865, 1991.
89. JL Whalen, ML Brown, R McLeod, RH Fitzgerald Jr. Limitations of indium leukocyte imaging for the diagnosis of spine infections. Spine 16(2): 193–197, 1991.

13

Postoperative Infections of the Spine and Treatment Options

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I. INTRODUCTION

Infection of the spine can complicate any invasive diagnostic spinal procedure or surgery whether noninstrumented or instrumented, and, generally, its incidence increases with the complexity of the operation (1).

Postoperative spinal infections can be thought of as two mainly different and distinct entities: infection without spinal instrumentation, particularly after diskectomy, and infection after spinal instrumentation. Postoperative infection of the spine after instrumentation may be manifested as an early or late (delayed) complication. Early infection is not an uncommon complication and, if not treated promptly and appropriately, may have significant implications. Delayed spinal infection after elective spinal instrumentation and fusion is uncommon, and the diagnosis is frequently challenging (2).

Complications of postoperative spinal infections can be classified into three categories: local complications, general complications, and socioeconomic problems. Postoperative spinal wound infection can have devastating consequences, from enormous social implications to jeopardy to the patient's life. The best treatment is prevention, by paying special attention to the so-called reversible risk factors. Successful outcomes in terms of restoring the purpose of the original surgery can be achieved by prompt diagnosis and appropriate treatment, as we attempt to outline in this chapter.

We first address the postoperative infection after diskectomy, then the early postoperative infection after spinal instrumentation, and, last, the late or delayed instrumented spinal infections. Suggested treatment options are based on available medical reports.

A. Socioeconomic Problems

The magnitude of the socioeconomic problem of spinal infections is enormous; consequently, the reduction of infection rates is of paramount importance (3).

The prognosis of diskitis varies markedly in different series. Clinical studies generally support the concept that when treatment is instituted early in the process of infection the prognosis is definitely better (4,5).

Available clinical studies indicate that after spondylodiskitis complicating diskectomy, 50% to 87.5% of patients were unable to resume their previous occupation (6–10).

The socioeconomic aspect of postoperative spinal instrumentation infections was well outlined in a prospective, multicenter study by Thalgott and associates (11). For mild infections, necessitating only one surgical débridement-irrigation treatment, the average hospital stay was 14 days (ranging from 8 to 28 days) with an average hospital cost of $42,000 (ranging from $14,000 to $87,000). In more severe infections, the patients required multiple hospital admissions and an average of three surgeries per patient (ranging from one to seven) to resolve their infections. The average hospital stay was 51.6 days (ranging from 8 to 180 days), and the average hospital cost was $128,000 (ranging from $10,500 to $778,000).

Patients with severely infected wounds, with extensive tissue damage and myonecrosis (group III), required an average of six surgeries per patient (ranging from four to eight) and eventually necessitating muscle flaps for closure. The average hospital stay was 77.5 days (ranging from 65 to 90 days), and the average hospital cost was $437,000.

II. RISK FACTORS

There are several risk factors that predispose a patient to postoperative spinal infection, particularly to early postoperative spinal infection after spinal instrumentation. To a lesser extent, however, these factors may also play a role in late infections and infections after noninstrumented spinal surgery, particularly after diskectomy. On the basis of available reports (11–18), the medical conditions widely accepted as risk factors are listed in Table 1.

The surgical approach also has an important bearing on surgical infections. The infection rate for spinal instrumentation through an anterior approach has been reported to range between 0% and 0.1% (13,18), as opposed to a relatively high infection rate when the posterior approach for instrumentation was used

Table 1 Risk Factors Predisposing to Spinal Surgical Wound Infections

Preoperative factors
Concomitant infections—acute or chronic (skin, visceral, pressure sores, etc.)
Immunocompromised host (cancer, chemotherapy, HIV, etc.)[a]
Corticosteroid therapy
Rheumatoid arthritis
Advanced age
Obesity
Malnutrition
Diabetes mellitus (uncontrolled)
Smoking
Previous spinal surgery
Cardiovascular disease
Intraoperative factors
Posterior spinal instrumentation greater than anterior
Prolonged duration of surgery (more than 5–7 hours)
High-volume blood loss (average 1600 mL)
High-volume operating room personnel traffic
Violation of sterile conditions
Use of allograft
Postoperative factors
Paralysis (incontinence, genitourinary infections, etc.)
Prolonged hospital bed rest
Skin maceration (dressing, orthosis, etc.)
Contamination of wound drains

[a] HIV, human immunodeficiency virus.

(13). It is postulated that the extensive surgical exposure required for posterior instrumentation, compounded by prolonged retraction of the paraspinal muscles (large retractors, etc.), renders the soft tissue avascular and devitalizes the paraspinal muscles. The ensuing liquefaction necrosis predisposes the tissue to colonization by contaminated microorganisms, which eventually leads to sepsis. Long surgical time (over 5 hours) and a high volume of blood loss (mean volume 1620 mL) (14,19) have also been implicated as risk factors for the development of postoperative infections. The presence of relatively large numbers of people in or moving through the operating room during spine surgery is also a consideration. The number of colony-forming units per cubic foot has been shown to be almost proportional to excessive traffic and number of persons in the operating room (20,21).

A history of previous surgery was noted in 37% of infected cases in one report (1). Additionally, biomaterials may make the adjacent tissues susceptible to both immediate and delayed infection by impeding host defense mechanisms (22), suggesting that the presence of instrumentation may be a risk factor by itself

(23). This instrumentation may protect inoculated microorganisms, allowing them to form a nidus of infection, making treatment more difficult.

The length of the patient's hospital stay may also be a risk factor for infection. An extended preoperative hospital stay leads to colonization of the patient with hospital flora, which may increase the incidence of postoperative infections (24). Additionally, the patient's nutritional status may be a risk factor for postoperative infection. One study reports that the prevalence of nutritionally challenged patients undergoing elective spinal surgery was noted in 25% of cases, with a higher number (42%) encountered in the older population group (25). Preoperative nutritional status is an extremely significant independent predictor of postoperative complications in patients undergoing elective lumbar spinal fusion; 85% of postoperative infectious complications were noted in malnourished patients in one report (26). Weight loss greater than 10 lb should be considered indicative of malnutrition. Finally, diabetes mellitus has been widely accepted as a risk factor for infection; however, a 2000 study challenges this conclusion (27). Uncontrolled diabetes mellitus, particularly when associated with cardiovascular or renal complications, should be considered as a potential risk factor. It seems that the presence of more than two or three risk factors predisposes the patient to infection (13).

III. LABORATORY INVESTIGATIONS

This section discusses some laboratory investigations that conventionally have been considered useful in the management of infections and addresses their response in reference to spinal infections.

A. Erythrocyte Sedimentation Rate

In the majority of patients, erythrocyte sedimentation rate (ESR) increases to peak levels about 4–5 days after surgery (28,29), followed by a slow and irregular decrease, usually with a return to normal after 2 weeks (28). However, ESR may remain elevated even 21–42 days after surgery (29). More specifically, the maximal mean peak values seen 4 days after disk surgery were 45–75 mm/h (5,28,29) and exceeded 100 mm/h after spinal fusion (28). When deep wound infection complicates spinal surgery, ESR values exceed the corresponding mean values by +2 SD. In delayed spinal infection, ESR was elevated in 87.5% of cases, averaging 57 mm/h.

B. C-Reactive Protein

The normal values for C-reactive protein (CRP) are usually less than 10 mg/L (μg/mL). These values can increase to certain peak levels, without reflecting

infection, after different types of spine surgery, such as microdiskectomy (46 ± 21 mg/L), anterior fusion (70 ± 23 mg/L), conventional diskectomy (92 ± 47 mg/L), and posterolateral intertransverse fusion (173 ± 39 mg/L). These values reach peak levels on the second and third postoperative days and tend to normalize in 5–14 days. The expected rapid decline in CRP is often interrupted by a second rise or CRP level remains persistently elevated if infection supervenes (30). CRP may be a better index than erythrocyte sedimentation rate for early detection of postoperative infection (30).

C. White Blood Cell Count

White blood cell count (WBC) usually is not expected to show any changes after uncomplicated spinal surgery, even in the presence of infection. Usually, this test is not a reliable index of infectious activity. Total WBC was found to be slightly elevated in only 20% of patients with acute postoperative spinal infection (28) and in 25% of patients with delayed postoperative infection after instrumentation (2).

D. Tissue Cultures

Tissue cultures usually yield the offending organism (13). According to different reports, the most commonly isolated microorganism for early infections is *Staphylococcus aureus*, with an incidence of instrumented spinal infections ranging from 50% to 63%. Multiple organisms are isolated in approximately 20% to 52%, and no growth in 10% (1,13,14) (Table 2).

However, for delayed infection after spinal instrumentations, the flora are typically different, characterized by apparently low-virulence organisms such as *Staphylococcus epidermidis* and *Proprionibacterium acnes* with negative culture finding rates ranging between 0% and 12.5% (Table 3).

E. Imaging Resources

Reports indicate that magnetic resonance imaging (MRI) alone, at least in the early stages, is not a good diagnostic tool for infection complicating diskectomy (5,31).

Computed tomography (CT) scan and MRI may not play a major diagnostic role in the presence of metallic implants but may be useful to indicate whether epidural abscess or diskitis is complicating the infection. For more details, see Chapter 12.

Scintigraphy has been widely used in joint infections (32). However, more emphasis is given to the clinical diagnosis in this situation and radionuclide testing should not create unnecessary delays of treatment. Radionuclide imaging

Table 2 Most Common Microorganism in Early Spinal Infection after Instrumentation

Microorganism	Authors
Staphylococcus aureus	
53%	Levi et al. 1987 (13)
17%	Dall et al. 1987 (4)
6%	Sponseller et al. 2000 (16)
63%	Weinstein et al. 2000 (1)
54.5%	Massie et al. 1992 (14)
Staphylococcus epidermidis	
50%	Dall et al. 1987 (4)
36%	Massie et al. 1992 (14)
Gram-negative	
40%	Massie et al. 1992 (14)
30%	Dall et al. 1987 (4)
43%	Sponseller et al. 2000 (16)
Polymicrobial	
29%	Levi et al. 1987 (13)
19%	Weinstein et al. 2000 (1)
59%	Massie et al. 1992 (14)
52%	Sponseller et al. 2000 (16)
25%	Dall et al. 1987 (4)
No organism	
16%	Dall et al. 1987 (4)
4.5%	Weinstein et al. 2000 (1)
6%	Levi et al. 1987 (13)

Table 3 Offending Organism in Delayed Infections

	Viola et al. (2)	Richards (23)	Heggeness et al. (100)	Schofferman et al. (104)
Staphylococcus epidermidis	75%	20%	16.6%	43%[a]
Proprionibacterium ances	12.5%	50%	16.6%	
Streptococcus morbillorium			16.6%	
Staphylococcus aureus			50%	
Micrococcus varians		10%		
Diphtheroids				57%[a]
Coagulase-negative *staphylococcus* spp.		10%		
No growth	12.5%	10%	0%	0%

[a] Polymicrobial with predominant diphtheroids or *Staphylococcus epidermidis*.

after removal of hardware is a useful tool for assessing the treatment and evaluating the infectious process (32).

F. Test for Nutrition Status

Lymphocyte count and serum albumin levels are good indices of nutritional status; therefore, these tests should be performed before any major elective surgery (17). Serum albumin level less than 3.5 g/dL and total lymphocyte count less than 1500–2000 cells/mm^3 are considered to represent clinical malnutrition (3,33,34).

Additional tests that can be helpful to evaluate the nutritional status include creatinine height indices, transferring levels, height-to-weight ratios, and skin fold thickness (3,35).

G. Other Tests

A blood culture, widely accepted as a good and reliable test, should be obtained in the presence of spiking fevers.

IV. POSTDISKECTOMY LAMINECTOMY INFECTION

Diskitis or spondylodiskitis (for appropriate terminology see Chapter 12) may have serious implications and therefore should be treated expeditiously. Unfortunately, spondylodiskitis after diskectomy is frequently missed or detected too late because of false interpretation of postoperative clinical presentation (29).

Most reports indicate infection rates less than 1% (Table 4), which increase with the addition of fusion (without instrumentation) to between 2.4% and 6.2% (1,36). With instrumentation, the incidence of infection is even higher (see Sec. V).

The influence of the use of microscopes on the rate of postoperative spondylodiskitis is a moot point. Some authors have demonstrated a negative impact of increasing the infection rate from 0% to 25% (26) and even higher to 5% (24). Others have claimed a positive influence of reducing the infection rate from 2.8% to 0.4% (37).

Minimally invasive surgery, such as percutaneous diskectomy, seems to have a lower incidence of infection, ranging from 0% to 0.26% (38,39), and these infections usually resolve without sequelae (38). The rate of disk space infections after other diagnostic or therapeutic procedures, such as diskography or chemonucleolysis, was reported to be 2.3% (40,41).

Table 4 Reported Infection Rates after Conventional Diskectomy

Complication rate	Authors
3.0%	Pilgaard 1969 (8)
3.1%	Weight 1970 (117)
0.6%	Horvitz et al. 1975 (36)
0.8%	El-Gindi et al. 1976 (49)
0.75%	Lindholm and Phylkkanen 1982 (7)
0.7%	Puranen et al. 1984 (8)
5.0%	Leung 1988 (118)
0.6%	Heller et al. 1992 (24)
3.7%	Rodhe et al. 1998 (44)
0.86%	Weinstein et al. 2000 (1)

Most of the older reports, however, may not reflect the exact incidence of postdiskectomy infection because of the retrospective nature of the studies and compromised diagnostic accuracy due to lack of availability of MRI facilities.

A. Clinical Manifestation

The onset of postdiskectomy diskitis symptoms usually occurs at 15–27 days (averaged days) after an apparently uneventful operation (4,5,42–44).

One clinical study (29) assessed four clinical parameters commonly used for evaluating infection and noted that, in 97% of patients after an uneventful diskectomy, CRP values were less than 2.5 μg/mL, ESR values were less than 45 mm/h, temperature was less than or equal to 37.5°C, and MRI findings (in the first 10 days) were normal. Therefore, changes beyond these values should serve as a "red flag" for possible postoperative diskitis (29). According to one report, the ESR averaged 60 mm/1st hour at the time of diagnosis of diskitis.

B. Pathogenesis

The infection is assumed to be the result of a direct contamination of the avascular disk space at the time of surgery, most likely by skin flora or the environment. It was observed that retrodiskal infection might also lead to diskitis (29).

On the basis of animal experiments, Fraser and colleagues (45) postulate that after a period of approximately 6 weeks a disk infected with *Staphylococcus aureus* may become "aseptic." They demonstrated that vascular granulation tissue from the subchondral bone invades, absorbs, and controls the infectious process. This mechanism may explain the relatively mild course of some cases of

spondylodiskitis, which may not require any treatment with antibiotic therapy. It is well known that not infrequently primary hematogenous pyogenic spondylodiskitis may lead to epidural abscess and sepsis with devastating consequences, including death (46).

It is our distinct impression that secondary postdiskectomy infection has a less aggressive course than primary hematogenous spondylodiskitis, which is subject to higher risk factors (47). Reports also indicate that spondylodiskitis in the lumbar region has a lower rate of neurological complications as compared to a more cephalad involvement (46).

C. Management

Conventional wisdom dictates that samplings from the lesion (biopsy or aspirate) should provide the best diagnostic confirmation of infection (46,48–50). Opponents of this idea (5,8) argue that, since *Staphylococcus* spp. are by far the most common offending organisms, there is no need for diagnostic sampling and therefore antibiotic treatment can be instituted empirically.

There is no consensus of opinion as to the most effective use of antibiotics in the treatment of postoperative spondylodiskitis. Intravenous (IV) antibiotics that have been successfully used alone include tobramycin, cephazolin, clindamycin, and cephalothin (51,52). Antibiotics used successfully in combination include methicillin, nafcillin, rifampin, cephazolin, penicillin, vancomycin, and cephalothin. Intravenous antibiotics are given for an average of 4–6 weeks, followed by oral administration if necessary (4,5,17,44) (Table 5). When treatment with IV antibiotics is instituted early, the ESR predictably falls to normal values within almost 90 days (4).

In the first author's series, we have encountered four cases of postdiskectomy laminectomy infection (1.3%). Two cases were complicated with pyogenic spondylodiskitis and epidural abscess, caused by *Serratia marcescens*. One of these patients underwent microdiskectomy at the L5-S1 level. The other patient had microlaminectomy and foraminotomy at the L4-L5 level for spinal stenosis. Within the first week, both cases were complicated with an epidural abscess. In the first case, there was also an associated spondylodiskitis. The second case was subsequently complicated with spondylodiskitis, suggesting that the infection spread from the epidural space to the intervertebral disk space. A similar observation was previously reported by others (29). Both cases were treated successfully with a combination of surgery and antibiotics. Surgery was performed approximately 10 days after the original operation (débridement-irrigation and closure over drains for 3 days) and antibiotics were administrated intravenously for 6 weeks and then orally for another 6 weeks. The other two cases were complicated by infection confined to the disk space. Both patients had a concomitant remote infection. One suffered from prostatitis (*Escherichia coli*),

Table 5 Comparison of Commonly Used Antibiotics and Their Antimicrobial Activity[a]

	Cephalosporin generation						
	First	Second	Vancomycin	Clindamycin	Penicillin	Ciprofloxacin	Tobramycin
Staphylococcus aureus (MSSA)	S	S	S	S	S	S	S
Staphylococcus aureus (MRSA)	R	R	S	R	R	R	R
Staphylococcus epidermidis	S	S	S	S	S	S	S
Escherichia coli	S/I	S	R	R	S	S	S
Klebsiella pneumoniae	S	S	R	R	R	S	S
Proteus mirabilis	S	S	R	R	S	S	S
Proteus indole (+)	R	R	R	R	R	S	S
Pseudomonas aeruginosa	R	R	R	R	R	S	S
Beta-hemolytic *Streptococcus* spp.	S	S	S	S	S	I	R
Enterobacter spp.	R	R	R	R	R	S	S
Serratia marcescens	R	I	R	R	R	S	S
Gram-negative	R	V	S	S	R	S	S

[a] MSSA, methicillin-sensitive *S. aureus*; MRSA, methicillin-resistant *S. aureus*; S, sensitive; R, resistant; V, variable; I, intermediate.
* Cefazolin and cephalothin.
** Cefoxitin and cefamandole.

and the other from infected facial acne (*Staphylococcus aureus*). We have been using cefuroxime (a second-generation cephalosporin), 1.5 g IV, just before induction of anesthesia, and 750 mg IV 6 hours after surgery in the recovery room, as a routine prophylactic antibiotic. This antibiotic was not expected to cover the organism in the first three cases and probably was ineffective in the fourth case. The last two cases should have been treated prophylactically with more specific and culture-directed antibiotics.

On the basis of available reports (29) and our experience with the management of hematogenous pyogenic spondylodiskitis (46,48,53) and postoperative infections (41), we recommend the following guidelines for the management of postdiskectomy infections (Fig. 1):

If the infection is confined to the disk space, one may elect a conservative treatment with IV antibiotics (29), unless it fails (7,8,46,49).

If the infection spreads to form a retrodiskal abscess (epidural abscess), we recommend a more aggressive approach with surgical drainage, débridement, and irrigation as the treatment of choice (29,46,50,54).

Minimally invasive surgery, such as transpedicle diskectomy and drainage of infection, has proved to be a cost-effective treatment in the management of primary hematogenous pyogenic diskitis, provided it is not complicated by a serious neurological deficit or destructive bony lesions (46,54).

Most available reports advocate some type of immobilization by means of either bed rest until the patient is comfortable (7,44,50) or orthotic

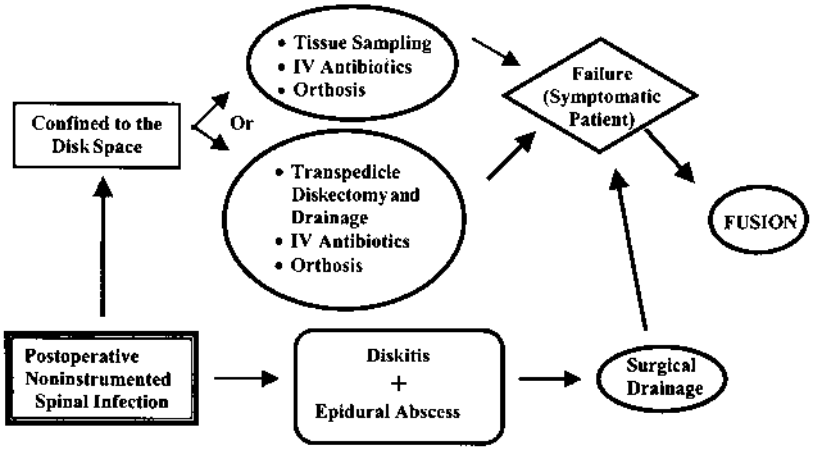


Figure 1 Management of spinal infection without instrumentation.

devices (50). We recommend the use of rigid or semirigid orthosis until fibrous or bony ankylosis takes place.

Finally, we recommend interbody fusion, when conservative treatment, débridement-irrigation, or transpedicle diskectomy fails (54).

V. EARLY POSTOPERATIVE SPINAL INFECTION AFTER INSTRUMENTATION

By far the most common infections encountered after spinal instrumentation surgery are superficial and deep wound infections (13). Fortunately, less common complications are osteomyelitis, diskitis (spondylodiskitis), epidural abscess, infected meningocele with or without cerebrospinal fluid leak, meningitis, sepsis, and even death (19). In general, epidural abscesses complicating spinal surgery represent 16% of all presentations (55).

With the advent of spinal implants, infection has become more prevalent, with reported rates reaching as high as 20%, but averaging 7.24% (Table 6).

A. Pathogenesis

The organism may have been inoculated during surgery and any number of sources may be responsible. The source of gram-negative organisms is a matter of speculation (14). Polymicrobial infections are more likely to inoculate the wound either at the time of surgery or secondarily through drains and wound contamination in the presence of urinary bladder or bowel incontinence.

The most commonly isolated organisms are gram-positive; *Staphylococcus aureus* is the most common organism, with incidence rates ranging from 50% to 75%, followed by *Staphylococcus epidermidis* with incidence rates ranging from 11% to 50%. Negative culture findings are not unusual (10%–16%) and multiple organisms are found in approximately 20% to 59% of infections (1,4,13,14,16) (Table 2).

In paraplegic patients, the flora seem to be different: gram-negative organisms (*Enterobacter* spp., 35%, *Escherichia coli*, 28%, *Proteus* spp., *Acinetobacter* spp., and *Pseudomonas* spp.) are seen as often as gram-positive organisms (coagulase-negative *Staphylococcus* spp., 50%, *Enterococcus* spp., *Streptococcus* spp., and *Staphylococcus aureus*) and are polymicrobial in 50% of cases (16). Arguably, the presence of enteric organisms suggests fecal contamination (16).

B. Clinical Manifestation

The most common clinical presentation is partial wound dehiscence associated with drainage of fluid that may or may not appear purulent, approximately 15 to

Table 6 Reported Infection Rates for Spinal Surgery after Posterior Instrumentation

Complication rate	Authors
11.0%	Tamborino et al. 1964 (119)
20%	Moe 1967 (62)
8.0%	Levine et al. 1970 (120)
4.0%	Keller and Pappas 1972 (61)
8.0%	Kostuik et al. 1973 (121)
9.3.%	Lonstein et al. 1973 (70)
13%	Swank et al. 1979 (122)
8.0%	Swank et al. 1981 (123)
9.0%	McCarthy et al. 1986 (124)
6.0%	Roy-Camille et al. 1986 (52)
6.0%	Luis et al. 1986 (125)
7.0%	Micheli et al. 1986 (126)
0%	Allen and Ferguson 1988 (127)
6.0%	Zuckerman et al. 1988 (128)
0%	Gurr and McAfee 1988 (129)
6.0%	Thalgott et al. 1989 (130)
7.5%	Whitecloud et al. 1989 (131)
4.0%	Esses and Saches 1991 (132)
11.9%	Kretzler and Banta 1992 (133)
2.6%	Davne and Meyers 1992 (102)
6.0%	Massie et al. 1992 (14)
3.7%	Abbey et al. 1995 (57)
3.6%	Wimmer and Gluch 1996 (101)
9.7%	Perry et al. 1997 (134)
7.2%	Levi et al. 1997 (13)
8.7%	Szoke et al. 1998 (65)
4.6%	Aydinly et al. 1999 (135)
3.2%	Picarda et al. 2000 (136)
12%	Sponseller et al. 2000 (16)
7.24%	**Average**

17 days after surgery (ranging from 4 to 80 days) (1,14,17,19) (see also risk factors). Other common manifestations are pain and redness around the wound. Fever is uncommon (2,13) and, at most, pyrexia at presentation was reported in 30% of cases (1). Unexplained hyperglycemia in diabetic patients, malaise, exacerbation of back pain, and sweat and chills, particularly at night, are important clues for prompt diagnosis of suspected infection (14). The mean age ranges from 44 to 57.2 years (17,19). We would like to emphasize that usually early diagnosis is established on clinical grounds.

C. Pseudoarthrosis and Spinal Infection

Available reports tend to indicate that, in contrast to delayed infection after spinal instrumentation, in which increased rates of pseudoarthrosis are observed, early infections do not significantly alter the rate of pseudoarthrosis (1,17,19). One report, however, implicated the use of an allograft and extension of the graft mass to the sacrum as a risk factor for pseudoarthrosis (56).

VI. TREATMENT

The most appropriate surgical method for managing early wound infection after spinal instrumentation has been widely debated. For this reason we attempt here to analyze the different concepts and methods of treatment in an objective fashion.

The surgical management of early spinal infections after instrumentation is divided into two different camps. One group thinks that the presence of spinal instrumentation precludes successful treatment of spinal infection (23,57), and therefore all the hardware should be removed. This option, however, may result in an unstable spine. The majority of surgeons (11,13,19,58,59) try to salvage the instrumentation at least until fusion takes place.

The principle of maintaining internal fixation in the presence of infection has been well recognized in the management of long bone fracture (60) that consolidates satisfactorily despite the infection. This concept also has been applied successfully in the management of instrumented spinal infections (61,62).

The objective of treating spinal infection with instrumentation is to eradicate the infection without removing the hardware, which is required to maintain alignment of the spine, especially after extensive laminectomy, until the fusion consolidates. This precludes the need for additional surgery and even orthosis.

Three main, different, and distinct surgical techniques are available for salvaging infected spinal instrumentation, until fusion takes place. In general, these surgical methods are known as *surgical débridement-irrigation*, *constant antibiotic irrigation-suction*, and *muscle flaps*. The surgeon may choose any combination of these techniques, depending on the local wound condition and the general physical status of the patient.

A. Guidelines for Surgical Treatment

For a rational method of treating postoperative infection after spinal instrumentation, Thalgott and colleagues (11) have developed a classification scheme in which the patients have been categorized according to two parameters. The first

deals with the severity of infection, and the second takes into account the host response or physiological classification of the patient. This classification system is based on the clinical staging system for adult osteomyelitis developed by Cierny and coworkers (63). The severity of infection is divided into three groups: group I involves a single-organism infection, either superficial or deep; group II is a multiple-organism deep wound infection; and group III is a multiple-organism infection with myonecrosis. The host response is divided into three classes: class A requires normal systemic defenses and metabolic capabilities and vascularity; class B patients demonstrate local or multiple systemic diseases, including effects of cigarette smoking; class C is an immunocompromised or severely malnourished host (Fig. 2).

According to Thalgott and associates (11), patients in group I can be managed by single surgical débridement-irrigation and closure over suction-drainage tubes without the use of an inflow-outflow irrigation system. The group II patients, with a multiple-organism infection, require more surgical débridement-irrigation sessions and, usually at the completion of the third débridement-irrigation treatment, the installation of a closed inflow-outflow device for constant irrigation with antibiotics. They found that patients in this group responded better with this technique when compared with surgical débridement-irrigation with a simple suction drainage system without constant inflow irrigation. The group III patients with multiple-organism infections and myonecrosis have a poor prognosis and are best managed with muscle flaps.

B. Surgical Techniques

1. Surgical débridement–irrigation method

Surgical débridement should be carried out in the operating room with general anesthesia. The surgeon should meticulously remove all the infected tissues, necrotic material, and nonviable bone grafts or substitutes by aggressive débridement and obtain tissue for immediate Gram stain and culture. Then the wound should be thoroughly irrigated by antibiotic-containing saline solution (5–9 L, depending on the situation), preferably by using a pulsatile lavage system. All the subfascial plains should be cultured, débrided, and irrigated separately in a systematic order. We advocate bacitracin, 50,000 units in 1000 mL, because its soapy quality adds a detergent effect to the solution. This practice has been supported experimentally as well (64).

One report argues that a single suction irrigation treatment does not allow a second look for further débridement of necrotic tissue that is not apparent during the initial procedure (1). However, we believe that if the wound looks clean, with relatively minimal tissue damage, good vascularity, and no severe infection, the objective of surgery has been achieved. Furthermore, if the patient's condition is

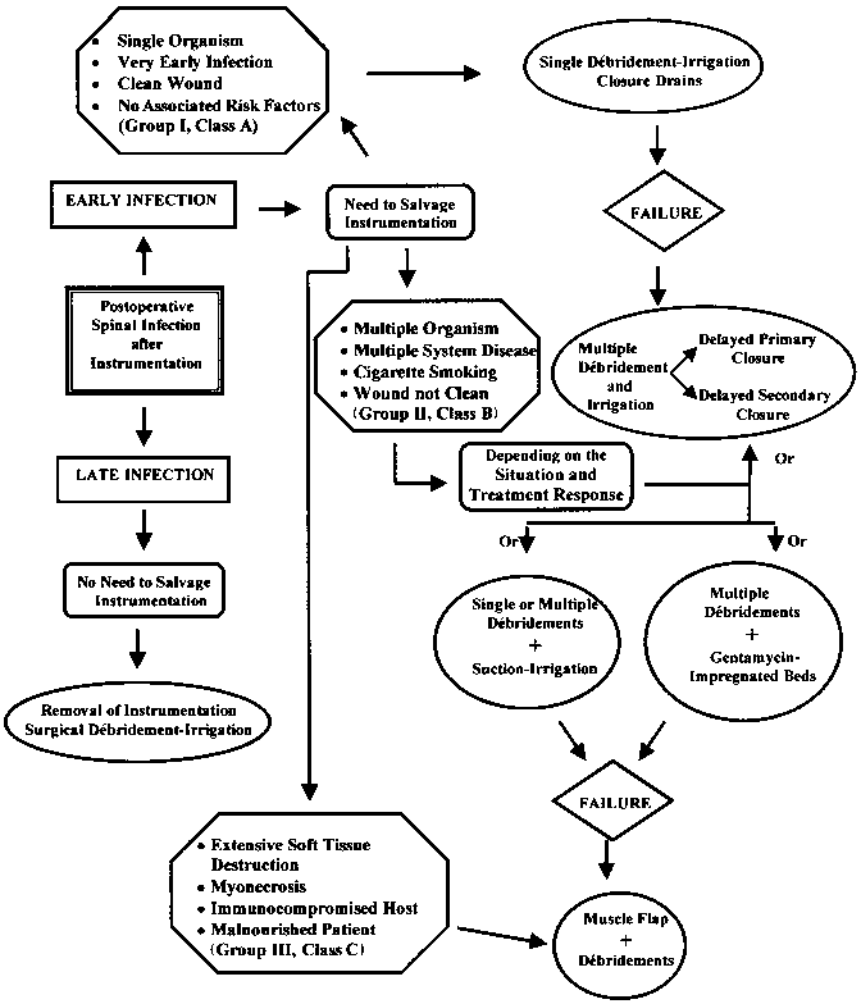


Figure 2 Guidelines for management of early postoperative infection after instrumentation.

stable and the patient does not appear ill from sepsis and has normal systemic and metabolic capabilities, the surgeon could choose to close the wound primarily (11) over suction drainage, as a single procedure. The drains are usually left in place for 4–5 days.

Instead of the method outlined, the surgeon may elect the option of packing the wound open with gauze, soaked preferably in half-strength Dakin's solution.

The surgeon may repeat the same procedure every 48 hours until the wound is clean, and then as needed every 4–5 days (this may be done on the wards under good analgesia-sedation preparation) until the formation of granulation tissue. This process requires an average of four to six sessions.

When the wound is suitable for secondary closure, the surgeon either elects to manage the wound by means of primary delayed closure or allows it to heal by secondary intent. The dressings are changed frequently on the ward or at home, until the wound eventually heals spontaneously by secondary intention (Fig. 3). Because this method, however, is a long, disabling, and expensive process (59), most surgeons prefer a delayed primary surgical closure, after the formation of good granulation tissue.

A culture should be done at each successive débridement for adjusting the antibiotics because of the potential for flora changes in the wound (11). The timing of wound closure depends on different parameters such as erythrocyte sedimentation rate, white blood count, nutritional status, fever, and overall appearance of the wound. The status of the wound is assessed according to the presence or absence of necrotic tissue, persistence and aggressiveness of infection, and presence of granulation tissue. Local bacterial counts are a good indicator that the wound can be managed with a more definitive procedure such as closure or reconstruction with muscle flaps (59).

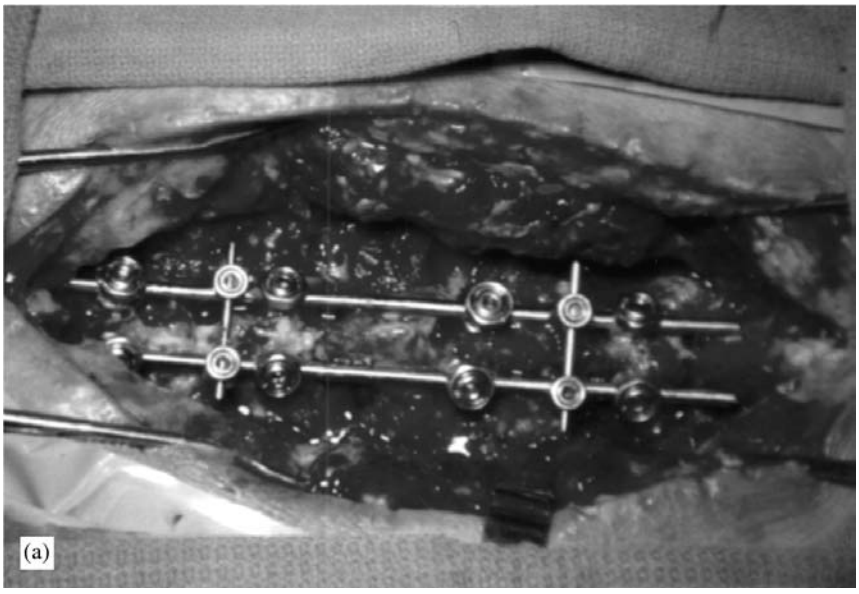
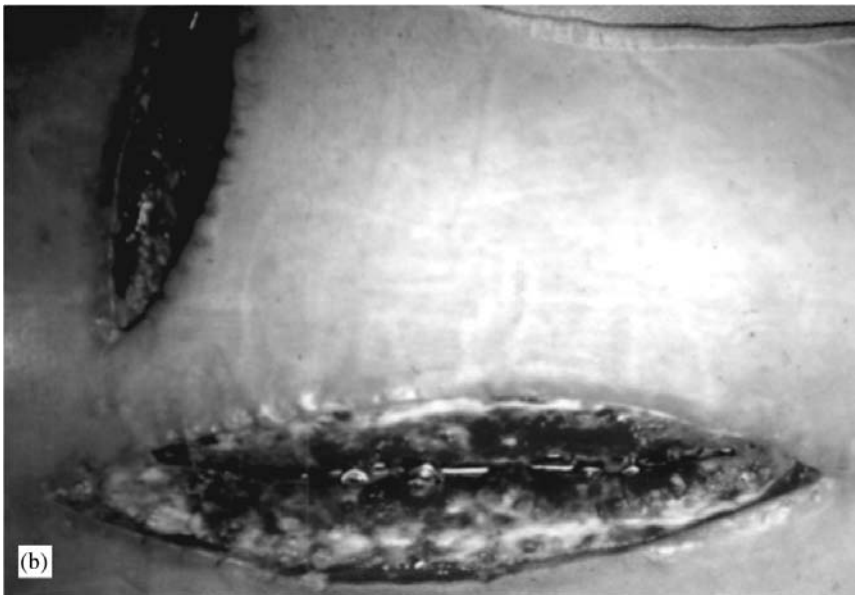


Figure 3 (a) Serosanguinous discharge on the fifth postoperative day.



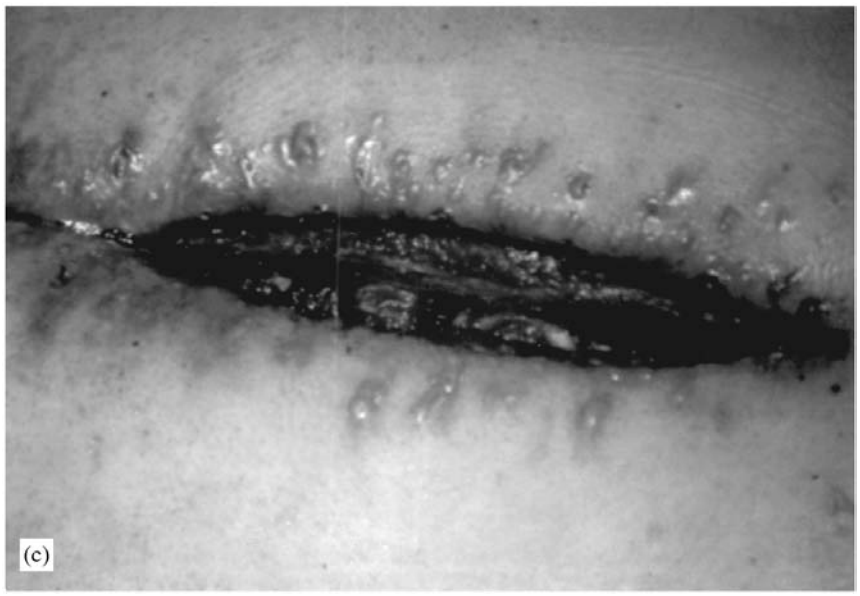


Figure 3 (b) Note, after meticulous surgical débridement and irrigation, absence of pus. (c) Primary wound closure over four suction drains.

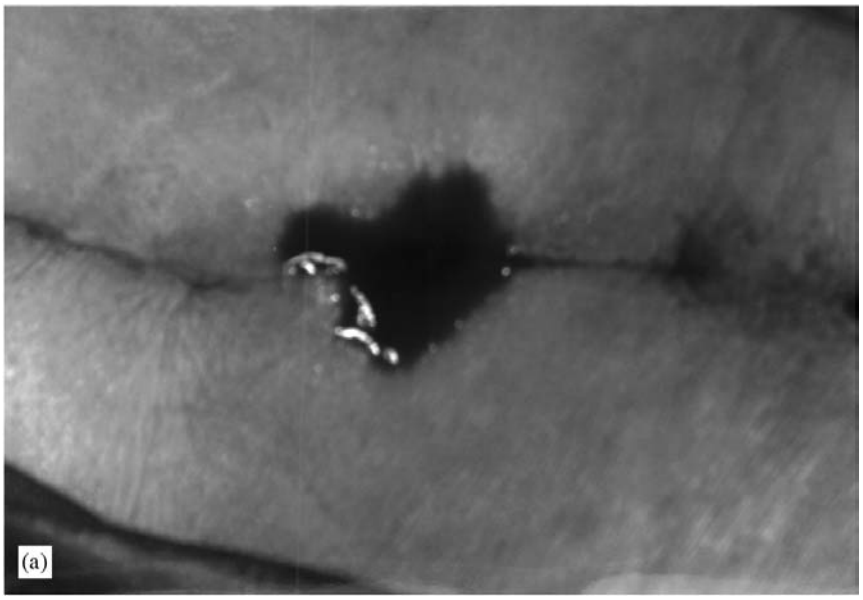


Figure 4 (a) Infection of an instrumented thoracic spine surgery in a 60-year-old female patient, treated by serial surgical débridement-irrigation.

In terms of available reports, vigorous débridements in the operating room with general anesthesia, appropriate antibiotic coverage, and delayed primary (17) or secondary (65) intent closure (depending on the virulence of infection) can be successful, with no necessity to remove the instrumentation (1,15,66).

Failure of débridement to control infection was reported in 28% of cases in one study (16) and in 18% in another study (1). Both cases were treated successfully by removing the instrumentation in the first case and using muscle flaps to salvage the instrumentation in the second situation.

Repeat débridements and delayed primary closure, overall, constitute a simple surgical technique, but when it is used indiscriminantly for all types of deep wound infection, we have observed complications in 68% of cases, including seroma/hematoma, persistence of infection, and wound dehiscence (59) (Table 8). This procedure, when used for early instrumented spinal infections with relatively minimal tissue damage and especially after noninstrumented surgeries, has an excellent rate of successful outcome (11,46,67). We have treated several cases successfully in this fashion, especially when the procedure was carried out early (within 5–10 days).

This record is highlighted with the following example of a 65-year-old retired policeman suffering from chronic low back pain and onset of right sciatica

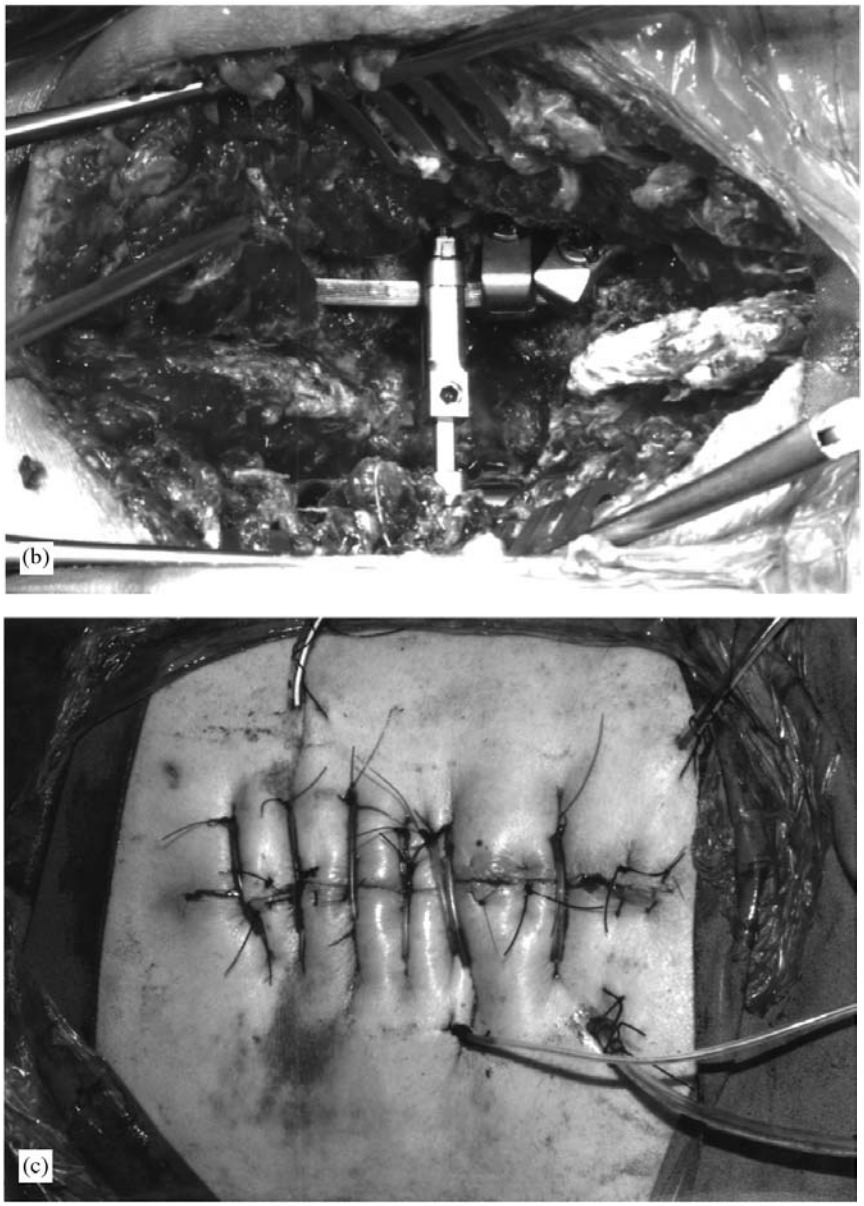


Figure 4 (b) The surgeon elected treatment by means of secondary intention closure. Note healthy granulation tissue creeping to cover the entire spine and instrumentation 4 weeks later. (c) Almost complete healing of the wound is seen in 8 weeks. Although it took a long time, the results were excellent. Fusion was successful and because the instrumentation was prominent under the skin, it was removed uneventfully 2 years later.

associated with weakness of dorsiflexion of the foot in the past 6 months, with gradual deterioration to complete incapacity. He was treated in the local hospital with analgesics, nonsteroidal anti-inflammatory drugs, and complete bed rest with bathroom use for 3 weeks. The patient had well-controlled diabetes mellitus. He was transferred to the first author's institution, where imaging studies revealed a right lateral stenosis at the L4-L5 and L5-S1 levels and grade I L4-L5 degenerative spondylolisthesis. He had microdecompression of the right L4-L5 and L5-S1 regions, foraminotomy, and laminotomy. Unfortunately, there was no substantial relief of his pain except some improvement of the right foot dorsiflexion. Postoperative conservative treatment with the administration of a tapering dose of methylprednisolone (Medrol Dosepak) over 5 days, ranging from 24 mg on day 1 to 8 mg on day 5, failed to relieve the pain and on the sixth postoperative day he underwent a complete L4 laminectomy, partial bilateral L3-L5 laminectomy, wider L4-L5 and L5-S1 right foraminotomies, transpedicle instrumentation from L3 to the sacrum, and intertransverse compound bone graft. He had an excellent response to this treatment. On the fifth postoperative day, while he was getting ready to be discharged from the hospital, he had an asymptomatic serosanguinous discharge. ESR was 106 mm/h, WBC was 14,230, and CRP level was 6.34. The diagnosis of a potential infection was made, and the patient had surgical débridement and irrigation, under general anesthesia, with 6 L of normal saline solution containing 80 mg of gentamycin and 500 mg/L fucidic acid. Because the wound was clean at the end of the procedure, with no excessive necrotic tissue, and the Gram stain finding was negative (the patient was class I and group I), he was treated with primary closure over suction drains (Fig. 4) for 3 days. As an adjunctive to the antibiotics the patient received during the procedure, he was given 500 mg vancomycin IV for 4 days and 750 mg cefuroxime IV for 3 days. The patient had an uneventful and complete recovery and was treated with culture result–directed antibiotics.

The risk factors in this situation were prolonged hospitalization with bed rest (>3 weeks), previous surgery, administration of steroids, and comorbid diabetes mellitus.

We share with others (14) the opinion that the benefits of early surgical intervention of suspected spinal instrumented infections, with aggressive débridement and irrigation, outweigh the risk of delaying surgery even if surgery yields no evidence of infection (Table 8 outlines the guidelines in an algorithmic approach).

2. Constant closed antibiotic irrigation-suction technique

After a thorough débridement and irrigation, as described earlier, the surgeon inserts the irrigation suction device. This consists primarily of inflow catheters and outflow drains that are usually placed both deep and superficial with respect

to lumbosacral fascia, and, if required, an additional irrigation-suction system is placed in the donor bone graft site (13). Antibiotics agents are added to the irrigation bags. The surgeon may also choose to achieve this effect by using a single-inflow Jackson-Pratt drain and close the skin over single-outflow hemovac drains (11).

The inflow-outflow tubes are sutured to the skin. The fascia is closed with several nonabsorbable interrupted N^{o} 0 sutures. The skin is closed with N^{o} 0 retention sutures and watertight running 3-0 nylon (13).

The rate of irrigation is usually maintained at a continuous flow ranging from 25 to 150 mL/h, depending on the severity of the infection. The irrigation system is usually placed for 5–7 days and the drainage tubes are kept in place for an additional day (13). The irrigant of 1 L of normal saline solution contains 500 mg of vancomycin and 1000 units of heparin. Successful outcome resulting from this treatment has been reported by several authors (11,13,14,58,61,68,69). Thalgott and associates (11) advocate combining this method with two or three previous surgical débridements.

Risk of *Pseudomonas* sp. superinfection is a serious drawback of this treatment (70,71).

3. Muscle flaps

When infected wounds involve exposed bony spine or hardware, the optimal goal for successful closure is a two-layered well-vascularized closure. The deep layer is made up of muscle and then covered with the skin (72). For this reason, muscle flaps are preferred to random and fasciocutaneous flaps in this situation (73–77).

Muscle flap coverage of infected instrumentation in the extremities has become a standard practice, and, with some guidelines and experience, the surgeon can easily apply this principle to the spine (59,72,78).

Animal model studies and clinical research have demonstrated the superiority of muscle flaps in inhibiting bacterial growth and promoting wound healing by providing well-vascularized tissue for delivery of antibiotics, immune cells, and oxygen (73–75,77,79–81).

Muscle flaps are indicated for extensive wounds when primary closure is not possible, such as in the so-called hostile back (82) (Fig. 5). This term describes the most complex back wounds, which are characterized by a large surface area defect (greater than 200 cm^2), exposed hardware, and a history of complex infection (other conditions also may be responsible, such as post-radiation necrosis). This also may be associated with other problems such as an osteodestructive process, spinal instability, multiple failed attempts at reconstruction (82), and, at worst, a cerebrospinal fluid leak.

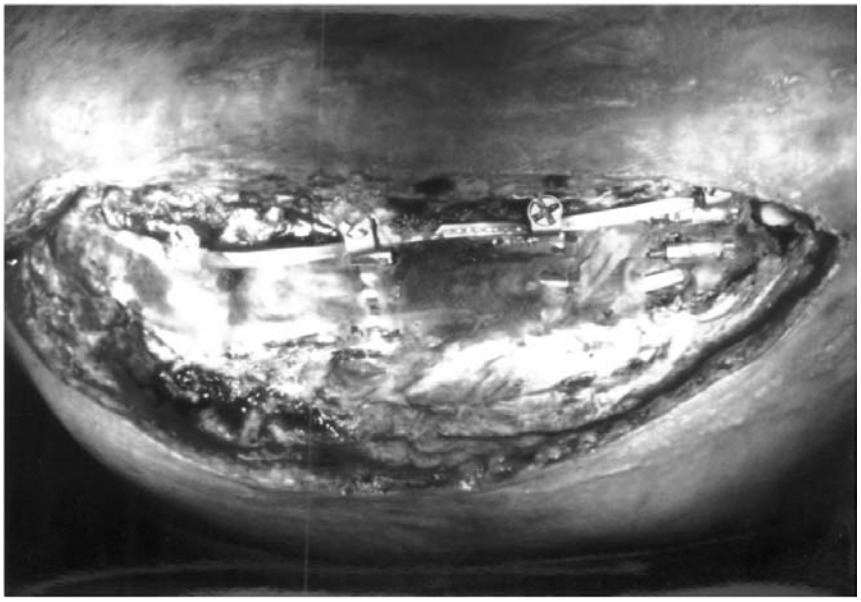


Figure 5 "Hostile" wound infection. Note wide complete wound dehiscence, with extensive necrotic tissue without evidence of granulation tissue.

We found that the average wound length for muscle flap coverage spans about five to six vertebral bodies (except in scoliosis surgery). In our experience, muscle flaps can cover any defect in the spine.

Many different methods for managing infected wounds using various muscle flaps have been reported. Latissimus dorsi, trapezius, gluteus maximus, and paraspinous muscles with their associated fasciocutaneous flaps have been described as *bipedicle or unipedicle advancement*, *rotation*, *turnover*, and *free island flaps*. These have been used individually or in combination (83).

In our experience, a higher complication rate was found in wounds closed in a delayed primary fashion (68%) than in those reconstructed with muscle flaps (20%) (59). For this reason, we have started using a paraspinous sliding flap as a primary reconstruction for infected spinal instrumentation in the lumbar region, after the initial two or three surgical débridements.

Postoperative infection after spine surgery, with extensive deep wound myonecrosis, deep space infection, exposed orthopedic hardware, bone, and dura mater is amenable to muscle flap reconstructive surgery with a predictable excellent outcome (for controlling the infections). This is performed either as a single one-stage surgery (84), after repeated débridements (1), or as a salvage procedure when other methods have failed (1,11,85).

Postoperative spinal infection after instrumentation complicated by dehiscence, a large defect, and cerebrospinal fluid (CSF) leak is a serious and potentially life-threatening complication, which fortunately is rare, can be managed satisfactorily with muscle flap reconstruction (51,72,83,86). One of our patients treated with spinal instrumentation had complications of spinal infection, wound dehiscence, and CSF leak and eventually died.

Flap selection. Flap selection for spinal wound reconstruction is based on the anatomical location of the lesion. Cervical, thoracic, and upper lumbar spinal wounds can be reconstructed with trapezius and latissimus muscles. Lower lumbar spinal wounds are best reconstructed with gluteus maximus flaps, bilateral bipedicled skin flaps (87), and free latissimus dorsi muscle flaps (85). Upper lumbar spine and especially the mid- and lower lumbar spine are best reconstructed with turnover paraspinous muscle flaps (72) or bipedicle sliding paraspinous muscle flaps (59) (Fig. 6).

Large midline back defects may require multiple flaps such as paraspinous muscles combined with latissimus or gluteus muscles (72,83).

Gluteus maximus muscle. The gluteus maximus muscle flap is useful for the lowermost region of the spine (lumbosacral region). Either the entire gluteus maximus (88) or the superior portion, as a turnover flap, can be used (80,84,89). It is important to preserve function on the inferior portion of the gluteus maximus in ambulatory patients (84), so the superior one-half segment of this muscle is used. Usually the patients do not have subjective symptoms related to removal of the superior portion of the gluteus maximus (85). The surgeon first dissects it off the posterior iliac crest, then separates it from the underlying gluteus medius muscle, and finally raises and turns it about 160 degrees to move it from the greater trochanteric region to the inferior lumbar and sacral region. One should take care not to damage its vascular pedicle while maneuvering the flap (84,85).

Deepithelialized myocutaneous turnover of a gluteus maximus island flap based on the superior gluteal vessels has been successfully used for closure of a CSF leak (83) (Fig. 7).

Trapezius muscle flap. The trapezius muscle flap is usually indicated for lesions in the higher cervical region (86). The vascular pedicle enters the muscle about 7–8 cm lateral to the seventh cervical spinous process. The surgeon elevates the muscle off the paraspinous musculature and divides it on its lateral aspect, and, under direct vision, carries out the dissection with the vascular pedicle remaining on the medial segment of the muscle and then transports it proximally. One complication of this technique is a shoulder drop.

Latissimus dorsi flap. The latissimus dorsi muscle flap is indicated for reconstruction or hardware coverage of thoracic or upper lumbar spinal wounds. Because the pedicle of the latissimus dorsi is in the axillary region, the arc of

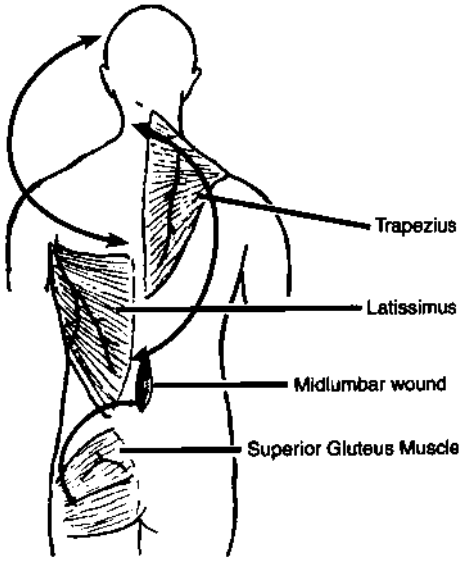


Figure 6 Illustration demonstrating selection of muscle flaps. For cervical, thoracic, and upper cervical regions, the trapezius and latissimus dorsi flaps can be used. The lower lumbar region is distal to latissimus dorsi arc of rotation. The lower lumbar region is amenable to superior gluteus maximus muscle flap, and the midlumbar (or whole lumbar region) to paraspinous bipedicle sliding muscle flap. (From Ref. 59.)

rotation of the latissimus dorsi muscle precludes its use for reconstruction of mid- and lower lumbar lesions (85,90) (Fig. 8).

Depending on the situation, the surgeon either dissects the latissimus dorsi muscle from the underlying paraspinal muscles and transposes it as an island based on the thoracodorsal vessels or chooses to turn over the muscle based on its segmental perforators along the spine (91,92). This turnover or reverse latissimus flap is not a reliable option for wound closure after spinal procedures because the spinal perforators may have been divided for a previous spinal instrumentation exposure.

Free flaps. The free flap method is usually indicated when the local tissue conditions are very poor and spine fusion is not performed. The superior gluteal muscle (92) or the latissimus muscle (85), with its overlying soft tissues, is commonly harvested for this technique and, in general, has been used for reconstructing lumbar wounds. The muscle flaps can be anastomosed to different vessels such as local lumbar perforators, the 11th intercostal, the superior gluteal vessels, and local lumbar perforators. The 11th intercostal vessels may be too

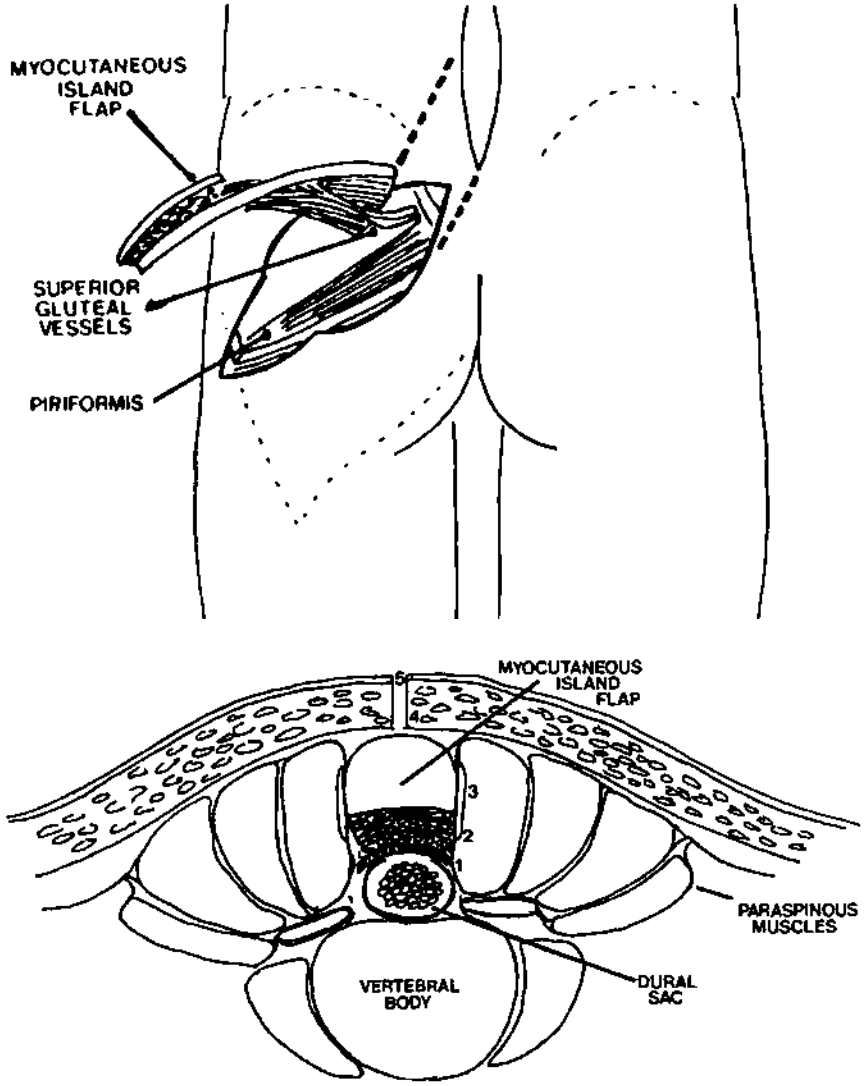


Figure 7 (a) Lower lumbar wounds reconstructed with gluteus maximus flap. The heavy broken line represents the subchondral tunnel through which the flap is being passed to reach the intended target. This skin muscle flap with deepithelialized skin can also be used to patch dural defect. (b) A cross-sectional demonstration of the flap within the defect. The deepithelialized skin can be seen patching the dural defect (1). The layer of subcutaneous tissue of the flap (2) and the gluteus maximus muscle (3) provide another two layers for closure. After undermining of the lumbar skin edges, these are closed in another two layers. (From Ref. 83.)

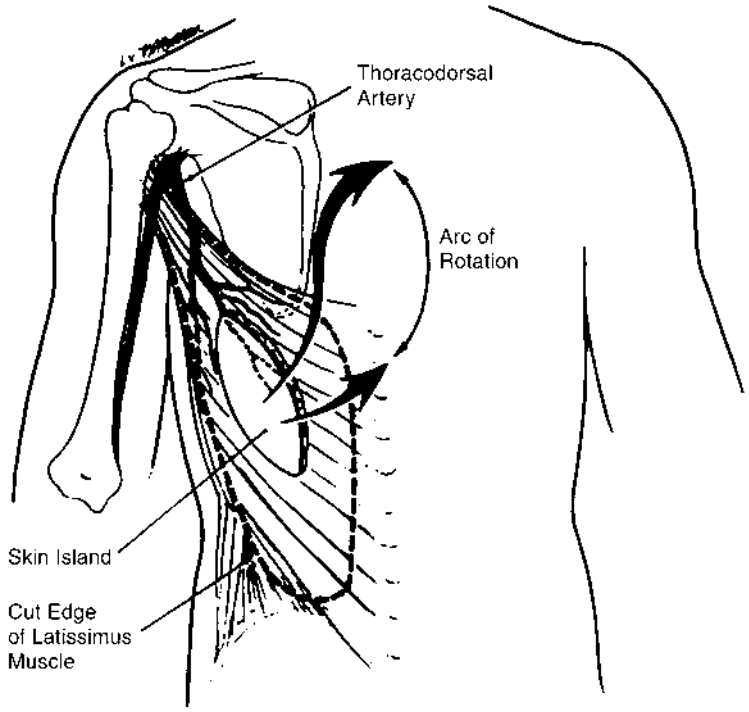


Figure 8 Latissimus dorsi flap is indicated for the upper lumbar and mienly thoracic spine regions. Midlumbar wounds are inferior to arc rotation for latissimus and superior to gluteus muscle. We advocate the use of paraspinous muscle for this level. (From Ref. 59.)

small to match the diameter of the thoracodorsal vessels (85). The superior gluteal vessels are short, and, for that reason, reversed saphenous vein grafts are required when using these recipient vessels for anastomoses to the free muscle flap (85). One of the problems of using local perforators to anastomose the flap is the great difficulty encountered when dissecting out these donor vessels adjacent to the spine. After stabilization procedures, these target vessels are rarely available (82,85,93,94). An alternative method is to use interposition of long vein grafts such as the saphenous or cephalic vein (82) (as long as 28 cm) to anastomose the flap either to the thoracodorsal vessels or to the femoral artery or external carotid.

Paraspinal muscle flaps. Local paraspinous muscles neighboring the spine can be used (72) to provide muscle coverage in the lumbar region, which is involved in most spinal surgery (95). The medially based, turnover paraspinous muscle flaps (72) may not be an option for spinal wound reconstruction after

posterior spinal instrumentation procedures because the spinal perforators may have been divided and sacrificed. The paraspinous muscles are also known as the *erector spinae muscles*, which include the longissimus, iliocostalis, and spinalis portions. The erector spinae muscles were also formerly called the *sacrospinalis muscles* (96). The paraspinous muscles are located deep to the latissimus dorsi muscles and thoracolumbar fascia, originate inferiorly from the spinous processes and the iliac crest, and insert superiorly into the posteriomedial aspect of the ribs (Fig. 9).

The paraspinous muscles are found by incising the thoracolumbar fascia medially and then elevating them from the underlying serratus posterior inferior muscles. The portion of the paraspinous muscle required for spinal bone or hardware coverage is released from its origin on the spine. Then this portion of the paraspinous muscle is bluntly elevated from the multifidus muscle, transverse processes, intertransversarii muscles, and transversalis fascia, from the medial to the lateral direction. This blunt dissection allows for mobilization and advance-

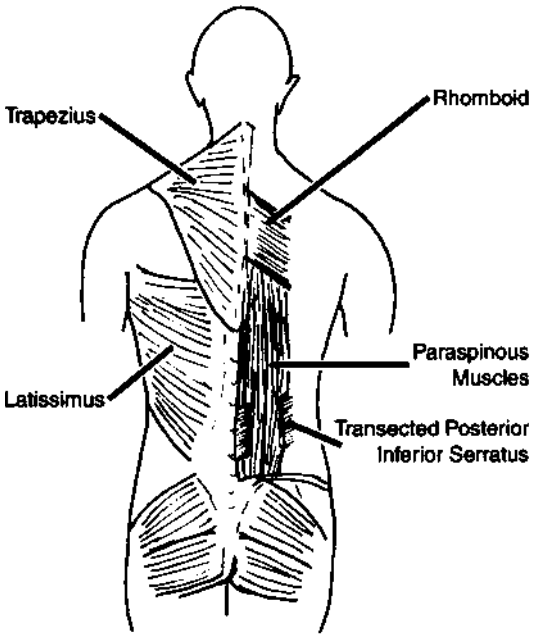


Figure 9 Diagram of paraspinous muscles on patient's right side, located deep to trapezius, rhomboid, latissimus dorsi, posterior inferior serratus, and thoracolumbar fascia. (From Ref. 59.)

ment of the paraspinous muscles in the medial direction, while preserving its lateral perforator vessels (59) (Fig. 10). Sometimes perforator vessels, which enter the muscle along its deep surface, limit muscle advancement to the midline, necessitating ligation of the medial column of perforator vessels. Because the blood supply to the paraspinous muscle is segmental, and is therefore a type IV muscle, the integrity of the superior and inferior muscle continuity must be preserved (80). Therefore, only the medial column of perforators corresponding to the area requiring muscle elevation and advancement is ligated with impunity (59). The muscle bodies are sutured in the midline. Then, the skin adjacent to the defect is undermined, medially advanced, and approximated over closed suction drains. We recommend use of several drains for closed suction (about five to six) strategically located for a prolonged period (usually 10 days).

The long and narrow configuration of most spinal wounds lends itself to the use of the longitudinal alignment of the paraspinous muscles for advancement in wound closure. Other advantages of the use of the paraspinous muscles for reconstructing lower lumbar spinal wounds include its technical simplicity, short

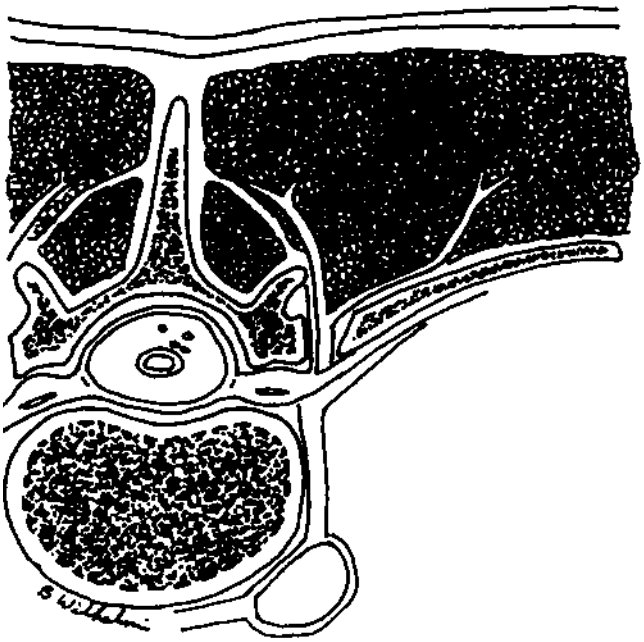


Figure 10 This cross section of the lumbar spine depicts the medial and lateral paraspinous perforator arteries from the posterior intercostalis artery originating from the aorta. (From Ref. 59.)

operative time, and elimination of the requirement of additional incision for muscle dissection.

According to the biomechanics of spinal support using the four-column support concept, the adult spine tolerates the transfer of the paraspinous muscles without difficulty (97).

Except defects at the two ends of the spine, the majority of wounds are amenable to bipedicle sliding paraspinous muscle flaps. One should not worry about loss of paraspinal muscle function in the situation of infected spinal arthrodesis with instrumentation because spinal motion at this level is already lost.

4. Other suggested treatments

Antibiotic-impregnated beads. Antibiotic-impregnated beads have been used successfully to salvage instrumented lumbar fusions complicated by infection (19,98). The beads are used as a vehicle for delivering a high local concentration of antibiotics with minimal, nontoxic systemic levels (99). This procedure does not have the complexity of an inflow-outflow device, but repeated surgeries are required. The technique allows maintenance of antibiotic levels between débridement procedures by using a closed drainage system (19). The reported success rate was 80% and the fusion rate over 90% (19).

VII. DELAYED POSTOPERATIVE SPINAL INFECTION AFTER INSTRUMENTATION

Late infections may occur up to 7 years after surgery (100) but are a rare entity with an incidence of 1.9% of all posteriorly instrumented spinal surgeries (101).

A. Pathogenesis

Both hematogenous sources (100) and introduction of infection at the time of surgery (23,102) have been implicated in the pathogenesis of delayed spinal infections. The microorganism may become active when the host's resistance is compromised (103).

B. Clinical Manifestation

The clinical manifestation of delayed spinal infection after instrumentation is milder than that of early infections. Characteristically, it has an indolent nature and a paucity of diagnostic criteria (104) that cause delay in diagnosis. Incisional swelling or drainage may develop after several months of nonspecific symptoms

(2). In terms of available reports, increased back pain (60% of cases) (23), especially after a prolonged period of normal postoperative recovery, is a good diagnostic clue, particularly when combined with an elevated ESR. In 78% to 87.5% of patients, the average elevation of ESR ranged from 39 to 57 mmHg/h (2,23). According to one report, mild elevation of WBC (usually high range of normal 9000–12,000) was noted in 25% of patients (2).

1. Pseudoarthrosis

A high pseudoarthrosis rate, ranging between 20% and 62% (2,23,58) of cases, has been observed. This suggests an association between pseudoarthrosis and delayed spinal infection (2).

C. Treatment

Most authors advocate surgical débridement and irrigation, as well as removal of instrumentation, in the treatment of delayed spinal infections, with a high rate of success (18,23,105). In this situation, the hardware is typically covered with glycocalix, an avascular enveloping exopolysaccharide resistant to both antibiotics and the host's immune system. Stability for the spine is not a major concern, as it is in the early postoperative infections, and therefore removal of hardware is thought to be an important aspect of the treatment in this situation (23).

VIII. ADJUNCTIVE TREATMENT

A. Antibiotics

Administration of antibiotics alone in the management of infected spinal surgery after instrumentation is not effective in the majority of cases (24,70,106). In this situation, it is our strong opinion that surgical débridement is the definitive treatment and administration of antibiotics can be considered an adjunctive therapy. However, for noninstrumented spinal infections the mainstay of treatment is the administration of intravenous antibiotics. One may select a combination of intravenous vancomycin and oral rifampin as the antibiotic of choice (13,107) until specific tissue culture results and antibiotic sensitivity are available. The duration of intravenous antibiotics may be individualized according to the severity of infection from 1 to 6 weeks and then followed by a course of oral antibiotics for approximately another 6 weeks. When a prolonged use of intravenous antibiotics is needed to facilitate early discharge from the hospital, a Groshong or Hickman intravenous catheter insertion is required. In general, for class B or C patients (see Thalgott and coworkers' classification) a 6-week course

of parenteral antibiotics followed by an additional 6 weeks of oral antibiotics administration is usually given (11).

1. Hyperalimentation

Hyperalimentation is advocated in group II and group III infections in order to improve the host response (11).

IX. PREVENTION OF ''REVERSIBLE'' RISK FACTORS

Close attention should be paid to the perioperative risk factors of patients undergoing spinal surgery, particularly when instrumentation is being used. It behooves the surgeon, before undertaking major elective spinal surgery, to deal first with risk factors that can be controlled, the so-called reversible risk factors:

The patient should be encouraged to quit smoking (11,13).

Steps should be taken to minimize operating room (OR) contamination (108). Proper sterile OR techniques should be followed, traffic in the OR should be minimized, and access doors should be kept closed. Filtered air should be exchanged at a rate of 25 times per hour (21). Laminar airflow systems may play a role in spine surgery as in hip surgery.

The surgeon should treat intercurrent infection and use prophylactic administration of antibiotics (109). The role of prophylactic antibiotics in spinal surgery is well established. The recommended administration is just before the induction of anesthesia and continued for at least 24 hours after surgery. Poor penetration of cefalozin (a first-generation cephalosporin) and oxacillin was demonstrated in animal experiments (110,111), suggesting the uncertainty of their therapeutic effect. Certainly supplemental intraoperative antibiotics should be administered in more length operations. For cases without a suspected potential concomitant infection, first- or second-generation cephalosporins have proved cost-effective.

Animal experiments (112) have demonstrated the efficacy of prophylactic antibiotics for spinal instrumentation and arthrodesis and have also shown that a single preoperative dose of cefazolin was as effective as 48-hour postoperative administration of cefazolin in eradicating wound infections.

This conventionally accepted method has been challenged for disk surgery. Animal experiments (113) demonstrated that intervertebral disk penetration may not be achieved 2 hours after an IV bolus injection, suggesting that it would be safer to administer prophylactic antibiotics at least 60 minutes before surgery. A retrospective study of a large number of posterior fusions (7000 cases) revealed

that prophylactic administration of antibiotics significantly reduced the rate of postoperative infection from 4.4% to 1.2% (58). Similar findings have been reported by others (71), who were able to decrease the rate of infection from 7% to 3.6% after Harrington instrumentation. Another large series confirmed this practice by demonstrating a drop in the infection rate from 9.3% to 1% (36) when prophylactic antibiotics were administrated.

In another relatively large prospective clinical study, it was noted that the patients who had spinal instrumentation and received three doses of 2 g/day cefamandole after surgery for 3 days had a rate of early and late postoperative infection of only 0.6% (69).

One clinical study (44), using a different method of prophylactic administration of antibiotics, reported a dramatic drop in postdiskectomy infections, from 3.7% to 0%. In this study, a collagenous sponge containing gentamycin was placed in the diskectomy region. Bactericidal gentamycin levels in the drainage fluid could be detected 48–72 hours after surgery (114), indicating the effectiveness of this method. Other prophylactic techniques include the following:

An irrigant solution containing a mixture of neomycin, 5% bacitracin (25,000 units/L), and polymixin (25 mg/L) was proved sufficient to eradicate 19 commonly found strains of gram-negative and gram-positive pathogens common in orthopedic surgery (115), thus rendering this solution ideal for wound irrigation. This is a relatively safe usage, although one case of anaphylaxis has been reported in a patient who had been previously exposed to the same irrigant (116).

It has been conventionally accepted that avoiding certain pitfalls during a posterior surgical procedure may contribute to a reduction in the surgical risks for infection (13,108). This includes careful dissection of the ligamentous attachments of the paraspinal muscles (decreases tissue necrosis and blood loss), intermittent release of paraspinal muscle retractors (reduces hypoperfusion and alleviates muscle ischemia), meticulous hemostasis, insertion of surgical drains (eliminates hematoma), and meticulous wound closure (eliminates dead space and provides an airtight barrier against bacterial infiltration).

When a procedure that requires two surgical approaches (anterior and posterior) is anticipated to take a long time and will be performed in one sitting, the surgeon may decrease the risk factor for infection by performing a two-stage procedure on 2 different days.

Since the anterior approach is associated with diminished risk factors for development of infection after spinal instrumentation (13), it is preferable to use an anterior rather than a posterior approach, provided both exposures are equally effective for the given type of spinal surgery.

Close attention should be given to the preoperative nutritional status of patients undergoing lumbar spinal surgery. Patients with suboptimal nutritional parameters should have supplementation and replenishment before elective surgery (25).

In paraplegic patients, because of potentially gram-negative microorganism and polybacterial contamination of the wound, more targeted preventive strategies such as broad-spectrum antibiotics with activity against gram-negative organisms should be used for prophylaxis (16), coupled with impermeable wound dressings and other hygiene measures (16).

X. SUMMARY

Postoperative spinal infections carry a great cost, both medically and socio-economically, and the surgeon must consider and minimize the risks of such infection. Preventive measures should be instituted before and during the surgical intervention.

If, however, infection occurs despite prophylaxis, treatment should be instituted quickly and aggressively to prevent or reduce sequelae. Antibiotic therapy, which may take the form of intravenous, intramuscular, or oral administration or placement of antibiotic-impregnated beads, is the first line of defense after noninstrumented procedures, although débridement may also become necessary. In cases of infection that follow spinal instrumentation, débridement is the initial approach and antibiotic therapy is the adjunctive step. Antibiotic therapy should be designed with the infecting organism(s) in mind. Late postinstrumentation infection may necessitate removal of the instrumentation along with débridement. Closure of wounds after infection may be accomplished by delayed primary closure or closure by secondary intention. In some cases, muscle flaps may be required for reconstruction.

REFERENCES

1. MA Weinstein, JP McCabe, FP Cammisa JR. Postoperative spinal wound infection: a review of 2,391 consecutive index procedures. J Spinal Disord 13:422–426, 2000.
2. RW Viola, HA King, SM Adler, CB Wilson. Delayed infection after elective spinal instrumentation and fusion: a retrospective analysis of eight cases. Spine 20:244–250, 1997.
3. JE Jensen, RG Jensen, TK Smith, DA Johnston, SJ Dudrick. Nutrition in orthopaedic surgery. J Bone Joint Surg 62A:1263–1972, 1982.
4. BE Dall, DE Rowe, WG Odette, DH Batts. Postoperative discitis: diagnosis and management. Clin Orthop 224:138–146, 1987.

5. F Postacchini, G Ginotti, D Perugia. Post-operative intervertebral discitis: evaluation of 12 cases and study of ESR in the normal postoperative period. Ital J Orthop Traumatol 19:57–69, 1993.
6. AM Frank, AE Trappe. The role of magnetic resonance imaging (MRI) in the diagnosis of spondylodiscitis. Neurosurg Rev 13:279–283, 1990.
7. TS Lindholm, P Phylkkanen. Discitis following removal of the intervertebral disc. Spine 7:618–622, 1982.
8. S Pilgaard. Discitis (closed space infection) following removal of lumbar intervertebral disc. J Bone Joint Surg 51A:713–716, 1969.
9. J Puranen, J Makela, S Lahde. Postoperative intervertebral discitis. Acta Orthop Scand 55:461–465, 1984.
10. D Stolke, V Seifert, U Kunz. Die postoperative discitis intervertebralis lumbalis: Eine ubersicht uber einen 15-jahresitraum und 7493 operationen. Z Orthop Ihre Grenzgeb 126:666–670, 1988.
11. JS Thalgott, HB Cotler, RC Sasso, H LaRocca, V Gardner. Postoperative infections in spinal implants: classification and analysis—a multicenter study. Spine 16:981–984, 1991.
12. PJE Cruse, R Ford. A five-year prospective study of 23,649 surgical wounds. Arch Surg 107:206–210, 1973.
13. AD Levi, CA Dickman, VK Sonntag. Management of postoperative infections after spinal instrumentation. J Neurosurg 86:975–980, 1997.
14. JB Massie, JG Heller, JJ Abitbol, D McPherson, SR Garfin. Postoperative posterior spinal wound infections. Clin Orthop 284:99–108, 1992.
15. JW Perry, J Montgomerie, S Swank, DS Gilmore, K Maederi. Wound infections following spinal fusion with posterior segmental spinal instrumentation. Clin Infect Dis 24:558–561 1997.
16. PD Sponseller, DM LaPorte, MW Hungerford, K Eck, KH Bridwell, LG Lenke. Deep wound infections after neuromuscular scoliosis surgery: a multicenter study of risk factors and treatment outcomes. Spine 25:2461–2466, 2000.
17. JL Stambough, D Beringer. Postoperative wound infections complicating adult spine surgery. J Spinal Disord 3:227–285, 1992.
18. C Wimmer, H Gluch, M Franzreb, M Ogon. Predisposing factors for infection in spine surgery: a survey of 850 spinal procedures. J Spinal Disord 11:124–128, 1998.
19. SD Glassman, JR Dimar, RM Puno, JR Johnson. Salvage of instrumental lumbar fusions complicated by surgical wound infection. Spine 21:2163–2169, 1996.
20. MA Ritter. Surgical wound environment. Clin Orthop 190:11–13, 1984.
21. MA Ritter, HE Eitzen, JB Hart, ML French. The surgeons garb. Clin Orthop 153:204–209, 1980.
22. AG Gristina, Y Shibata, G Giridhar, A Kreger, QN Myrvik. The glycocalyx, biofilm, microbes, and resistant infection. Semin Arthroplasty 5(4):160–170, 1994.
23. BS Richards. Delayed infections following posterior spinal instrumentation for the treatment of idiopathic scoliosis. J Bone Joint Surg 77A:524–529, 1995.
24. JG Heller. Postoperative infection of the spine. In: RH Rothman, FA Simeone, eds. The spine. 3d ed. Philadelphia: WB Saunders, 1992:1817.

25. JD Klein, LA Hey, CS Yu, BB Klein, FJ Coufal, EP Young, LF Marshall, SR Garfin. Perioperative nutrition and postoperative complications in patients undergoing spinal surgery. Spine 21:2676–2682, 1996.
26. JD Klein, SR Garfin. Nutritional status in the patients with spinal infection. Orthop Clin North Am 27:33–36, 1996.
27. JA Bendo, J Spivak, R Moskovich, M Neuwirth. Instrumented posterior arthrodesis of the lumbar spine in patients with diabetes mellitus. Am J Orthop 29(8):617–620, 2000.
28. B Jonsoon, R Soderholm, B Stromqvist. Erythrocyte sedimentation rate after lumbar spine surgery. Spine 16:1049–1050, 1991.
29. KP Schulitz, J Assheuer. Discitis after procedures on the intervertebral disc. Spine 19:1172–1177, 1994.
30. U Thelander, S Larsson. Quantitation of C-reactive protein levels and erythrocyte sedimentation rate after spinal surgery. Spine 14:400–404, 1992.
31. P Grane, A Josephsson, A Seferlis, T Tullberg. Septic and aseptic post-operative discitis in the lumbar spine-evaluation by MR imaging. Acta Radiol 39:108–115, 1998.
32. A Hadjipavlou, F Cesani-Vazquez, J Villaneuva-Meyer, JT Mader, JT Necessary, W Crow, RE Jensen, G Chaljub. The effectiveness of gallium citrate Ga 67 radionuclide imaging in vertebral osteomyelitis revisited. Am J Orthop 27:179–183, 1998.
33. SC Dickhaut, JC DeLee, CP Page. Nutritional status: importance in predicting wound healing in amputations. J Bone Joint Surg 66A: 71–75, 1984.
34. BA Feed, M Corliss, RS Bergman. Serum albumin levels and total lymphocyte a predictors of morbidity and mortality in patients undergoing abdominal surgery (abstract). J Parenter Enteral Nutr 6:584, 1982.
35. RD Zoma, RD Sturrock, WD Fisher, PA Freeman, DL Hambleden. Surgical stabilization of the rheumatoid spine: a review of indications and results. J Bone Joint Surg 69B:8–12, 1987.
36. NH Horwitz, JA Curtin. Prophylactic antibiotics and wound infections following laminectomy for lumbar disc herniation. J Neurosurg 43:727–731, 1975.
37. WA Dauch. Infection of the intervertebral space following conventional and microsurgical operation on the herniated lumbar intervertebral disc: a controlled clinical trial. Acta Neurochir 82:43–49, 1986.
38. Bonaldi G, Belloni G, Prosetti D, Moschini L. Percutaneous discectomy using Onik's method: 3 years' experience. Neuroradiology 33:516–519, 1991.
39. JL Schaffer, P Kambin. Percutaneous posterolateral lumbar discectomy and decompression with a 6.9-millimeter cannula. Analysis of operative failures and complications. J Bone Joint Surg 73A(6):822–831, 1991.
40. RD Fraser, OL Osti, B Vernon Roberts. Discitis after discography. J Bone Joint Surg 69B:26–35, 1987.
41. RD Fraser. Chymopapaine for the treatment of intervertebral disc herniation: the final report of a double-blind study. Spine 1:815–818, 1984.
42. M Klinger. Spondylitis: a complication following lumbar disc operations. Adv Neurosurg 10:394–399, 1982.
43. WP Piotrowski, MA Krombhol, B Muhl. Spondylodiscitis after lumbar disc surgery. Neurosurg Rev 17:189–193, 1994.

44. V Rohde, B Meyer, C Schaller, W Hassler. Spondylodiscitis after lumbar discectomy: incidence and a proposal for prophylaxis. Spine 23:615–620, 1998.
45. RD Fraser, OL Osti, B Vernon-Roberts. Iatrogenic discitis: the role of intravenous antibiotics in prevention and treatment. An experimental study. Spine 14:1025–1032, 1989.
46. AG Hadjipavlou, JT Mader, JT Necessary, AJ Muffoletto. Hematogenous pyogenic spinal infection and their surgical management. Spine 25:1668–1679, 2000.
47. AG Hadjipavlou. The management of postoperative pyogenic infection of the spine. The 10th University Congress of Osteosynthesis. Patras, Greece, March 22–24, 2001.
48. S Arya, W Crow, A Hadjipavlou, H Nauta, A Borowski, L Vierra, E Walser. Percutaneous transpedicular management of discitis. J Vasc Interv Radiol 7(suppl):921–927, 1996.
49. S El-Gindi, S Afer, M Salama, J Andrew. Infection of the intervertebral disc space after operation. J Bone Joint Surg 58B:114–116, 1976.
50. GA McCain, M Harth, A Bell, TF Disney, T Austin, E Ralph. Septic discitis. J Rheumatol 8:100–109, 1981.
51. SS Ramasastry, B Schlechter, M Cohen. Reconstruction of posterior trunk defects. Clin Plast Surg 22:167–185, 1995.
52. R Roy-Camille, G Saillant, C Mazel. Internal fixation of the lumbar spine with pedicle screw plating. Clin Orthop 203:7–17, 1986.
53. AM Borowski, WN Crow, AG Hadjipavlou, G Chaljub, J Mader, F Cesani, E van Sonnenberg. Interventional radiology case conference: The University of Texas Medical Branch: percutaneous management of spondylodiscitis. Am J Roentgenol 170:1587–1592, 1998.
54. A Hadjipavlou, WN Crow, A Borowski, JT Mader, A Adesokan, RE Jensen. Percutaneous transpedicular discectomy and drainage in pyogenic spondylodiscitis. Am J Orthop 27:188–197, 1998.
55. AS Baker, RG Ojemann, MN Swartz, EP Richardson Jr. Spinal epidural abscess. N Engl J Med 293:463–468, 1975.
56. LE Weiss, AR Vaccaro, G Scuderi, M McGuire, SR Garfin. Pseudoarthrosis after postoperative wound infection in the lumbar spine. J Spinal Disord 10:482–487, 1997.
57. DM Abbey, DM Turner, JS Warson, TC Wirt, RD Scalley. Treatment of postoperative wound infections following spinal fusion with instrumentation. J Spinal Disord 8:278–283, 1995.
58. JE Lonstein. Management of Musculoskeletal Infections. Philadelphia: WB Saunders, 1989:243–249.
59. B Wilhelmi, N Snyder, T Colquhoun, A Hadjipavlou, L Philips. Bipedicle paraspinous muscle flaps for spinal wound closure: an anatomic and clinical study. Plast Reconstr Surg 106:1305–1311, 2000.
60. WR MacAusland, RG Eaton. Management of sepsis following intramedullary fixation for fractures of the femur. J Bone Joint Surg 45A:1643–1653, 1963.
61. RB Keller, AM Pappas. Infection after spinal fusion using internal fixation instrumentation. Orthop Clin North Am 3:99–111, 1972.
62. JH Moe. Complications of scoliosis treatment. Clin Orthop 53:21–30, 1967.

63. G Cierny, JT Mader, JJ Penninck. A clinical staging system for adult osteomyelitis. Contemp Orthop 10:17–37, 1985.
64. BD Rosestein, FC Wilson, CH Funderburk. The use of bacitracin irrigation to prevent infection in postoperative skeletal wounds. J Bone Joint Surg 71A:427–430, 1989.
65. G Szoke, G Lipton, F Miller, K Dabney. Wound infection after spinal fusion in children with cerebral palsy. J Pediatr Orthop 18:727–733, 1998.
66. R Picada, RB Winter, JF Lonstein, F Denis, MR Pinto, MD Smith, JH Perra. Postoperative deep wound infection in adults after posterior lumbosacral spine fusion with instrumentation: incidence and management. J Spinal Disord 13:42–45, 2000.
67. PD Dernbach, H Gomez, J Hahn. Primary closure of infected spinal wounds. Neurosurgery 26:707–709, 1990.
68. K Ido, K Shimzu, Y Nakayama, J Shikata, M Matsushita, T Nakamura. Suction/irrigation for deep wound infection after spinal instrumentation: a case study. Eur Spine J 5:345–349, 1996.
69. C Wimmer, M Nogler, B Frischhut. Influence of antibiotics on infection in spinal surgery: a prospective study of 110 patients. J Spinal Disord 11:498–500, 1998.
70. J Lonstein, R Winter, J Moe, D Gaines. Wound infection with Harrington instrumentation and spine fusion for scoliosis. Clin Orthop 96:222–233, 1973.
71. EE Transfeldt, JE Lonstein. Wound infections in elective reconstructive spinal surgery. Orthop Trans 9:128–129, 1985.
72. LA Casas, VL Lewis Jr. A reliable approach to the closure of large acquired midline defects of the back. Plast Reconstr Surg 84:632–631, 1989.
73. JP Anthony, SJ Mathes, BS Alpert. The muscle flap in the treatment of chronic lower extremities osteomyelitis. Plast Reconstr Surg 88:311–318, 1991.
74. W Calderon, N Chang, SJ Mathes. Comparison of the effect of bacterial inoculation in musculocutaneous and fasciocutaneous flaps. Plast Reconstr Surg 77:785–794, 1986.
75. N Chang, SJ Mathes. Comparison of the effect of bacterial inoculation in musculocutaneous and random-pattern flaps. Plast Reconstr Surg 70:1–10, 1982.
76. SJ Mathes, F Nahai. A systemic approach to flap selection. In: SJ Mathes, F Nahai, eds. Clinical Applications for Muscle and Musculocutaneous Flaps. St Louis: Mosby, 1982:1–358.
77. RC Russell, DR Graham, AM Feller, EG Zook, A Mathur. Experimental evaluation of the antibiotic carrying capacity of a muscle flap into a fibrotic cavity. Plast Reconstr Surg 81:162–170, 1988.
78. ME Manstein, CH Manstein, G Manstein. Paraspinous muscle flaps. Ann Plast Surg 40:458–462, 1998.
79. I Eshima, SJ Mathes, P Paty. Comparison of the intracellular bacterial killing activity of leukocytes in musculocutaneous and random-pattern flaps. Plast Reconstr Surg 86(3):541–547, 1990.
80. SJ Mathes, BS Alpert, N Chang. Use of the muscle flap in chronic osteomyelitis: experimental and clinical correlation. Plast Reconstr Surg 69:815–829, 1982.
81. RC Murphy, MC Robson, JP Heggers, M Kadowski. The effect of microbial contamination on musculocutaneous and random flaps. J Surg Res 41:75–80, 1986.

82. JW Few, JR Marcus, MJ Lee, S Ondra, GA Dumanian. Treatment of hostile midline back wounds: an extreme approach. Plast Reconstr Surg 105:2448–2451, 2000.
83. C Hill, M Riaz. A new twist to the myocutaneous turnover flap for closure of a spinal defect. Plast Reconstr Surg 102:1167–1160, 1998.
84. JR Wendt, VO Gardner, JI White. Treatment of complex postoperative lumbosacral wounds in nonparalyzed patients. Plast Reconstr Surg 101(5):1248–1253, 1998.
85. HC Chen, HH Chen, WJ Chen, YB Tang. Chronic osteomyelitis of the spine managed with a free flap of latissimus dorsi: a case report. Spine 21:2016–2018, 1996.
86. AE Seyfer, AS Joseph. Use of trapezius muscle for closure of complicated upper spinal defects. Neurosurgery 14:341–345, 1984.
87. TS Moore, TM Dreyer, AG Bevin. Closure of large spina bifida cystica defects with bilateral bipedicle musculocutaneous flaps. Plast Reconstr Surg 73:288–292, 1984.
88. JO Stallings, JR Delgado, JM Converse. Turnover island flap of gluteus maximus muscle for the repair of sacral decubitus ulcer. Plast Reconstr Surg 54:52–54, 1974.
89. SJ Mathes, LO Vasconez, MJ Jurkiewitz. Extensions and further applications of muscle flap transposition. Plast Reconstr Surg 60:6–12, 1977.
90. J Bostwick III, M Scheflan, F Nahai, MJ Jurkiewitz. The "reverse" latissimus dorsi muscle and musculocutaneous flap: anatomic and clinical considerations. Plast Reconstr Surg 65:395–399, 1980.
91. TR Stevenson, RJ Rohrich, RA Pollock, RO Dingman, J Bostwick. More experience with reverse latissimus dorsi musculocutaneous flap: Precise location of blood supply. Plast Reconstr Surg 74:237–243, 1984.
92. T Fujino, T Harashina, F Aoyagi. Reconstruction for aplasia of the breast and pectoral region by microvascular transfer of a free flap from the buttock. Plast Reconstr Surg 56:178–181, 1975.
93. GR Evans, GP Reece. Lower back reconstruction: an approach to wound closure in the cancer patient. Plast Reconstr Surg 96:635–642, 1995.
94. P Giesswein, CG Constance, DR Mackay, EK Manders. Supercharged latissimus muscle flap for coverage of the problem wound in the lower back. Plast Reconstr Surg 94:1060–1063, 1994.
95. DA Capen, RR Calderon, A Green. Perioperative risk factors for wound infections after lower back fusions. Orthop Clin North Am 27:83–86, 1996.
96. CD Clemente. Anatomy: a regional atlas of the human body, 3d ed. Baltimore: Urban & Schwarenberg, 1987.
97. RS Stahl, FD Burstein, JV Lieponis, MJ Murphy, JM Piepmeier. Extensive wounds of the spine: a comprehensive approach to debridement and reconstruction. Plast Reconstr Surg 85:747–753, 1990.
98. A Harle, R VanEnder. Management of wound sepsis after spinal fusion surgery. Acta Orthop Belg 57:242–246, 1991.
99. D Seligson, S Metha, K Voos, SL Henry, JR Johnson. The use of antibiotic-impregnated polymethylmethacrylate beads to prevent the evolution of localized infection. J Orthop Trauma 6:401–406, 1992.
100. MS Heggeness, SI Esses, T Errico, HA Yuan. Late infection of spinal instrumentation by hematogenous seeding. Spine 18:492–496, 1993.
101. C Wimmer, H Gluch. Management of postoperative wound infection in posterior spinal fusion with instrumentation. J Spinal Disord 9:505–508, 1996.

102. SH Davne, DL Myers. Complications of lumbar spinal fusion with transpedicular instrumentation. Spine 17(suppl):S184–S189, 1992.
103. JM Davis, B Wolff, TF Cunningham, L Drusin, P Dineen. Delayed wound infection. An 11-year survey. Arch Surg 117:113–117, 1982.
104. L Schofferman, J Zucherman, J Schofferman, K Hsu, H Gunthorpe, G Picetti, N Goldthwaite, A White. Diphtheroids and associated infections as a cause of failed instrumented stabilization procedures in the lumbar spine. Spine 16:356–358, 1991.
105. J Dubousset, H Shufflebarger, D Wagner. Late "infection" with Cotrel-Dubousset instrumentation. Orthop Trans 18:121, 1994.
106. JG Heller, SR Garfin. Postoperative infection of the spine. Semin Spine Surg 2:268–282, 1990.
107. RF Gagnon, GK Richards, R Subang. Experimental staphylococcus epidermidis implant infection in the mouse. Kinetics of rifampin and vancomycin action. ASAIO J 38:M596–M599, 1992.
108. JG Heller, MJ Levine. Postoperative infection of the spine. Semin Spine Surg 8:105–114, 1996.
109. RL Rimoldi, W Haye. The use of antibiotics for wound prophylaxis in spinal surgery. Orthop Clin North Am 27:47–52, 1996.
110. FJ Eismont, SW Wiesel, CT Brighton, RH Rothman. Antibiotic penetration into rabbit nucleus pulposus. Spine 12:254–256, 1987.
111. MJ Gibson, MRK Karpinski, RCB Slack, WA Cowlishaw, JK Webb. The penetration of antibiotics into the normal intervertebral disc. J Bone Joint Surg 69B:784–786, 1987.
112. JP Guiboux, B Ahlgren, J Patti, M Bernhard, M Zervos, H Herkowitz. The role of prophylactic antibiotic in spinal instrumentation: a rabbit model. Spine 23:653–656, 1998.
113. BL Currier, K Banovac, FJ Eismont. Gentamycin penetration into normal rabbit nucleus pulposus. Spine 19:2614–2618, 1994.
114. C von Hasselbach. Klinik und pharmakokinetik von kollagen-gentamycin als adjuvente Lokaltherapie knocherner infektionen. Ulfallchirurg 92:459–479, 1989.
115. DD Scherr, TA Dodd. In vitro bacteriological evaluation of the effectiveness of antimicrobial irrigating solution. J Bone Joint Surg 58A:119–122, 1976.
116. PA Netland, JE Baumgartner, BT Andrews. Intraoperative anaphylaxis after irrigation with bacitracin: a case report. Neurosurgery 21:927–928, 1987.
117. RL Wright. Septic Complications of Neurological Spinal Procedures. Springfield, IL: Thomas, 1970.
118. PC Leung. Complications in the first 40 cases of microdiscectomy. J Spinal Disord 1:306–310, 1988.
119. JM Tambornino, EN Armbrust, JH Moe. Harrington instrumentation in correction of scoliosis. J Bone Joint Surg 46A:313–323, 1964.
120. DB Levine, RL Wilson, JH Dohedry. Surgical management of idiopathic scoliosis: a critical analysis of 67 cases. Clin Orthop 52:34–47, 1971.
121. JP Kostuik, J Israel, JE Hall. Scoliosis surgery in adults. Clin Orthop 93:225–234, 1973.

122. SM Swank, DS Cohen, JC Brown. Spine fusion in cerebral palsy with L-rod spinal instrumentation: a comparison of single and two-state combined approach with ielke instrumentation. Spine 14:1750–1753, 1979.
123. S Swank, JE Lonstein, JH Moe, RB Winter, DS Bradford. Surgical treatment of adult scoliosis. J Bone Joint Surg 63A:268–287, 1981.
124. RE McCarthy, RD Peek, RT Morrissy, AJ Hough Jr. Allograft bone in spinal fusion for paralytic scoliosis. J Bone Joint Surg 68A:370–375, 1986.
125. R Louis. Fusion of the lumbar and sacral spine by internal fixation. Clin Orthop 203:28–33, 1986.
126. LJ Micheli, JE Hall. Complications in the management of adult spinal deformities. In: CH Epps Jr, ed. Complications in Orthopaedic Surgery. Vol 2. 2d ed. Philadelphia: JB Lippincott, 1986:1227–1229.
127. BL Allen Jr, RL Ferguson. The Galveston experience with L-rod instrumentation for adolescent idiopathic scoliosis. Clin Orthop 229:59–69, 1988.
128. J Zuckerman, K Hsu, A White, G Wynne. Early results of spinal fusion using variable spine plating system. Spine 13:570–579, 1988.
129. KR Gurr, PC McAfee. Cotrel-DuBousset instrumentation in adults: a preliminary report. Spine 13:510–520, 1988.
130. JS Thalgott, H LaRocca, M Agei, AP Dwyer, BE Razza. Reconstruction of the lumbar spine using AO DCP plate fixation. Spine 14:91–95, 1989.
131. TS Whitecloud III, JC Butler, JL Cohen, PD Candelora. Complications with the variable spinal plating system. Spine 14:472–476, 1989.
132. SI Esses, BL Saches. Complication of pedicle screw fixation. 1991 North American Spine Society Meeting. Keystone, CO, August 1991.
133. J Kretzler, J Banta. Wound infections following spinal fusion surgery: Transactions of the 1991 meeting of the Pediatric Orthopaedic Society of North America. J Pediatr Orthop 12:264, 1992.
134. JW Perry, JZ Montgomerie, S Swank, DS Gilmore, K Maeder. Wound infections following spinal fusion with posterior segmental spinal instrumentation. Clin Infect Dis 24:558–561, 1997.
135. U Aydinli, O Karaeminogullari, K Tiskaya. Postoperative deep wound infection in instrumented spinal surgery. Acta Orthop Belg 65:182–187, 1999.
136. R Picada, RB Winter, JF Lonstein, F Denis, MR Pinto, MD Smith, JH Perra. Postoperative deep wound infection in adults after posterior lumbosacral spine fusion with instrumentation: incidence and management. J Spinal Disord 13:42–45, 2000.

14

Granulomatous Infections of the Spine

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I. INTRODUCTION

Granulomatous infection of the spine includes tuberculosis, fungal infections such as blastomycosis, histoplasmosis, and coccidioidomycosis and brucellosis. The characteristic feature of these infections is the formation of a granuloma. The term *granuloma* refers to a microorganism-induced response, which results in cellular hyperactivity. In its most classic form, it consists of concentric layers of cells that form a distinctive lesion. At the center of the lesion, there is often a focus of necrosis that is surrounded by a layer of specialized macrophages, called *epithelioid cells*, and multinucleated giant cells that form as the result of fusion of macrophages. The next layer is predominantly lymphocytes, and the outer layer is most often fibroblasts that are attempting to cordon the area of inflammation with fibrous connective tissue. Other cell types may also be present.

The necrotic area in tuberculosis is caseatious, whereas in some fungal infections this type of lesion may not develop. Coccidioidomycosis and histoplasmosis often exhibit caseatious necrosis. In this chapter, actinomycosis is discussed with fungal infections. Although actinomyces is a gram-positive bacteria that causes pyogenic infection, it morphologically branches as fungus does and resembles fungal infections, which can become extremely chronic and are poorly transmissible from person to person. Brucellosis, a bacterial infection

caused by an aerobic, gram-negative coccobacillus commonly found in domestic animals, has the ability to induce granulomatous reaction.

II. SPINAL TUBERCULOSIS

A. Introduction

Tuberculosis (TB) is a granulomatous infection caused most commonly by *Mycobacterium tuberculosis*. Percival Pott first described spinal involvement of tuberculosis with characteristic gibbus formation and paraplegia in 1779. For this reason, spinal tuberculosis is also called *Pott's disease*. Tuberculosis of the spine is almost always a secondary infection and is characterized by an insidious onset and silent clinical course. By the time the disease becomes symptomatic, it has already provoked impressive pathological changes as depicted by imaging modalities.

Spinal tuberculosis is the most dangerous form of skeletal tuberculosis because of its ability to cause bone destruction, spinal deformity, and paraplegia. Paraplegia is more common in tuberculosis than in pyogenic spondylitis (1,2).

B. Incidence and Risk Factors

According to the World Health Organization (WHO), TB has become the world's most deadly infectious disease, killing nearly 3 million people per year (3). Each year there are 8 million new cases of tuberculosis, and 50% of them represent active infections. There are approximately 20 million active cases, and 1.7 billion people (one-third of the world's population) are, or have been, infected with the tuberculosis bacillus. In some East and Central African countries, the reported cases of tuberculosis have nearly doubled in the recent years. One of the main reasons for the resurgence of tuberculosis is the spread of human immunodeficiency virus (HIV) infection (3).

There is an increased risk for tuberculous infections in older population adults, immunocompromised patients (HIV patients, transplant patients, etc.) (4), and individuals with chronic debilitating conditions (5), including substance-abusing individuals. Populations in developing countries are not spared; however, an increase of drug-resistant tuberculosis has been noticed in the former Soviet Union (6).

In HIV-negative patients, spinal involvement occurs in 1% of all individuals who suffer from tuberculosis. In contrast, the spine is affected in 60% of the cases in patients who are HIV-positive (7,8). In addition, HIV-positive patients have a 170-fold increased risk of reactivation of an old dormant tuberculosis (9).

C. Pathophysiological Characteristics

Spinal tuberculosis represents 50%–60% of cases of musculoskeletal tuberculosis (8,10) and is almost always secondary to hematogenous spread of mycobacteria from primary foci in the lung or genitourinary tract (11,12). The route of infections is controversial. The arterial route of transmission is considered the most important (13). However, some investigators believe that the paravertebral venous plexus of Batson provides the primary pathway for dissemination of the tuberculous bacilli into the vertebra column (14,15). It is also possible that lymphatic drainage of the pleura or kidney may involve the para-aortic lymph nodes, which may secondarily affect the vertebra (16).

The disease most commonly affects the thoracolumbar region of the spine, followed by the thoracic and the lumbar spine. Rarely, it can affect the cervical spine and, even more rarely, the sacral region (8,17). At times the disease may exhibit multiple lesions in the spine, mimicking other conditions, such as metastatic cancer (18).

The initial site of vertebral involvement is the anterior-inferior corner of the vertebral body and then spreading along the anterior longitudinal ligament to involve the adjacent vertebral body. Destruction of the anterior vertebral body results in acute vertebral wedging that gives rise to the classic focal kyphosis, or the so-called gibbus of Pott's disease (19).

The intervertebral disk is not affected in the early stages of the disease (Fig. 1). In the late stages, intervertebral disk involvement ranges from 46% to 72% of cases as seen in magnetic resonance images (7,20).

Abscesses are common findings in spinal tuberculosis and have a prevalence of 55% to 96% (21). Tracking of the abscess follows tissue planes. Extension posteriorly into the spinal canal can occur at any level of the spine.

The intervertebral disk is involved by direct spread from affected neighboring vertebrae or soft tissue. Alternatively, the pathological process may involve the center of the vertebral body or the paradiskal region (22). Central destruction of the vertebral body results in "concertina collapse." When the paravertebral abscess strips the periosteum and ligaments away from the vertebral body, the blood supply becomes compromised and avascular necrosis of the vertebral body results. The devitalized anterior vertebral body is further attacked by the pathological process, forming anterior scalloping that is referred to as *aneurysmal syndrome*. Involvement of the paradiskal region usually occurs on either side of the intervertebral disk, resulting in narrowing of the disk space. Destruction of two or three vertebrae may result in subluxation or dislocation of the spine. Other malalignments of the spine that may arise from tuberculosis are reversed spondylolisthesis in the lumbar region and scoliotic deformity.

Tuberculosis can also have an unusual or atypical form such as primary involvement of the posterior elements of the spine (2%–10%) (23,24) (i.e.,

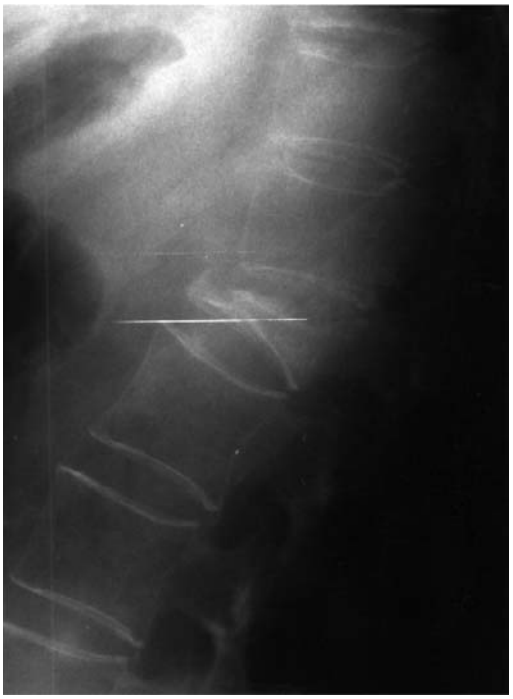
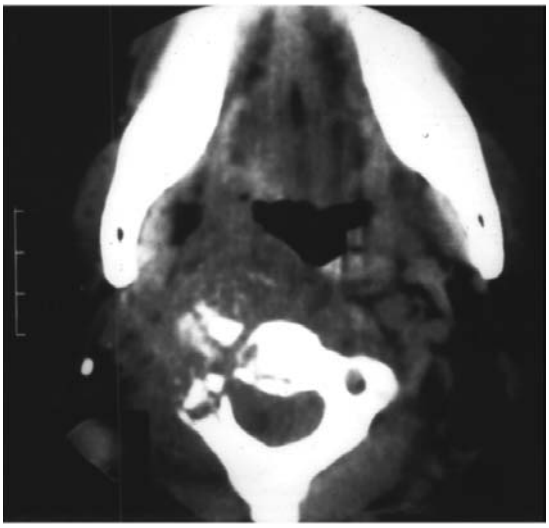


Figure 1 Plain radiograph demonstrating a kyphotic deformity with telescoping of T12 into the L1 vertebra. Note that the intervertebral disk is intact.

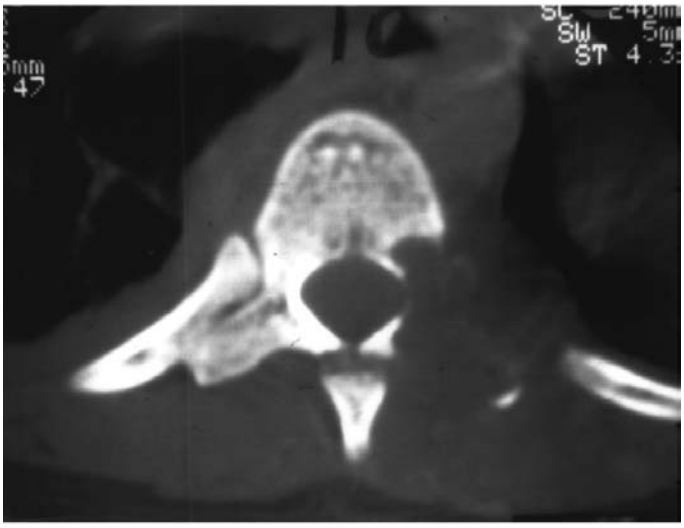
lamina, spinous process, and pedicle) (Fig. 2) or localization at the intervertebral disk in early stages of the infection process (7).

Paraplegia or severe paraparesis is more frequently encountered at the T4-T5 level of the thoracic spine, which has the poorest vascular supply of the spinal cord (25); therefore, the disease process can easily compromise the tenuous nature of the local vascular anatomical features.

Necrotic bone and caseous tuberculosis abscess material can cause cord compression in active disease and, occasionally, can even displace an intervertebral disk. Cord compression can also occur with spinal kyphosis caused by vertebral destruction and spinal subluxation. Spinal artery thrombosis is probably unrelated to the compression effect and its ensuing paraplegia has the gloomiest prognosis (21). Tuberculous pachymeningitis usually results in a severe and spastic form of paraplegia caused most likely by scar contraction (22). The majority of patients with posterior element involvement have severe neurological deficits (23,24).

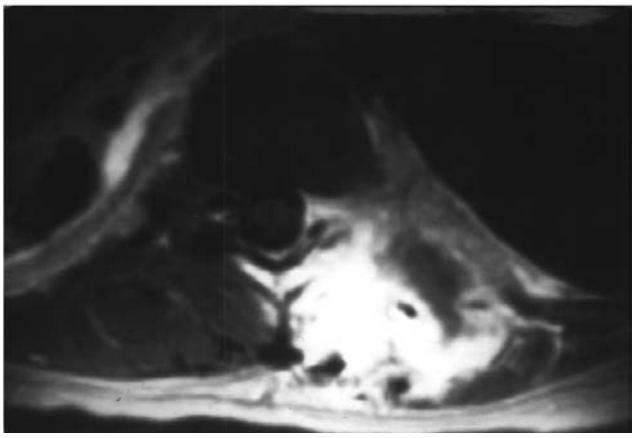


(a)



(b)

Figure 2 (a) Rare forms of TB spondylitis affecting the lateral mass and facet joint of the C2 vertebra and (b) pedicle of T10 with posterior paravertebral abscess, as seen on CT scan.
CT, computed tomography; MRI, magnetic resonance imaging.



(c)

Figure 2 (c) MRI, magnetic resonance imaging; TB, tuberculosis.

Late onset of paraplegia, in inactive disease, has been observed when a progressive kyphotic deformity mechanically compromises the cord.

Tuberculosis also can directly affect the neural elements of the spine and corresponds of 2% to 5% of all central nervous system (CNS) tuberculomas (26,27). When intramedullary tuberculoma is localized in the conus medullaris, it can be confused with a conus tumor, and diagnosis in this condition can only be established by surgery (28).

D. Histopathological Characteristics

Gross examination of the tubercular tissues shows they are thickened and edematous and frequently studded with grayish small nodules with opaque centers (granulomas). Granulomas often become confluent, producing larger areas of white necrotic material, so-called caseation (or cheese) necrosis (29).

On microscopic examination, the typical tubercle consists of a central necrotic area surrounded by a pale histiocytes, referred to as *epithelioid cells*. Among the epithelioid cells are some scattered giant cells, the nuclei of which are typically arranged at the margin of the cell and are called *Langerhans giant cells*. At the periphery of the tubercle is a rim of mixed chronic inflammatory cells. Often the tubercles are confluent, resulting in extensive central caseation necrosis (29). Typically the acid-fast bacilli can be demonstrated with the Ziehl-Neelsen stain and are characteristically seen in the giant cells and at the margins of the caseous area.

E. Clinical Manifestation

Back pain and gibbus, with or without an associated neurological involvement, highlight the symptomatic clinical picture of spinal tuberculosis. Usually the onset is insidious and the symptoms mild and months up to 2 or 3 years may pass before diagnosis is established (30). In contrast, pyogenic spondylodiskitis is characterized by an acute onset of severe pain. Weight loss, fever, and malaise may be associated with chronic tuberculosis illness and often precede manifestation of the spinal lesion. Therefore, the delayed diagnosis may hinder the institution of appropriate early treatment and may result in spinal deformity and spinal cord compression, with variable degrees of neurological deficit. In the late stages, bone destruction with its antecedent instability may give rise to pain with mechanical characteristics. Cervical involvement may produce torticollis, neck pain, stiffness, dysphagia, and even respiratory stridor (31,32).

Cold abscess adjacent to the spinous processes of the characteristic "gibbus" is not an unusual finding. A paraspinal abscess, which is highly characteristic of tuberculous infection, may be so prominent that it may compress the bronchial tree, producing symptoms simulating asthmatic bronchitis (asthma milleri). Cold abscesses also may be present in the groin, buttock, trochanteric region, or loin. Mobility of the spine is limited; therefore, the patient flexes the hips when asked to bend over during physical examination.

According to Hodgson and Yau (33), paraplegia or paraparesis can be caused either by an active disease process or by a progressive kyphotic deformity in the healed phase.

Symptoms from other affected organs such as the urinary tract or the pulmonary and lymphatic systems may not be obvious; therefore, it behooves the physician to scrutinize the patient clinically.

F. Laboratory Tests

The white blood cell (WBC) count is variable. Erythrocyte sedimentation rate (ESR) often is elevated, but may also be normal in up to 25% of cases. Purified protein derivative (PPD) skin test typically yields a positive result, indicating either active or previous disease. This test may have false-negative results, particularly in malnourished or immunocompromised patients. Polymerase chain reaction (PCR) is a fast and reliable test for the diagnosis of tuberculosis (34).

The most effective and rapid identification of the pathological process relies on needle biopsy. Needle biopsy yields a positive result in 82% of cases (35).

G. Imaging Resources

The most common early findings on plain radiography are narrowing of the disk space and vertebral osteolysis. In more advanced stages of the disease, a

paravertebral shadow, indicating extension of the tuberculous granulation tissue and the formation of abscess in the paravertebral region, can be seen. Later, vertebral collapse, angulation of the spine, subluxation, and even dislocation may occur. As opposed to pyogenic infection of the spine, tuberculosis less frequently causes reactive sclerotic bone and sclerosis. However, in the healing phase of tuberculosis, the ostoblastic response may prevail (36).

Radionuclide imaging is not helpful in these cases because the false-negative finding rates for technetium (^{99m}Tc) and gallium-67 scans are very high: 33% and 70%, respectively (10,30).

Computed tomography (CT) scans of the involved areas are helpful in identifying the nature and extent of the vertebral involvement as well as the association with soft tissue masses. Four types of lesions can be observed in CT scan: (1) fragmentary, which appear as numerous residual small bone fragments; (2) osteolytic, when most of the vertebral elements are destroyed; (3) subperiosteal; and (4) localized destruction with sclerotic margins when few residual bone fragments are seen within a lytic area (37).

The most characteristic and frequent (47%) type of bone destruction is the fragmentary type (37) with fragments frequently migrating into the associated soft tissue mass and epidural space. This appearance is probably due to the tuberculous inflammatory exudates' lack of proteolytic enzymes, which are required to lyse bone (38).

CT scans are not capable of distinguishing granulation tissue from frank abscess formation. CT scans are recommended in planning treatment, especially when surgical intervention is contemplated, in order to assess the structural integrity of the spine.

Magnetic resonance imaging (MRI) is probably the imaging modality of choice, providing excellent definition of the extent of vertebral involvement, abscess formation, and degree of spinal canal compromise. MRI is useful for evaluation and for follow-up studies of spinal tuberculosis.

The signal intensity of the vertebral marrow is decreased on T_1-weighted images and increased on T_2-weighted images as a result of replacement of the normal fat content by the edematous inflammatory process (39). Loss of the intranuclear cleft within the disk and high signal intensity on T_2-weighted images are signs of inflammation (7,20). Epidural extension of vertebral infection (7,20) with neurocompression is detected on 61% of MRIs. Paraspinal soft tissue masses are shown in 71% of cases (7). These inflammatory soft tissues are seen well on post-contrast-enhanced, fat-suppressed sequences. Rim enhancement around intraosseous abscesses on gadolinium-enhanced MRIs is suggestive of granulation tissue. Also, on contrast-enhanced sequences a thick rim enhancement around paraspinal abscesses is seen. The height of disk space is preserved until the late stages of the infection. According to one report (20) mixed signal intensity was present in 32% of cases.

Follow-up MRI studies are useful for monitoring response to therapy. The earliest sign of healing is a reduction in the amount of inflammatory soft tissue.

H. Treatment

There is still significant controversy regarding the preferred treatment for spinal tuberculosis. Conservative treatment is indicated when the patient seeks medical attention early with minimal destruction of the spine. The duration of the chemotherapy is usually 9 to 12 months. The most common combination of drug administration is standard triple chemotherapy (isoniazid, rifampin, and pyraminazide) (Table 1) (40–42). When the response to antituberculous treatment is slow, the triple chemotherapy can be administered for 18 months, or a four-drug regimen can be used (isoniazid, rifampin, pyraminazide, and ethambutol) for 12 months. According to one report (40), a course of chemotherapy based on two drugs (rifampin and isoniazid) for 6 months can be as effective as the 18-month course of isoniazid and paraamino salicylic acid (PAS). Others (41) have reported that 6 months of three-drug chemotherapy with surgical eradication of the tuberculous lesion in the spine was as effective as treatment with the same regimen for 9 and 18 months. In addition, early in the disease process, nonsteroidal anti-inflammatory drugs may be useful for the management of nonspecific synovial membrane inflammation. This adjunct treatment may also inhibit or minimize bone resorption by prostaglandin (42).

Table 1 Pharmacological Treatment of Adults for Spinal Tuberculosis

Drug	Dosage	Side effects
Isoniazid	300 mg PO/day for 12 months	Hepatitis, peripheral neuropathy, and pharmacological fever
Rifampin	600–900 mg PO/day for 12 months	Hepatitis, flulike symptoms (rare)
Pyraminazide	1.5–2 mg PO/day	Hepatitis, hyperuricemia
Streptomycin	0.75–1 mg IM/day for 2–3 months	Kidney toxicity, ear toxicity, hepatitis, nausea, and vomiting
Ethambutol	15 mg/kg PO/day for 2–4 months	Posterior eyeball neuritis (rare, but most severe), arthritis, urichemia, gastrointestinal effects, and peripheral neuropathy

Clinical studies by the First Medical Research Council (MRC) of Britain (43–47) compared the effectiveness of (1) ambulant chemotherapy alone, or in combination with either rest or immobilization; (2) surgical débridement without fusion; and (3) anterior radical excision of the pathological process with fusion. The chemotherapeutic regimen used was daily isoniazid (INH) and PAS for 18 months, with or without concomitant streptomycin for the first 3 months. The conclusion of this study was that at 3-, 5-, and 10-year follow-up, patients attained favorable results in all groups. However, the results did not take into account fusion rate, symptomatic relief, or angle of kyphosis (36) (Fig. 3). In the second study, which began in 1986 (47), a short course of chemotherapy (6 to 9 months of INH and rifampin with or without streptomycin) was used. The 3-year follow-up findings were more favorable for that group of patients who had combined radical operation in the regimen, as compared to ambulant chemotherapy alone, except in Madras. The patients treated with anterior radical excision and fusion had almost no increased kyphotic deformity, as opposed to those treated with débridement or conservative therapy alone. The increase in the kyphotic deformity of the patients treated conservatively is worrisome. Table 2 shows the changes in the angle of kyphosis at 5- and 10-year follow-up. It is well known that spinal kyphosis is a disabling, and even dangerous, deformity because of its detrimental effect on the spinal cord.

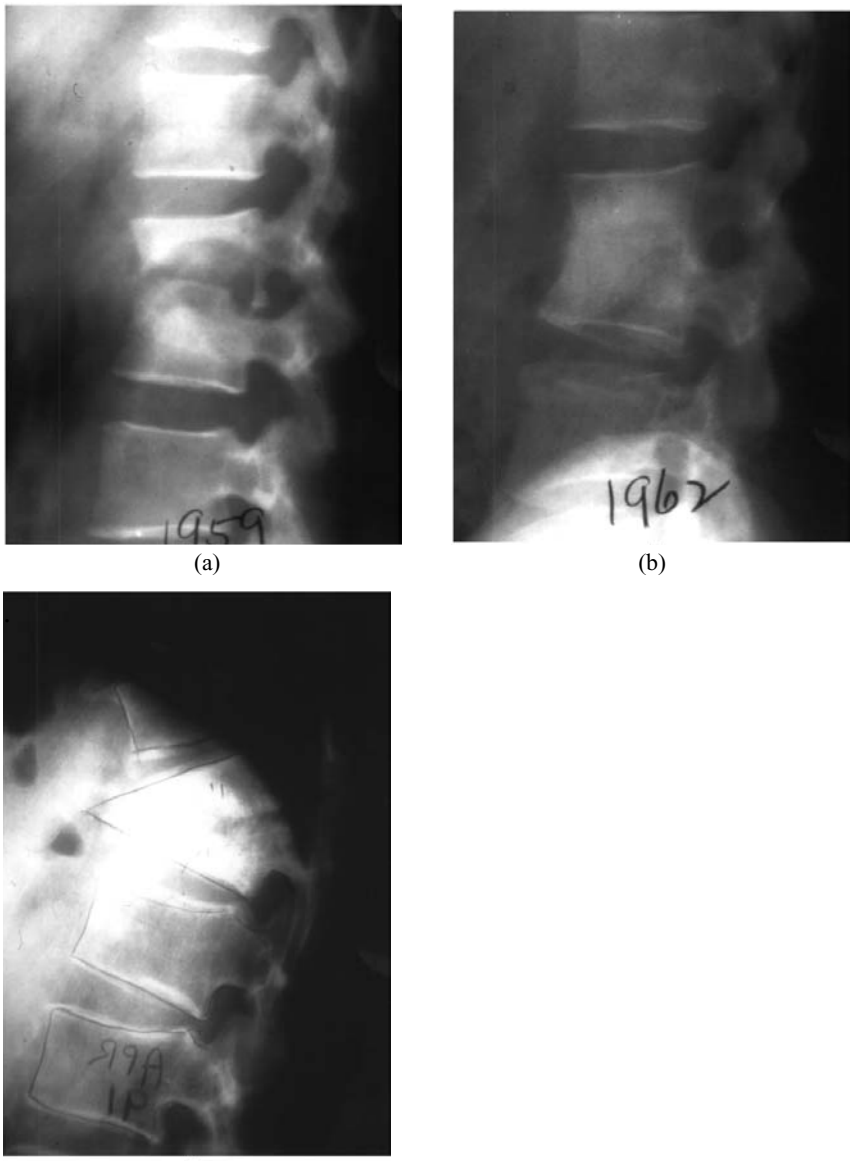
The conclusion of these findings is that surgical excision of the disease process and fusion deals better with the deforming effect of spinal tuberculosis. Antituberculosis chemotherapy alone (the mainstay of treatment) can heal the disease and may even reverse neurological deficit but obviously cannot control the deformities or prevent late neurological or musculoskeletal complications arising from kyphotic deformities. According to Leong (36) anterior radical resection of the tuberculous lesion combined with spinal fusion involves several aspects: (1) it dramatically improves the patient's condition by evacuating the abscess, (2) established paraplegia can be corrected rapidly, (3) early fusion is anticipated with insertion of a strut graft under compression, and (4) late paraplegia and late deformity can be prevented (36) (Fig. 4).

On the basis of these principles, the senior author has surgically treated 25 patients with spinal tuberculosis with vertebral destruction, kyphotic deformities, epidural abscesses, and severe neurological deficits, including five patients with complete paraplegia. The surgical approach consisted of anterior decompression, fusion, and posterior stabilization with instrumentation (transpedicular screws or laminal hooks) without laminectomy (Figs. 5 and 6). All patients had an excellent outcome, including the paraplegic patient, who had complete recovery. A report indicated that the fusion rate in radical anterior surgery for spinal tuberculosis is expected to be between 80% and 94% with an average time for fusion of 22.2 months (ranging from 7 to 42 months) (48).

Table 2 Changes in the Angle of Kyphosis

	Increased Kyphosis							
	5-Year follow-up				10-Year follow-up			
	Patients assessed	11°–30°	31°–50°	51°–70°	Patients assessed	11°–30°	31°–50°	51°–70°
Radical excision and fusion (Hong Kong)	60	9	0	0	23	4	0	0
Débridement (Bulawayo)	38	11	3	0	33	9	3	0
Conservative therapy (Korea)	271	88	31	12	160	52	27	9

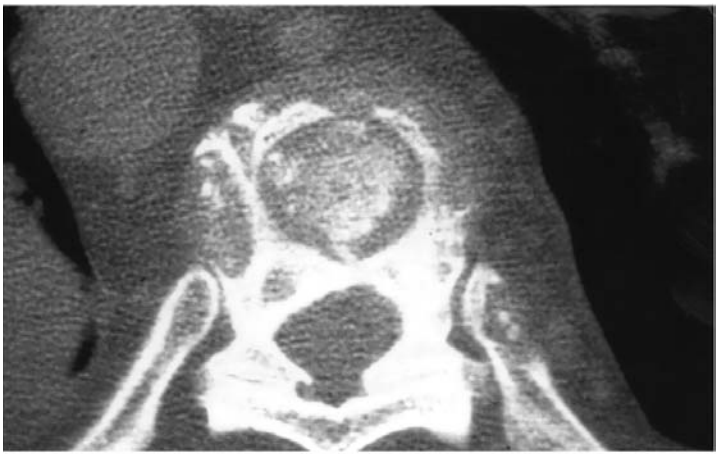
Source: Ref. 143.



(a) (b)

(c)

Figure 3 (a) TB of the L2 vertebral body telescoping the intervertebral disk; (b) treated successfully with anti-TB medication and bracing, resulting in complete fusion with minimal and asymptomatic kyphosis. (c) Similar treatment in another patient resulted in severe painful kyphotic deformity.
(TB, tuberculosis.)



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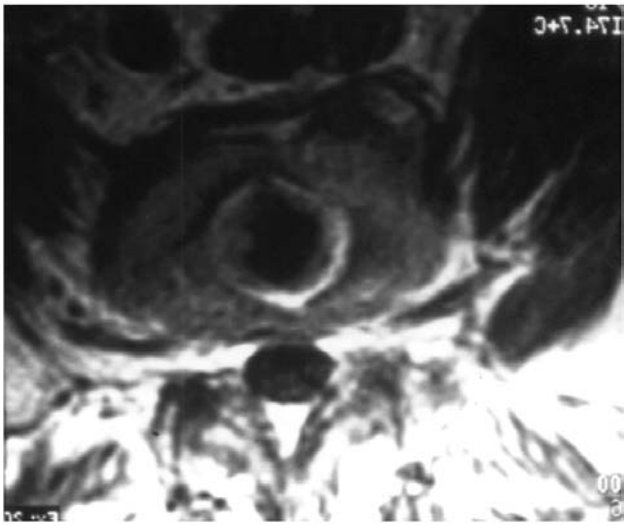
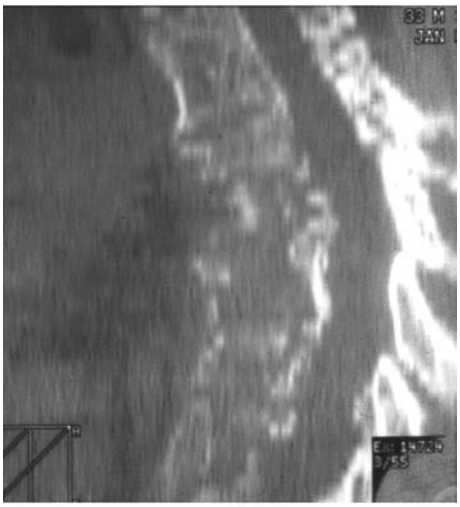


(b)

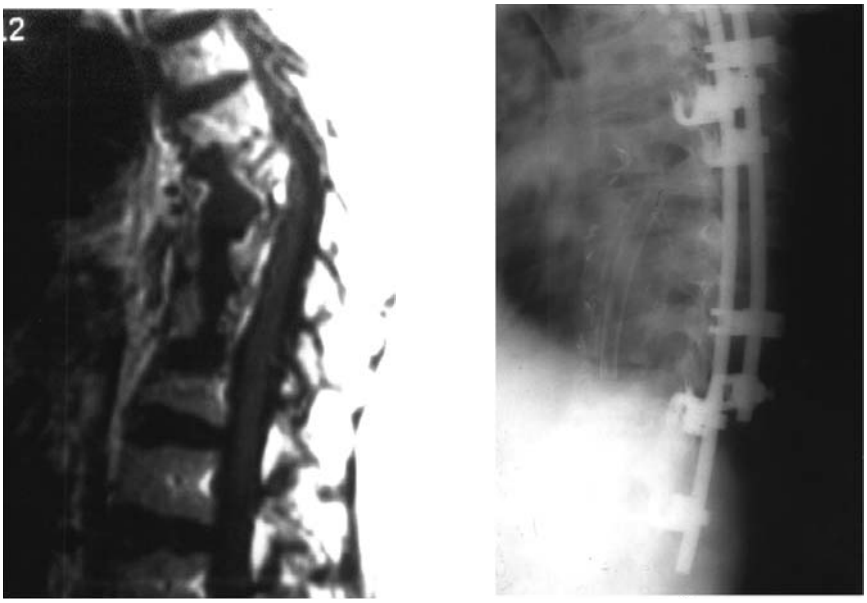
Figure 4 (a) Cystic tuberculosis of the thoracolumbar spine vertebral bodies. The cavity is filled with caseous necrotic material as seen on axial CT scan; (b) MRI.
CT, computed tomography; MRI, magnetic resonance imaging.

(c)



(d)

Figure 4 (c) Excised during surgery. (d) Sagittal reformatted CT image.



(e) (f)

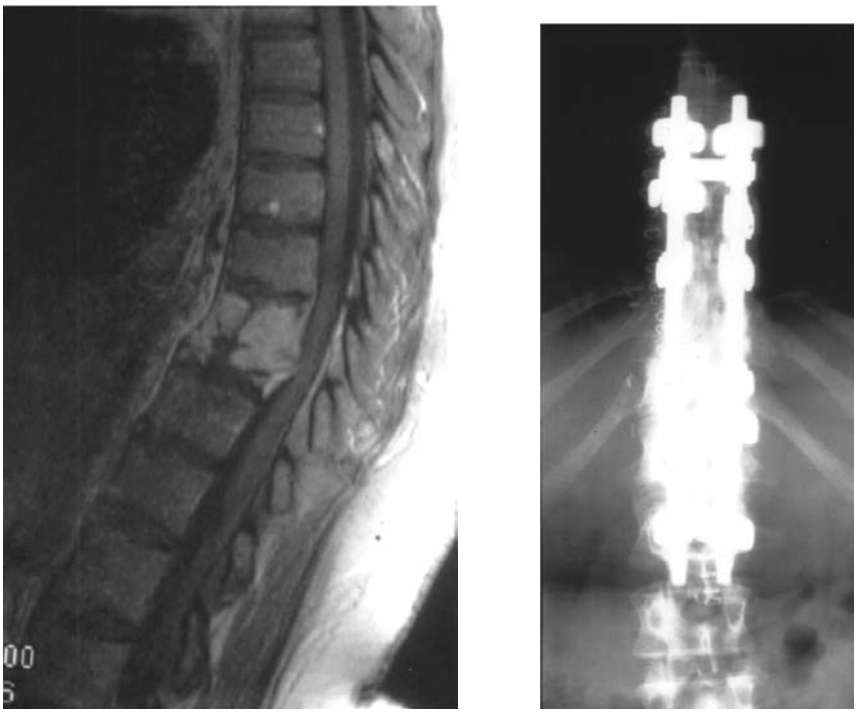
Figure 4 (e) Sagittal MRI T_1-weighted image demonstrate the extent of the cavity. (f) The patient was treated by debulking of the affected tissue, reconstruction with rib graft, and posterior instrumentation.

The decision for the appropriate management of spinal tuberculosis should be based on the goals of treatment for each individual case. The preferred method of treatment is outlined through an algorithmic approach in Figure 7. There is no place for conservative treatment in cervical spine tuberculosis (36). In the lumbar spine, if the common iliac vessels and segmental vessels are encased in the abscess itself, conservative therapy is indicated for control of the abscess, because the invading inflammatory tissue may result in friable wall vessels, thus increasing the risk of massive bleeding (36). If deformity cannot be prevented, then a late reconstruction can be performed with potentially less difficulty. However, early surgery (débridement and fusion) is indicated (36,49), if the technical expertise is available, because the kyphotic deformity is painful and unacceptable.

III. FUNGAL INFECTIONS OF THE SPINE

A. Introduction

Fungal infections of the spine are noncaseating, acid-fast-negative infections that occur primarily as opportunistic infections in immunocompromised patients (50). Most fungal infections are granulomatous infections.

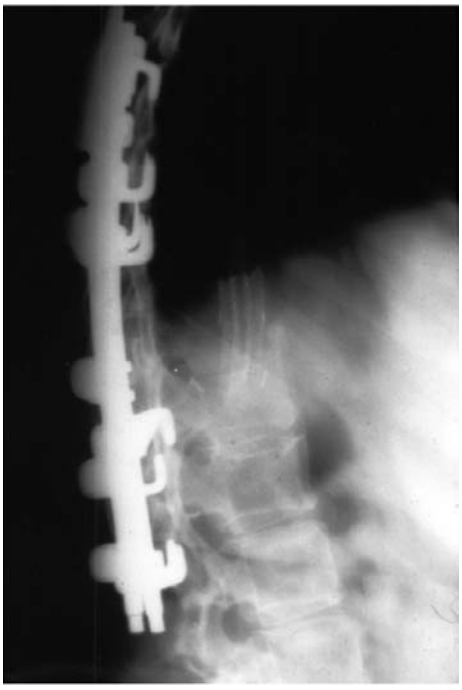


(a) (b)

Figure 5 (a) Sagittal MRI gadolinium-enhanced T_2-weighted image demonstrating TB spondylitis of T12 vertebra with extension of inflammatory tissue compromising the cord and producing paraparesis. Note that the intervertebral disks are spared. (b) The patient recovered completely after surgery consisting of anterior decompression, rib graft, and posterior stabilization with claw-rods instrumentation system. (MRI, magnetic resonance imaging.)

Fungi can appear microscopically as either rounded, budding forms (yeastlike organisms) or hyphae (molds). Yeastlike colonies are smooth, whereas mold colonies are fuzzy. Dimorphic ("having two forms") organisms are rounded in tissue but grow as molds do when cultured at room temperature (Table 3). Some *Candida* species appear in tissue as both budding yeasts and tubular elements called *pseudohyphae*.

Most fungi that are pathogenic for humans are saprophytes in nature. They cause infection when airborne spores reach the lung or paranasal sinus or when hyphae or spores are accidentally inoculated into the skin. Acquisition of infection from another person or an animal is very rare in deep mycoses. Thus,



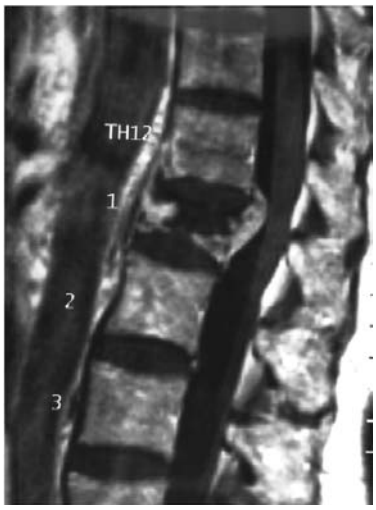
(c)

Figure 5 (Continued.)

hospitalized patients do not require special isolation. Inhalation is the route of inoculation for the agents of most deep mycoses. *Candida albicans*, a normal commensal in the mouth and intestine, reaches deeper tissues only when mucosal or cutaneous barriers are breached by disease, surgery, trauma, or catheterization. Histoplasmosis, blastomycosis, coccidioidomycosis, and paracoccidioidomycosis have been called endemic mycoses to emphasize their preferential geographical

Table 3 Fungal Infections

Yeastlike organism	Moldlike organism	Dimorphic organism
Candida spp.	*Aspergillus* spp.	Coccidioidomycosis
Cryptococcus spp.	*Rizopus* spp.	Blastomycosis
		Sporotrichosis
		Histoplasmosis
		Paracoccidiomycosis



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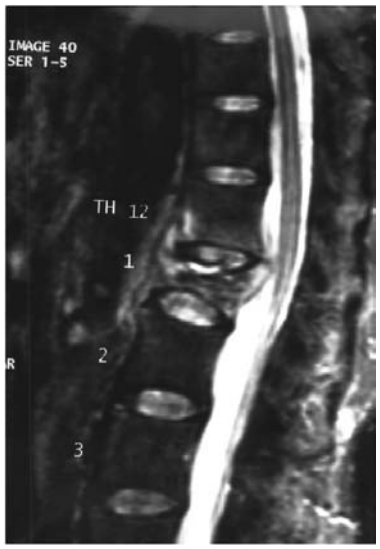

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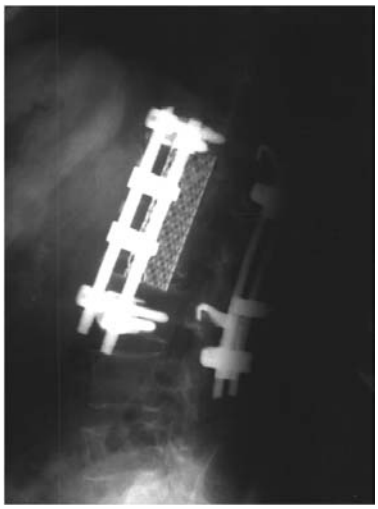


(c)

Figure 6 (a) Sixty-year-old female patient with low back pain progressively deteriorating over the last few months and before admission to the hospital experienced severe weakness in the lower extremities. (b) Sagittal MRI T_1-weighted image demonstrates complete destruction of L1 vertebra, with intact adjacent intervertebral disks. (c) Sagittal T_2-weighted image shows high-intensity signal suggestive of purulent material. The patient was treated successfully by means of excision of the affected T12 and L1 vertebrae, anterior reconstruction with titanium mesh cage filled with the excised ribs, and anterior and posterior instrumentation. (MRI, magnetic resonance imaging.)

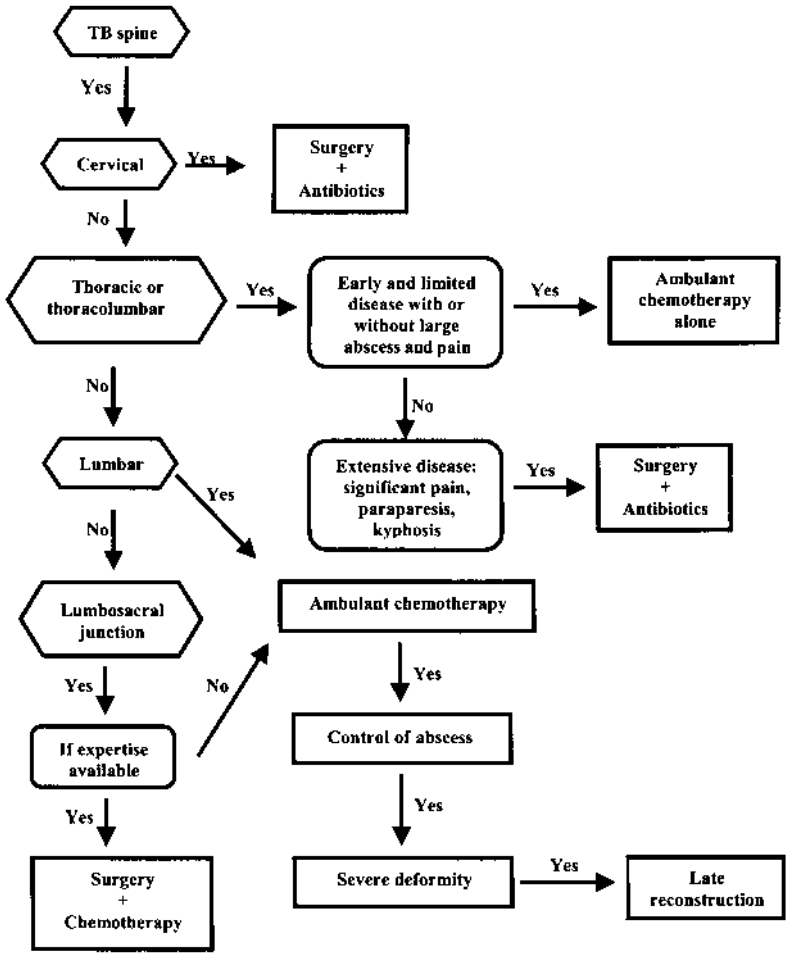


Figure 7 Algorithm approach for the management of spinal tuberculosis.

distribution. Some fungi, such as *Candida* and *Aspergillus* spp., are said to be opportunists in that they usually infect hosts with compromised immunity, but this distinction is not always absolute (51).

The clinical and imaging pictures of most fungal infections of the spine are nonspecific, and there is a spectrum of appearances. Cryptococcosis, blastomycosis, and coccidioidomycosis can be confused with other destructive bone lesions caused by actinomycosis, tuberculosis, bacterial infections, or metastatic carcinomas (52,53). Fungal infection should always be considered when an

abscess or draining sinus has unusual manifestations. In blastomycosis and coccidioidomycosis, there is indiscriminate involvement of the vertebral bodies as in tuberculosis. In tuberculosis and cryptococcosis, the posterior elements of the vertebral body are usually spared (54). Coccidioidomycosis (52,55) and blastomycosis (56), however, affect all bony elements. Disk space involvement varies with respect to the causative fungus (57). It can be found in the early stages of blastomycosis (53,58), but this observation is not universal (57). In coccidioidomycosis there is a relative sparing of the disk space (52,55). Decreased disk-space height caused by a destructive process is a common finding in candidiasis. Postdiskectomy infections due to *Candida* (50) and *Aspergillus* spp. have also been reported.

B. Imaging Resources

MRI and CT are valuable in determining the presence and extent of involvement by the granulomatous disease. The advantage of CT is its ability to show bone architecture better than MRI. MRI, on the other hand, can depict pathological changes of the soft tissue, spinal canal, and cord in much more detail than other imaging modalities (57). The appearance of granulomatous lesions on non-enhanced MR images can be variable. Most lesions are hyperintense on T_2-weighted images. Intravenous gadolinium on T_1-weighted images shows marked solid enhancement of granulomatous lesions, as opposed to the ring enhancement characteristic of purulent abscess. Gadolinium-enhanced MR images are valuable indicators of the disease activity and response to therapy (59,60). T_1- and T_2-weighted images do not always distinguish between a burnt-out infection and an ongoing one, since the abnormal changes of the infection process tend to remain somewhat permanent. ^{67}Ga-enhanced bone scan can reliably monitor the disease activity and the response to treatment, as advocated by Lisbona and associates (61).

C. Bacteriological Investigation

The diagnosis of a mycosis requires demonstration of the pathogenic fungus in appropriate patient specimens. Visualization of the fungus by smear or histological testing is a rapid but less precise and less sensitive diagnostic method than culture. Demonstration of fungi in tissue sections usually requires slide preparation with potassium hydroxide and special stains, such as Gomori's methenamine silver or periodic acid–Schiff (PAS) stain. A diagnostic biopsy can be done as a needle biopsy or excisional biopsy. Percutaneous transpedicular biopsy offers the best approach for diagnosing spinal lesions (62). The biopsy usually yields good results, and special culture can identify the causative fungi.

D. Treatment

1. Antimycotic drug therapy

Treatment of fungal spondylitis is often delayed by difficulty in establishing the diagnosis (50,63,64). Long-term clinical outcome does not seem to be related to the specific species of fungus, but rather to the interval between the onset of the symptoms and the treatment of the infection. Medical treatment includes the use of antimycotic agents, which unfortunately are potentially toxic and have a high incidence of complications.

a. Amphotericin B. Amphotericin B is the mainstay of medical treatment. Histoplasmosis, blastomycosis, paracoccidioidomycosis, candidiasis, and cryptococcosis are the most responsive mycoses to this drug. Coccidioidomycosis, extra-articular sporotrichosis, aspergillosis, and mucormycosis are less sensitive. The usual dose is 0.5 to 0.7 mg/kg daily. The goal is to achieve a total therapeutic dosage of 30 mg/kg, which usually takes 6 to 10 weeks. Infusions are generally given in 5% dextrose over 2 to 4 hours. At the onset, amphotericin B may occasionally cause a marked febrile reaction and is poorly tolerated by adult patients with limited cardiac or pulmonary functions. Therefore, a test dose of 1 mg intravenously in 20 mL of 5% dextrose is recommended with close observation of vital signs over the next 4 hours. If no adverse reaction is observed, an initial dose of 0.25 mg/kg in 5% dextrose is given intravenously over 4 hours. The dose is advanced slowly over 5 days to achieve 0.5 mg/kg. If the drug is withheld for more than 5 days because of adverse reactions, it should be repeated at 0.25 mg/kg with gradual increment. Premedication with aspirin or acetaminophen or the addition of hydrocortisone (25 mg) to the infusion solution decreases the likelihood of chills and fever. This is a drug with serious side effects. Nephrotoxicity, which depends on the daily dose, is not unusual. Saline solution infusions have been advocated to reduce azotemia. Permanent loss of renal function is related to the total accumulated dose of amphotericin B and is generally noted in adults who have received more than 3 g of the drug. Other side effects include bone marrow suppression (anemia), hypokalemia, nausea, anorexia, weight loss, phlebitis, and, occasionally, hypomagnesemia (65).

Recently, lipid complex, colloidal dispersion, and liposomal formulation of amphotericin became available. The nephrotoxicity of all three drugs is minimal.

b. Flucytosine. Flucytosine is a synthetic oral drug useful in cryptococcosis, candidiasis, and chromoblastomycosis. Drug resistance appears rather rapidly when flucytosine is used alone. For this reason, the drug is generally used in combination with amphotericin B. The usual dose of flucytosine is 25 to 37.5 mg/kg orally every 6 hours. Even modest reductions in renal function may elevate flucytosine blood levels into the toxic range with significant incidence of

neutropenia and thrombocytopenia. Another toxic effect is colitis. Allergic rash may also develop.

c. Ketoconazole. Ketoconazole is effective in blastomycosis, histoplasmosis, paracoccidioidomycosis, and some forms of disseminated coccidioidomycosis. The usual adult dose is 400 mg orally, once daily. Absorption of ketoconazole is variable among individuals and is not affected by food, but in patients who have acquired immunodeficiency syndrome (AIDS) it is poorly absorbed. Ketoconazole at a dose of 600 mg to 800 mg orally per day has a cure rate for blastomycosis of 81% to 100%. Treatment may be required up to 12 months.

d. Itraconazole. This triazole analogue of ketoconazole is superior to the parent compound in safety and efficacy. Hormonal suppression and hepatotoxicity are less marked with itraconazole than with ketoconazole. Clinical indications for its use involve all those cited for ketoconazole but also include selected cases of sporotrichosis, cryptococcosis, and aspergillosis. The usual dose is 200 mg once or twice a day by mouth with food. For blastomycosis, at daily doses of 200–400 mg, a cure rate up to 90% is reported (66).

2. Surgery

Operative intervention is indicated (1) to obtain tissue for diagnosis, (2) to débride the spine and drain an abscess, (3) to decompress the neural elements, or (4) to treat cases that are refractory to antimycotic treatment (50). Drainage and antifungal treatment can cure the disease but certainly cannot control the pain and neurological deficit caused by deformity and osseous element neurocompression. It seems advisable to institute surgery at a rather early stage, particularly when failure of antimycotic drug therapy or toxicity is evident (67,68).

In the cases of progressive deformity (kyphoscoliosis) and spinal canal compromise, reconstructive surgery is indicated to decompress the spinal canal, eradicate pockets of any residual infection, and reconstruct and align the spine. The anterior spinal surgical approach proved to be an excellent surgical option because it provides adequate access for radical excision of pathological tissue and simultaneously allows a one-stage rigid reconstructive procedure (57). Many studies conclude that anterior decompression and stabilization yield predictably better results than laminectomy for patients with or without neural compression. When infection is destroying the vertebral body anteriorly, laminectomy removing the posterior elements produces only instability of the spine (50), resulting in progressive kyphosis or even dislocation of the spine (67–69).

Because mycosis is not a glycocalyx-producing infection, there are no contraindications to the use of anterior device instrumentation for spinal stabilization (57). Biomechanically it has been shown that the Kaneda instrumentation

is rigid enough and can be used as the sole device, without the need for posterior instrumentation (70).

E. Types of Fungal Infections

1. Blastomycosis

a. Introduction. *Blastomyces dermatitides* is a dimorphic fungus that is endemic in southern, midwestern, and eastern parts of the United States, especially the Mississippi and Ohio River valleys (71). Blastomycosis has also been reported as a rare condition in southern Canada, South America, Africa, and Asia (72,73). All ages are affected, although there is a higher frequency in the third and fourth decades of life (51). The incidence of blastomycosis is much lower than that of either coccidioidomycosis or histoplasmosis (74). The severity of the disease ranges from asymptomatic to life-threatening. Blastomycosis is almost exclusively acquired by inhalation of airborne spores from soil, decomposed vegetation, or rotting wood, resulting in a primary lung infection. The initial pulmonary infection may heal spontaneously or become chronic. Whether or not the lung lesion resolves spontaneously, infection not uncommonly may spread hematogenously to other organs with variable involvement. Skin and bones are among the most common extrapulmonary sites, followed by the genitourinary tract (prostate), central nervous system, and oropharynx (71,75). Osseous involvement ranges from 14% to 60% of the disseminated form of the disease (76,77). The spine (with predilection for the lumbar and the thoracic region) is the most common site of skeletal involvement, followed by the skull, ribs, tibia, bones of the foot, and wrist (58).

b. Clinical Manifestation. The clinical and imaging manifestations can be confused with those of other destructive bone lesions (52,53). In blastomycosis there is an indiscriminate involvement of the vertebral bodies, but unlike tuberculosis (54), it can also commonly affect the posterior elements of the vertebral body (56). Some reports have shown that the disk space may also be involved in early stages of blastomycosis (53,58). However, this observation is not universal (57).

Spontaneous spinal fusion, a frequency occurrence in tuberculosis, has not been observed in blastomycosis (57). Soft tissue extension with formation of fluctuating paraspinal abscesses and ulceration is common (72), as in tuberculosis, but blastomycosis has a greater tendency to produce fistulae (57).

c. Laboratory Investigation. The diagnosis of blastomycosis involves skin testing, serological assays, and mycological cultures of involved tissue (78).

Blastomycin skin testing is used only for epidemiological studies. Most of the patients exposed to the fungus have a positive skin test result that usually becomes negative over the ensuing years.

Serological tests include complement fixation, immunodiffusion, indirect enzyme immunoassay, sandwich enzyme immunoassay, Western blot, and radioimmunoassay (78).

All currently available serological tests are characterised by their lack of sensitivity as well as cross-reactivity with other fungal infections, particularly histoplasmosis, which has a similar endemic preference. The only definitive diagnosis of blastomycosis is based on identification of the organism in tissue specimens or cultures. Blastomycosis colonies may take several weeks to grow in culture media, and diagnosis of blastomycosis should not be disregarded until culture results remain negative for at least 4 weeks (79,80).

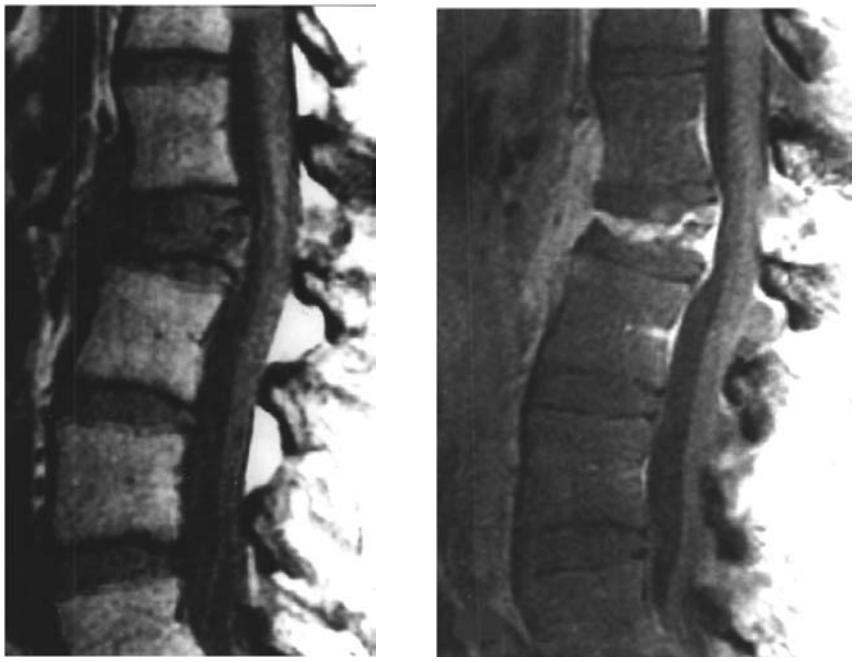
d. Treatment. Before the advent of chemotherapy, blastomycosis had an unrelenting course and mortality rates were reported to be as high as 78% (81). Some authors believe that in immunocompetent patients with uncomplicated pulmonary forms of the disease, therapy may not be necessary (82–84). However, considering the dreadful complications of blastomycosis and the relative safety of oral antifungal medication, antifungal therapy is recommended by some, even for the mildest form (57,66,85,86).

Amphotericin B (0.4 mg/kg daily for 10 weeks) was previously considered the treatment of choice for all forms of blastomycosis, but as this drug has serious side effects and the infection is not fulminant, other drugs, such as itraconazole and ketoconazole, are recommended. However, amphotericin B remains the drug of choice for patients who are severely immunocompromised or have a disseminated form of the disease with a life-threatening condition. The cure rate of amphotericin B was reported to be 87% when a 1-g course of therapy was used, and 97% when a 2-g course of treatment was used.

Absolute indications for surgery are progressive deformity and spinal canal compromise with neurocompression (57) (Figs. 8, 9, and 10).

2. Coccidioidomycosis

a. Introduction. *Coccidioides immitis* has two forms (dimorphic), growing as a mold on most culture media, but as a nonbudding spherical form (a spherule) in host tissue or under specialized conditions. *C. immitis* is a soil saprophyte found in certain arid regions of the United States, Mexico, Central America, and South America. Within the United States, most cases of infection with *C. immitis* are acquired in California, Arizona, and western Texas. It is particularly prevalent in central California, where it carries the name of *San Joaquin Valley fever*. Infection in humans results from inhalation of wind-borne arthrospores from soil sites.

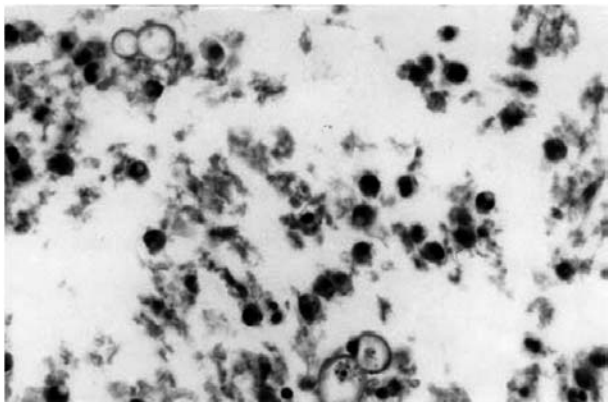


(a) (b)

Figure 8 (a) MRI of the lumbar spine pre- and post-gadolinium. (b) Sagittal T_1-weighted image reveals replacement of the normal fatty signal of L2. Sagittal post gadolinium with fat saturation images reveals abnormal enhancement of the L2 vertebral body with spread via both psoas muscles. The disks are relatively spared. (MRI, magnetic resonance imaging.)

b. Clinical Manifestation. The usual course of pulmonary infection is complete healing, although an area of pneumonitis (detected on radiographs) may heal by forming a coinlike lesion called a *coccidioidoma*. Dissemination is an uncommon, but dreaded, complication. *Coccidioides immitis* is the most infectious of all fungi capable of producing systemic disease. Although the disease occurs in all ages, it is most prevalent in the age group between 25 and 55 years of age, with a tendency for greater dissemination in males. The disseminated form is 10 times more common in blacks than in whites and is of even greater hazard to Filipinos. Other susceptible individuals to the disseminated form are Native Americans, Mexican Americans, pregnant women, and immunosuppressed patients, including those with AIDS (51).

C. immitis incites a chronic granulomatous reaction in host tissue, often with caseation necrosis. Lung and hilar node lesions may show calcification.



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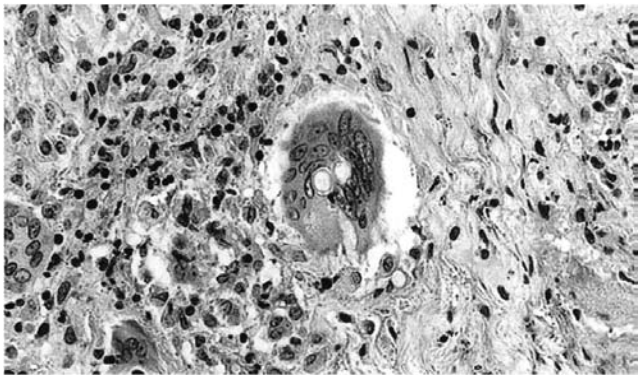
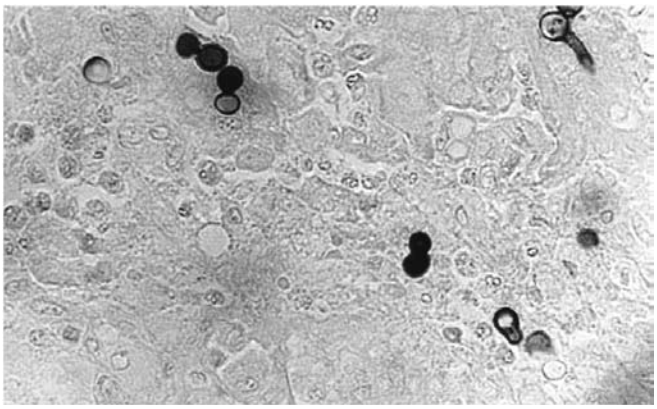


(b)

Figure 9 (a) Aspirated material from the spine showing double-contour, thick-walled budding yeasts with surrounding acute inflammatory cells. (b) Histological section of bone showing double-contour, thick-walled budding yeast in multinucleated giant cells and adjacent inflammation with extracellular organism.

Most bony lesions are lytic in nature and indiscriminately involve the vertebrae by affecting both the anterior and posterior bony elements (52,55). Often, multiple spinal lesions are found. Paraspinal masses can be seen with contiguous rib involvement and usually are extensive (87). Despite extensive bone destruction, the disk space is relatively spared (52,75); therefore, disk height preservation is a characteristic radiographic finding. However, MRI often demonstrates abnormal densities at the intervertebral disks. The disk typically shows low signal intensity



(c)

Figure 9 (c) Budding yeast highlighted by Gomori's methenamine silver stain with germ tube form (right upper corner).

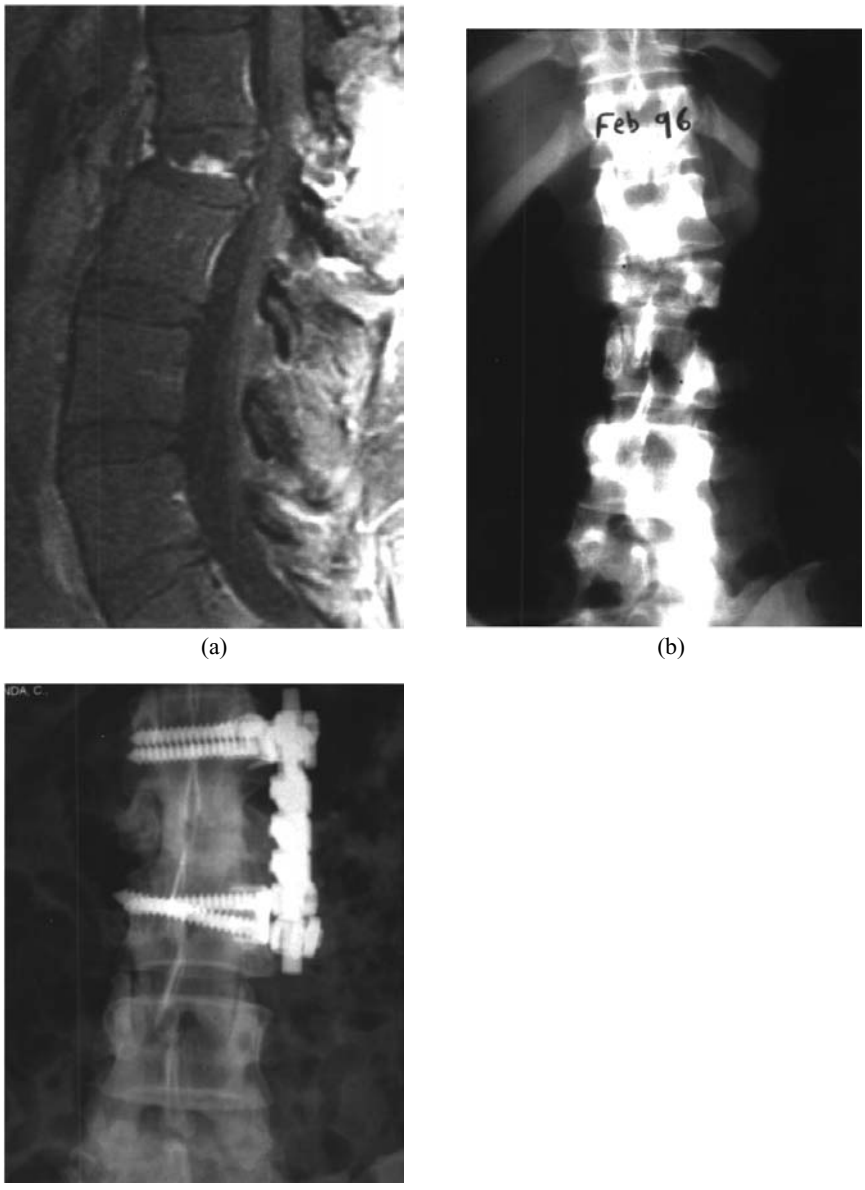
on T_1-weighted images and high signal intensity on T_2-weighted images. Commonly, epidural extension of inflammatory, nonliquefactive tissue is seen beneath the longitudinal ligament on MR images (87). Vertebral body marrow typically shows heterogenous changes. So the more common pattern of MRI appearance is mild disk involvement with extensive heterogenous bone marrow and soft tissue involvement (87) (Fig. 11).

When coccidioidomycosis is suspected, sputum, urine, and pus from the lesion should be examined for *C. immitis* by wet smear and culture. On biopsy, the appearance of the mature spherule, the hallmark of diagnosis, helps to distinguish coccidioidomycosis from nonbudding forms of *Blastomyces* and *Cryptococcus* spp. Specimens must be handled with extreme care to prevent infection of laboratory personnel.

Serological tests are very helpful in the diagnosis of coccidioidomycosis. The complement fixation test is more specific and accurate than latex agglutination and apgar gel diffusion tests.

c. Treatment. Neither spontaneous cure nor spontaneous spinal fusion, a feature of tuberculosis infection, has been observed in coccidioidomycosis (57,88). Patients respond poorly to pharmacological therapy alone and often require surgery (89,90). The goal of surgery is to decompress the neural element with radical excision of the infectious process and stabilize the spine with instrumentation to prevent deformities.

Patients who have severe or rapidly progressing disseminated coccidioidomycosis are initially treated with intravenous amphotericin B at a dose of 0.5 to



(a) (b)

(c)

Figure 10 (a) MRI 5 months after therapy reveals decreased enhancement on gadolinium T_1-weighted image with fat saturation. Anteroposterior radiographs (b) before and (c) after instrumentation.
(MRI, magnetic resonance imaging.)

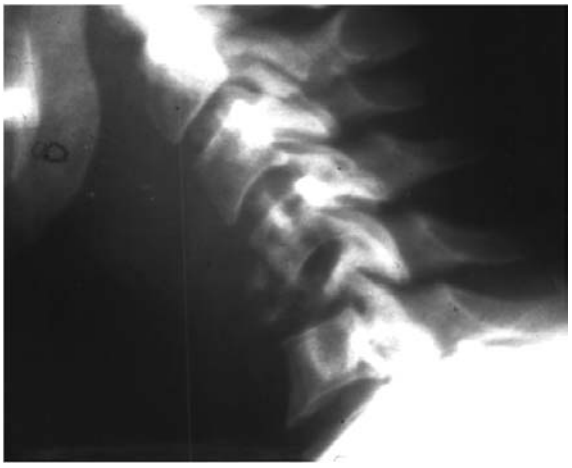
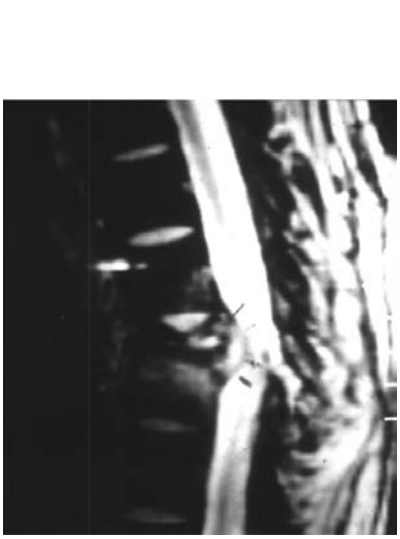


Figure 11 Coccidioidal spondylodiskitis with almost complete destruction of C5 vertebra. The intervertebral disks are spared.

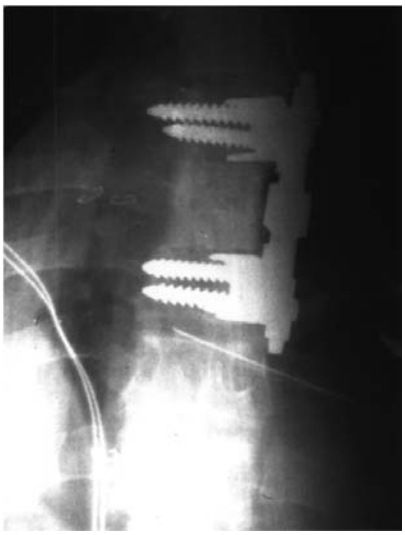
0.7 mg/kg daily. Ketoconazole (400 mg daily), itraconazole (200 mg twice daily), or fluconazole (400 to 600 mg daily) is used for indolent disseminated forms or after successful treatment of the severe form with amphotericin B, which usually takes 2 to 3 months. These oral agents are also useful for long-term suppression of infection, and treatment should be continued for years, to prevent relapse of the disease activity. Of the six patients referred to the senior author, there were two recurrences because of inadequate treatment and one eventually died. Five of these patients were treated successfully. Anterior decompression, femoral allograft reconstruction, and fixation with screw and plates were performed on two patients (Fig. 12). The other three were treated by combined anterior reconstruction with a femoral allograft and stabilization with plate and screws, and augmented posteriorly by instrumentation to maintain the correction of deformities (Fig. 13).

3. Candidiasis

a. Introduction. *Candida albicans* is the most common cause of candidiasis, but *C. tropicalis*, *C. parapsilosis*, *C. glabrata*, and some other species can also cause candidiasis that may even be fatal. Candidiasis belongs to opportunistic deep mycosis. It is often preceded by increased colonization of the mouth, vagina, and stool with *Candida* spp. due to broad-spectrum antibiotic therapy.



(a)



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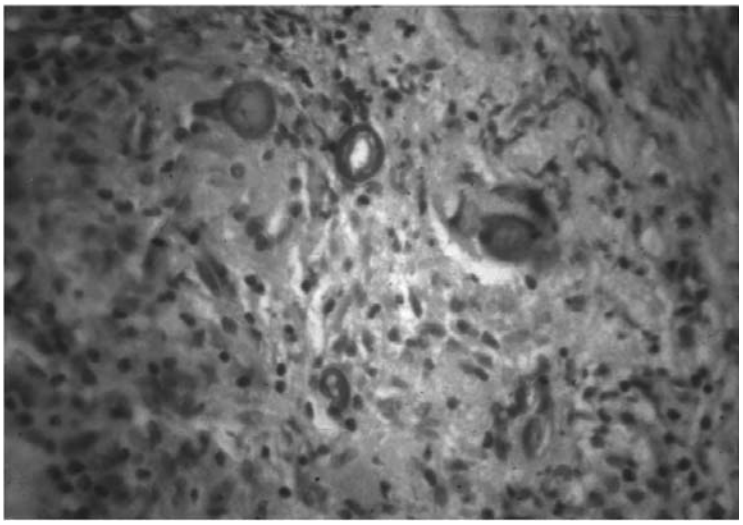
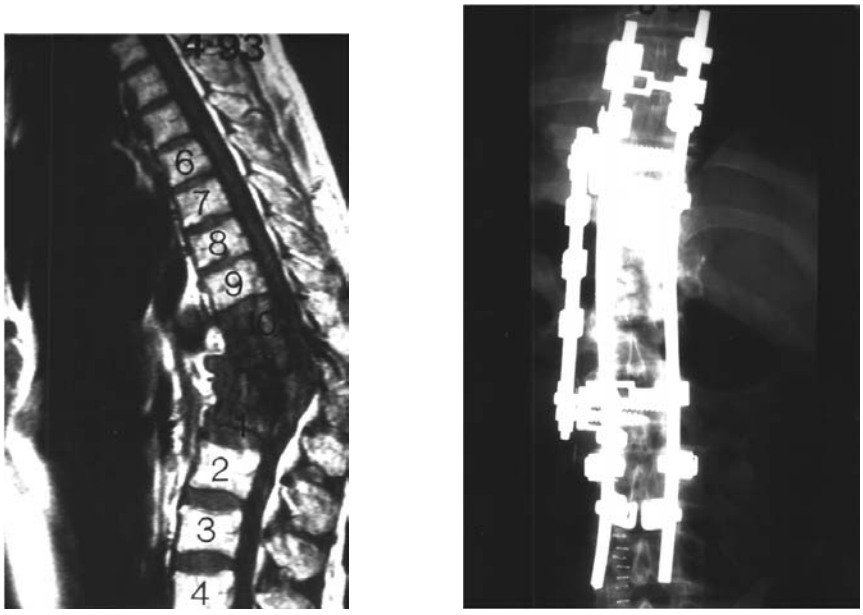


(c)

Figure 12 (a) Coccidioidal spondylodiskitis with complete destruction of T5 vertebra and cord compression with serious neurological deficit. (b) The patient was treated successfully by means of anterior T5 corpectomy, tibial allograft and Kaneda instrumentation. (c) Tubercle-like structure that contains the characteristic spherules (sporangia) of coccidioidomycosis. The sporangia in this figure contain endospore.

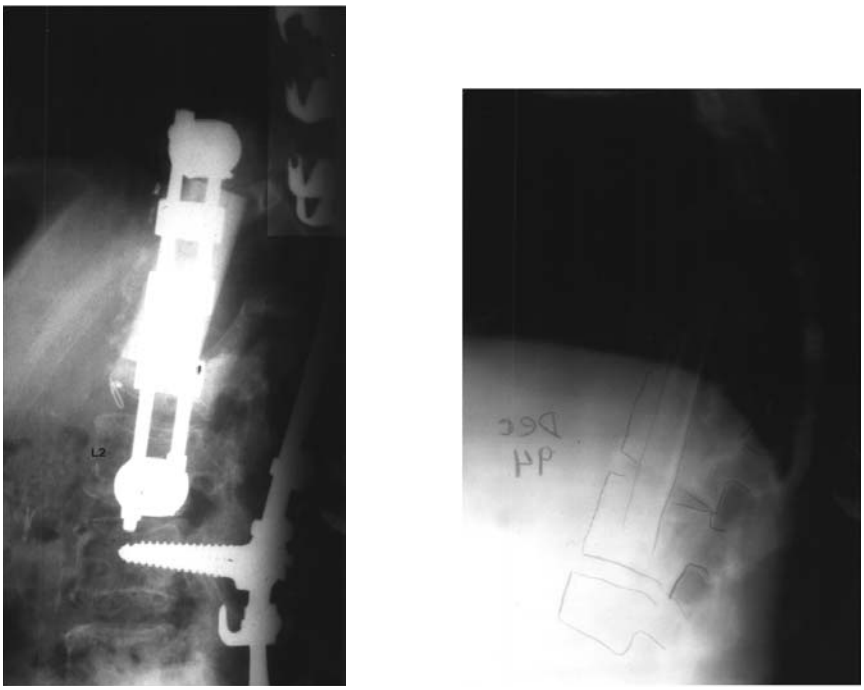


(a) (b)

Figure 13 (a) Sagittal T_1-weighted image demonstrating extensive destruction and resorption of T11, T12, and L1 vertebrae with concertina collapse and kyphotic deformity causing severe neurocompression and paraparesis. Bone marrow edema is seen throughout T10, T11, T12, and L1 vertebrae. Treatment consisted of complete anterior excision of T11 and T12, partial excision of L1, femoral allograft, and anterior and posterior stabilization with instrumentation as seen on (b) AP and (c) lateral view. (See page 452.)

b. Clinical Manifestation. Candidal spondylodiskitis is a rare condition (91). Cases of postdiskectomy infection have been reported with the causative agents *C. albicans* and *C. parapsilosis* (50). Neurological deterioration occurs in 21% of patients (91). Spinal cord lesions in candidal spondylodiskitis are produced by either vertebral collapse, spinal cord infarct, or epidural abscess (91–93). Twenty-three percent of the cases described in the literature occurred in intravenous drug users, and candidiasis should be suspected when para- or tetraplegia occurs in these patients (91).

c. Treatment. The treatment of choice is amphotericin B. The amount of amphotericin B and its antecedent toxicity can be decreased by combining the drug with flucytosine. In the absence of progressive neurological deficit, suspected abscess formation, or significant loss of spinal alignment, intravenous amphotericin B with brace immobilization is the initial treatment of choice. A



(c) (d)

Figure 13 (d) A year later the instrumentation and bone graft were infected with *Staphylococcus aureus*, necessitating excision of the instrumentation. The defect was reconstructed with vascular fibular graft with excellent response. AP, anteroposterior.

combination of antifungal therapy and surgical débridement and spinal fusion can be used in selected cases. Thoracic infections usually require early surgery, whereas patients with lumbar disease may do well with nonoperative management (94). In a 2001 report, Frazier and associates concluded that the fact that 10 of 11 patients required spinal surgery suggests that antifungal management alone may not produce acceptable results (50). The authors treated one case of L3-L4 candidiasis of a patient who had poorly controlled diabetes mellitus who responded well to amphotericin B and surgical decompression of lumbar spine abscess.

4. Torulopsosis

a. Introduction. *Torulopsis glabrata* is a yeastlike fungus that is closely related to the *Candida* species (95) but does not form hyphae or pseudohyphae.

Yeast from *T. glabrata* is the same size as the yeast from *Histoplasma capsulatum* (51). Like *Candida* spp., it is an opportunistic pathogen that can cause urinary tract infections, pneumonitis, endocarditis, and esophagitis (96). It can also cause complications in immunocompromised hosts such as patients with cancer or diabetes mellitus and patients who receive corticosteroids and broad-spectrum antibiotics (97).

T. glabrata can also cause spinal osteomyelitis with neurological deficits. Radiographic changes are indistinguishable from those of candidiasis and the therapeutic approach is similar to that described for candidiasis (94).

5. Aspergillosis

a. Introduction. *Aspergillus fumigatus* is the most common cause of aspergillosis, but *A. flavus*, *A. niger*, *A. nodulans*, and *A. terreus* can also cause disease. *Aspergillus* sp. is a mold with septate hyphae. All the common species of *Aspergillus* are widely found in the environment, growing on dead leaves, stored grain, compost piles, hay, and other decaying vegetation (51).

b. Clinical Manifestation. *Aspergillus* species commonly invade the respiratory tract, where they usually reside as harmless inhabitants. Invasion of lung tissue is confined almost entirely to immunosuppressed or chronically ill patients, such as patients with AIDS and those receiving chemotherapeutic or immunosuppressive treatment (98). Aspergilloma can develop in patients who have chronic cavitation or allergic bronchitis (67,99).

Aspergillus sp. is a common cause of skeletal mycosis, predominantly affecting the spine (100). In children, aspergillus spondylodiskitis is usually related to contiguous spread from the lungs to the spine (99). However, in adults these infections mostly arise through hematogenous spread from pulmonary, gastrointestinal, or cerebral locations (100). Infection with *Aspergillus* sp. is also described after diskectomy (101). Aspergillosis of the spine can also affect patients without predisposing risk factors (99).

Radiographic appearance is similar to that of other granulomatous infections with extensive destruction of disk and vertebral bodies. The diagnostic process is often difficult. Serological tests are available, but false-negative results are not uncommon. Needle biopsy does not always provide a definitive diagnosis (67,99).

c. Treatment. Treatment consists of medical therapy alone (102) or in combination with surgery. Radiation therapy has also been used (100). Intravenous amphotericin B (1.0 to 1.5 mg/kg daily) is the drug of choice. Itraconazole (200 mg twice daily) is useful for immunocompetent patients with indolent forms of the infection (102). Surgical treatment is favored if the response to medical treatment is not satisfactory or in the presence of neurological complications

(67,98–100). One of the authors' patients had aspergillous T5-T6 spondylodiskitis with epidural abscess and paraplegia as a complication of high doses of steroid for Wegener's granulomatosis. He had anterior surgical decompression, fusion, and posterior stabilization with incomplete neurological improvement (Fig. 14).

6. Histoplasmosis

a. Introduction. *Histoplasma capsulatum* is a dimorphic fungus that grows as a mold in nature. Hyphae bear both large and small spores, which are used for identification. Despite its name, the fungus is unencapsulated. Infection with *H. capsulatum* has been encountered in many regions of the world but is much more frequent in certain areas. Within the United States, infection is most common in the southeastern, mid-Atlantic, and central states (51).

b. Pathological Characteristics. Small spores of *H. capsulatum* reach the alveoli on inhalation and are transformed there to budding forms. With time, an intense granulomatous reaction occurs. Caseation necrosis or calcification may mimic tuberculosis. Transient dissemination may leave calcified granulomas in the spleen.

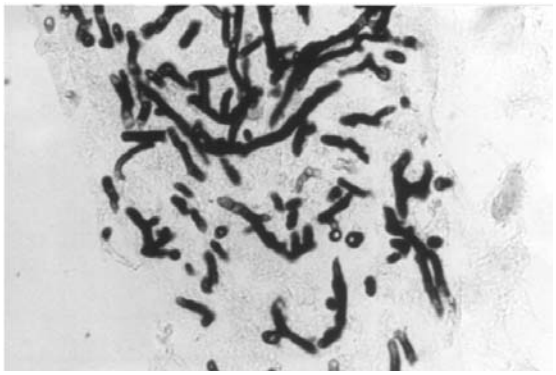
c. Clinical Manifestation and Treatment. In a small portion of patients, histoplasmosis becomes progressive and potentially fatal. When the spine is affected, the same principle of treatment is applied as for other fungal infections.

7. Cryptococcosis

a. Introduction. Cryptococcosis is an infection caused by a yeastlike fungus, *Cryptococcus neoformans*. It occurs widely in nature and is found in large numbers in pigeon roosts. Infection is thought to be acquired by inhalation of fungus into the lungs. Pulmonary infection has a tendency toward spontaneous resolution and is frequently asymptomatic (51). Approximately three-fourths of patients have a predisposing condition, such as leukemia, lymphoma, Hodgkin's disease, sarcoidosis, tuberculosis, or diabetes or are receiving supraphysiological doses of glucocorticoids (103,104). *Cryptococcus* sp. infects 7% to 10% of patients with AIDS (105). In these patients the mycosis disseminates and is difficult to cure. Less commonly, healthy individuals are affected. The majority of patients have meningoencephalitis at the time of the diagnosis. Osseous involvement including the spine is usually a manifestation of disseminated cryptococcosis, appearing in 5% to 10% of cases (103).

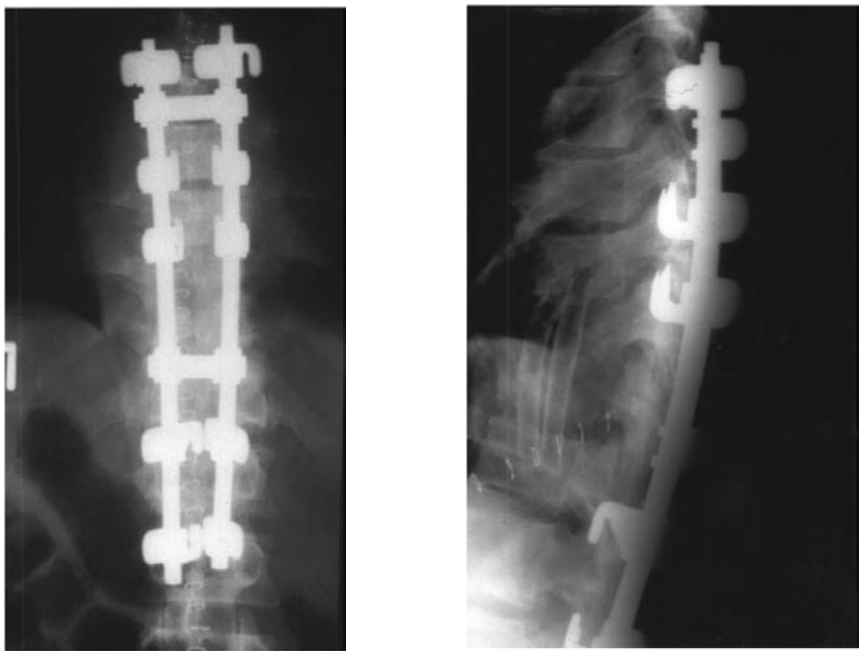
b. Imaging Resources. The radiological features of spinal involvement are nonspecific, and there is a spectrum of appearances. A lytic lesion within a vertebral body can resemble the cystic form of tuberculosis, with discrete margins

(a)



(b)

Figure 14 Sixty-year-old male patient with Frankel B paraplegia caused by *Aspergillus* sp. spondylodiskitis. The patient had been on high-dose steroids for Wegener's granulomatosis. (a) Sagittal MRI image demonstrated destruction of T5-T6 disk and adjacent vertebrae with posterior extension of purulent material. (b) Biopsy obtained during anterior vertebrectomy demonstrates branching septate hyphae (Gomori's methenamine silver stain, magnified $\times 400$).



(c) (d)

Figure 14 Treated successfully by means of anterior debulking of the destroyed tissue, reconstruction with rib bone graft, and posterior stabilization with claw-rods instrumentation system (c and d). (MRI, magnetic resonance imaging.)

and surrounding sclerosis. The infection may appear as a permeative lesion involving mainly a single vertebral body with collapse. In the latter stage, the infection may spread to a contiguous vertebra, forming also paravertebral soft-tissue masses suggestive of spinal tuberculosis (104), and as in tuberculosis, the posterior elements are usually spared (106). Therefore, tissue diagnosis is recommended for appropriate antibiotic treatment.

c. Treatment. Skeletal lesions respond variably to treatment, and spontaneous healing has been observed. The antifungal agent of choice is amphotericin B. Addition of flucytosine allows a lower daily dose of amphotericin B.

8. Actinomycosis

a. Introduction. The actinomycetes are a heterogeneous group whose morphological characteristics suggest they are a fungus but that are classified as bacteria. Actinomycetes infections include actinomycosis, nocardiosis, and actinomycetoma. They resemble fungi infections characterized by chronicity and

poor transmissibility from person to person. These organisms are gram-positive higher bacteria that branch as fungus does but have the diameter, nuclear organization, cell wall composition, antibiotic susceptibility, and ability to induce neutrophilic inflammatory reaction similar to those of other bacteria (107,108).

The most common infective organism in humans is *Actinomyces israelii*. Many actinomycotic infections are polymicrobial in the sense that they very often are contaminated by other bacteria such as *Bacteroides*, *Staphylococcus*, and *Streptococcus* spp. This contamination occurs through fistulae that are commonly found in *Actinomycetes* sp. infection (107). However, the extent to which these bacteria contribute to pathogenesis of the infectious process is uncertain.

Disruption of the mucosal barrier allows the actinomycetes to invade beyond their endogenous habitat in the mouth, lower gastrointestinal tract, and female genitourinary tract and to provoke local infection. In rare cases, distant hematogenous spread may occur.

Acute and chronic inflammatory tissue resembles that of pyogenic infections. The initial acute inflammation is followed by the characteristic chronic, indolent phase. Lesions usually appear as single or multiple indurations and, in the absence of suppuration, can be misconstrued as neoplastic growth. Once established, actinomycosis spreads contiguously in a slow and progressive manner, ignoring tissue planes. Sinus tracts can close and reopen spontaneously. The incidence of spinal actinomycosis is less than 5% of all actinomycotic infections (109,110). The infection spreads to the spine usually from adjacent soft-tissue infection or through hematogenous seeding (111).

b. Imaging Resources. On plain radiography the intervertebral disk space appears intact (112). This can help in differential diagnosis from tuberculosis or other bacterial infections. Adjacent pedicles, transverse processes, and the adjacent end of the ribs can be affected. The lesion is a slow destructive process with reactive bone formation, which on radiography has a characteristic honeycomb architecture or the appearance of sawtoothed borders (109,112,113).

The technetium bone scan is a sensitive method that shows abnormal radionuclide uptake at an early stage of the disease activity before any radiological changes occur. MRI, which is sensitive but not specific, demonstrates the full extent of infection, especially paravertebral masses and epidural soft tissue extension on the thecal sac. On T_1-weighted sequence, an isointense signal involving the bodies of infected vertebrae can be seen, with hyperintense signals on T_2-weighted sequences. Characteristically the disk signal is usually normal.

c. Histological and Bacteriological Characteristics. Diagnosis of spinal actinomycosis in the early phase is difficult, and it is usually detected late. The disease must be confirmed histologically and microbiologically. Sulfur granules in foamy macrophages are characteristic histological findings. They consist of

Actinomyces israelii aggregated into microcolonies that grow in a radial configuration, with the peripheral layer of organisms having club-shaped ends (114). Bacteriological diagnosis is more challenging since *Actinomyces* spp. are slow-growing microorganisms and are frequently outnumbered by contamination of anaerobic or aerobic bacteria.

d. Treatment. Intravenous administration of 18 to 24 million units of penicillin for 6 weeks, followed by oral therapy with penicillin or amoxicillin for another 6 to 12 months, is a reasonable approach for serious infections. Less extensive disease may require less intensive therapy. For the treatment of penicillin-allergic patients, tetracycline has been used most extensively. Minocycline, clindamycin, and first-generation cefalosporins are other suitable alternatives. Although the role of concomitant infection with other bacteria is not clear, the use of a therapeutic regimen that covers these organisms is a reasonable approach, particularly in critically ill patients.

Since antimicrobial therapy alone can cure extensive disease, it is unclear how often surgical intervention is actually necessary. Moreover, percutaneous drainage has become an alternative option. However, combined medical-surgical therapy is still advocated by some authorities. Spinal actinomycosis with predominant paraspinal infection and relatively minor epidural involvement, with no neurological deficits, responds well to antibiotic therapy alone (111,115). Emergency decompression is indicated when epidural spread is associated with progressive deterioration of neurological status, particularly in the presence of cord compression (111,116–119). There is no need to débride all the infected material within the spinal canal aggressively because of the risk of uncontrollable bleeding and increased morbidity rate. Systemic antibiotics can complete the job of eradicating residual infection (107,120).

IV. SPINAL BRUCELLOSIS

A. Introduction

Brucellosis is a systemic infection caused by an aerobic, gram-negative coccobacillus commonly found in domestic animals and transmitted to humans by direct contact, by ingestion of contaminated products, and possibly by inhalation of aerosols (121,122).

Human brucellosis is predominantly caused by three different variants of *Brucella*: *B. melitensis*, acquired from goats, sheep, and camels; *B. abortus*, a bovine brucella; and *Brucella suis*, which can be acquired from hogs. *Brucella canis* (dogs) and *Brucella ovis* have also been described, although they rarely cause human disease (123). These bacilli are unencapsulated, nonmotile, non-spore-forming facultative intracellular parasites. Brucellae are killed by boiling or

pasteurization of milk and milk products. They survive for up to 8 weeks in unpasteurized white soft cheese made from goat's milk and are not killed by freezing.

Geographical areas with high prevalence include the Mediterranean basin, the Arabian Gulf, the Indian subcontinent, and parts of Mexico and Central and South America; it is very rarely seen in the United States or Europe. Some reports indicate that, even in developed countries, the true incidence of brucellosis may be up to 26 times higher than the reported incidence. In the United States, about 200 new cases are reported per year; however, this is estimated to represent only 4% to 10% of recognized cases (121). Consumption of imported cheese, travel abroad, and occupation-related exposures are the most frequently identified sources of infection in the United States. Men are affected more often than women because of occupational hazards. Brucellosis of the spine is a well-known complication of *Brucella* spp. infection and is a frequent cause of spondylitis in Mediterranean countries (124).

B. Pathophysiological Characteristics

The invading organism localizes in tissues of the reticuloendothelial system in the liver, spleen, lymph nodes, and bone marrow and is spread by lymphatics and through the bloodstream (121). Complications may result in osteomyelitis, septic arthritis, spinal infections, and central nervous system involvement. Multisystem disease can occur if the host resistance is weakened (125). *Brucella* sp. spondylitis may develop a neurological complication in 74% of cases (126). In 10% of patients the organism may also affect the central nervous system through the bloodstream or through direct extension from a spondylitic lesion. Compressive myelopathy or radiculopathy may occur as a result of infected disk herniation, epidural abscess, or granuloma formation (127–130). Other neurological complications are arachnoiditis, myelopathy, localized neuritis (cranial neuritis, radiculitis), and demyelination (Guillain-Barré syndrome) as the result of a *Brucella* sp.–induced immunological reaction (127,129,131).

C. Clinical Manifestation

Brucella sp. infections are often asymptomatic and may render immunity in more than 90% of cases. When symptomatic, it is characterized by low-grade fever, weakness, sweats, headache, lymphadenopathy, hepatosplenomegaly, and generalized musculoskeletal symptoms (myalgia and arthralgia) that may develop after an incubation period, which varies from a few days to several weeks. Most patients recover from the acute infection within 3 to 6 months, but in some cases the infection may remain active for years, causing variable degrees of generalized weakness (132).

Spinal involvement is usually a late complication and occurs in 2% to 53% of *Brucella* sp. infections (123,133,134). Among those with spondylitis, 10% to 20% have paraspinal abscess, and 10% to 43% have some degree of neurological compromise (126).

Localized spinal pain is the earliest sign of spondylitis (122). Younger patients may report low backache resembling sacroiliac joint arthritis. Because of its nonspecific presentation, brucellosis can easily be overlooked.

D. Imaging Resources

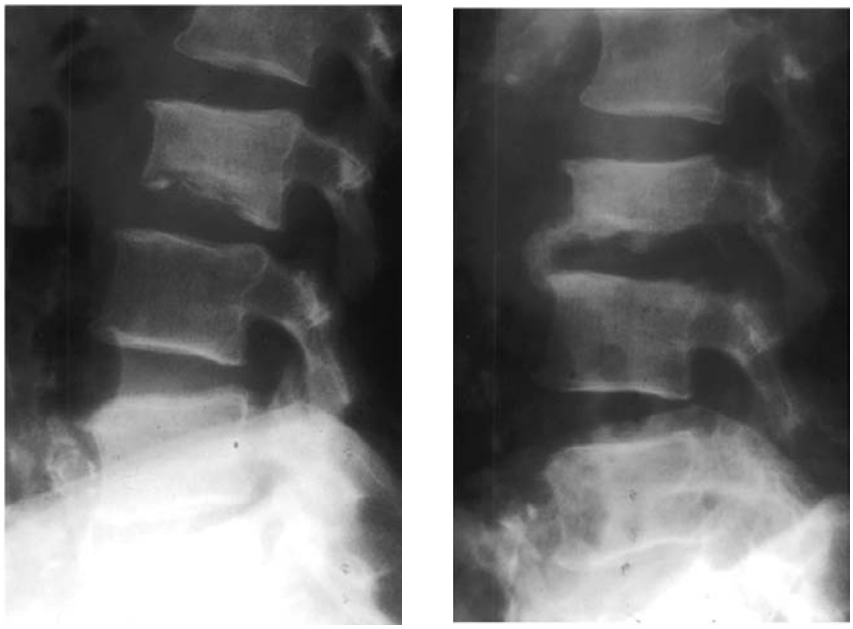
Brucella sp. spondylitis has a characteristic predilection for the lower thoracolumbar spine, which is affected in 45% (123) to 75% (135,136) of cases. The L4-L5 vertebral level is the most commonly affected region. Early radiological findings, which usually appear 3 months after the onset of symptoms (132,137), are nonspecific and may include evidence of bone destruction in the superior vertebral endplate and new bone formation as a result of the healing process leading to a typical "parrot beak" osteophyte (121,123,132). The disk space in the early stage usually is not affected (Fig. 15). The infection can involve the entire vertebral body and may extend as a secondary process to the adjacent disk space and adjacent vertebrae (134). Although reported rates of disk involvement range as high 66% and 100%, these incidences probably represent late and chronic stages of the disease process (135,136,138).

MRI lesions in *Brucella* sp. spondylitis are less impressive than in other spinal infections. Even in severe spinal involvement, no vertebral collapse, gibbous deformity, or spinal cord compression is usually seen (136). Abscess formation is also less frequently seen (Fig. 16). These features help differentiate it from tuberculous spondylitis. At times, arachnoiditis or demyelination may also appear (134).

E. Bacteriological Characteristics and Diagnostic Tests

The diagnosis is usually made by demonstrating a high or rising serum antibody titer to *Brucella* sp. (123,139). The *Brucella* sp. agglutination test is quite reliable; 97% of infected persons have a positive result within 3 weeks of exposure.

Brucella sp. can be cultured from the blood during a bacteremic episode and from involved lymph nodes, from bone marrow, or from the granuloma later in the course of the disease (121,123). The organism is fastidious, and unless the disease is suspected and appropriate media are used, culture results are usually negative (123). The finding of *Brucella* sp. organisms in blood culture is diagnostic, but positive blood culture result rates are less than 20% (140).

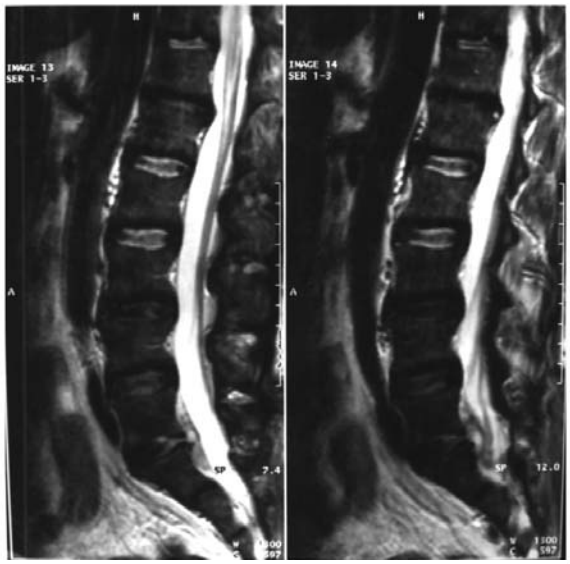


(a) (b)

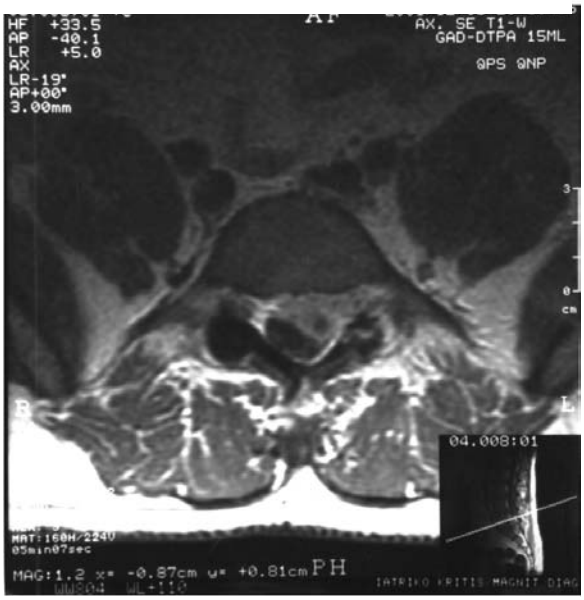
Figure 15 Lateral radiograph showing destruction of the anterior inferior region of the L3 vertebra. Six months later the distraction proceeded to involve almost the entire inferior portion of the vertebra. Note: (a) The intervertebral disk apparently is not destroyed; (b) evidence of reparative process is demonstrated with sclerosis of the margins of the vertebral bodies and large anterior osteophyte-like "parrot beak" bridging the intervertebral disk to fuse with the L4 vertebra.

F. Treatment

Antibiotics are the mainstay of treatment for brucellosis. Single-agent therapy leads to a high incidence of failure and relapse and the potential development of resistance. Relatively short courses of treatment with combinations of different antibiotics have similarly been associated with high rates of recurrences. A minimal course of at least 3 months is recommended. The combination of doxycycline and an aminoglycoside (streptomycin, gentamicin, or preferable netilmicin) for 6 weeks followed by the combination of doxycycline and rifampicin for another 6 to 8 weeks is quite effective treatment, which the authors have applied routinely in their practice. Doxycycline is administered orally 100 mg twice daily. Netilmicin is administered intramuscularly to outpatients or



(a)



(b)

Figure 16 Rare case of *Brucella* sp. diskitis with abscess formation of L5-S1 disk. (a) Severe radiculopathy as seen on sagittal MRI T_2-weighted image, and (b) axial T_1 image. (MRI, magnetic resonance imaging.)

intravenously to inpatients in a dose of 2 mg/kg every 12 hours. The drug level should be monitored regularly in the plasma in order to maintain constant levels. An alternative regimen consists of the doxycycline-rifampicin combination given for 12 weeks. Rifampicin is administered as a single daily dose of 600 mg to 900 mg. The doxycycline-netilmicin combination is more effective than the doxycycline-rifampicin combination in that rifampin reduces levels of doxycycline in plasma. Co-trimoxazole alone or usually in combination with rifampicin can also be used (123).

Brucella sp. antibody titers seem the most accurate way of assessing response to treatment. Antibiotics should be continued until the titer is 1 : 160 or less and there is associated clinical and radiographic improvement (123). Careful and long-term follow-up is recommended because of a high recurrence rate.

Brucellar granulomas or abscesses may resolve spontaneously without treatment (132,133,141). However, it is doubtful that spontaneous resolution of *Brucella* sp. spondilitis is always possible (133,142).

Adjunct treatments are rest and orthosis. Complete bed rest (except in the acute phase) should be discouraged. The spine is immobilized with a rigid orthosis until the resolution of back pain, which usually occurs after 3 to 4 months. Elderly patients may not show prompt response even with adequate antibiotic treatment.

Many authors consider operation for brucellar abscess as a last resort because of the good response to antibiotic treatment (132,141). A relative indication for surgery is neurological deficit with severe pain. Severe neurological deficit caused by bone deformities and purulent epidural abscesses are absolute indications for surgery because of possible irreversible neural damage.

Over the past two years the authors have surgically treated nine patients in our institution. Two had surgery for predominantly mechanical back pain and seven for severe neurological deficit and back pain. The patients who had mechanical back pain had posterior stabilization and transpedicular drainage of the purulent material. One of the patients had a recurrence despite adequate antibiotic treatment of 3 months' duration. All patients with neurological deficit made an excellent recovery. Two patients with spondylitis and epidural abscess had laminectomy. Two patients who had rare cases of isolated diskitis also underwent laminectomy. Two patients with spondylodiskitis of the lumbar spine and anterior epidural abscess had anterior decompression, fusion, and posterior stabilization. One patient, who was treated adequately with antibiotics, experienced severe myelopathy and paraparesis caused by pathological fracture and kyphotic deformity and was treated effectively by means of anterior corpectomy (T12) and reconstruction with vertebral body cage and anterior plate fixation.

V. SUMMARY

The spectrum of granulomatous spinal infections is broad, and each variety of infection has its unique characteristics and clinical course. These diseases share the common characteristic of formation of granulomas in infected tissue. MRI is generally the imaging modality of choice to identify and evaluate these lesions. Anti-infective medical therapy is generally the mainstay of treatment once the specific infecting organism has been identified through biopsy, but surgical intervention is often required to correct deformity, débride infected tissue, or resolve neurocompression.

REFERENCES

1. MS Moon, KY Ha, DH Sun, JL Moon, YW Moon, JW Chung. Pott's paraplegia—67 cases. Clin Orthop 323:122–128, 1996.
2. PR Pattison. Pott's paraplegia: an account of the treatment of 89 consecutive patients. Paraplegia 24:77–91, 1986.
3. World Health Organization. World tuberculosis toll on the rise. Asian Med News 3:9–12, 1991.
4. S Govender, K Annamalai, KPS Kumar, UG Govender. Spinal tuberculosis in HIV positive and negative patients: immunological response and clinical outcome. Int Orthop 24:163–166, 2000.
5. GW Comstock. Epidemiology of tuberculosis. Am Rev Respir 125(suppl):8–15, 1982.
6. MK Viljanen, BI Vyshnevskiy, TF Otten, E Vyshnevskya, M Marjamaki, H Soini, PJ Laippala, AV Vasilyef. Survey of drug-resistant tuberculosis in Northwestern Russia from 1984 through 1994. Eur J Clin Microbiol Infect Dis 17:177–183, 1998.
7. S Lindahl, RS Nyman, J Brismar, C Hugosson, C Lundstedt. Imaging of tuberculosis IV: spinal manifestations in 63 patients. Acta Radiol 37:506–511, 1996.
8. MS Moon. Tuberculosis of the spine controversies and a new challenge. Spine 22:1791–1797, 1997.
9. JJ Ellner. Review: the immune response in human tuberculosis—implications for tuberculosis control. J Infect Dis 176:1351–1359, 1997.
10. AG Fam, J Rubenstein. Another look at spinal tuberculosis. J Rheumatol 20:1731–1740, 1993.
11. AR Hodgson. Infectious disease of the spine. In: RH Rothman, FA Simeone, eds. The Spine. Philadelphia: WB Saunders, 1975:567.
12. P Weaver, RM Lifeso. The radiological diagnosis of tuberculosis of the adult spine. Skeletal Radiol 12:178–186, 1984.
13. HS Sharif. Role of MR imaging in the management of spinal infections. Am J Roentgenol 158:1333–1345, 1992.

14. OV Batson. The function of the vertebral veins and their role in the spread of metastases. Ann Surg 112:138–139, 1940.
15. D Resnick, G Niwayama. Osteomyelitis, septic arthritis, and soft tissue infection: organisms. In: D Resnick, ed. Diagnosis of Bone and Joint Disorders. Vol 4, 3d ed. Philadelphia: WB Saunders, 1995:2467–2474.
16. DC Yao, DJ Sartosis. Musculoskeletal tuberculosis. Radiol Clin North Am 33:679–689, 1995.
17. T Patankar, A Krishnan, D Patkar, H Kale, S Prasad, J Shah, M Castillo. Imaging in isolated sacral tuberculosis: a review of 15 cases. Skeletal Radiol 29:392–396, 2000.
18. MC Haddad, HS Sharif, MS Jared, BM Sammak, MS al Shahed. Premature tracheobronchial, laryngeal and costochondral cartilage calcification in children. Clin Radiol 47(1):52–55, 1993.
19. MJ Post, G Sze, RM Quencer, FJ Eismont, BA Green, H Gahbauer. Gadolinium enhanced MR in spinal infection. J Comput Assist Tomogr 14:721–729, 1990.
20. FA Al-Mulhim, EM Ibrahim, AY el-Hassan, HM Moharram. Magnetic resonance imaging of tuberculous spondylitis. Spine 20:2287–2292, 1995.
21. MA Whelan, DP Naidich, JD Post, NE Chase. Computed tomography of spinal tuberculosis. J Comput Assist Tomogr 7:25–30, 1983.
22. AR Hodgson, OK Skinsnes, JCY Leong. The pathogenesis of Pott's paraplegia. J Bone Joint Surg 49A:1147–1156, 1967.
23. N Rahman. Atypical forms of tuberculosis. J Bone Joint Surg 62B:162–169, 1980.
24. K Kumar. A Clinical study and classification of posterior spinal tuberculosis. Int Orthop 9:147–152, 1991.
25. R Djindjian. Angiography of the Spinal Cord. Baltimore: University Park Press, 1970.
26. C Arseni, DC Samitca. Intraspinal tuberculous granulomas. Brain 83:285–292, 1960.
27. SK Lin, T Wu, YY Wai. Intramedullary spinal tuberculomas during treatment of tuberculous meningitis. Clin Neurol Neurosurg 96:71–78, 1994.
28. T Suzer, T Coskun, K Tahta, H Bayramoglou, E Duzkan. Intramedullary spinal tuberculoma presenting as a conus tumor: a case report and review of the literature. Eur Spine J 7:168–171, 1998.
29. PG Bullough. Tuberculosis. In: PG Bullough, ed. Bullough and Vigorita's Orthopaedic Pathology. 3d ed. London: Mosby-Wolfe, 1997:122–126.
30. A Smith, S Blaser. Infectious and inflammatory process of the spine. Radiol Clin North Am 29:809–827, 1991.
31. D Fang, JC Leong, HS Fang. Tuberculosis of the upper cervical spine. J Bone Joint Surg 65B:47–50, 1983.
32. LC Hsu, JC Leong. Tuberculosis of the lower cervical spine (C2 to C7): a report on 40 cases. J Bone Joint Surg 66B:1–5, 1984.
33. AR Hodgson, A Yau. Pott's paraplegia: a classification based the living pathology. Paraplegia 5:1–16, 1967.
34. RH Berk, M Yazici, N Atabey, OS Ozdamar, U Pabuccuoglu, E Alici. Detection of Mycobacterium tuberculosis in formaldehyde solution-fixed, paraffin-embedded

tissue by polymerase chain reaction in Pott's disease. Spine 21(17):1991–1995, 1996.
35. IM Francis, DK Das, UK Luthra, Z Sheikh, M Sheikh, M Bashir. Value of radiologically guided fine needle aspiration cytology (FNAC) in the diagnosis of spinal tuberculosis: a study of 29 cases. Cytopathology 10:390–401, 1999.
36. J Leong. Pyogenic infection. In: J Weinstein, S Wiesl, eds. The Lumbar Spine. Philadelphia: WB Saunders, 1990:699–723.
37. R Jain, S Sawhney, M Berry. Computed tomography of vertebral tuberculosis: patterns of bone destruction. Clin Radiol 47:196–199, 1993.
38. J Edeiken, AF DePalma, H Moskowitz, V Smythe. "Cystic" tuberculosis of bone. Clin Orthop 28:163–168, 1963.
39. A Gouliamos, D Kehegias, S Lahanis, A Athanasopoulou, E Moulopoulou, A Kalovidouris, S Trakadas, L Vlachos. MR imaging of tuberculous vertebral osteomyelitis: pictorial review. Eur Radiol 11:575–579, 2001.
40. DL Griffiths. Short-course chemotherapy in the treatment of spinal tuberculosis (abstract). J Bone Joint Surg 68B:158, 1986.
41. SS Upadhyay, MJ Saji, CMC Yau. Duration of antituberculous chemotherapy in conjunction with radical surgery in the management of spinal tuberculosis. Spine 21:1898–1903, 1996.
42. MS Moon, L Kim, YK Woo, YO Park. Conservative treatment of tuberculosis of the thoracic and lumbar spine in adults and children. Int Orthop 11:315–322, 1987.
43. Medical Research Council Working Party on Tuberculosis of the Spine (First report). A controlled trial on ambulant outpatient treatment and inpatient rest in bed in the management of tuberculosis of the spine in young Korean patients on standard chemotherapy: a study in Masan, Korea. J Bone Joint Surg 55B:678–697, 1973.
44. Medical Research Council Working Party on Tuberculosis of the Spine (Third report). A controlled trial of debridement and ambulatory treatment in the management of tuberculosis of the spine in patients on standard chemotherapy: a study in Bulawayo, Rhodesia. J Trop Med Hyg 77:72–92, 1974.
45. Medical Research Council Working Party on Tuberculosis of the Spine (Fifth report). A five-year assessment a controlled trial of outpatient and inpatient treatment and plaster of paris jackets for tuberculosis of the spine in children on standard chemotherapy: studies in Masan and Pusan, Korea. J Bone Joint Surg 58B:399–411, 1976.
46. Medical Research Council Working Party on Tuberculosis of the Spine (Sixth report). A five-year assessment a controlled trial of ambulatory treatment debridement and anterior spinal fusion in the management of tuberculosis of the spine. J Bone Joint Surg 60B:163–177, 1978.
47. Medical Research Council Working Party on Tuberculosis of the Spine (Tenth report). A controlled trial of 6-months VS. 9-months regimens of chemotherapy in patients undergoing radical surgery for tuberculosis of the spine in Hong Kong. Tubercule 67:243–259, 1986.
48. AR Hodgson, FE Stock. Anterior spine fusion for the treatment of tuberculosis of the spine. J Bone Joint Surg 42A:295–310, 1960.

49. WK Pun, SP Chow, KD Luk, CL Cheng, LC Hsu, JC Leong. Tuberculosis of the lumbosacral junction: long-term follow-up of 26 cases. J Bone Joint Surg 72B:675–678, 1990.
50. DD Frazier, DR Campbell, TA Garvey, S Wiesel, HH Bohlman, FJ Eismont. Fungal infections of the spine: report of eleven patients with long-term follow-up. J Bone Joint Surg 83A:560–565, 2001.
51. J Bennett. Fungal infections. In: JD Wilson, E Braunwald, KJ Isselbacher, RG Petersdorf, JB Martin, eds. Harrison's Principles of Internal Medicine. 12th ed. New York: McGraw-Hill, 1991:743–751.
52. MK Dalinka, WH Greendyke. The spinal manifestations of coccidioidomycosis. J Can Assoc Radiol 22:93–99, 1971.
53. DA Detrisac, WG Harding, ASL Greiner, GR Dunn, FH Mayfield. Vertebral North American blastomycosis. Surg Neurol 13:311–312, 1980.
54. HP Doub, CE Badgley. The roentgen signs of tuberculosis of the vertebral body. Am J Roentgenol 27:827–832, 1932.
55. D Miller, JW Birsner. Coccidioidal granuloma of bone. Am J Roentgenol 62:229–236, 1949.
56. MC Arvin, RL Gehring, JL Crecelius, MF Curfman. Man with progressive lower back pain. Radiol Clin Indiana Med 84:554–556, 1991.
57. AG Hadjipavlou, JT Mader, HJW Nauta, JT Necessary, G Chaljub, A Adesokan. Blastomycosis of the lumbar spine: case report and review of the literature, with emphasis on diagnostic laboratory tools and management. Eur Spine J 7:416–421, 1998.
58. JA Gehweiler, MP Capp, EW Chick. Observations on the roentgen patterns in blastomycosis of bone: a review of cases from the blastomycosis cooperative study of the Veterans' Administration and Duke University Medical Center. Am J Roentgenol 108:497–510, 1970.
59. MJD Post, G Sze, RM Quencer, FJ Eis-mont, BA Green, H Gahbouer. Gadolinium enhanced MR in spine infection. J Comput Assist Tomogr 14:721–729, 1990.
60. A de Roos, EL van Persijn van Meerken, JL Bloem, RG Bluemm. MRI of tuberculosis spondylitis. Am J Roentgenol 147:79–82, 1986.
61. R Lisbona, V Derbekyan, J Novales-Diaz, A Veksler. Gallium-67 scintigraphy in tuberculous or nontuberculous infectious spondylitis. J Nucl Med 34:853–859, 1993.
62. AG Hadjipavlou, A Arya, W Crow, W Maggio, P Lander, EM Nardone. Percutaneous transpedicular biopsy of the spine. J Interv Radiol 11:103–108, 1996.
63. VP Kushwaha, BA Shaw, JA Geraldi, WL Oppenheim. Musculoskeletal coccidiomycosis: a review of 25 cases. Clin Orthop 332:190–199, 1996.
64. FA Broner, DE Garland, JE Zigler. Spinal infections in the immunocompromised host. Orthop Clin North Am 27(1):37–46, 1996.
65. JE Bennett. Antifungal agents. In: AG Gilman, TW Rall, AS Nies, P Taylor, eds. Goodman and Gilman's The Pharmacological Basis of Therapeutics. 8th ed. New York: Pergamon Press, 1990:1165–1179.
66. LM Lagging, CM Breland, DL Kennedy, TW Milligan, ML Sokol-Anderson, TU Westblom. Delayed treatment of pulmonary blastomycosis causing vertebral osteo-

myelitis, paraspinal abscess and spinal cord compression. Scand J Infect Dis 26:111–115, 1994.
67. KH Bridwell, JW Campbell, SJ Barenkamp. Surgical treatment of haematogenous vertebral osteomyelitis. Spine 15:281–285, 1990.
68. JL Seres, H Ono, EJ Benner. Aspergillosis presenting as spinal cord compression. J Neurosurg 36:221–224, 1972.
69. AG Hadjipavlou, JT Mader, JT Necessary, AJ Muffoletto. Hematogenous pyogenic spinal infections and their surgical management. Spine 25(13):1668–1679, 2000.
70. K Kaneda, H Taneichi, K Abumi, T Hasimoto, S Satoh, M Fujiya. Anterior decompression and stabilization with the Kaneda device for thoracolumbar burst fracture associated with neurological deficits. J Bone Joint Surg 79A:69–83, 1997.
71. RW Bradsher. Blastomycosis. Clin Infect Dis 14(suppl 1):82–90, 1992.
72. SW Chapman. Blastomyces dermatitides. In: GL Mandell, RG Douglas Jr, JE Bannett, eds. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases. 4th ed. New York: Churchill Livingstone, 1995:2353–2364.
73. N Guler, A Palanduz, U Ones, A Ozturk, A Somer, N Saalman, I Yalcin. Progressive vertebral blastomycosis mimicking tuberculosis. Pediatr Infect Dis J 4:816–818, 1995.
74. GA Sarosi, SF Davies. Blastomycosis. Am Rev Respir Dis 120:911–938, 1979.
75. PB McDonald, GB Black, R MacKenzie. Orthopaedic manifestations of blastomycosis. J Bone Joint Surg 72A:860–864, 1990.
76. HG Riegler, LF Goldstein, RF Betts. Blastomycosis osteomyelitis. Clin Orthop 100:225–231, 1974.
77. JW Rippon. Blastomycosis. In: JW Rippon, ed. Medical Mycology: The Pathogenic Fungi and the Pathogenic Actinomycetes. 2d ed. Philadelphia: WB Saunders, 1982:428–458.
78. JP Areno, GD Campbell, RB George. Diagnosis of blastomycosis. Semin Respir Infect 12:252–262, 1997.
79. SF Davies, GA Sarosi. Epidemiological and clinical features of pulmonary blastomycosis. Semin Respir Infect 12:206–218, 1997.
80. SD Green, MW Owens, RB George. Update on blastomycosis. Clinical Pulm Med 8:346–350, 2001.
81. DS Martin, DT Smith. Blastomycosis: a review of the literature. Am Rev Tuberc 39:275–304, 1939.
82. FR Cockerill, GD Roberts, JE Rosenblatt, JP Utz, DC Utz. Epidemic of pulmonary blastomycosis (namekagon fever) in Wisconsin canoeists. Chest 86:688–692, 1984.
83. LD Recht, JR Philips, MR Eckman, GA Sarosi. Self-limited blastomycosis: a report of thirteen cases. Rev Respir Dis 120:1109–1112, 1979.
84. GA Sarosi, KJ Hammerman, RS Tosh Kronenberg. Clinical features of acute pulmonary blastomycosis. N Engl J Med 290:540–543, 1974.
85. RW Bradsher, DC Rice, RS Abernathy. Ketoconazole therapy for endemic blastomycosis. Ann Intern Med 103:872–879, 1985.
86. WE Dismukes, RW Bradsher, GC Cloud, SW Chapman, RB George, DA Stevens, WM Girard, MS Saag, C Bowles-Patton. Intraconazole therapy for blastomycosis and histoplasmosis. Am J Med 93:489–497, 1992.

87. EM Olson, AC Duberg, LD Herron, P Kissel, D Smilovitz. Coccidioidal spondylitis: MR findings in 15 patients. AJR Am J Roentgenol 171(3):785–789, 1998.
88. WG Winter Jr, RK Larson, MM Honeggar, DT Jacobsen, D Pappagianis, RW Huntington Jr. Coccidioidal arthritis and its treatment—1975. J Bone Joint Surg 57A:1152–1157, 1975.
89. LD Herron, P Kissel, D Smilovitz. Treatment of coccidioidal spinal infection: experience in 16 cases. J Spinal Disord 10:215–222, 1997.
90. JM Bried, JN Galgiani. Coccidioides immitis infections in bones and joints. Clin Orthop 21:235–243, 1986.
91. C Hennequin, P Bourèe, C Hiesse, B Dupont, B Charpentier. Spondylodiscitis due to Candida albicans: reports of two patients who were successfully treated with fluconazole and review of the literature. Clin Infect Dis 23:176–178, 1996.
92. JC Gathe Jr, RL Harris, B Garland, MW Bradshaw, TW Williams Jr. Candida osteomyelitis: report of five cases and review of the literature. Am J Med 82:927–937, 1987.
93. P Derkinderen, F Bruneel, O Bouchaud, B Regnier. Spondylodiscitis and epidural abscess due to Candida albicans. Eur Spine J 9:72–74, 2000.
94. M Curran, L Lenke. Torulopsis glabrata spinal osteomyelitis involving two contiguous vertebrae: a case report. Spine 21:866–870, 1996.
95. J Bruns, T Hemker, G Dahmen. Fungal spondylitis: a case of Torulopsis glabrata and Candida tropicalis infection. Acta Orthop Scand 57:563–565, 1986.
96. KA Gustke, KK Wu. Torulopsis glabrata osteomyelitis: report of a case. Clin Orthop 154:197–200, 1981.
97. G Samonis, D Bafaloukos. Fungal infections in cancer patients: an escalating problem. In Vivo 6:183–194, 1992.
98. A van Ooij, JMH Beckers, MJH Herpers, GHI Walenkamp. Surgical treatment of aspergillus spondylodiscitis. Eur Spine J 9:75–79, 2000.
99. S Govender, R Rajoo, IE Goga, RW Charles. Aspergillus osteomyelitis of the spine. Spine 16:746–749, 1991.
100. C Castelli, F Benazzo, L Minoli, P Marone, R Seghezzi, CN Carlizzi. Aspergillus infection of the L3-L4 disc space in an immunosuppressed heart transplant patient. Spine 15:1369–1373, 1990.
101. JR Mawk, DL Erickson, SN Chou, EL Seljeskog. Aspergillus infection of the lumbar disc spaces. Report of three cases. J Neurosurg 58:270–274, 1983.
102. B Cortet, R Richard, X Deprez, L Lucet, RM Flipo, X Le Loet, B Duquesnoy, B Delcambre. Aspergillus spondylodiscitis: successful conservative treatment in 9 cases. J Rheumatol 21:1287–1291, 1994.
103. J Chleboun, S Nade. Skeletal cryptococcosis. J Bone Joint Surg 59A:509–514, 1977.
104. E Govender, E Mutasa, AH Parbhoo. Cryptococcal osteomyelitis of the spine. J Bone Joint Surg 81B:459–461, 1999.
105. K Matsushsita, K Suzuki. Spastic paraparesis due to cryptococcal osteomyelitis: a case report. Clin Orthop 196:279–284, 1985.
106. KW Lie, YL Yu, IK Cheng, E Woo, WT Wong. Cryptococcal infection of the lumbar spine. J R Soc Med 82:172–173, 1989.

107. A Boda, S Aranyi, T Varföldi, G Elo. A case of spinal actinomycosis involving seven vertebral bodies. Eur J Orthop Surg Traumatol 7:199–201, 1997.
108. J Bennett. Actinomycosis and nocardiasis. In: Harrison's Principles of Internal Medicine 12th ed. New York: McGraw-Hill, 1991:752–753.
109. J Ernst, E Ratjen. *Actinomycosis* of the spine: report of two cases. Acta Orthop Scand 42:35–44, 1971.
110. AH Kaplan, DJ Weber, EZ Oddone, JR Perfect. Infection due to Actinobacillus actinomycetem comitans: 15 cases and review. Rev Infect Dis 11:46–63, 1989.
111. VS Cope. *Actinomycosis* of bone with special reference to infection of the vertebral column. J Bone Joint Surg 33B:205–214, 1951.
112. WB Young. *Actinomycosis* with involvement of the vertebral column: case report and review of the literature. Clin Radiol 11:175–182, 1960.
113. RN Crank, M Sundaram, JB Shields. Case report 197: cervical actinomycosis with spinal involvement. Skeletal Radiol 8:164–167, 1982.
114. JR Brown. Human actinomycosis: a study of 181 subjects. Hum Pathol 4:319–330, 1973.
115. T Lane, S Goings, DW Frase, K Ries, J Petrozzi, E Abrutyn. Disseminated actinomycosis with spinal cord compression: report of two cases. Neurology 29:890–893, 1979.
116. R Alday, MO Lopez-Ferro, M Fernandez-Guerrero, P Ruiz-Barnes. Spinal intrathecal empyema due to Actinomyces israelii. Acta Neurochir 101:159–162, 1989.
117. DW Kannangara, T Tanaka, H Thadepalli. Spinal epidural abscess due to Actinomycosis israelii: a case report. Neurology 31:202–204, 1981.
118. PG Muller. *Actinomycosis* as a cause of spinal cord compression: a case report and review. Paraplegia 27:390–393, 1989.
119. RL Nolan, JD Ross, SW Chapman. Thoracid actinomycosis presenting as spinal cord compression. J Miss State Med Assoc 31:41–45, 1990.
120. B Yung, J Cheng, T Chan, T Loke, J Lo, P Lau. Aggressive thoracid actinomycosis complicated by vertebral osteomyelitis and epidural abscess leading to spinal cord compression. Spine 25:745–748, 2000.
121. D Kaye. Brucellosis. In: JD Wilson, E Braunwald, KJ Isselbacher, RG Petersdorf, JB Martin, eds. Harrison's Principles of Internal Medicine. 12th ed. New York: McGraw-Hill, 1991:625–626.
122. JD Keenam, CW Metz Jr. Brucella spondylitis: a brief review and case report. Clin Orthop 82:87–91, 1972.
123. RM Lifeso, E Harder, SJ McCorkell. Spinal brucellosis. J Bone Joint Surg 67B:345–351, 1985.
124. H Serre, F Blotman, J Sany, L Simon. Spondylodiscites infectieuses: aspect symptomatiques et évolutifes. Rev Rhum 40:243–253, 1973.
125. RI Wise. Brucellosis in the United States. JAMA 24:2318–2322, 1980.
126. ARM Mousa, SA Muhtaseb, DS Almudallal. Osteoarticular complications of brucellosis: a study of 169 cases. Rev Infect Dis 9:531–543, 1987.
127. R Bashir, MZ Al-Kawi, EJ Harder, J Jinkins. Nervous system brucellosis: diagnosis and treatment. Neurology 35:1576–1581, 1985.
128. N Çeviker, K Baykaner, M Göksel, L ener, H Alp. Spinal cord compression due to Brucella granuloma. Infection 17:304–305, 1989.

129. AM Mousa, RH Bahar, GF Araj, TS Koshy, SA Muhtaseb, DS al-mudallal, AA Marafie. Neurological complications of Brucella spondylitis. Acta Neurol Scand 81:16–23, 1990.
130. RR Sharma, MJ Chandy, SD Lad. Extradural brucellosis granuloma with 'subtle' spondylosis: a rare cause of spinal cord compression. Br J Neurosurg 4:441–445, 1990.
131. RA Shakir, AN Al-Din, FG Araj, AR Lulu, AR Mousa, MA Saadah. Clinical categories of neurobrucellosis: a report on 19 cases. Brain 110:213–223, 1987.
132. YH Tekkök, M Berker, OE Özcan, T Özgen, E Akalin. Brucellosis of the spine. Neurosurgery 33:838–844, 1993.
133. W Ganado, AJ Craig. Brucellosis myelopathy. J Bone Joint Surg 40A:1380–1388, 1958.
134. HS Sharif, OA Aideyan, DC Clark. Brucellar and tuberculous spondylitis: comparative imaging feature. Radiology 171:419–425, 1989.
135. GS Wilson, AA Miles. Topley and Wilson's Principles of Bacteriology and Immunity. 5th ed. Baltimore: Williams & Wilkins, 1964.
136. ID Farrell, L Robertson, PM Hinchliffe. Serum antibody response in acute brucellosis. J Hyg 74:23–28, 1975.
137. M Cordero, I Sanchez. Brucellar and tuberculous spondylitis. J Bone Joint Surg 73B:100–103, 1991.
138. D Ozaksoy, K Yucesoy, M Yucesoy, I Kovanlykaya, A Yuce, S Naderi. Brucellar spondylitis: MRI findings. Eur Spine J 10:529–533, 2001.
139. JD Colmenero, JM Reguera, A Fernandez-Nebro, F Cobrera-Franquelo. Osteoarticular complications of brucellosis. Ann Rheum Dis 50:23–26, 1991.
140. Y Samra, M Hertz, Y Shaked, S Zwas, G Altman. Brucellosis of the spine: a report of 3 cases. J Bone Joint Surg 64B:429–431, 1982.
141. J Ariza, F Gudiol, J Valverde, R Pallares, P Fernandez-Viladrich, G Rufi, L Espadaler, F Fernandez-Nogues. Brucellar spondylitis: a detailed analysis based on current findings. Rev Infect Dis 7:656–664, 1985.
142. MMS Glasgow. Brucellosis of the spine. Br J Surg 283–288, 1976.
143. J Leong. Pyogenic infection. In: JN Weinstein, SW Wiesel, eds. The Lumbar Spine. Philadelphia: WB Saunders, 1990:699–723.

15
Pediatric Osteomyelitis

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I. INTRODUCTION

Osteoarticular infections are unique in children. Unlike adults, children have a propensity to development of osteoarticular infections through the hematogenous route. Since children tend to have frequent episodes of bacteremia, it is no wonder that acute hematogenous osteomyelitis and septic arthritis are important disease processes in this age group. The morbidity associated with a pediatric osteoarticular infection is potentially devastating, yet early diagnosis and treatment can prevent most complications. Proper treatment and follow-up are important; undertreatment can result in relapse and improper or broad use of antibiotics carries risks of the development of resistant organisms. This chapter focuses primarily on acute hematogenous osteomyelitis (AHO), since it is the most common form of osteoarticular infection in children. Septic arthritis, subacute and chronic osteomyelitis, and puncture wounds of the foot are also discussed.

II. EPIDEMIOLOGICAL CHARACTERISTICS

Acute hematogenous osteomyelitis occurs in children less than 13 years old at a rate of 1 in 5000 (1). There is a male predominance in most series. AHO is particularly common in neonates, in whom 75% to 100% of cases of septic

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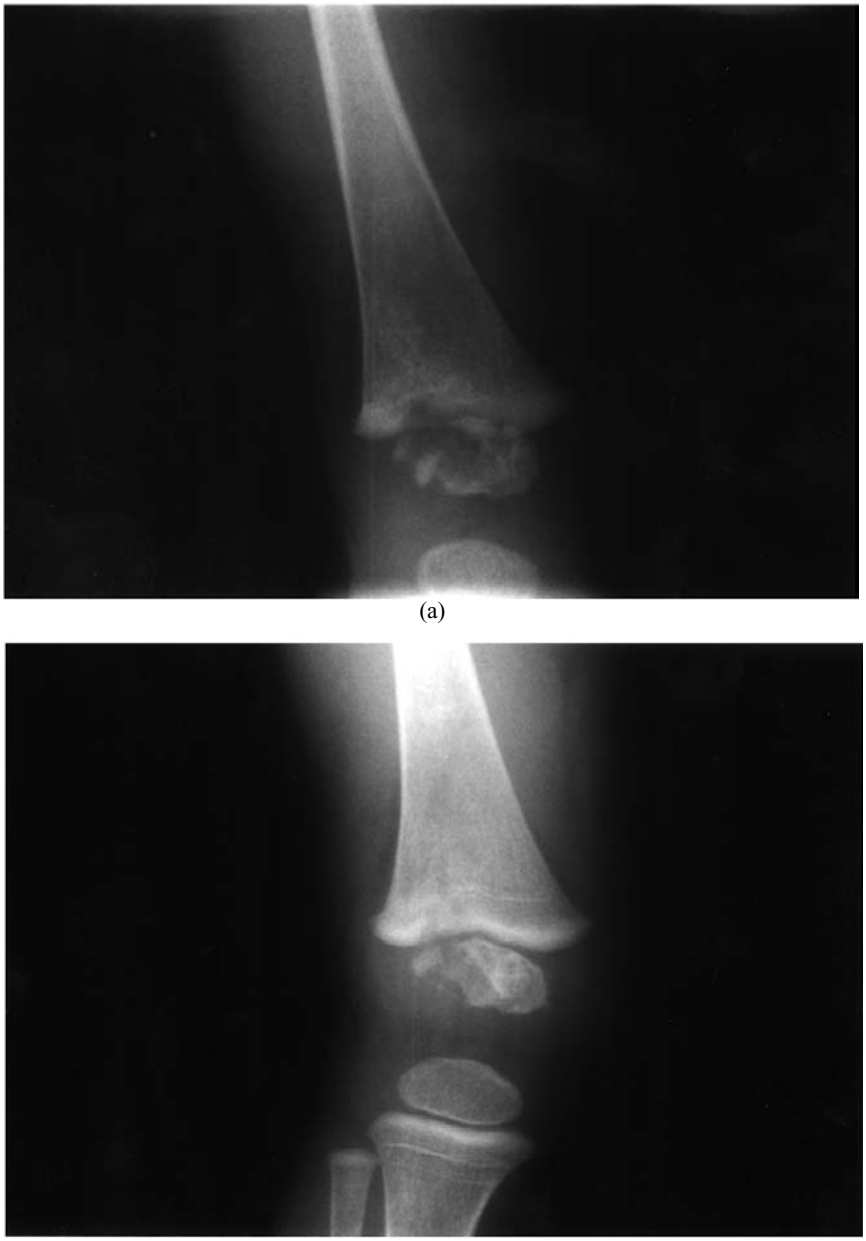
arthritis are secondary to osteomyelitis. Overall, 10% to 16% of cases of septic arthritis are attributable to underlying osteomyelitis (2). The character of AHO of the long bones in children has changed over the past three decades. In the United Kingdom, *Staphylococcus aureus* still accounts for almost a third of cases (31%), but that proportion is down from 54% in the early 1970s. The overall incidence of long bone infection decreased from 84% in the early 1970s to 57% in the late 1990s. The proportion of children with subacute infection has increased from 12% to 42% (3). These changes may be due to the trend toward the use of broad-spectrum antibiotics early in the course of childhood illness, increased awareness, and earlier presentation to a medical facility (4). Certainly the trend toward more invasive procedures in the neonatal intensive care unit makes this population uniquely susceptible to hospital-acquired long bone sepsis.

III. PATHOGENESIS

Primary hematogenous osteomyelitis occurs mainly in infants and children. The metaphyses of the long bones (tibia, femur) are most frequently involved. The anatomical features of the metaphyseal region explain this clinical localization (5). The area adjacent to the growth plate has a normally low oxygen tension and a low pH, prerequisites for normal physeal function. Nonanastomosing capillary ends of the nutrient artery make sharp loops under the growth plate and enter a system of large venous sinusoids, where the blood flow becomes slow and turbulent. Bacteria can become lodged in these sharp capillary loops, where they may proliferate in the relatively acidic and anaerobic environment. The metaphyseal capillaries lack phagocytic lining cells, and sinusoidal veins contain functionally inactive phagocytic cells (6). The combination of sluggish flow, low oxygen tension, low pH, and lack of phagocytic reaction in the area can result in infection. Minor trauma also makes the area more susceptible to inoculation from transient bacteremia (7). Trauma to the physis produces a small hematoma, vascular obstruction, and subsequent bone necrosis.

The acute infection initially produces a local cellulitis that results in infiltration by leukocytes, increased bone pressure, further decrease in pH, and decreased oxygen tension. The cumulative effects of these physiological factors further compromise the medullary circulation and enhance the spread of infection. The infection may proceed laterally through the Haversian and Volkmann's canal systems, perforate the bony cortex, and lift the periosteum from the surface of the bone. When this occurs in the presence of medullary extension, both the periosteal and endosteal circulations are lost, and large segments of dead cortical and cancellous bone are formed. In the infant, medullary infection may spread to the epiphysis and joint surfaces through capillaries that cross the growth plate (Fig. 1). In the child above 1 year of age the infection is usually confined to the metaphysis and diaphysis since the growth plate is avascular. The joint is spared



(a)

(b)

Figure 1 This 13-month-old child suffered a bout of right distal femoral osteomyelitis as a neonate. Note damage on both sides of the growth plate. (b) At age 16 months, note the intact Harris line indicating symmetrical growth of the distal femoral physis.

unless the metaphysis is intracapsular. Thus, cortical perforation at the proximal radius, humerus, or femur may infect the elbow, shoulder, or hip joint, respectively, regardless of the age of the patient.

A single pathogenic organism is usually recoverable from the bone. In infants, *Staphylococcus aureus*, *Streptococcus agalactiae*, and *Escherichia coli* are most frequently isolated from blood or bones, whereas in children above 1 year of age, *S. aureus*, *Streptococcus pyogenes*, and *Haemophilus influenzae* are most commonly isolated. The incidence of *H. influenzae* infection decreases after 4 years of age. However, the overall incidence of *H. influenzae* as a cause of osteomyelitis is decreasing because of the new *H. influenzae* vaccine now given to children (8). In adults, *S. aureus* is the most common organism isolated.

IV. SIGNS AND SYMPTOMS

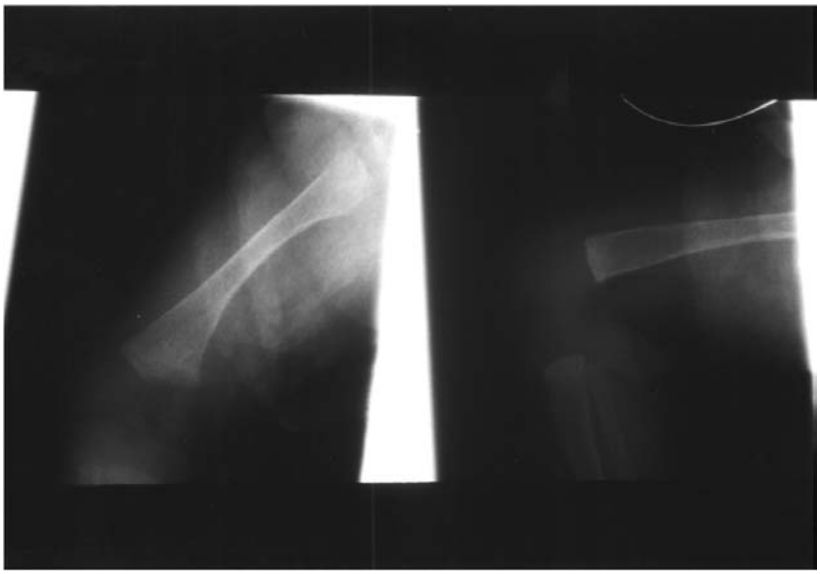
Neonatal osteomyelitis is characterized by a paucity of systemic and local findings (9). Local findings include edema and decreased motion of a limb, commonly known as *pseudoparalysis*. A joint effusion adjacent to the bone infection is present in approximately 60% of cases. Often fever is absent and the erythrocyte sedimentation rate (ESR) is normal despite fulminant infection; therefore, a high level of suspicion is required in this age group.

Children with hematogenous osteomyelitis may experience abrupt fever, irritability, lethargy, and local signs of inflammation 3 weeks or less in duration (10). They may limp or refuse to bear weight on the involved limb. If septic arthritis is present, passive motion of the joint may be painful. However, 50% of children have vague complaints, including pain of the involved limb of 1 to 3 months in duration and minimal, if any, temperature elevation.

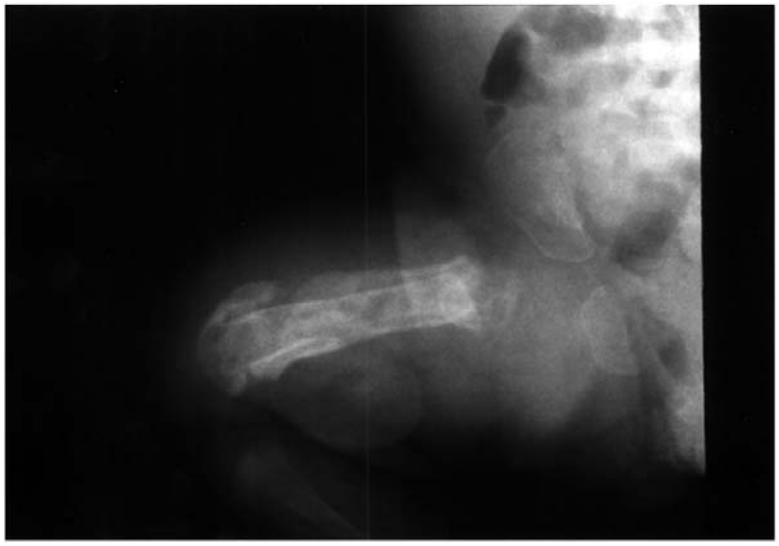
Infants and children with hematogenous osteomyelitis usually have normal soft tissue enveloping the infected bone and are capable of a very efficient metabolic response to infection. Therefore, children have the potential to resorb large sequestra and generate a significant periosteal response to the infection. This latter feature leads to substantial formation of bone formed at the margin of the infection (involucrum) (Figs. 2 and 3). The involucrum affords skeletal continuity and maintenance of function during the healing phase. If antimicrobial therapy directed at the responsible pathogen is begun before extensive bone necrosis, the patient has an excellent probability of disease arrest.

V. DIAGNOSIS

The presumptive diagnosis of osteomyelitis can be based on the combination of signs, symptoms, and radiographic results. *Bone pain plus fever in a child*



(a)



(b)

Figure 2 (a) Oblique and lateral femur radiographs of a 3-month-old 24-week premature infant with pain and tenderness in the right thigh. At initial exam the radiographs show no obvious bony abnormality. (b) Twenty-four days later there is obvious exuberant periosteal reaction. Note the "bone within a bone" appearance of the involucrum.

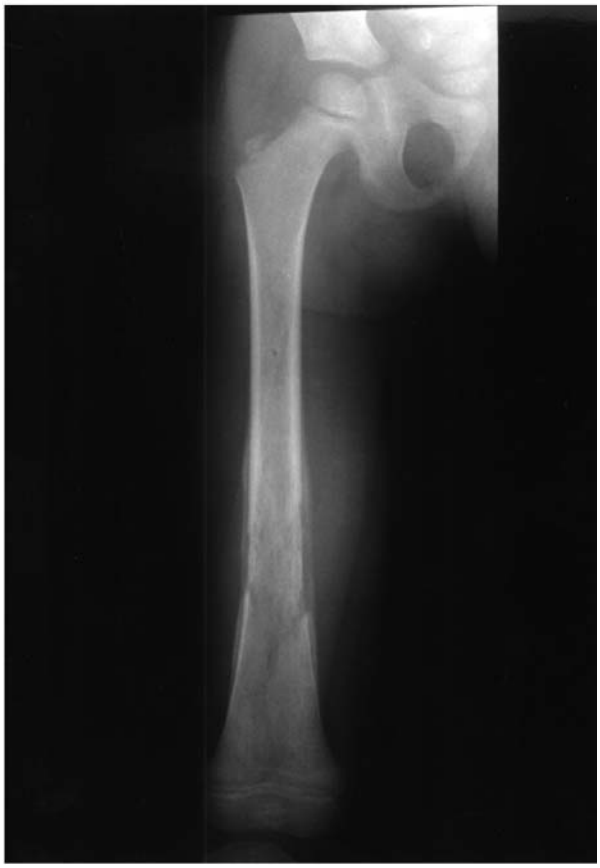


Figure 3a This 3-year-old African-American female with sickle-cell disease had a 3-week history of pain and tenderness in the right thigh. AP and lateral radiographs of the femur show the involucrum, or "bone within a bone." Unlike AHO in otherwise healthy children, AHO in sickle-cell patients is often diaphyseal.

constitutes osteomyelitis until proved otherwise. Definitive diagnosis rests on the obligatory isolation of the pathogen from the bone lesion or blood culture. In hematogenous osteomyelitis, positive blood culture results can often obviate the need for a bone aspirate or biopsy when there is radiographic evidence of osteomyelitis. Blood culture results are positive in up to 50% of children with osteoarticular bacterial infections (1,11). They should be drawn immediately once osteomyelitis or septic arthritis is suspected. Any joint effusion should be tapped and fluid sent for culture, Gram stain, and cell count. A white blood cell count of 50,000 per high-powered field (hpf) in joint fluid is diagnostic of septic

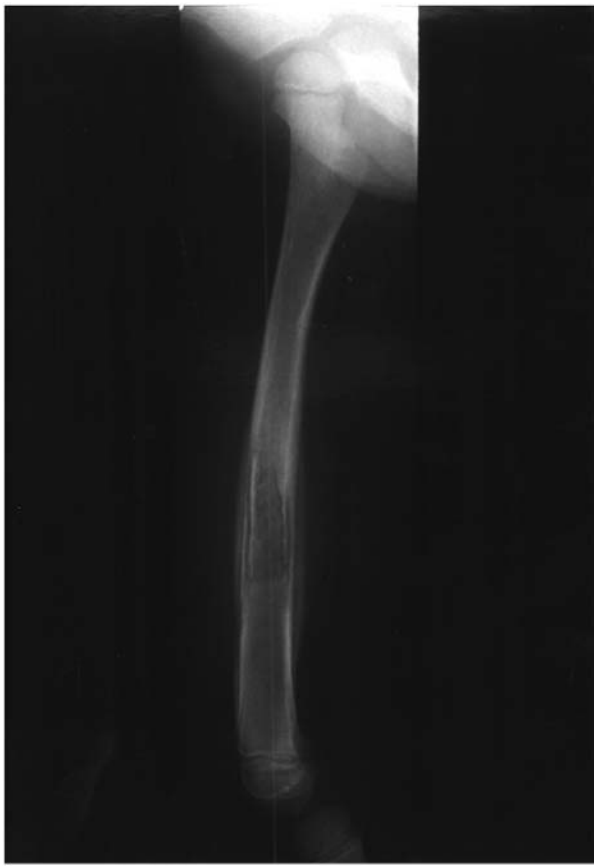


Figure 3b This 3-year-old African-American female with sickle-cell disease had a 3-week history of pain and tenderness in the right thigh. Lateral radiograph of the femur showing the involucrum is shown here.

arthritis. In the case of osteomyelitis, the bone should be aspirated. The aspiration of bone through an area of overlying cellulitis is not likely to cause osteomyelitis. In most children, an 18 gauge spinal needle can be atraumatically inserted at the point of maximal tenderness, usually without, or with minimal, sedation. As the needle reaches the cortex, the syringe should be aspirated. If pus is obtained, then a subperiosteal abscess is present. If no pus is obtained, the needle should be gently inserted through the cortex and into the cancellous bone of the metaphysis. Again, if pus is obtained then the diagnosis of abscess is made. If only blood is returned on aspiration of the marrow, then it should be sent for culture and Gram stain. Between 50% and 87% of bone aspirates yield bacteriological

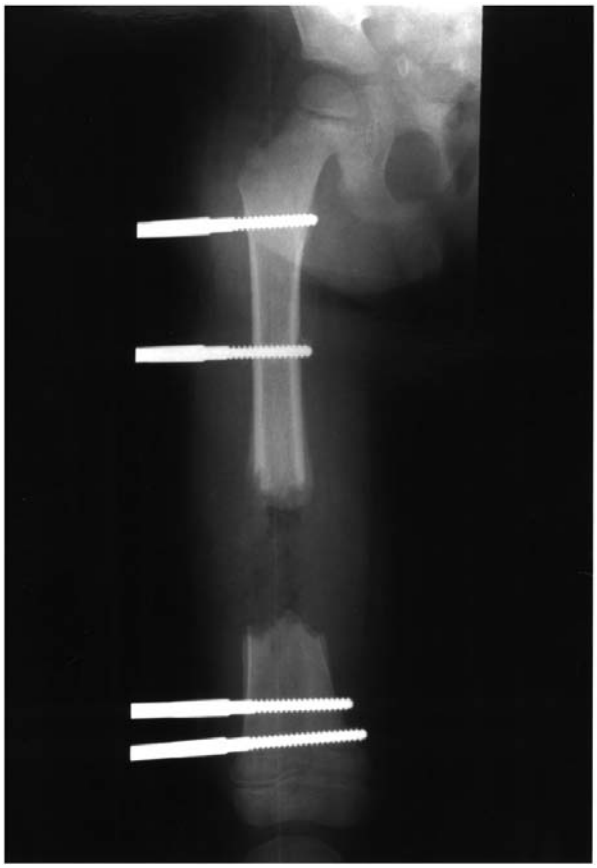


Figure 3c This 3-year-old African-American female with sickle-cell disease had a 3-week history of pain and tenderness in the right thigh. The patient was treated with diaphysectomy and application of an external fixator.

diagnoses (11–14). All culture specimens must be obtained before antibiotics are administered.

A. Laboratory Studies

Laboratory studies should include a complete blood count (CBC), ESR, and C-reactive protein. In most cases of long bone osteomyelitis, the ESR is elevated, usually above 40 (11). However, the ESR is not a reliable predictor for neonates or in children with sickle cell anemia. It is not as reliable an indicator of improvement as C-reactive protein, which is elevated in 98% of cases of AHO at

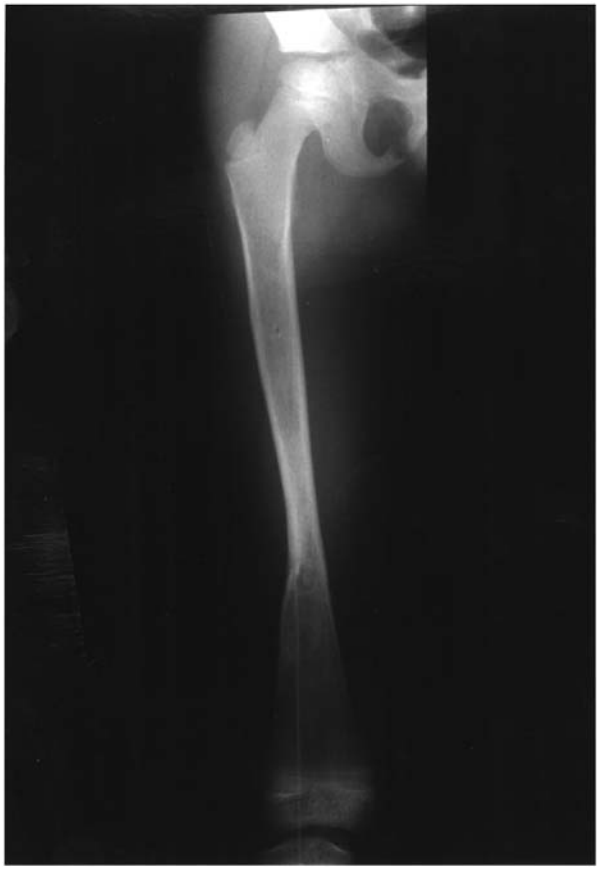


Figure 3d This 3-year-old African-American female with sickle-cell disease had a 3-week history of pain and tenderness in the right thigh. The fixator was removed 4 months later after regrowth of a normal diaphysis Three-year follow-up. AP of the femur is shown here.

presentation and approaches normal values within 1 week of the initiation of clinically effective therapy (15). Therefore, whenever an ESR is drawn as part of the work-up, a C-reactive protein should be used as a baseline to evaluate the eventual response to therapy. Peripheral WBC count is less reliable as a diagnostic indicator as it is elevated in only 50% of cases of AHO.

B. Radiographic Studies

In acute hematogenous osteomyelitis, radiographic changes accurately reflect the destructive process but lag at least 2 weeks behind the evolution of infection. The

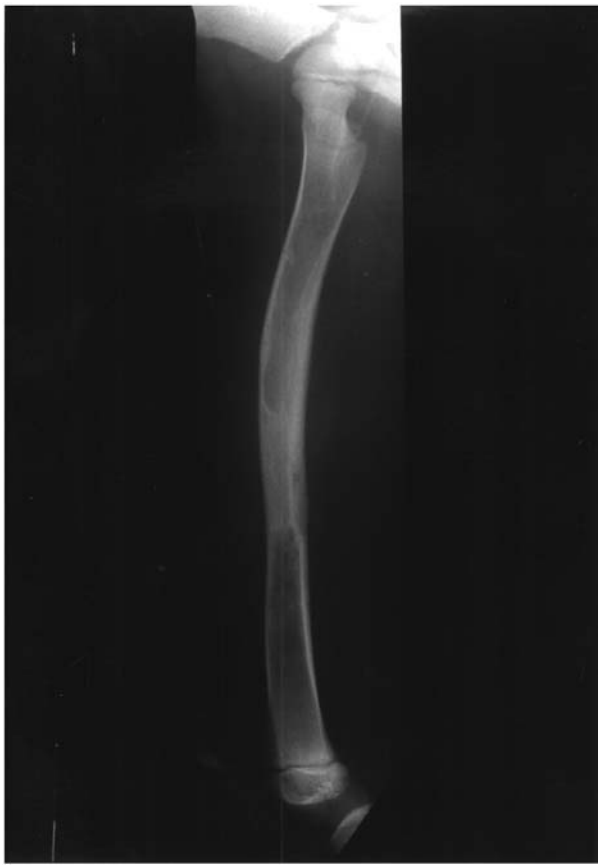


Figure 3e This 3-year-old African-American female with sickle-cell disease had a 3-week history of pain and tenderness in the right thigh. Three-year follow-up lateral of the femur is shown here.

earliest changes are swelling of the soft tissue, periosteal thickening and/or elevation, and focal osteopenia. Periosteal new bone formation may be evident at 5 to 7 days. At least 50%–75% of the bone matrix must be destroyed before radiographs show lytic changes. Radiographic improvement may lag behind clinical recovery, even when the patient is receiving appropriate antimicrobial therapy (16). In contiguous focus and chronic osteomyelitis, the radiographic changes are subtle, are often found in association with other nonspecific radiographic findings, and require a careful clinical correlation to achieve diagnostic significance.

C. Radionuclide Studies

Radionuclide scans may be obtained to clarify an ambiguous diagnosis of osteomyelitis or to help gauge the extent of bone and soft tissue inflammation. In general, it is not usually necessary to obtain these scans for the diagnosis of long bone osteomyelitis. The actual mechanism of bone labeling with radiophatmaceuticals is still unclear. The technetium polyphosphate ^{99m}Tc scan demonstrates increased isotope accumulation in areas of increased blood flow and reactive new bone formation (17). In biopsy-confirmed cases of hematogenous osteomyelitis, it usually yields positive findings as early as 48 hours after the initiation of the bone infection (18). It is not a reliable test in neonates or in infections of the foot and ankle because the false-negative rate is high in these circumstances. Negative ^{99m}Tc scans findings in documented cases of osteomyelitis may reflect impaired blood supply to the infected area (19).

A second class of radiopharmaceuticals used for the evaluation of osteomyelitis includes gallium citrate. Gallium attaches to transferrin, which leaks from the bloodstream into areas of inflammation. The gallium scan also shows increased isotope uptake in areas concentrating polymorphonuclear leukocytes, macrophages, and malignant tumors (20). Since the gallium citrate scan does not show bone detail well, distinguishing between bone and soft tissue inflammation is often difficult. Comparison with a ^{99m}Tc scan result helps to resolve this problem (21). Gallium citrate is found to accumulate in areas of reactive bone (20).

Indium-labeled leukocyte scans are less useful in the evaluation of osteomyelitis. Indium leukocyte scans yield positive results in approximately 40% of patients with acute osteomyelitis and 60% of patients with septic arthritis (22). Patients who have chronic osteomyelitis, bony metastases, and degenerative arthritis often have negative scan findings.

D. Computed Tomography

Computed axial tomography (CT) may play a role in the diagnosis of osteomyelitis. Increased marrow density occurs early in the infection (23), and intramedullary gas has been reported in patients with hematogenous osteomyelitis (24). The CT scan can also help to identify areas of necrotic bone and to assess the involvement of the surrounding soft tissues. In a recalcitrant infection, the CT scan may assist in identifying the surgical approach and augment débridement (23,25). One disadvantage of this study is the scatter phenomenon, which occurs when metal is present in or near the area of bone infection. This scatter results in a significant loss of image resolution. The CT scan should not be used as a substitute for the obligatory aspiration of bone in the suspected area of osteomyelitis whenever possible.

E. Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) has been recognized as a useful modality for diagnosing the presence and scope of musculoskeletal sepsis (26–28). The spatial resolution of MRJ makes it useful in differentiating between bone and soft tissue infection, often a problem with radionuclide studies (29). Unlike the radionuclide studies, MRI is not useful for whole-body examinations. Metallic implants in the region of interest may produce focal artifacts, thereby decreasing the utility of the image (30).

VI. TREATMENT

The components of osteomyelitis treatment include patient evaluation, staging assessment, identification and sensitivity of microorganism(s), administration of antibiotics, débridement surgery, dead space management, and, if necessary, stabilization (31–33). Reconstruction is considered at the first surgery.

A. Acute Hematogenous Osteomyelitis

In children, acute hematogenous osteomyelitis is primarily a medical disease. Identification of the causative pathogen is essential. The infection is usually susceptible to specific antimicrobial therapy. Mismanagement with inappropriate antibiotic(s) encourages disease extension, necrosis, and sequestra formation. The decision for surgical intervention hinges on the result of aspiration of the infected bone or joint. Surgical intervention is indicated if the patient has evidence of a soft tissue or intramedullary abscess, or joint sepsis or if the patient has not responded to specific antimicrobial therapy within 48 hours. If no abscess is found on aspiration, a parenteral antimicrobial regimen is begun to cover the clinically suspected pathogens. A positive culture finding of an aspirate or a positive blood culture result along with radiographic findings consistent with osteomyelitis establish the diagnosis. Once the organism is identified, the antibiotic regimen may be continued or changed on the basis of sensitivity results (34). If all culture results are negative, a bone biopsy is indicated unless clinical improvement with empirical therapy has been dramatic. The patient is treated for 4 to 6 weeks with appropriate parenteral antimicrobial therapy, dated from the initiation of therapy or after the last major débridement surgery. If the initial medical management fails and the patient is clinically compromised by a recurrent infection, medullary and/or soft tissue débridement is necessary in conjunction with another 4- to 6-week course of antibiotics.

Initial antibiotic therapy should cover the most likely pathogens for the age of the child. In general, neonates should receive cefotaxime at 100–120 mg/kg of

body weight/24 h or some other appropriate coverage for *S. aureus*, group B *Streptococcus* spp., and gram-negative rods. Infants and children are most likely to be infected with *S. aureus* and should receive cefazolin at 100 mg/kg/24 h. Clindamycin is an appropriate substitute for a child who is allergic to penicillin or cephalosporins. Nafcillin may be used instead of cefazolin if *Streptococcus* spp. infection is strongly suspected on a clinical basis. Routine coverage for *H. influenzae* is no longer recommended if the child is above 18 months old and is up to date on immunizations. Sickle-cell disease patients should have coverage for *S. aureus* and *Salmonella* spp. with cefotaxime at 100–120 mg/kg/24 h or with oxacillin and ampicillin or chloramphenicol.

Oral antibiotic therapy can be used for treatment of childhood osteomyelitis. It should be reserved for cases of short duration with a culture-proven pathogen and rapid response to initial antibiotic therapy. It is recommended that the patient initially receive 2 weeks of parenteral antibiotic therapy before changing to an oral regimen (35,36). In addition, the patient must be compliant and have close outpatient follow-up. Absorption and activity of the orally administered antibiotic should be monitored. Pediatric patients should not be given oral antimicrobial therapy with quinolones (37,38).

B. Subacute and Chronic Osteomyelitis (Brodie's Abscess)

Brodie's abscess is the name given to a localized, well-circumscribed bone abscess that is not associated with systemic illness. The most common site of involvement is the distal part of the tibia. The lesion is typically single and located near the metaphysis. Seventy-five percent of the patients are less than 25 years of age. It is usually due to a form of subacute osteomyelitis. Patients who have subacute cases appear less ill and less toxic than children with AHO. They frequently seek medical attention later in the course of their disease. Pain is usually mild, fever is occasionally present, and loss of function is minimal. Subacute osteomyelitis is associated with prior antibiotic therapy in up to 40% of cases (39). The ESR is usually elevated. Subacute osteomyelitis, like AHO, is usually metaphyseal but may occur in the epiphysis as well. Primary epiphyseal osteomyelitis is almost always subacute. Most cases of subacute osteomyelitis are caused by *S. aureus*, though isolation of the organism is possible only 50% of the time. At surgery, granulation tissue, not pus, is present. Surgical débridement and culture-directed antibiotics are often curative (40,41). Chronic osteomyelitis may also cause a Brodie's abscess that is indicated radiographically, but the patients are often afebrile and report longstanding dull pain. As in the subacute form, surgical débridement and parenteral antibiotics may be necessary for symptomatic patients.

C. Septic Arthritis

In neonates, septic arthritis is almost always due to underlying or contiguous osteomyelitis; however, in older infants and children primary hematogenous septic arthritis is a frequent occurrence (Fig. 4). Careful consideration should be given to whether there is contiguous osteomyelitis because the duration of intravenous antibiotic administration can be shortened for uncomplicated septic arthritis. The knee and the hip are the most commonly affected joints. The most likely pathogens are the same as in AHO, as is the diagnostic work-up. Aspiration is essential for definitive diagnosis and determination of the need for surgical drainage. If hip sepsis is suspected, ultrasonography of the hip reveals the presence of an effusion in most cases (Fig. 5). Fluoroscopy aids in the placement of the needle for aspiration of the hip. Any effusion of the knee should be detectable clinically and aspiration can be accomplished under local anesthesia without sedation. Any septic joint in an individual older than 12 years should be considered to be gonococcal (GC) until proved otherwise. If GC is suspected, the lab should be immediately alerted and the specimen sent on charcoal or some other medium favorable to the fastidious gonococcal organism.

(a)

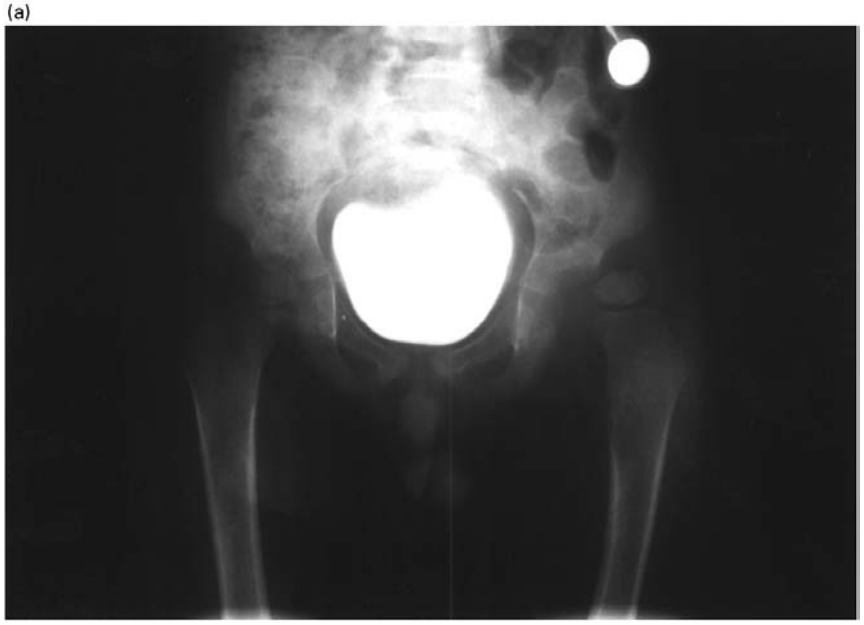


Figure 4 (a) This 2-year-old boy had a 3-week history of fever and left hip pain. Note the dislocation of the left hip due to the presence of pus in the joint.

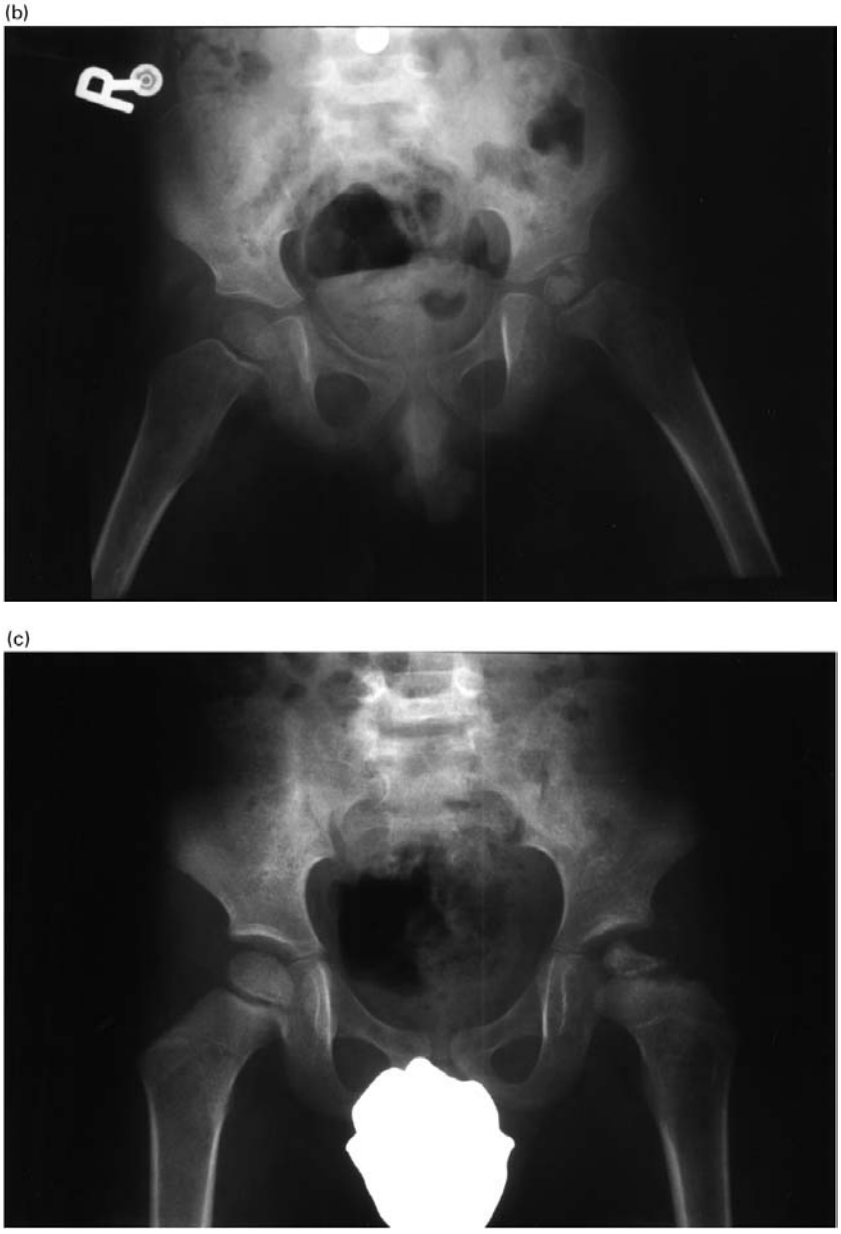


Figure 4 (b) Six weeks after open reduction, débridement, and application of abduction casts, the hip shows evidence of avascular necrosis and chondrolysis. (c) At 2 years post infection, the hip is moderately stiff but is nonpainful. The head has not yet reconstituted.

The differential diagnosis of a joint effusion in a child should include the inflammatory arthritides. Juvenile rheumatoid arthritis, human leukocyte antigen B27 (HLA-B27) disease, post streptococcal disease, and gout can all cause a monoarticular effusion that mimics septic joint. Inflammatory disease produces a joint aspirate with a cell count of 20,000 to 50,000/hpf, negative culture findings, and minimal systemic toxicity. A prodromal illness such as mononucleosis, sore throat, or documented streptococcus infection should also raise suspicions of inflammatory arthritis. Even if a noninfectious cause is strongly suspected, a joint fluid WBC count of greater than 50,000/hpf indicates immediate surgical drainage. Definitive diagnosis should be made in retrospect so that drainage of a possible septic joint is not delayed.

VII. PUNCTURE WOUNDS TO THE FOOT

Puncture wounds of the foot are common in children, and the foot is uniquely susceptible to penetrating trauma because of its weight bearing status. Multiple

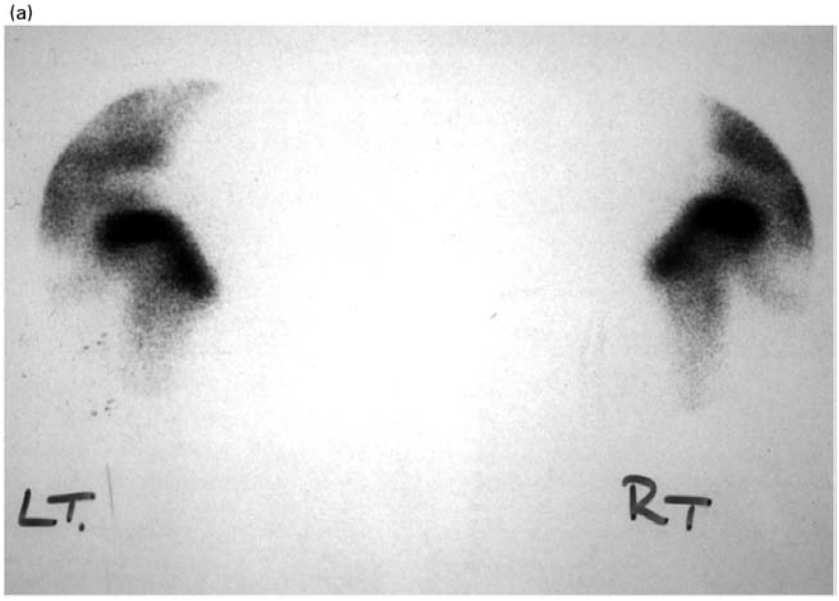


Figure 5 This 23-month-old boy refused to bear weight on his left leg. His erythrocyte sedimentation rate was 41 and his peripheral white blood cell count was 16,000. (a) Bone scan showed relative decreased uptake in the left femoral head when compared to that in the right. This was thought to be consistent with disruption of blood flow due to fluid under pressure in the hip joint.

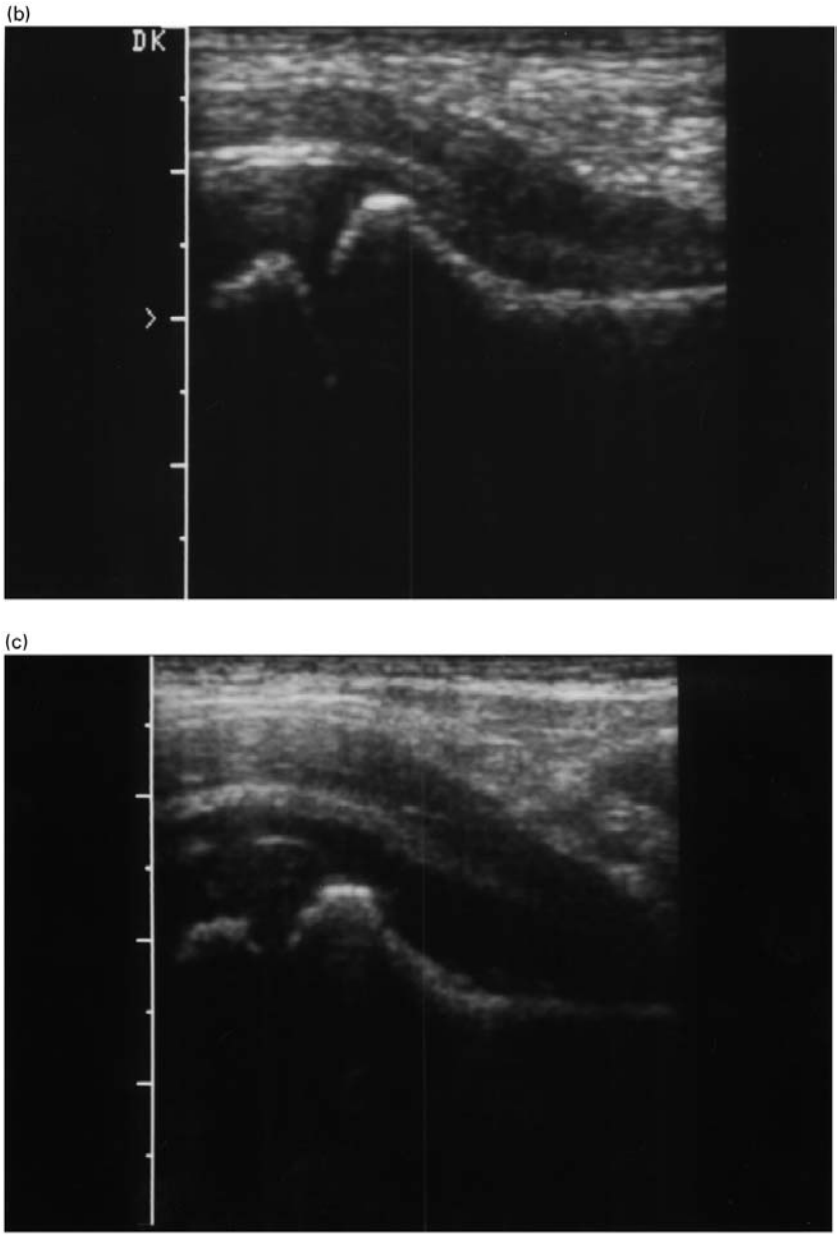


Figure 5 (b) Ultrasound of the left hip, however, yielded a negative finding for the presence of excess fluid. (c) Five days later, after the patient's symptoms had not improved, repeat ultrasound showed bulging of the capsule. Purulent fluid was tapped from the joint.

bones and joints are vulnerable to injury by foreign objects that often must traverse the septic environment of the sneaker before entering the foot. Thus, the bacterial milieu is also unique. *Pseudomonas* spp. and *S. aureus* are the two most common pathogens in these infections. The presentation is variable. If the patient seeks attention within a few hours after stepping on a foreign object, testing should be directed toward determining whether a residual foreign body is still present in the tissues. A radiograph should be obtained and the shoe should be inspected for missing fragments. A careful history should be taken to determine whether the offending object was withdrawn intact or whether it could have broken off in the foot. If a retained foreign body is suspected, formal débridement in the operating room is necessary. If a foreign body is not suspected, the wound may be débrided and irrigated under local anesthesia in the clinic or emergency room. Close follow-up is required. Prophylactic antibiotics should not be given, as there is a risk of selecting out *Pseudomonas* spp. if oral antistaphylococcals are administered.

If a patient seeks medical care several days after a puncture wound for a swollen, red, painful foot, radiographs should first be taken to search for any foreign body or bone involvement. Care should be taken to determine whether any of the joints of the foot is involved. Puncture wounds in the area of the metatarsal heads have a high likelihood of involving one of the metatarsophalangeal (MTP) joints. Pain on passive range of motion of the suspected joint establishes the need for a formal arthrotomy and débridement. Treatment should include débridement of the tract, curettement of the bone, irrigation and drainage of the infected joints or tendons, culture, and open packing of the wound. Antibiotics should be administered parenterally and should include adequate coverage for *Pseudomonas aeuriginosa* and *S. aureus* (42). The patient's tetanus immunization status should be investigated in every case of a puncture wound to the foot and prophylaxis should be administered if necessary (43).

VIII. SUMMARY

Osteoarticular infections are unique in children in that they are relatively common compared to those in adults and are usually hematogenous in origin. The unique characteristics are due to the specialized anatomical characteristics of the metaphyseal blood supply in the growing child. Because of their proximity to the physis, infections have the potential to cause long-term damage to the growing child. However, because of the exceptional healing powers of children, long-term sequelae are rare when proper diagnosis and treatment are initiated early. The ability to make the diagnosis rests on the combination of a high level of suspicion, a careful and complete history and physical examination, and the willingness to obtain blood and bone or marrow aspirate for culture. An under-

standing of the appropriate use of antibiotics, especially in terms of duration and method of administration, is critical.

REFERENCES

1. GM Sonnen, NK Henry. Pediatric bone and joint infections: diagnosis and antimicrobial management. Pediatr Clin North Am 43:933–947, 1996.
2. KM Song, JF Sloboda. Acute hematogenous osteomyelitis in children. J Am Acad Orthop Surg 9:166–175, 2001.
3. MAC Craigen, J Watters, JS Hackett. The changing epidemiology of osteomyelitis in children. J Bone Joint Surg 74B:541–545, 1992.
4. JP Dormans, DS Drummond. Pediatric hematogenous osteomyelitis: new trends in presentation, diagnosis and treatment. J Am Acad Orthop Surg 2:333–341, 1994.
5. J Trueta, JD Morgan. The vascular contribution to osteogenesis. I. Studies by the injection method. J Bone Joint Surg 42B:97–109, 1960.
6. T Hobo, Zur pathogenese de akuten haematogenen Osteomyelitis, mit Berucksichtigung der Vitalfarbungslehre. Acta Sch Med Univ Imp Kioto 4:1–29, 1922.
7. RT Morrissy, DW Haynes. Acute hematogenous osteomyelitis: a model with trauma as an etiologic agent (abstract). Kappa Delta Paper 2. American Academy of Orthopaedic Surgeons 51st Annual Meeting, Atlanta: 1984.
8. M De Jonghe, G Glaesener. Type B *Haemophilus influenzae* infection: experience at the pediatric hospital of Luxembourg. Bull Soc Sci Med Grand Duche Luxemb 132:17–20, 1995.
9. MR Ish-Horowicz, P McIntyre, S Nade. Bone and joint infections caused by multiply resistant *Staphylococcus aureus* in a neonatal intensive care unit. Pediatr Infect Dis J 11:82–87, 1992.
10. BF Morrey, HA Peterson. Hematogenous pyogenic osteomyelitis in children. Orthop Clin North Am 6:935–951, 1975.
11. RJ Scott, MR Chrtistofersen, WW Robertson Jr, RS Davidson, L Rankin, DS Drummond. Acute osteomyelitis in children: a review of 116 cases. J Pediatr Orthop 10:649–652, 1990.
12. LB Dali , AL Hoyland, J Dramsdahl, P1 Kaaresen. Acute osteomyelitis in children: a population-based retrospective study 1965–1994. Scand J Infect Dis 30:573–577, 1998.
13. CB Howard, M Einhorn, R Dagan, P Yagupski, S Porat. Fine-needle biopsy to diagnose osteomyelitis. J Bone Joint Surg 76B:311–314, 1994.
14. A Karwowska, HD Davies, T Jadavji. Epidemiology and outcome of osteomyelitis in the era of sequential intravenous-oral therapy. Pediatr Infect Dis J 17:1021–1026, 1998.
15. L Unkila-Kallio, M Kallio, H Peltola. The usefulness of C-reactive protein levels in the identification of concurrent septic arthritis in children who have acute hematogenous osteomyelitis. J Bone Joint Surg 76A:848–853, 1994.
16. WP Butt. The radiology of infection. Clin Orthop 96:20–30, 1973.

17. AG Jones, MD Francis, MA Davis. Bone scanning: radionuclide reaction mechanisms. Semin Nucl Med 6:3–18, 1976.
18. S Treves, J Khettry, FH Broker, RH Wilkinson, H Watts. Osteomyelitis: early scintigraphic detection in children. Pediatrics 57:173–186, 1976.
19. LD Russin, EV Staab. Unusual bone-scan findings in acute osteomyelitis: case report. J Nucl Med 17:617–619, 1976.
20. M Deysine, H Rafkin, I Teicher, L Silver, R Robinson, J Manly, AH Aufses Jr. Diagnosis of chronic and postoperative osteomyelitis with gallium 67 citrate scans. Am J Surg 129:632–635, 1975.
21. R Lisbona, L Rosenthall. Observations of the sequential use of ^{99m}Tc phosphate complex and ^{67}Ga imaging in osteomyelitis, cellulitis, and septic arthritis. Radiology 123:123–129, 1977.
22. SL Propst-Proctor, MF Dillingham, IR McDougall, D Goodwin. The white blood cell scan in orthopedics. Clin Orthop 168:157–165, 1982.
23. JP Kuhn, PE Berger. Computed tomographic diagnosis of osteomyelitis. Radiology 130:503–506, 1979.
24. PC Ram, S Martinez, M Korobkin, RS Breiman, HR Gallis, JM Harrelson. CT detection of intraosseous gas: a new sign of osteomyelitis. AMJ Am J Roentgenol 137:721–723, 1981.
25. SE Seltzer. Value of computed tomography in planning medical and surgical treatment of chronic osteomyelitis. J Comput Assist Tomogr 8:482–487, 1984.
26. LD Ma, FJ Frassica, DA Bluemke, EK Fishman. CT and MRI evaluation of musculoskeletal infection. Crit Rev Diagn Imaging 38:535–568, 1997.
27. WA Erdman, F Tamburro, HT Jayson, PT Weatherall, KB Ferry, RM Peshock. Osteomyelitis: characteristics and pitfalls of diagnosis with MR imaging. Radiology 180:533–539, 1991.
28. J Tehranzadeh, F Wang, M Mesgarzadeh. Magnetic resonance imaging of osteomyelitis. Crit Rev Diagn Imaging 33:495–534, 1992.
29. E Unger, P Moldofsky, R Gatenby, W Hartz, G Broder. Diagnosis of osteomyelitis by MR imaging. AJR Am J Roentgenol 150:605–610, 1988.
30. MT Modic, W Pflanze, DH Feiglin, G Belhobek. Magnetic resonance imaging of musculoskeletal infections. Radiol Clin North Am 24:247–258, 1986.
31. G Chierny, JT Mader. Adult chronic osteomyelitis. Orthopedics 7:1557–1564, 1984.
32. G Cierny, JT Mader. The surgical treatment of adult osteomyelitis. In: CMC Evarts, ed. Surgery of the Musculoskeletal System. New York: Churchill Livingstone, 1983:15–35.
33. JT Mader, M Ortiz, JH Calhoun. Update on the diagnosis and management of osteomyelitis. Clin Podiatr Med Surg 13:53–61, 1996.
34. HM Ericcson, JC Sherris. Antibiotic sensitivity testing: report of an international collaborative study. Acta Pathol Microbiol Scand 227(suppl B):1–90, 1971.
35. TR Tetzloff, GH McCracken, FD Nelson. Oral antibiotic therapy for skeletal infections in children. II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr 92:485–490, 1978.

36. JD Nelson. A critical review of the role of oral antibiotics in the management of hematogenous osteomyelitis. In: RS Remington, MN Swartz, eds. Current Clinical Topics in Infectious Diseases. Vol. 4. New York: McGraw-Hill, 1983:64–74.
37. W Lehnert, T Ulbrich. Specific toxicologic aspects of the quinolones. Rev Infect Dis 10(suppl l):141–146, 1988.
38. DG Mayer. Overyiew of toxicological studies. Drugs 34(suppl 1):150–153, 1987.
39. JM Roberts, DS Drummond, AL Breed, J Chesney. Subacute hematogenous osteomyelitis in children: a retrospective study. J Pediatr Orthop 2:249–254, 1982.
40. W Miller, W Murphy, L Gilula. Brodie abscess: reappraisal. Radiology 132:15–23, 1979.
41. EC Dunn, L Singer. Operative treatment of Brodie's abscess. J Foot Surg 30:443–445, 1991.
42. TA DeCoster, RA Miller. Management of traumatic foot wounds. J Am Acad Orthop Surg 2:226–230, 1994.
43. AS Inaba, DD Zukin, M Perro. An update on the evaluation and management of plantar puncture wounds and *Pseudomonas* osteomyelitis. Pediatr Emerg Care 8:38–44, 1992.

16
Antibiotic Activities and Toxicities

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I. INTRODUCTION

In order to understand antibiotic activity and toxicity, the antibiotics are grouped into categories based on their mechanisms of action. These categories include cell wall–active antibiotics, ribosomal-active antibiotics, ribonucleic acid– (RNA)-active antibiotics, deoxyribonucleic acid– (DNA)-active antibiotics, antimetabolites, and the reducing compounds.

The initial choice of antibiotics for gram-positive, gram-negative, and anaerobic organisms is shown in Tables 1, 2, and 3. The initial antibiotic regimen is modified, if necessary, by culture and sensitivity results.

II. CELL WALL–ACTIVE ANTIBIOTICS

The cell wall–active antibiotics include penicillins, β-lactamase inhibitors, cephalosporins, other β-lactam antibiotics, and vancomycin.

A. Penicillins

The penicillin class of antibiotics is frequently used for the treatment of musculoskeletal infections. The penicillins can be divided into general groups

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Table 1 Gram-Positive Organisms: Initial Choice of Antibiotics for Therapy (Adult Dosages)

Organism	Antibiotics of first choice	Alternative antibiotics
Methicillin-sensitive		
Staphylococcus aureus	Nafcillin 2 g q4h or clindamycin 900 mg q8h	Cefazolin Vancomycin
Coagulase-negative *Staphylococcus* sp.	Nafcillin 2 g q6h or clindamycin 900 mg q8h	Cefazolin Vancomycin
Methicillin-resistant		
Staphylococcus aureus	Vancomycin 1 g q12h or linezolid 600 mg q12h	SMZ-TMP[a] or minocycline ± rifampin
Coagulase-negative *Staphylococcus* sp.	Vancomycin 1 g q12h or linezolid 600 mg q12h	SMZ-TMP[a] or minocycline ± rifampin, clindamycin[b]
Group A streptococcus *Strep. pyogenes*	Penicillin G2 × 10^6 u q4h or ampicillin 2 g; q6h	Clindamycin, cephalosporin vancomycin
Group B streptococcus *Strep. agalactiae*	Penicillin G2 × 10^6 u q4h or ampicillin 2 g q6h	Clindamycin, cephalosporin vancomycin
Sensitive		
Strep. pneumoniae	Penicillin G2 × 10^6 u q4h	Clindamycin, erythromycin,
Intermediate		
Strep. pneumoniae	Cefotaxime 1 g q8h Erythromycin	Clindamycin
Resistant		
Strep. pneumoniae	Vancomycin 1 g q12h or levofloxacin 500 mg/day	Quinupristin & dalfopristin Linezolid
Sensitive		
Enterococcus sp.	Ampicillin 1 g q6h[c] vancomycin 1 g q12h	Ampicillin-sulbactam Linezolid
Resistant		
Enterococcus faecium	Quinupristin/dalfopristin 7.5 mg/kg q8h Linezolid 600 mg q12h	Chloramphenicol and rifampin

[a] Sulfamethoxazole-trimethoprim.
[b] If sensitive to clindamycin.
[c] In a serious *Enterococcus* spp. infection, ampicillin plus an aminoglycoside is used.

Table 2 Gram-Negative Organisms: Initial Choice of Antibiotics for Therapy (Adult Dosages)

Organism	Antibiotics of first choice	Alternative antibiotics
Acinetobacter sp.	Ceftazidime 1 g q8h + levofloxacin 500 mg/day or imipenem 500 mg q6h	Ampicillin-sulbactam
Enterobacter sp.	Cefotaxime 1 g q6h or imipenem 500 mg q6h	Levofloxacin, mezlocillin, ticarcillin-clavulanate
Escherichia coli	Ampicillin-sulbactam 3 g q6h	Cefazolin, levofloxacin, gentamicin, SXT[a]
Haemophilus influenzae	Cefotaxime 1 g q8h or ampicillin-sulbactam 3 g q6h	Levofloxacin, SMZ-TMP[a] ampicillin,[b] azithromycin
Klebsiella sp.	Cefotaxime 1 g q6h or levofloxacin 500 mg/day	Ampicillin-sulbactam gentamicin
Proetus mirabilis	Ampicillin 1 g q6h or levofloxacin 500 mg/day	Cefazolin, SMZ-TMP[a] Gentamicin
Proteus vulgaris *Proteus rettgeri* *Morganella morganii*	Cefotaxime 2 g q8h or imipenem 500 mg q6h or levofloxacin 500 mg/day	Mezlocillin, gentamicin ticarcillin-clavulanate
Neisseria gonorrhoeae	Cefriaxone 125 mg, IM once + azithromycin 1 g PO once	Levofloxacin and azithromycin
Providencia sp.	Cefotaxime 2 g IV qh or levofloxacin 500 mg/day	SMZ-TMP,[a] amikacin, imipenem
Pseudomonas aeruginosa	Cefepime[c] 2 g q12h or piperacillin[c] 3 g q6h or imipenem 500 mg q6h	Ticarcillin-clavulanate, tobramycin, amikacin, ciprofloxacin[d]
Serratia marcescens	Cefotaxime 2 g q6h	Levofloxacin, gentamicin, imipenem

[a] Sulfamethoxazole-trimethroprim.
[b] Non-β-lactamase-producing strain of *H. influenzae*.
[c] In a serious infection should be used with an aminoglycoside: gentamicin or tobramycin 5 mg/kg/day q8.
[d] Increasing resistance to the quinolones including ciprofloxacin.

Table 3 Anaerobic Organisms: Initial Choice of Antibiotics for Therapy (Adult Dosages)

Organism	Antibiotic of first choice	Alternative antibiotics
Bacteroides fragilis group	Clindamycin 900 mg q8h or metronidazole 500 mg q8h	Ampicillin-sulbactam, ticarcillin-clavulanic acid
Prevotella sp.	Clindamycin 900 mg q8h or metronidazole 500 mg q8h	Ampicillin-sulbactam, cefotetan
peptostreptococcus sp.	Penicillin G 2×10^6 U q4h or clindamycin 900 mg q8h	Clindamycin, metronidazole
Clostridium sp.	Clindamycin 900 mg q8h or penicillin G 2×10^6 U q4h	Ampicillin-sulbactam, metronidazole

on the basis of their antibacterial activity. The major penicillin groups of interest to an orthopedic surgeon are natural penicillins, aminopenicillins, penicillinase-resistant penicillins, antipseudomonal penicillins (carboxypenicillins), and extended-spectrum penicillins (ureidopenicillins). Overlap among these groups exists; the differences are usually pharmacological in nature.

The major side effects of all the penicillins are hypersensitivity reactions that range in severity from rash to anaphylaxis (1). Immediate hypersensitivity reactions occur in 0.0004%–0.15% of patients, urticaria occurs in 1%–5% of these cases, and rash occurs in 2%–9%. Hemolytic anemia and central nervous toxicities can also occur with penicillin administration. Serum sickness rarely occurs with penicillins. Additionally, exfoliative dermatitis and erythema multiforme are rare forms of allergic reactions to penicillin.

Penicillin G is the major natural penicillin. Although penicillin G has a half-life of 30 to 60 minutes, it can be combined with procaine or benzathine to produce a repository penicillin. Penicillin is the drug of choice for the treatment of *Streptococcus pyogenes*, *Strep. agalactiae*, and *Clostridium perfringens*. In addition, penicillin has a good anaerobic spectrum of activity except for the *B. fragilis* group. *Strep. pneumoniae* continues to become more resistant to penicillin. Currently, *Strep. pneumoniae* has an intermediate resistance of 15% and a high-level resistance of 15% to penicillin.

The major side effects of the natural penicillins are immediate hypersensitivity reactions with anaphylaxis, bronchospasm, and hives and delayed reactions including skin rashes (2). Other potential side effects are renal failure, Coombs' test–positive hemolytic anemia, and seizure activity, which usually occurs with aqueous penicillin doses greater than 20 million units per day.

The parenteral penicillinase-resistant penicillins are methicillin, nafcillin, and the isoxazolyl penicillins (including oxacillin, cloxacillin, dicloxacillin, and

flucloxacillin). The most active parenteral semisynthetic penicillins are nafcillin and oxacillin. These drugs are resistant to staphylococcal β-lactamase and are used when methicillin-sensitive *S. aureus* is present or suspected. The semisynthetic penicillins are also active against *Strep. pyogenes* and *Strep. pneumoniae*. However, they have no activity against *Enterococcus* sp. or gram-negative bacilli.

Methicillin is associated with the greatest potential for producing intersitial nephritis (3). Nafcillin and oxacillin may cause interstitial nephritis, leukopenia, and reversible hepatic dysfunction (4,5). Cloxacillin and dicloxacillin are the oral semisynthetic penicillins of choice in the United States and have fewer side effects than the parenteral semisynthetic penicillins.

The major aminopenicillins include ampicillin and amoxicillin. Ampicillin may be given parenterally or orally, whereas amoxicillin is only an oral agent. The antibacterial activity of the aminopenicillins is similar. They are the antibiotics of choice for the treatment of the *Enterococcus* spp. (*E. faecalis*, *E. faecium*) (6). The aminopenicillins are also active against many highly susceptible gram-negative rods, such as *Escherichia coli* and *Proteus mirabilis*. They are not stable to β-lactamase and are less active than penicillin G against *Strep. pyogenes* and *Strep. agalactiae*. The aminopenicillins may cause skin rashes; an idiosyncratic rubella-form rash occurs in 99% of the patients who have mononucleosis and are given the aminopenicillins.

Ticarcillin (carboxypenicillin) is an antipseudomonal penicillin. Ticarcillin has a β-lactam ring and is susceptible to β-lactamase of both gram-positive and gram-negative organisms. Ticarcillin has a gram-negative spectrum of activity similar to that of ampicillin but is more active than ampicillin against *Pseudomonas* sp., *Enterobacter* sp., *Serratia* sp., and certain strains of the *B. fragilis* group. Ticarcillin has poor activity against *Klebsiella* sp. (7). The side effects of this class of penicillins include sodium loading and bleeding problems secondary to platelet dysfunction (8).

The extended-spectrum penicillins (ureidopenicillins) include mezlocillin and piperacillin. These penicillins have an antibacterial spectrum similar to that of ticarcillin. In vitro, these antibiotics are active against *Enterococcus* sp., and *Streptococcus* sp. and inhibit the majority of *Klebsiella* spp. They are also more active than ticarcillin against *Haemophilus influenzae* and the *B. fragilis* group (9,10). These drugs act in synergy with the aminoglycosides against *Pseudomonas aeruginosa* and most of the Enterobacteriaceae. They have the same side effects as ticarcillin, except that they cause less sodium loading and bleeding dysfunction.

Penicillins as a group have a number of drug interactions. However, generally, these interactions are uncommon. The carboxypenicillins and ureidopenicillins inactivate the aminoglycosides (11,12). This drug interaction is seen in those patients who have underlying renal dysfunction (13,14). Probenecid inhibits tubular secretion of the penicillins and increases the drug half-life of these agents (15).

B. β-Lactamase Inhibitors

Clavulanic acid, sulbactam, and tazobactam are potent inhibitors of β-lactamase produced by gram-positive and gram-negative organisms (16). β-Lactamase of gram-positive species is an exoenzyme. Clavulanic acid, sulbactam, and tazobactam have been shown to inhibit β-lactamase for a number of clinically important gram-positive organisms including *S. aureus* and *S. epidermidis* (17). β-Lactamase of both gram-negative and most anaerobic organisms is situated in the periplasmic space and is chromosome- and plasmid-encoded (18). Clavulanic acid, sulbactam, and tazobactam inhibit β-lactamase of many gram-negative organisms, including most *E. coli*, *Klebsiella* sp., and *Bacteroides* sp. Currently, clavulanic acid is commercially available with amoxicillin (Augmentin) and ticarcillin (Timentin). Sulbactam is available with ampicillin (Unasyn). Tazobactam is combined with piperacillin (Zosyn). The β-lactam inhibitors enhance the gram-positive coverage and, to a lesser extent, the gram-negative spectrum of these antibiotics. The side effects are the same as those of the penicillin class of antibiotics.

C. Cephalosporins

The cephalosporins have been divided into first-, second-, third-, and fourth-generation agents. The first-generation cephalosporins, which include cephalothin, cephapirin, sodium, cephradine, and cefazolin, are active against *S. aureus*, *S. epidermidis*, and *Streptococcus* spp. They have limited gram-negative activity but are active against *E. coli*, *Klebsiella* sp., and *P. mirabilis*. The first-generation cephalosporins are safe antibiotics but are occasionally associated with the production of allergic reactions, drug eruptions, phlebitis, and diarrhea. Cefazolin is the first-generation cephalosporin used by the orthopedic community for the treatment of staphylococcal infections including osteomyelitis. The large amounts of β-lactamase produced by *S. aureus* (10^9 organisms/tissue) will inactivate cefazolin (19). However, high numbers of *S. aureus* are not the norm in staphylococcal osteomyelitis: 10^5 or fewer organisms per gram of bone are usually found. Cefazolin has a longer half-life and higher serum concentration than the other first generation cephalosporins (20). The remainder of the first-generation cephalosporins are comparable. They are all more stable to β-lactamase than cefazolin.

There are many second-generation cephalosporins, the major parenteral ones include cefamandole, cefoxitin, cefotetan, and cefuroxime. The major oral ones include cefuroxime, cefprozil, and loracarbef. The second-generation cephalosporins have somewhat greater activity against gram-negative organisms as compared to the first generation but are less active than the third-generation agents. Cefoxitin and cefotetan are more active than the other first- or second-

generation cephalosporins against the anaerobes, especially the *B. fragilis* group (21). The second-generation cephalosporins have the same toxicity potential as the first-generation cephalosporins with the exception of those that have a methylthiotetrazole (MTT) side chain.

The major third-generation cephalosporins include cefotaxime, ceftriaxone, ceftizoxime, cefoperazone, and ceftazidime. The third-generation cephalosporins are generally less active than the first-generation cephalosporins against gram-positive organisms but are more active against the Enterobacteriaceae (22). Cefotaxime, ceftriaxone, and ceftizoxime are third-generation cephalosporins with similar antibacterial activity. They are highly resistant to β-lactamase and have activity against gram-positive organisms with the exception of the *Enterococcus* spp. They have good activity against most gram-negative organisms except *Peudomonas aeruginosa*. Cefotaxime, ceftizoxime, and ceftriaxone have half-lives of 1.1, 1.7, and 8 hours, respectively.

Ceftazidime is similar in activity to cefotaxime, ceftizoxime, and ceftriaxone against the Enterobacteriaceae, but it has superior activity against *Pseudomonas aeruginosa* (23). For serious *Pseudomonas aeruginosa* infections it should be combined with an aminoglycoside (24). Ceftazidime is half as active against gram-positive organisms as are cefotaxime, ceftizoxime, and ceftriaxone.

The fourth-generation cephalosporins are represented by cefepime. Cefepime has excellent activity against aerobic gram-positive organisms including methicillin-sensitive *S. aureus* and gram-negative organisms including *Pseudomonas aeruginosa*. In vitro data suggest increased activity of cefepime against multiresistant *Enterobacter* spp. Like other cephalosporins, cefepime has no activity against *Enterococcus* spp.

In general, the cephalosporins have a low incidence of adverse reactions. There is a cross-reactivity of 3% to 7% in those patients who are allergic to penicillin. This may be a true cross-reactivity (allergy) or those patients may be more allergenic. The allergic reactions to the cephalosporins include a type one immediate hypersensitivity reaction that includes bronchospasm, hives, and skin rashes that occur 3 to 5 days after the initiation of therapy. Fever, lymphadenopathy, eosinophilia, and serum sickness reactions may also occur. The cephalosporins cause a Coombs' test–positive anemia in approximately 3% of patients. Neutropenia occurs in approximately 1% of patients, usually after 3 weeks of the therapy. Liver function abnormalities, with liver enzyme level elevation, occur in 1% to 7% of patients. Antibiotic-associated colitis is associated with cephalosporin administration as well.

Some second- and third-generation cephalosporins have the MTT side chain. These include cefotetan and cefamandole (second generation) and moxalactam disodium and cefoperazone (third generation). Antibiotics with the MTT side chain can cause a disulfiram-like reaction when a patient drinks alcohol (25–29) and are also associated with hypoprothrombinemia (30–34).

The cephalosporins have very few reported drug-drug and drug-food interactions.

D. Other β-Lactam Antibiotics

Aztreonam is a monocyclic β-lactam antibiotic, which is active against most Enterobacteriaceae, *Pseudomonas aeruginosa* (35–37), all *Neisseria meningitidis*, *N. gonorrhoeae* (36), β-lactamase, and non-β-lactamase-producing strains of *H. influenzae* (37). Aztreonam has no appreciable antibacterial activity against aerobic gram-positive or anaerobic bacteria.

Aztreonam may be administered intramuscularly or intravenously; absorption after oral administration is poor. The serum half-life in patients with normal renal function is 1.5 to 2.1 hours (38). The serum half-life in anephric patients is 6 to 8 hours (39).

Aztreonam has been effective in the treatment of gram negative osteomyelitis (40,41). It has also been successful in treating mixed soft tissue infections in combination with clindamycin.

No major adverse reactions have been reported with this antibiotic (42,43). Minor reactions with aztreonam include nausea, vomiting, and diarrhea. On occasion the drug may cause elevated liver transaminase levels. Aztreonam has a low probability of cross-reactivity (allergy) in penicillin- or cephalosporin-allergic patients.

Imipenem is an antimicrobial agent belonging to the β-lactam class of antibiotics. Biochemically, it is a carbapenem. Imipenem has excellent in vitro activity against aerobic gram positive organisms including *S. aureus*, *S. epidermidis*, and *Streptococcus* spp. Imipenem has excellent gram-negative activity against the Enterobacteriaceae and *Pseudomonas aeruginosa*, among others. Imipenem also inhibits most anaerobic species including the *B. fragilis* group (44). The broad antimicrobial spectrum of imipenem is attributable to its low rate of hydrolysis by β-lactamases.

The serum half-life is approximately 1-hour. When impinem is administered every 6 hours to patients with normal renal function, serum levels do not accumulate (45).

Imipenem has been shown to be effective in the treatment of mixed soft tissue infections, diabetic foot infections, and osteomyelitis (46,47). Nausea, vomiting, and diarrhea may occur with imipenem therapy. Penicillin cross-reactivity occurs with imipenem. Grand mal seizures occur in 1% to 4% of the patients receiving this antibiotic. The incidence of seizures is increased among patients who have renal dysfunction (48,49) and/or a history of seizure activity. Finally, resistance of *Pseudomonas aeruginosa* and fungal superinfection may develop during therapy.

E. Meropenem

Meropenem is a carbapenem that is a derivative of thienamycin. In general, meropenem is slightly more active than imipenem in vitro against aerobic, gram-negative bacilli and slightly less active against aerobic gram-positive cocci (50). There are no significant differences between anaerobes except that meropenem is less active against *C. difficile* (50,51).

The pharmacokinetic properties of meropenem are similar to those of imipenem. In clinical tnals, there are similar outcomes in skin structure infections (52). The side effects of meropenem are less than those of imipenem. Meropenem produces fewer seizures, less nausea and vomiting, and less severe inflammation at the intravenous administration site.

F. Vancomycin

Vancomycin exerts its main bactericidal effect by inhibiting the biosynthesis of the major structural polymer of the bacterial cell wall, peptidoglycan (53).

Vancomycin has excellent activity against *S. aureus*, *S. epidermidis*, and *Enterococcus* spp. It is the antibiotic of choice for individuals who are unable to tolerate either the penicillins or the cephalosporins (54). Vancomycin is also the antibiotic of choice for the treatment of methicillin-resistant *S. aureus* (55), coagulase-negative *Staphylococcus* spp. (56), and cellulitis and osteomyelitis (57–59).

Vancomycin is given only by the intravenous route for systemic infections. Fifty to sixty percent of this drug is bound to serum albumin. The drug has a plasma half-life of about 6 to 10 hours in neonates, 4 hours in older infants, 2 to 3 hours in children, and 4 to 8 hours in normal adults. The usual intravenous dose of vancomycin is 500 mg every six hours or 1 g every 12 hours in adults with good renal function. The bone-to-serum ratio of vancomycin concentration of 10% increases to 20%–30% in infected bone (60).

The postantibioitic effect relates to the ability of an antimicrobial agent to suppress bacterial regrowth for a period after limited exposure to the drug. Studies with vancomycin suggest that the duration of the in vitro postantibiotic effect is about 1.5 to 3 hours against *S. aureus* (61,62), but the actual in vivo postantibiotic effect may be longer.

Hemodialysis removes small amounts of vancomycin, with a mean elimination half-life of 7.5 days. Recommended dosage for hemodialysis patients is an initial 1-g load followed by 500 mg every 8 days (63). Peritoneal dialysis may reduce serum concentrations by 35–40% (64). Vancomycin should be administered over 30–60 minutes to prevent toxicity.

Reports in 1978 of vancomycin-resistant *Enterococcus* spp. (56) dictate increased vigilance and caution (57,58).

When vancomycin is used as monotherapy, end-organ toxicity is minimal. The "red-man syndrome" (65,66) may be observed with vancomycin therapy. This syndrome includes flushing of the head, neck, and upper torso and is often associated with hypotension. It occurs in 5% to 13% of patients, especially when the infusion is given for less than 1 hour. Allergic reactions rarely occur with vancomycin therapy. Vancomycin may be associated with nephrotoxicity (67–70) or ototoxicity, especially when given concurrently with the aminoglycoside. Vancomycin may also cause neutropenia (71,72) and thrombocytopenia (73,74).

III. RIBOSOMAL–ACTIVE ANTIBIOTICS

The ribosomal-active antibiotics include clindamycin; macrolides, including quinupristin/dalfopristin; tetracyclines; oxazolidinones; and aminoglycosides.

A. Clindamycin

Ciindamycin is one of the most active antibiotics against clinically significant anaerobic bacteria, particularly the *B. fragilis* group. However, clindamycin is ineffective against 10% to 20% of clostridial species other than *C. perfringens* (75). In addition to its anaerobic activity, clindamycin is effective against *S. aureus*, coagulase-negative *Staphylococcus* spp., and the *Streptococcus* spp.

Clindamycin is absorbed rapidly and almost completely after oral administration. It has a half-life of 2.4 hours and is ideally given every 8 hours (76). Clindamycin demonstrates good penetration into most tissues including bone (77) and penetrates well into abscesses (78). Clindamycin accumulates in polymorphonuclear leukocytes, alveolar macrophages, and abscesses (78). Bone, joint capsule, and synovial fluid concentrations of clindamycin were approximately 40%–45% of serum concentrations in one study (79), and its activity appears to be the same regardless of bone type (cortical or cancellous).

Clindamycin is relatively nontoxic but may cause diarrhea and pseudomembranous colitis in approximately 8% of patients (80). Of those patients in whom antibiotic-associated diarrhea develops, 10% experience pseudomembranous colitis secondary to toxin produced by the overgrowth of *Clostridium difficile*. Hypersensitivity reactions, including rashes, urticaria, and erythema multiforme, may occur with clindamycin administration. Clindamycin drug interactions are rare, but clindamycin may potentiate action of the neuromuscular blocking agents (81–83).

B. Macrolides

Erythromycin is the prototype of the macrolide class of antibiotics (84). These agents work at the ribosomal level and are bacteriostatic. Erythromycin has in vitro activity against *Streptococcus* spp., *Listeria monocytogenes*, *Moraxella catarrhalis*, *Mycobacterium pneumoniae*, *Legionella pneumophila*, and *Chlamydia pneumoniae*. The new macrolides (clarithromycin and azithromycin) can inhibit *M pneumoniae*, *Legionella* spp., and *Chlamydia pneumoniae* at lower concentrations. They are also more active against *H. influenzae*, *Mycobacterium avium-intracellulare* (MAI), and other atypical mycobacteria. The new macrolides are active against the agent of Lyme disease, *Borrelia burgdorferi*. Because of its high intracellular concentration, azithromycin is more active against *C. trachomatis* and *Toxoplasmosis gondii*, and clarithromycin is very active against *Helicobacter pylori*. The macrolides are indicated for the treatment of upper and lower respiratory tract infections and skin structure infections. The new macrolides are agents of choice for *Mycobacterium avium-intracellulare* infections.

The peak serum concentration of azithromycin after a 500-mg dose is approximately 0.4 μg/mL, fivefold lower than that of a comparable dose of clarithromycin. However, tissue concentrations are significantly higher. The terminal half-life of azithromycin exceeds 40 hours, allowing once-daily dosage, whereas clarithromycins's half-life of 4 to 5 hours requires twice-daily dosage (85).

The macrolides are generally considered to be very safe drugs. The macrolide antibiotics have the propensity to cause gastrointestinal reactions including nausea, vomiting, and abdominal cramps in approximately 20% of patients. These problems are less frequent with newer erythromycins such as azithromycin and clarithromycin. The macrolides have a number of drug interactions. They stimulate bepatic microsomal activity with cytochrome P-450 complexes. This stimulation causes increased levels of theophylline, warfarin, cyclosporin, carbamazepine, and cisapride. Azithromycin has the least drug interaction potential of the macrolides.

C. Quinupristin/Dalfopristin

Quinupristin/dalfopristin (Synercid) is a fixed combination of two streptogramins in a ratio of 30 : 70. This antibiotic produces in vitro inhibitory and bactericidal activity against most gram-positive organisms, including vancomycin-resistant *Enterococcus faecium* (86).

Quinupristin/ dalfopristin acts at different sites on the ribosome and inhibits protein synthesis. The recommended dosage is 7.5 mg/kg every eight hours intravenously. No adjustments are necessary for patients with renal or

hepatic impairment (87). This drug combination has a postantibiotic effect of 6 to 8 hours.

In two prospective studies with 396 patients with *E. faecium* infections that included bacteremia, intra-abdominal and urinary tract infections, catheter-related bacteremia, and skin infections, quinupristin & dalfopristin had a clinical success rate of 73.6%, a bacteriological rate of 70.5%, and a favorable safety profile (88).

Quinupristin/dalfopristin also has a role in the treatment of methicillin-resistant *S. aureus* and coagulase-negative *Staphylococcus* spp. infections in patients who cannot tolerate vancomycin therapy. Adverse reactions to quinupristin & dalfopristin appear to be mild; they include self-limited, but local, reactions such as itching, pain, and burning, as well as vomiting and diarrhea (84,87). The major side effect is phlebitis, especially in the smaller veins. The antibiotic should be given into a central line. The drug causes severe myalgia (89) in approximately 15% to 20% of the patients receiving this antibiotic.

D. Tetracyclines

The tetracyclines are divided into three groups: the short-acting compounds (chlortetracycline, oxytetracycline, tetracycline), an intermediate group (demeclocycline), and the more recently developed longer-acting group (doxycycline and minocycline). The tetracyclines are primarily bacteriostatic. They are useful drugs for the treatment of relatively uncommon diseases including brucellosis and granuloma inguinale. Tetracyclines are also active against mycoplasma, rickettsia, and Lyme disease (*Borrelia burgdorferi*). The tetracyclines are also useful in the treatment of chlamydial diseases including lymphogranuloma venereum, psittacosis, and trachoma. Minocycline is the most active drug of the tetracycline class against *Staphylococcus aureus*. Minocycline is often used in combination with rifampin for the oral treatment of methicillin-resistant *S. aureus* and coagulase-negative *Staphylococcus* spp.

The tetracyclines have excellent tissue distribution, probably because of their high lipid solubility. Minocycline is the most lipid-soluble tetracycline. The high lipid solubility and diffusion make it useful for the treatment of metabolically inactive organisms. Tetracyclines accumulate in bone.

Most tetracyclines should be avoided by patients with renal insufficiency, because substantial increases in serum levels as a result of diminished renal filtration may lead to hepatotoxicity. Because of the long elimination half lives of doxycycline and minocycline, once- or twice-daily dosage is possible.

The tetracyclines have significant side effects including anorexia, nausea, vomiting, and diarrhea. Tetracyclines also cause hepatotoxicity, especially in pregnant females. The tetracyclines should not be given to children less than 12 years of age. Tetracycline administration in this age group causes gray-brown-yellowish discoloration of teeth and may impair bone growth. Tetracyclines are

catabolic and aggravate preexisting renal failure. Tetracyclines have a propensity to cause major photosensitivity reactions. Other side effects include esophageal ulcers and hypersensitivity reactions. Minocycline causes vestibular toxicity in some patients.

Tetracycline antibiotics have a number of drug interactions. Divalent metals including calcium, magnesium, and aluminum (antiacids) (90–92), when given concurrently, lead to decreased absorption of the tetracycline. A number of drugs produce an increase of the hepatic metabolism of the tetracyclines, which causes a decreased half-life of this class of antibiotics.

E. Oxazolidinones

The oxazolidinones (linezolid and eperezolid) (93,94) are a new synthetic class of antimicrobials. These agents have bacteriostatic activity against a number of important organisms including methicillin-resistant *S. aureus*, penicillin-resistant *Streptococcus pneumoniae*, and vancomycin-resistant *Enterococcus* spp. (95).

Linezolid works by inhibiting the initiating complex at 30S ribosome early in protein synthesis (93). It has efficacy when administered either parenterally or orally, of a dosage of 400 mg every 12 hours. The drug is eliminated by the kidney and has a 1-hour postantibiotic effect. Linezolid is currently being used in clinical trials for gram-positive pneumonia, bacteremia, and skin structure infections.

Side effects include nausea, vomiting, diarrhea, skin rash, and an increase in liver and renal function test results.

F. Aminoglycosides

The aminoglycosides include gentamicin, tobramycin, amikacin, and netilmicin. The aminoglycosides are the standard by which other antibiotics are measured for the treatment of aerobic gram-negative infections. The aminoglycosides generally have poor activity against gram-positive organisms. Initially, they may be used for the treatment of *S. aureus*, but resistance may develop rapidly (96,97). They have no effect against the *Streptococcus* spp. or anaerobes. The aminoglycosides have excellent activity against the Enterobacteriaceae and *Pseudomonas aeruginosa*. The aminoglycosides may be inactivated by enzymatic modification. Amikacin has fewer available sites than the other aminoglycosides for enzymatic inactivation. Consequently, the percentage of strains susceptible to amikacin is greater than for tobramycin. gentamicin, or netilmicin (98). There is no evidence to support amikacin's having greater or lesser activity than the other aminoglycosides.

Aminoglycosides cannot be administered orally because of poor oral absorption; therefore, parenteral administration is necessary to achieve adequate serum concentrations. Aminoglycosides have a volume of distribution that

approximates the extracellular space (99,100). An alteration in the extracellular fluid compartment (such as in the presence of congestive heart failure, dehydration, or ascites) results in a change in the volume of distribution that may require dosage modification. In adults with normal renal function, each aminoglycoside has approximately a 2-hour serum half-life. The half-life increases in patients with deteriorating renal function and may exceed 24 hours in patients with end-stage renal failure (101). Aminoglycosides are effectively removed by hemodialysis (102), and less by peritoneal dialysis (103). Low concentrations of aminoglycosides that are found in purulent fluids (characterized by low pH and oxygen tension) are probably due to local inactivation by deoxyribonucleic acid (DNA) released by leukocytes (104). Aminoglycosides usually achieve reasonable concentrations in bone and synovial fluid.

Currently, once-daily dosage of aminoglycosides is the norm, especially to people above 65 years of age. There are three meta-analyses of clinical trials comparing the efficacy of single daily dosages of the aminoglyeosides, which show no differences in clinical outcomes. There was decreased toxicity with single daily dosage. There are also multiple other studies and reviews on this subject (105–109). With a single daily dosage, trough levels should be obtained 18 hours after the second dose. Single daily dosage reduces the cost of therapy and allows for easier outpatient therapy (105–109).

The toxicity of the aminoglycosides includes nephrotoxicity and ototoxicity. Ototoxicity reactions include hearing loss, tinnitus, ear fullness, and vestibular problems including nausea, vomiting, vertigo, nystagmus, and difficulty with gait. Other aminoglycoside toxicities include neuromuscular blockade and hypersensitivity reactions.

The aminoglycosides have some drug interactions. There is an increase in nephrotoxicity and ototoxicity when cyclosporin, vancomycin, amphotericin B, ethacrynic acid, neuromuscular blocking agents, nonsteroidal, and radiographic contrast agents are given concurrently with the aminoglycosides.

IV. RIBONUCLEIC ACID–ACTIVE ANTIBIOTICS

The RNA-active antibiotic is rifampin.

A. Rifampin

Rifampin exhibits bactericidal activity against a wide variety of gram-positive and gram-negative organisms. Rifampin is the most active antistaphylococcal agent known (110). However, rifampin has less activity than the aminoglycosides against most gram-negative bacteria. When rifampin is used alone for the treatment of bacterial infections, a rifampin-resistant subpopulation rapidly

develops (111). Expression of rifampin resistance can be lessened by the addition of a second effective antibiotic. Rifampin in combination with a semisynthetic penicillin has been used to treat methicillin-sensitive *Staphylococcus* spp. osteomyelitis. Trimethoprim-sulfamethoxazole and minocycline plus rifampin have been used to treat methicillin-resistant *Staphylococcus* spp. osteomyelitis.

Peritoneal dialysis and hemodialysis do not appreciably eliminate rifampin. Rifampin is highly lipid-soluble and widely distributed into most body tissues and fluids, including synovial fluid and bone (112).

Rifampin has been used in combination with cloxacillin, vancomycin, minocycline, and trimethoprim-sulfamethoxazole to prevent the emergence of resistance. Rifampin and cloxacillin have been effective in interrupting the course of recurrent staphylococcal furunculosis (113).

Side effects of rifampin include orange-red discoloration of body fluids, gastrointestinal symptoms, hepatitis, and possibly mild immunosuppression. There are a number of rifampin drug interactions (114–116). The coadministration of rifampin with isonicotinic acid hydrazide (INH) leads to a higher rate of hepatotoxicity (117). Coadministration of rifampin with ketoconazole (118) can result in a failure of either drug. Food interferes with the absorption of rifampin, and this antibiotic must be taken on an empty stomach. Rifampin induces hepatic microsomal enzymes and can decrease the level of certain drugs (Table 4). Patients using these medications must be carefully monitored and have their drug dosages adjusted when indicated.

V. DEOXYRIBONUCLEIC ACID–ACTIVE ANTIBIOTICS

The DNA-active antibiotics are the fluoroquinolones.

Table 4 Rifampin Drug Interactions

Rifampin induces hepatic microsomal enzymes and can decrease the effect of the following drugs:

Acetaminophen	Oral anticoagulants	Barbiturates
Benzodiazepines	Beta-blockers	Chloramphenicol
Clofibrate	Oral contraceptives	Corticosteroids
Cyclosporin	Digitoxin	Disopyramide
Digoxin	Enalapril	Estrogens
Hydrantoins	Methadone	Mexiletine
Quinidine	Sulfones	Solfonylureas
Theophyllines	Tocainide	Verapamil

A. Fluoroquinolones

The quinolones are divided into four generations. The first-generation quinolone nalidixic acid is used to treat urinary tract infections. The second-, third-, and fourth-generation quinolones may be used to treat musculoskeletal infections including osteomyelitis (119).

The second-generation quinolones include ciprofloxacin and ofloxacin. Ciprofloxacin and ofloxacin provide adequate serum, tissue, and urine concentrations. Ciprofloxacin and ofloxacin have efficacy against most gram-negative organisms. Most streptococcal strains and anaerobic organisms are resistant to ciprofloxacin and ofloxacin. Reports of resistance in some *S. aureus* and *S. epidermidis* strains dictate caution. Ciprofloxacin is advantageous in the treatment of gram-negative bone infections, which previously required prolonged parenteral antibiotic therapy (119).

The third-generation quinolones include levofloxacin and gatifloxacin. Levofloxacin and gatifloxacin provide higher serum levels than either ciprofloxacin or ofloxacin. These agents have excellent activity against *Streptococcus* spp., including penicillin-intermediate and -resistant *Strep. pneumoniae*. These agents are also active against atypical respiratory pathogens (*M pneumoniae*, *Legionella* spp., and *Chlamydia pneumoniae*). These agents have efficacy against most gram-negative organisms as well.

The fourth-generation quinolones (trovafloxacin) have similar aerobic gram-positive and gram-negative coverage to the third-generation quinolones. Unlike the third-generation quinolones, fourth-generation quinolones have excellent anaerobic organism coverage (120,121). In a small number of patients, trovafloxacin was associated with serious liver injury leading to liver transplantation and/or death. This problem was reported with both short- and long-term therapy; treatment over 2 weeks was associated with an increased risk of liver injury. Currently, trovafloxacin may only be used for serious life- or limb-threatening infections in a hospital or nursing care facility.

None of the quinolones have reliable *Enterococcus* spp. coverage (122). The current quinolones have variable *S. aureus* and *S. epidermidis* coverage, and resistance to the second- and third-generation quinolones is increasing (123).

Although second-, third-, and fourth-generation quinolones are formulated for parenteral administration, the oral mode of these quinolones produces excellent serum concentrations, oral administration results in decreased length of hospitalization and reduced treatment costs. In most cases, the patient is begun on the parenteral quinolone and switched to oral quinolone therapy unless there is a contraindication to oral antibiotic therapy. The switch to oral therapy usually occurs at 1 to 2 days into therapy.

The fluoroquinolones have a prolonged postantibiotic effect against most gram-negative organisms, similar to that of the aminoglycosides. Hemodialysis

and peritoneal dialysis results in less than 14% elimination for all the available quinolones. Serum levels may be 1.5 to 3 times higher in elderly patients because of increased absorption and decreased renal clearance (124). Adjustments of the dosage with altered renal function depend on the quinolone drug.

Patients who have not completed puberty should not be given antimicrobial therapy with the quinolone class of antibiotics because altered bone growth has been found in young beagle dogs (178).

Overall, the toxicity of the quinolones is low (125). General reactions to the quinolones include gastrointestinal disturbances consisting of nausea, vomiting, and dyspepsia in 2% to 5% of patients. Central nervous system reactions including headache, dizziness, tiredness, and insomnia occur in 1% to 2% of patients. The quinolones may cause hypersensitivity reactions including skin rashes. Moderate to severe phototoxicity may be caused by some of the quinolones, especially lomefloxacin and sparfloxacin. The quinolones may cause tendinitis and Achilles tendon rupture. Rarely, this class of antibiotic may also cause acute interstitial nephritis. All quinolones cause mild toxicity, and individual quinolones have the propensity for certain side effects; for example, sparfloxacin causes prolongation of the QT interval (Table 5). The quinolones also have multiple drug-drug interactions (126). Antacids including sucralfate, iron, zinc, and calcium decrease the absorption and the efficacy of most quinolones. Certain quinolones have specific drug-drug interactions (Table 6).

Several anecdotal cases have implied clinically significant interactions between warfarin and quinolones. Any patient who is receiving a quinolone alone with warfarin anticoagulation should have prothrombin time closely monitored.

VI. ANTIMETABOLITES

The antimetabolites include the sulfonamides and trimethoprim-sulfamethoxazole.

Table 5 Toxicity by Specific Quinolone

Phototoxicity	Enoxacin, lomefloxacin, sparfloxacin
Central nervous system, insomnia	Ofloxacin
Seizures	Lomefloxacin
Prolonged QT interval	Sparfloxacin
Increased bilirubin level	Trovafloxacin
Dizziness	Trovafloxacin
Persistent hypoglycemia with glyburide	Ciprofloxacin

Table 6 Quinolone Drug Interactions

Drug	Quinolone	Effect
Antacids (sucralfate, iron, zinc and calcium)	All	Decreased absorption and efficacy
Theophylline	Enoxacine, ciprofloxacin	Theophylline toxicity
Caffeine	Enoxacin	Nervousness, insomnia
Warfarin	Enoxacin, ciprofloxacin ofloxacin	Increased PT time
Cyclosporin	Ciprofloxacin	Transient increase in levels of cyclosporine
Phenytoin	Ciprofloxacin	Increased or decreased phenytoin levels

A. Trimethoprim-Sulfamethoxazole

Trimethoprim-sulfamethoxazole is an antimetabolite composed of a fixed combination of a trimethoprim and sulfonamide. In vitro, these agents are more active together than either agent is alone (127). Aerobic gram-negative bacteria including *E. coli*, *P. mirabilis*, *H. influenzae*, and *Stenotrophomonas maltophilia* are consistently susceptible. In addition, *Klebsiella pneumoniae*, *Enterobacter* spp., *Serratia marcescens*, indole-positive *Proteus* spp., and non–*Pseudomonas aeruginosa Pseudomonas* spp. are frequently susceptible. The principal targets of trimethoprim-sulfamethoxazole are aerobic gram-negative organisms, but some gram-positive bacteria such as *S. aureus*, *Strep. pneumoniae*, and *Strep. pyogenes* are often susceptible (128). In some hospitals, the combination of trimethoprim-sulfamethoxazole and rifampin may be effective for the oral treatment of methicillin-resistant *S. aureus* and *S. epidermidis* (129). Trimethoprimsulfamethoxazole may be given either parenterally or orally. The combination is useful as suppressive therapy for osteomyelitis.

All the sulfonamides, including trimethoprim-sulfamethoxazole, have multiple side effects including gastrointestinal disturbances. Other side effects include blood dyscrasias such as acute hemolytic anemias, glucose-6-phosphate dehydrogenase (G6PD) deficiency problems, agranulocytosis, aplastic anemia, and thrombocytopenia. Hypersensitivity reactions include erythema multiforme, urticaria, and erythema nodosum. The sulfonamides may cause a focal or diffuse hepatitis and neurological symptoms consisting of headache, confusion, and peripheral neuropathy. A serum sickness–like syndrome can occur with the sulfonamides, and in 3% of patients on sulfonamides a drug fever develops. The sulfonamides have also been reported to cause nephrotoxicity and pruritus

without a rash. Trimethoprim-sulfamethoxazole should not be administered during the last month of pregnancy.

The sulfonamides have a number of drug interactions, which include increased anticoagulation effects of warfarin (130,131) and increased levels of phenytoin (132). They also potentiate hypoglycemic effects of the sulfonylurea compounds (133–136). Finally, the sulfonamides potentiate bone marrow suppression by methotrexate (137).

VII. REDUCING COMPOUNDS

The reducing compounds include metronidazole.

A. Metronidazole

Metronidazole is a useful and inexpensive antibiotic for the treatment of anaerobic organisms. This antibiotic is a reducing compound that leads to the formation of toxic oxygen radicals. Toxic oxygen radicals are lethal to strict anaerobic organisms, which lack the protective enzymes superoxide dismutase and catalase. Metronidazole is active against all anaerobic organisms except actinomycetes and microaerophilic streptococci (138). The drug is well absorbed and penetrates into tissues and abscesses.

Metronidazole is rapidly and almost completely absorbed orally (139,140). Serum levels are similar after equivalent intravenous and oral doses (141). Metronidazole penetrates all tissues and body fluids (142). The half-life in adults with normal renal and hepatic function is approximately 8 hours (140,143).

The excellent penetration of metronidazole into all tissues combined with its bactericidal activity make it effective for the treatment of serious anaerobic infections, including bone and joint infections and skin and soft tissue infections (140).

Side effects, which are rare, include metallic taste, seizures, cerebellar dysfunction, disulfiram. reaction with alcohol, and pseudomembranous colitis. Metronidazole may also have gastrointestinal side effects including anorexia, nausea, vomiting, diarrhea, abdominal pain, and pancreatitis.

VIII. SENSITIVITY TESTING

Once the organism(s) is isolated, the specific antibacterial activity of a variety of antibiotics can be determined by appropriate sensitivity techniques. The disk diffusion method is a commonly used method for susceptibility testing for fastidious and slow-growing organisms.

The diameter of a zone of inhibition around an antimicrobial impregnated paper disk relates approximately linearly to the antibiotic's $\log_2$ mean inhibitory concentration. Inhibition diameters are interpreted as signifying susceptibility, intermediate susceptibility, or resistance to each antimicrobial agent tested according to published criteria (144). Quantitative data are provided by methods that incorporate serial dilution of antibiotics in agar-containing or broth culture medium. Quantitative sensitivity testing by macro- or microdilution techniques is a prerequisite for the determination of the least concentration of the antibiotic required to inhibit (mean inhibitory concentration [MIC]) and kill (mean bactericidal concentration [MBC]) the isolated organisms (145). Clinical prejudice demands selection of an antibiotic or antibiotic combination having a low MIC/MBC activity relative to its expected serum concentration. Most clinical laboratories report only mean inhibitory concentrations.

IX. SERUM BACTERICIDAL CONCENTRATIONS

Peak and trough serum bacteriostatic and bactericidal levels described by Schlichter and MaClean (146) are often employed to assess the bacteriostatic and bactericidal capabilities of the treatment antibiotic(s). Initially, patient serum samples are obtained after dosage in order to obtain the peak and trough serum levels. The serum samples are then serially diluted and the dilution fractions are tested against an inoculum of the infecting bacterial species. Using this method, one can obtain an estimation of the antibiotic dosage necessary to obtain adequate serum inhibitory and bactericidal antibiotic levels. These results are expressed as minimal inhibitory dilution (MID) and minimum serum bactericidal dilution (MBD or SBT). The interpretation criteria and significance of the data vary for different laboratories (147–149). Most investigators strive for a peak minimum serum bactericidal dilution of 1 : 8 or greater (i.e., eightfold or higher dilution of a patient's serum is capable of having a bactericidal effect on the infecting bacterial species or strain) (150). In pediatric patients with osteomyelitis, minimum serum bactericidal dilutions have been utilized to ensure the adequacy of oral antibiotic therapy (151). In a typical osteomyelitis patient when optimal antibiotics are selected by MIC testing, the likelihood of success is governed by the adequacy of débridement surgery rather than by the adequacy of serum-cidal levels.

A. Concentration-Independent and -Dependent Killing of Antibiotics

All β-lactams, glycopeptides, macrolides, and clindamycin show little concentration-dependent bactericidal activity (152). Once the drug concentration exceeds a critical value, which appears to be two to four times the MIC for a given

organism, killing proceeds at a zero-order rate, and increasing the drug concentration does not increase the rate or extent of microbial death (153). Under these conditions, little correlation between peak serum concentrations is expected. These antibiotics exhibit concentration-independent or time-dependent killing; the duration of the concentration of the drug above its MIC for the pathogen at the site of infection is the best predictor of the clinical outcome.

In contrast, the aminoglycosides, fluoroquinolones, metronidazole, and amphotericin B kill most rapidly when their concentrations are appreciably above the MIC of the targeted microorganism (154,155). These antibiotics exhibit concentration-dependent or time-independent killings. It has been shown that aminoglycoside and fluoroquinolone agents eradicate organisms best at levels 10 to 12 times above the organism's MIC (156,157). If this drug-to-MIC ratio is obtained, most bacteria die within a short time. Consequently, the effect of the time of drug exposure is minimal.

X. ANTIBACTERIAL AGENTS IN PREGNANCY

Most antibiotics used during pregnancy are for the benefit of the mother; however, the fetus is also exposed to the antibiotic in varying degrees. Pharmacokinetic data on antibiotics from studies in pregnancy are limited because of ethical issues.

A doubling of renal plasma flow in pregnancy increases the glomerular filtration rate by 70% and the creatinine clearance by 50%; therefore, renal excretion of drugs is also increased. This leads to a lowered serum drug level of antibiotics during gestation.

Toxic effects of antibiotics vary with the period of gestation and the maturity of the fetus. The risk of teratogenesis is present from the moment of conception, but the embryo is most susceptible to teratogenic effects during the first trimester (days 1 to 70).

All antibiotics must be used with caution by the pregnant female (158). Antibiotics that have the best safety record include penicillins, cephalosporins, and erythromycin. Other antibiotics can cause problems, for example, the aminoglycosides can cause deafness. The sulfonamides, when given in the third trimester, displace bilirubin from albumin, leading to kernicterus. The tetracyclines alter bone growth and can cause pancreatitis and liver dysfunction in the pregnant female. Metronidazole is carcinogenic in rats. The quinolones alter cartilage growth in juvenile animals. Rifampin, trimethoprim, and clarithromycin either are teratogenic in rodents or cause adverse outcomes in nonhuman animal species.

Many antibiotics appear in breast milk if administered to lactating women. Antibiotics such as sulfonamides, quinolones, and chloramphenicol have been found in breast milk and can have adverse effects in infants. It is prudent to

discontinue breast-feeding temporarily during antibiotic therapy while maintaining mild flow via a breast pump. If there is any question concerning a specific antibiotic, specific references or specialists should be consulted (159).

XI. ANTIBIOTICS IN THE ELDERLY

The selection and dosage of antibiotics in the elderly require a clear comprehension of the physiological changes associated with aging and the higher frequency of adverse drug reactions. It is unclear whether drug absorption, hepatic metabolism, and drug response vary significantly with old age. It is evident that drug clearance, particularly through renal mechanisms, is decreased in aged persons. As a result of reduced muscle mass with age, the creatinine clearance is a more accurate estimate of renal function than serum creatinine (160).

Because of age-related decline in renal function, dose adjustments and monitoring of serum drug levels may be necessary for certain drugs. This can work to our advantage by reducing twice-daily dosage to once-daily dosage and allowing outpatient treatment.

Certain groups of antibiotics are associated with increased side effects in elderly patients, including β-lactam antibiotics (seizures, skin rash), aminoglycosides (renal and auditory and vestibular dysfunction), vancomycin (renal dysfunction), macrolides (nausea, abdominal cramps), and quinolones (seizures, hallucinations) (161). Additionally, drug interactions in the elderly are increased as a consequence of greater numbers of medications taken (162).

XII. ANTIBIOTIC RESISTANCE

One of the major infectious disease challenges of the modern era is fighting infections due to antibiotic-resistant microorganisms. Infection with antibiotic-resistant organisms is often associated with increased morbidity and mortality rates. In a 1998 report, the National Foundation for Infectious Diseases estimated that approximately $4 billion is spent annually in the United States to treat nosocomial infections due to antimicrobial-resistant and emerging infections (163).

Antibiotic resistance began with the advent of antibiotic therapy, when sulfonamides and penicillin were introduced. Today, antibiotic resistance is common in community-acquired pathogens and nosocomial pathogens, especially isolates from intensive care units. Many factors are involved in the development of antibiotic resistance, including the increased number of immunocompromised and critically ill patients, increased use of indwelling devices and invasive procedures, inappropriate use of antibiotics in the agricultural industry,

lack of strict adherence to infection control procedures, and increased and inappropriate use of antibiotic therapy (164–169).

Most antimicrobial resistance is caused by one of the following mechanisms: (1) enzymatic modification and inactivation of the antibiotic agent (e.g., β-lactamase-producing *S. aureus*); (2) alteration of the antibiotic target site (e.g., penicillin-resistant *Strep. pneumoniae* isolates that have acquired a penicillin-binding protein with reduced affinity to penicillin); (3) increased production of antibiotic target proteins (e.g., increased production of cytochrome p450 in *Candida* spp. treated with an azole); (4) decreased uptake of antibiotic by alteration of porins or channels through which antibiotics penetrate the bacterial cell membrane (e.g., *P. aeruginosa* resistant to imipenem) or the increased efflux of intracellular antibiotic (e.g., azole-resistant *Candida* spp.). Microorganisms may acquire antibiotic resistance by undergoing chromosomal mutations of the antibiotic target protein or the transport system that controls uptake of the drug, through acquisition of genetic material (plasmids, transposons, etc.) encoding resistance genes, or by expression of existing resistance genes through induction. Then, under selective pressure, organisms that have acquired resistance survive and multiply, despite the presence of antibiotics, and replace sensitive organisms.

Antimicrobial-resistant pathogens important in orthopedics include methicillin-resistant *S. aureus* (MRSA), vancomycin-intermediate *S. aureus* (VISA), vancomycin-resistant *S. aureus* (VRSA), coagulase-negative staphylococci, *Enterococcus* spp., *P. aeruginosa*, Enterobacteriaceae, and, rarely, azole-resistant *Candida* spp. (170–173).

Depending on the institution, 10% to 50% of *S. aureus* isolates are methicillin-resistant. One major source of infection is hospital personnel, since approximately 3% of health care workers are nasal carriers. Control of MRSA involves hand washing, isolation of suspected MRSA-infected or colonized patients, use of universal barrier precautions, and minimization of the hospital stay of patients. Treatment options include vancomycin, teicoplanin, co-trimoxazole, minocycline, clindamycin, and quinolones. The newer drugs quinupristin & dalfopristin and linezolid can be used to treat infections due to MRSA (174).

Resistance to vancomycin is rare in *S. aureus*. A limited number of cases have been reported in Europe, Asia, and the United States; VISA is more common than VRSA. These strains are usually isolated from patients who have been treated with vancomycin for an infection due to MRSA. Treatment can be challenging, and potential therapeutic candidates include linezolid and quinupristin & dalfopristin (174).

Coagulase-negative staphylococci are a major cause of nosocomial infections, especially among patients with indwelling catheters or prosthetic implants. Of this family, *S. epidermidis* is the most common cause of infections. A large number of coagulase-negative staphylococcus isolates are resistant to methicillin. Treatment is similar to that used for MRSA (174).

Vancomycin-resistant *Enterococcus* spp. (VRE) was first reported in 1986 in Europe, where avopracin, a glycopeptide antibiotic, had been in use for years in animal feed (175). In 2000, the National Nosocomial Infectious Surveillance (NAIS) system report stated that 24.7% of nosocomial enterococcal infections in intensive care units in the United States were caused by VRE (176). Although enterococci are not as virulent as other microorganisms, the emergence of VRE is a matter of concern because of the limited therapeutic options and potential for transfer of vancomycin-resistance genes from enterococci to other more virulent nosocomial pathogens, such as *S. aureus*. The Hospital Infection Control Practices Advisory Committee (HICPAC) has issued recommendations to control the spread of VRE (174). The highlights of these recommendations are strict adherence to infection control measures and judicious use of vancomycin. Since VREs are usually resistant to penicillin and aminoglycosides, treatment options are limited to linezolid and quinupristin & dalfopristin.

Since the advent of antimicrobial therapy, the treatment of *P. aeruginosa* infection has been a constant challenge to physicians. *P. aeruginosa* strains are resistant to the majority of commonly used antibiotics (177). This intrinsic resistance is primarily due to the low permeability of the outer cell membrane; however, other mechanisms of resistance may be involved as well. Antibiotics commonly used to treat resistant *Pseudomonas aeruginosa* include cephalosporins (third- and fourth-generation), piperacillin-tazobactam, ticarcillin-clavulanic acid, carbapenem, fluoroquinolones, and aminoglycosides. These same antibiotics can also be used to treat infections due to Enterobacteriaceae species.

Candida spp. are rarely the cause of musculoskeletal infections. Azoles are the first-line drugs for *Candida* spp. infections. Resistance to azoles has been described in certain *Candida* spp. (*C. krusei* and *C. glabrata*) (174). In these situations, amphotericin B is the treatment of choice.

XIII. SUMMARY

Antibiotics are classified on the basis of their mechanism of action. Antibiotics that inhibit cell wall synthesis include penicillins, cephalosporins, imipenem, aztreonam, and vancomycin, as well as β-lactamase inhibitors such as clavulanic acid and sulbactam. Inhibitors of bacterial protein synthesis include those antibiotics that act on the 50S ribosomal subunit (chloramphenicol, macrolides, clindamycin) and others that act on the 30S ribosomal subunit (tetracyclines, aminoglycosides, oxazolidinones). Sulfonamides and trimethoprim are inhibitors of nucleotide synthesis. Quinolones inhibit DNA synthesis, whereas rifampin inhibits messenger RNA (mRNA) synthesis. Metronidazole is a reducing compound antibiotic. Other classes of antibiotics include those that alter cell

membrane function (polymyxin, amphotericin B, azoles, nystatin) and those that have an uncertain method of action (isoniazide, pentamidine).

The development of antibiotics has allowed us to change the natural course of many bacterial diseases. As a result of the extensive use of antibiotics and various advances in medicine, resistance to antibiotics is becoming a major problem that threatens our success in treating bacterial diseases in the future. Resistance to antibiotics can only be limited, not eliminated, so our major efforts must be directed toward the appropriate and responsible use of antibiotics. This includes using them for the appropriate indication, for the appropriate amount of time, and through the appropriate route.

REFERENCES

1. Al Neugut, AT Ghatak, RL Miller. Anaphylaxis in the United States: an investigation into its epidemiology. Arch Intern Med 161(1):15–21:2001.
2. RD deShazo, SF Kemp. Allergic reactions to drugs and biologic agents. JAMA 278:1895–1906, 1997.
3. MD Yow, LH Taber, FF Barrett, AA Mintz, GR Blankinship, GE Clark, DJ Clark. A ten-year assessment of methicillin-associated side-effects. Pediatrics 58:329–334, 1976.
4. UG Hodgkin. Antibiotics in the treatment of chronic staphylococcal osteomyelitis. South Med J 68:817–823, 1975.
5. TM Onorato, JL Axelrod. Hepatitis from intravenous high-dose oxacillin therapy. Ann Intern Med 89:497–500, 1978.
6. HC Neu. Aminopenicillins:clinical pharmacology and use in disease states. Int J Clin Pharmacol Biopharm 11:132–144, 1975.
7. HC Neu. Carbenicillin and ticarcillin. Med Clin North Am 66:61–77, 1982.
8. HC Neu, GG Garvey. Comparative *in vitro* activity and clinical pharmacology of ticarcillin and carbenicillin. Antimicrob Agents Chemother 8:457–462, 1975.
9. KP Fu, HC Neu. Piperacillin a new penicillin active against many bacteria resistant to other penicillins. Antimicrob Agents Chemother 13:358–367, 1987.
10. MF Parry, D Folta. The *in vitro* activity of mezlocillin, against community hospital isolates in comparison to other penicillins and cephalosporins. J Antimicrob Chemother 11(suppl):97–102, 1983.
11. WA Kradjan, R Burger. In vivo inactivation of gentamicin by carbenicillin and ticarcillin. Arch Intern Med 140(12):1668–1670, 1980.
12. MS Chow, R Quintiliani, CU Nightingale. In vivo inactivation of tobramycin by ticarcillin:a case report. JAMA 247(5):658–659, 1982.
13. CE Halstenson, MO Wong, CS Herman, KL Heim-Duthoy, MA Teal, MB Affrime, JH Kelloway, WE Keane, WM Awni. Effect of concomitant administration of piperacillin on the dispositions of isepamicin and gentamicin in patients with end-stage renal disease. Antimicrob Agents Chemother 36:1832–1836, 1992.

14. GR Matzke, DR Luckham, AJ Collins, CE Halstenson. Effect of ticarcillin on gentamicin and tobramycin pharmacokinetics in a patient with end-stage renal disease. Pharmacotherapy 4(3):158–160, 1984.
15. DW Nierenberg. Drug inhibition of penicillin tubular secretion: concordance between in vitro and clinical findings. J Pharmacol Exp Ther 240(3):712–716, 1987.
16. HC Neu, KP Fu. Clavulanic acid: a novel inhibitor of β-lactamases. Antimicrob Agents Chemother 14:650–655, 1978.
17. C Reading, P Hepburn. The inhibition of staphylococcal β-lactamase by clavulanic acid. Biochem J 179:67–76, 1979.
18. MH Richmond, RB Sykes. The beta-lactamases of gram-negative bacteria and their possible physiological role. Adv Microb Physiol 9:31–88, 1973.
19. IW Fong, ER Engelking, WMM Kirby. Relative inactivation by *Staphylococcus aureus* of eight cephalosporin antibiotics. Antimicrob Agents Chemother 9:939–944, 1976.
20. WMM Kirby, C Regamey. Pharmacokinetics of cefazolin compared with other cephalosporins. J Infect Dis 128 (suppl):341–346, 1973.
21. EH Kass, DA Evans. Future prospects and past problems in antimicrobial therapy: the role of cefoxitin. Rev Infect Dis 1:1–2, 1973.
22. C Thornsberry. Review of in vitro activity of third-generation cephalosporins and other newer Beta-lactam antibiotics against clinically important bacteria. Am J Med 79(suppl 2A):14–20, 1985.
23. HC Neu, P Labthavikul. Antibacterial activity and β-lactam stability of ceftazidime, an aminothiazolyl cephalosporin potentially active against *Pseudomonas aeruginosa*. Antimicrob Agents Chemother 21:11–18, 1982.
24. BE Scully, HC Neu. clinical efficacy of ceftazidime: treatment of serious infection due to multiresistant pseudomonas and other Gram-negative bacteria. Arch Intern Med 144:57–62, 1984.
25. MK Buening, JS Wold, KS Israel, RB Krammer. Disulfiram-like reaction to beta-lactams. JAMA 245(20):2027, 1981.
26. RM Elenbaas, JL Ryan, WA Robinson, MJ Singsank, MJ Harvey, CD Klaassen. On the disulfiram-like activity of moxalactam. Clin Pharmacol Ther 32(3):347–355, 1982.
27. S Umeda, T Arai. Disulfiram-like reaction to moxalactam after celiac plexus alcohol block. Anesth Analg 64:377, 1985.
28. SS Kline, VF Mauro, RB Forney, EH Freimer, P Somani. Cefotetan-induced disulfiram-type reactions and hypoprothrombinemia. Antimicrob Agents Chemother 31(9):1328–1331, 1987.
29. RA Fromtling, HH Gadebusch. Ethanol-cephalosporin antibiotic interactions: an animal model for the detection of disulfiram (Antabuse)-like effects. Methods Find Exp Clin Pharmacol 5(9):595–600, 1983.
30. HR Freedy, AB Cetnarowski, RM Lumish, FJ Schafer. Cefoperazone-induced coagulopathy. Drug Intell Clin Pharm 20(4):281–283, 1986.
32. D O'Donnell. Hypoprothrombinaemia associated with use of cefamandole. Aust N Z J Surg 61(6):471–472, 1991.
33. P Cristiano. Hypoprothrombinemia associated with cefoperazone treatment. Drug Intell Clin Pharm 18(4):314–316, 1984.

34. A Conjura, W Bell, JJ Lipsky. Cefotetan and hypoprothrombinemia. Ann Intern Med 108(4):643, 1988.
35. RB Sykes, DP Bonner, K Bush. Aztreonam: a synthetic monobactam active against aerobic Gram-negative bacteria. Antimicrob Agents Chemother 21:85–92, 1982.
36. V Fainstein, S Weaver, GP Bodey. Comparative in vitro study of SQ26, 776. Antimicrob Agents Chemother 21:294–298, 1982.
37. MF Parry. Aztreonam susceptibility testing: a retrospective analysis. Am J Med 88:75–115, 1990.
38. EA Swabb, SM Singhvi, MA Leitz, M Frantz, AA Sugerman. Metabolism and pharmacokinetics of aztreonam in healthy subjects. Antimicrob Agents Chemother 24:394–400, 1983.
39. JCL Mihindy, WM Scheld, ND Bolton, DA Spyker, EA Swabb, WB Bolton. Pharmacokinetics of aztreonam in patients with various degrees of renal dysfunction. Antimicrob Agents Chemother 24: 252–261, 1983.
40. WJ Simons, TJ Lee. Aztreonam in the treatment of bone and joint infections caused by gram-negative bacilli. Rev Infect Dis 7(suppl 4):S783-S788, 1085.
41. C Pribyl, R Salzer, J Beskin, RJ Haddad, B Pollock, B. Bevillile. Aztreonam in the treatment of serious orthopedic infections. Am J Med 78:51–56, 1985.
42. G Alvan, CE Nord. Adverse effects of monobactams and carbapenems. Drug Saf 12(5):305–313, 1995.
43. WC Hellinger, NS Brewer. Carbapenems and monobactams: imipenem, meropenem, and aztreonam. Mayo Clin Proc 74(4):420–434, 1999.
44. HC Neu, P Labthavikul. Comparative *in vitro* evaluation of *N*-formimidoyl thienamycin against Gram-positive and Gram-negative aerobic and anaerobic species and its 13-lactamase stability. Antimicrob Agents Chemother 21:180–187, 1982.
45. GL Drysano. An overview of the pharmacolocy of imipenem/cilastatin. J Antimicrob Chemother 18(suppl):79–92, 1986.
46. RR MacGregor, LO Gentry. Imipenem/cilastatin in the treatment of osteomyelitis. Am J Med 78:100–105, 1985.
47. ML Grayson, GW Gibbons, GM Habershaw, DV Freeman, FB Pomposelli, BI Rosenblum, E Levin, AW Karchmer. Use of ampicillin/sulbactam versus imipenem/cilastatin in the treatment of limb-threatening foot infections in diabetic patients. Clin Infect Dis 18:683–693, 1994.
48. J Zazgornik, W Schein, K Heimberger, FA Shaheen, F Stockenhuber. Potentiation of neurotoxic side effects by coadministration of imipenem to cyclosporine therapy in a kidney transplant recipient–synergism of side effects or drug interaction? Clin Nephrol 26(5):265–266, 1986.
49. C Bosmuller, W Steurer, A Konigsrainer, J Willeit, R Margreiter. Increased risk of central nervous system toxicity in patients treated with cyclosporin and imipenem/cilastatin. Nephron 58(3):362–364, 1991.
50. LR Wiseman, AJ Wagstaff, RN Brogden, HM Bryson. Meropenem: a review of its antibacterial activity, pharmacokinetic properties and clinical efficacy. Drugs 50:73–101, 1995.

51. JR Edwards. Meropenem: a microbiological overview. J Antibicrob Chemother 36(suppl A):1–17, 1995.
52. RL Nichols, JW Smith, RW Geckler, SE Wilson. Meropenem versus imipenem/cilastatin in the treatment of hospitalized patients with skin and soft tissue infections. South Med J 88:397–404, 1995.
53. PF Reynolds. Structure, biochemistry, and mechanism of action of glycopeptide antibiotics. Eur J Clin Microbiol Infect Dis 8:943–950, 1989.
54. JE Geraci, PE Hermans. Vancomycin. Mayo Clin Proc 58:88–91, 1983.
55. TC Sorrell, DR Packham, S Shanker, M Foldes, MR Munro. Vancomycin therapy for methicillin-resistant *Staphylococcus aureus*. Ann Intern Med 97:344–350, 1982.
56. GL Archer. Antimicrobial susceptibility and selection or resistance among *Staphylococcus epidermidis* isolates recovered from patients with infections of indwelling foreign devices. Antimicrob Agents Chemother 14:353–359, 1978.
57. FV Cook, WE Farrar. Vancomycin revisited. Ann Intern Med 88:813–818, 1978.
58. PE Herman, MP Wilhem. Vancomycin. Mayo Clin Proc 62:901–905, 1987.
59. BR Smith, JL LeFrock. Vancomycin update. AFP 35:223–225, 1987.
60. AL Graziani, LA Lawson, GA Gibson, MA Steinberg, RR MacGregor. Vancomycin concentrations in infected and noninfected human bone. Antimicrob Agents Chemother 32:1320–1322, 1985.
61. RW Bundtzen, AU Gerber, DL Cohen, WA Craig. Postantibiotic suppression of bacterial growth. Rev Infect Dis 3:28–37, 1981.
62. H Hanberger. Pharmacodynamic effects of antibiotics: studies on bacterial, morphology, initial killing, postantibiotic effect, and effective regrowth time. Scand J Infect Dis 81 (suppl):1–52, 1992.
63. V DeBock, D Verbeelen, V Maes, J Sennesael. Pharmacokinetics of vancomycin in patients undergoing haemodialysis and haemofiltration. Nephrol Dial Transplant 4:635–639, 1989.
64. HE Nielsen, I Sorensen, HE Hansen. Peritoneal transport of vancomycin during peritoneal dialysis. Nephron 24:274–279, 1979.
65. RE Polk. Red man syndrome. Ann Pharmacother 32(7–8):840, 1998.
66. MR Wallace, JR Mascola, EC Oldfield. Red man syndrome: incidence, etiology, and prophylaxis. J Infect Dis 164(6):1180–1185, 1991.
67. BF Farber, RC Moellering. Retrospective study of the toxicity of preparations of vancomycin from 1974 to 1981. Antimicrob Agents Chemother 23:138–141, 1983.
68. C Odio, GH McCracken, JD Nelson. Nephrotoxicity associated with vancomycin-aminoglycoside therapy in four children. J Pediatr 105(3):491–493, 1984.
69. DJ Pauly, DM Musa, MR Lestico, MJ Lindstrom, CM Hetsko. Risk of nephrotoxicity with combination vancomycin-aminoglycoside antibiotic therapy. Pharmacotherapy 10(6):378–382, 1990.
70. MY Munar, L Elzinga, R Brummett, TA Golper, WM Bennett. The effect of tobramycin on the renal handling of vancomycin. J Clin Pharmacol 31(7):618–623, 1991.
71. PF Smith, CT Taylor. Vancomycin-induced neutropenia associated with fever: similarities between two immune-mediated drug reactions. Pharmacotherapy 19(2):240–244, 1999.

72. HH Kesarwala, WJ Rahill, N Amaram. Vancomycin induced neutropenia. Lancet 1(8235):1423, 1981.
73. CE Howard, LA Adams, JL Admire, MA Chu, GL Alred. Vancomycin-induced thrombocytopenia: a challenge and rechallenge. Ann Pharmacother 31(3):315–318, 1997.
74. JC Kuruppu, TP Le, CU Tuazon. Vancomycin-associated thrombocytopenia: case report and review of the literature. Am J Hematol 60(3):249–250, 1999.
75. VL Sutter. *In vitro* susceptibility of anaerobes: comparison of clindamycin and other antimicrobial agents. J Infect Dis 135(suppl):7–12, 1977.
76. JL LeFrock, A Molavi. Clindamycin. Med Clinics North Am 66:103–120, 1982.
77. JD Panzer, DC Brown, WL Epstein, RL Lipson, HW Mchaffey, WH Atkinson. Clindamycin levels in various body tissues and fluids. J Clin Pharrnacol 12:259–262, 1972.
78. MS Klempner, B Styrt. Clindamycin uptake by human neutrophils. J Infect Dis 144:472–479, 1981.
79. NH Steigbigel. Erythromycin, lincomycin, and clindamycin. In: GL Mandell, RG Douglas Jr, JE Bennett, eds. Principles and Practice of Infectious Diseases. 3d ed. New York: Churchill Livingstone, 1990:308–317.
80. JL LeFrock, AS Klainer, S Chen, RB Gainer, M Omar, W Anderson. The spectrum of colitis associated with lincomycin and clindamycin therapy. J Infect Dis 131(suppl):108–115, 1975.
81. LD Becker, RD Miller. Clindamycin enhances a nondepolarizing neuromuscular blockade. Anesthesiology 45:84, 1976.
82. O al Ahdal, DR Bevan. Clindamycin-induced neuromuscular blockade. Can J Anaesth 42(7):614–617, 1995.
83. JA Best, All Marashi, LD Pollan. Neuromuscular blockade after clindamycin administration:a case report. J Oral Maxillofac Surg 57(5):600–603, 1999.
84. E Rubinstein, P Prokocimer, GH Talbot. Safety and tolerability of quinupristin/dalfopristin: administration guidelines. J Antimicrob Chemother 44(suppl A):37–46, 1999.
85. SC Piscitelli, LH Danziger, KA Rodvold. Clarithromycin and azithromycin: new macrolide antibiotics. Clin Pharmacol Ther 11:137–152, 1992.
86. RE Fuller, RH Drew, JR Perfect. Treatment of vancomycin-resistant enterococci with a focus on quinupristin-dalfopristin. Pharmacotherapy 16:584–592, 1996.
87. C Chant, MJ Rybak. Quinupristin/dalfopristin (RP59500); a new streptogramin antibiotic. Ann Pharmacother 29:1022–1030, 1995.
88. RC Moellering, PK Linden, J Reinhardt, EA Blumberg, F Bompart, GH Talbot. The efficacy and safety of quinupristin/dalfopristin for the treatment of infections caused by vancomycin-resistant *Enterococcus faecium*. Synercid Emergency Use Study Group. J Antimicrob Chemother 44:251–261, 1999.
89. KM Olsen, JA Rebuck, ME Rupp. Arthralgias and myalgias related to quinupristin-dalfopristin administration. Clin Infect Dis 32(4):E83–E86, 2001.
90. WH Barr, J Adir, L Garrettson. Decrease of tetracycline absorption in man by sodium bicarbonate. Clin Pharmacol Ther 12(5):779–784, 1971.

91. M Garty, A Hurwitz. Effect of cimetidine and antacids on gastrointestinal absorption of tetracycline. Clin Pharmacol Ther 28(2):203–207, 1980.
92. VX Nguyen, DE Nix, S Gillikin, JJ Schentag. Effect of oral antacid administration on the pharmacokinetics of intravenous doxycycline. Antimicrob Agents Chemother 33(4):434–436, 1989.
93. CW Ford, JC Hamel, D Stapert, JK Moerman, DK Hutchinson, MR Barbachyn, GE Zurenko. Oxazolidinones: new antibacterial agents. Trends Microbiol 5(5):196–200, 1997.
94. DI Diekema, RN Jones. Oxazolidinones: a review. Drugs 59(1):7–16, 2000.
95. LD Dresser, MJ Rybak. The pharmacologic and bacteriologic properties of oxazolidinones, a new class of synthetic antimicrobials. Pharmacotherapy 18:456–462, 1998.
96. CW Norden. Experimental osteomyelitis. V. Therapeutic trials with oxacillin and sisomicin alone and in combination. J Infect Dis 137:155–160, 1978.
97. SG Wilson, CC Sanders. Selection and characterization of strains of *Staphylococcus aureus* displaying unusual resistance to aminoglycosides. Antimicrob Agents Chemother 10:519–525, 1976.
98. CC Sanders, WE Sanders, RV Goering. *In vitro* studies with Sch 21420 and Sch 22591: activity in comparison with six other aminoglycosides and synergy with penicillin against enterococci. Antimicrob Agents Chemother 14:178–184, 1978.
99. LJ Riff, GG Jackson. Pharmacology of gentamicin in man. J Infect Dis 124(suppl):S98–S105, 1971.
100. GR Siber, P Echeverria, AL Smith, JW Paisley, DH Smith. Pharmacokinetics of gentamicin in children and adults. J Infect Dis 132:637–651, 1975.
101. WR Lockwood, JD Bower. Tobramycin and gentamicin concentrations in the serum of normal and anephric patients. Antimicrob Agents Chemother 3:125–129, 1973.
102. MC McHenry, JG Wagner, PM Hall, DG Vidt, TL Gavan. The pharmacokinetics of amikacin in patients with impaired renal function. J Infect Dis 134(suppl):S343–S348, 1976.
103. L Regeur, H Colding, H Jensen, JP Kampmann. Pharmacokinetics of amikacin during hemodialysis arid peritoneal dialysis. Antimicrob Agents Chemother 11:214–218, 1977.
104. P Vaudaux, FA Waldvogel. Gentimicin inactivation in purulent exudates: role of cell lysis. J Infect Dis 142:586–593, 1980.
105. SL Preston, LL Briceland. Single daily dosing of aminoglycosides. Pharmacology 15:297–316, 1995.
106. RB Drew III, GM Susig. Once daily aminoglycoside treatment. Infect Dis Clin Pract 5:12–24, 1996.
107. TC Baily, JR Little, B Littenberg, RM Reichley, WC Dunagon. A meta-analysis of extended-interval dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis 24:786–795, 1997.
108. MZ Ali, MB Goetz. A meta-analysis of the relative efficacy and toxicity of single daily dosing versus multiple daily dosing of aminoglycosides. Clin Infect Dis 24:896–809, 1997.

109. R Hatala, TT Dinh, DJ Cook. Single daily dosing of aminoglycosides in immunocompromised adults: a systemic review. Clin Infect Dis 24:810–815, 1999.
110. LD Sabath, C Garner, C Wilcox, M Findland. Susceptibility of *Staphylococcus aureus* and *Staphylococcus epidermidis* to 65 antibiotics. Antimicrob Agents Chemother 9:962–969, 1976.
111. RJ Faville, DE Zaske, EL Kaplan. *Staphylococcus aureus* endocarditis: combined therapy with vancomycin and rifampin. JAMA 240:1963–1965, 1978.
112. G Acocella. Pharmacokinetics and metabolism of rifampin in humans. Rev Infect Dis 5(suppl)428–433, 1983.
113. LJ Wheat, RB Kohler, FC Luft, A White. Long-term studies of the effect of rifampin on nasal carriage of coagulase-positive staphylococci. Rev Infect Dis 5(suppl 3):S459–S462, 1983.
114. JR Horn, PD Hansten. Drug interactions with antibacterial agents. J Fam Pract 41 (1):81–90, 1995.
115. G Acocella, R Conti. Interaction of rifampicin with other drugs. Tubercle 61(3):171–177, 1980.
116. VA Strayhorn, AM Baciewicz, TH Self. Update on rifampin drug interactions, III. Arch Intern Med 157(2l):2453–2458, 1997.
117. FC Hugues, N Moore, D Julien. Interactions of antitubercular drugs. Rev Pneumol Clin 44(6):278–285, 1988.
118. N Doble, R Shaw, C Rowland-Hill, M Lush, DW Warnock, EE Keal. Pharmacokinetic study of the interaction between rifampicin and ketoconazole. J Antimicrob Chemother 21(5):633–635, 1988.
119. DP Lew, FA Waldvogel. Quinolones and osteomyelitis: state-of-the-art. Drugs 49(suppl) 2:100–111, 1995.
120. ME Ernst, EJ Ernst, ME Klepser. Levofloxacin and trovafloxacin: the next generation of fluoroquinolones. Am J Health Syst Pharm 54:2569–2584, 1997.
121. AJ Wagstaff, JA Balfour. Grepafloxacin. Drugs 53(5):817–824, 1997.
122. DR Schamberg, WI Dillon, MS Terpenning. Increasing resistance of enterococci to ciprofloxacin. Antimicrob Agents Chemother 36:25233–2535, 1992.
123. HM Blumberg. D Rimland, DJ Carroll. Rapid development of ciprofloxacin resistance in methicillin-susceptible and -resistant *Staphylococcus aureus*. J Infect Dis 163:1279–1285, 1991.
124. DC Hooper, JS Wolfson. Fluoroquinolone antimicrobial agents. N Engl J Med 324: 384–394, 1991.
125. A De Sarro, G De Sarro. Adverse reactions to fluoroquinolones: an overview on mechanistic aspects. Curr Med Chem 8(4):371–384, 2001.
126. RE Polk, Drug-drug interactions with ciprofloxacin and other fluoroquinolones. Am J Med 87(5A):76S–81S, 1989.
127. SRM Bushby. Synergy of trimethoprim and sulfonamides: history and current status. In: D Woodbine, ed. Antibiotics and Antibiosis in Agriculture. London: Butterworths, 1977: 64–81.
128. GP Wormser, GT Keusch. Trimethoprim-sulfamethoxazole in the United States. Ann Intern Med 91:420–429, 1979.

129. TT Ward, RE Winn, AI Hartstein, DL Sewell. Observations relating to an interhospital outbreak of methicillin-resistant *Staphylococcus aureus*: role of antimicrobial therapy in infection control. Infect Control 2:453–459, 1981.
130. TH Self, W Evans, T Ferguson. Letter: interaction of sulfisoxazole and warfarin. Circulation 52(3):528, 1975.
131. LJ Sioris, RT Weibert, PR Pentel. Potentiation of warfarin anticoagulation by sulfisoxazole. Arch Intern Med 140(4):546–547, 1980.
132. JM Hansen, JP Kampmann, K Siersbaek-Nielsen, IB Lumholtz, M Arroe, U Abildgaard, L Skovsted. The effect of different sulfonamides on phenytoin metabolism in man. Acta Med Scand 624(suppl):106–110, 1979.
133. JB Field, M Ohta, C Boyle, A Remer. Potentiation of acetohexamide hypoglycemia by phenylbutazone. N Engl J Med 277(17):889–894, 1967.
134. SM Pond, DJ Birkett, DN Wade. Mechanisms of inhibition of tolbutamide metabolism: phenylbutazone, oxyphenbutazone, sulfaphenazole. Ciin Pharmacol Ther 22(5 Pt 1):573–579 1977.
135. HS Tucker, JI Hirsch. Sulfonamide-sulfonylurea interaction. N Engl J Med 286:110, 1972.
136. JF Johnson, ME Dobmeier. Symptomatic hypoglycemia secondary to a glipizide-trimethoprim/sulfamethoxazole drug interaction. DICP 24:250, 1990.
137. DS Zaharko, H Bruckner, VT Oliverio. Antibiotics alter methotrexate metabolism and excretion. Science 166(907):887–888, 1969.
138. JE Rosenblatt, RS Edson. Metronidazole. Mayo Clin Proc 58:154–157, 1983.
139. A Molavi, JL LeFrock. Metronidazole. Am Fam Physician 24:185–187, 1981.
140. SM Finegold, GE Methisen. Metronidazole. In: GL Mandell, JE Bennett, R Dolin, eds. Principles and Practice of Infectious Diseases. 4th ed. New York: Churchill Livingstone, 1995:329–334.
141. FP Tally, CE Sullivan. Metronidazole: in vitro activity, pharmacology, and efficacy in anaerobic bacterial infections. Pharmacotherapy 1:28–38, 1981.
142. SM Finegold. Metronidazole. Ann Intern Med 93:585–587, 1980.
143. AH Lau, NP Lam, SC Piscitelli, L Wilkes, LH Danziger. Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. Clin Pharmacokinet 23:328–364, 1992.
144. National Committee for Clinical Laboratory Standards. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically (Tentative Standard: M7-T). Villanova, PA, 1983.
145. HM Ericcson, JC Sherris. Antibiotic sensitivity testing: report of an international collaborative study. Acta Pathol Microbiol Scand 227(suppl B):1–90, 1971.
146. JG Schlicter, H MacLean. A method of determining the effective therapeutic level in the treatment of subacute bacterial endocarditis with penicillin. Am Heart J 34:209–211,1947.
147. FD Pein, KIL Vosti. Variation in performance of the serum bactericidal test. Antimicrob Agent Chemother 6:300–333, 1974.
148. LB Reller, CW Stratton. Serum dilution test for bactericidal activity. II. Standardization and correlation with antimicrobial assays and susceptibility tests. J Infect Dis 136:196–204, 1977.

149. CW Stratton, LB Reller. Serum dilution test for bactericidal activity. I. Selection of a physiologic diluent. J Infect Dis 136:187–195, 1977.
150. JE Rosenblatt. Laboratory tests used to guide antimicrobial therapy. Mayo Clin Proc 52:611–615, 1977.
151. TR Tetzloff, GH McCracken, FD Nelson. Oral antibiotic therapy for skeletal infections in children. II. Therapy of osteomyelitis and suppurative arthritis. J Pediatr 92:485–490, 1978.
152. WA Craig. Interrelationship between pharmacokinetics and pharmacodynamics in determining dosing regimens for broad-spectrum cephalosporins. Diagn Microb Infect Dis 22:89–96, 1995.
153. M Nishida, T Murakawer, T Kaminura. Bactericidal activity of cephalosporins in an in vitro model simulating serum levels. Antimicrob Agents Chemother 14:6–12, 1978.
154. MN Dudley. Pharmacodynamics and pharmacokinetics of antibiotics with special reference to the fluoroquinolones. Am J Med 91(suppl 6A):45S–50S, 1991.
155. JN Krieger, CS Dickins, M Rein. Use of a time-kill technique for susceptibility testing of *Trichomonas vaginalis*. Antimicrob Agents Chemother 27:332–336, 1985.
156. RD Moore, PS Lietman, CR Smith. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimum inhibitory concentration. J Infect Dis 155:93–99, 1987.
157. SL Preston, GL Drusano, AL Berman, CL Fowler, AT Chow, B Dornseif, V Reichl, J Natarajan, M Corrado. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. JAMA 279:125–129, 1998.
158. C Olesen, FH Steffensen, GL Nielsen, L de Jong-van den Berg, J Olsen, HT Sorensen. Drug use in first pregnancy and lactation: a population-based survey among Danish women. The EUROMAP Group. Eur J Clin Pharmacol 55(2):139–144, 1999.
159. GG Briggs, RK Freeman, SJ Yaffe. Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk. 5th ed. Baltimore: Williams & Wilkins, 1998.
160. TT Yoshikawa. Antimicrobial therapy for elderly patients. J Am Geriatr Soc 38:1353–1372, 1990.
161. I Nilsson-Ehle, B Ljungberg. Pharmacokinetics of antimicrobial agents with aging. In: TT Yoshikawa, DC Norman, eds. Antimicrobial Therapy in Elderly Patients. New York: Marcel Dekker, 1994:33–35.
162. S Rajagopalan, TT Yoshikawa. Antibiotic selection in the elderly patient. Antibiot Clinicians 3:51–56, 1999.
163. Institute of Medicine Forum on Emerging Infections. Antimicrobial Resistance: Issues and Options, Workshop Report. PF Harrison, J Lederberg, eds. Washington, DC: National Academy Press, 1998:8–74.
164. DA Goldman, RA Weinstein, RP Wenzel, OC Tabian, RJ Dunna, RP Gaynes, J Schlosser, WJ Martone. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals: a challenge to hospital leadership. JAMA 275:234–240, 1996.

165. NO Fishman, PJ Brennan. Optimizing use of antimicrobial agents: pitfalls and consequences of inappropriate therapy. Journal of Clinical Outcomes Management 4:25–33, 1997.
166. DM Shales, DN Gerding, JF John Jr, WA Craig, DL Bornstein, RA Duncan, MR Eckman, WE Farrer, WH Greene, V Lorian, S Levy, JE McGowen Jr, SM Paul, J Ruskin, FC Tenover, C Watanakunakorn. Society for Health Care Epidemiology of America and Infectious Diseases Society of America Joint Committee on the Prevention of Antimicrobial Resistance: Guidelines for the prevention of antimicrobial resistance in hospitals. Infect Control Hosp Epidemiol 18:275–291, 1997.
167. JE McGowen Jr, FC Tenover. Control of antimicrobial resistance in the health care system. Infect Dis Clin North Am 11:297–311, 1997.
168. MN Swartz. Use of antimicrobial agents and drug resistance (editorial). N Engl J Med 337:491–492, 1997.
169. MH Kollef, VJ Fraser. Antibiotic resistance in the intensive care unit. Ann Intern Med 134:298–314, 2001.
170. C Walsh. Molecular mechanisms that confer antibacterial drug resistance. Nature 406:775–781, 2000.
171. FC Tenover, JM Hughes. The challenges of emerging infectious diseases: development and spread of multiply-resistant bacterial pathogens. JAMA 275:300–304, 1996.
172. GA Jacoby, GL Archer. New mechanisms of bacterial resistance to antimicrobial agents. N Engl J Med 324:601–612, 1991.
173. PM Hawkey. The origins and molecular basis of antibiotic resistance. Br Med J 317:657–660, 1998.
174. Hospital Infection Control Practices Advisory Committee (HICPAC). Recommendations for preventing the spread of vancomycin resistance. MMWR Morb Mortal Wkly Rep 44:1–13, 1995.
175. BE Murray. Vancomycin-resistant enterococcal infections. N Engl J Med 342:710–721, 2000.
176. National Nosocomial Infections Surveillance (NNIS) system report, data summary from January 1992–April 2000, issued June 2000. Am J Infect Control 28:429–448, 2000.
177. M Pollack. *Pseudomonas aeruginosa*. In: GL Mandell, RG Douglas Jr, J Bennet, eds. Principles and Practices of Infectious Diseases. New York: Churchill Livingstone, 1990:1673–1691.
178. R Stahlmann, S Kuhner, M Shakibaei, J Flores, J Vormann, DC Van Sickle. Chondrotoxicity of ciprofloxacin in immature beagle dogs: immunochemistry, electron microscopy, and drug plasma concentrations. Arch Toxicol 73:564–572, 2000.

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Muscle Flaps

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I. INTRODUCTION

Osteomyelitis after compound fractures, especially in the lower extremities, is not uncommon. Infection is usually the result of the initial bacterial contamination compounded by devascularization of the soft tissue and bone from the injury and a prolonged delay in primary wound healing (1–3). The single greatest obstacle to the successful treatment of open fractures of the lower extremity is the prevention of, or the eradication of, posttraumatic osteomyelitis. In 1970, Ger and Efron (4) enumerated the factors associated with persistent infection after open fractures: (1) retention of devitalized or infected bone (sequestrum), (2) presence of dysvascular or infected soft tissues, (3) dead space in the surgical site, and (4) inadequate soft tissue coverage. The successful treatment of any form of osteomyelitis depends on radical débridement of devitalized bone, the poorly vascularized surrounding soft tissue (scar), and the infected granulation tissue. Once a healthy wound bed is obtained, the method for coverage of the open wound can be determined.

Stark first described muscle flap coverage for chronic osteomyelitis wounds in 1946 (5). Ger further documented the efficacy of muscle coverage for tibial osteomyelitis (6). The work of Chang and Mathes (7) and later Feng and associates (8) gave a physiological explanation for the improved results. In animal studies, they showed that muscle flaps were significantly more effective than random skin flaps in reducing bacterial counts and, thereby, more resistant to soft tissue infection. They also found that the oxygen tension of the wounds covered by vascularized muscle flaps was higher than that of wounds covered by random pattern flaps.

The successful treatment with aggressive débridement of all pathological tissue and the obliteration of dead space, combined with muscle flap coverage of such wounds and delayed osseous reconstruction, has been described by a number of investigators (9–11). These principles have now become axiomatic in the management of severe extremity trauma and posttraumatic osteomyelitis. The ability to perform free tissue transfer for coverage of complex extremity wounds has significantly expanded the possibilities for limb salvage in this setting.

II. WOUND COVERAGE TECHNIQUES

Once adequate débridement has been performed and all infected and potentially infected tissue has been removed, the resulting defect should be examined to determine the reconstructive procedure required to close the wound. The fundamental principles of the reconstructive ladder should be kept in mind. However, in most cases, after adequate débridement has been completed, the wounds are too large or too complicated for simple primary closure or skin grafting to complete the function of both closure of the wound and obliteration of the dead space resulting from the débridement. Most cases require the pedicled or free transfer of vascularized tissue to restore blood supply, replace lost or devitalized tissues, and provide stable coverage to these complex wounds.

The location and size of the defect, as well as the structures exposed, determine the nature of the reconstruction. Various local and distant flaps both free and pedicled have been described for wound coverage.

III. LOCATION-BASED WOUND RECONSTRUCTION

A. Upper Extremity

Most cases of osteomyelitis in the upper extremity are secondary to trauma or postoperative infections, especially in the presence of hardware.

1. Forearm

Open wounds over the forearm with exposed bone, nerve, or tendon substance require vascularized tissue coverage either from local or distant flaps (12). Local flaps available for soft tissue coverage of the forearm include the radial forearm flap, ulnar artery flap, posterior interosseous flap, lateral arm flap, and brachioradialis muscle flap. The distant pedicled flaps described include the groin flap, deltopectoral flap, and axial pattern hypogastric or thoracoepigastric flap. These flaps require two stages for closure of wounds. A pedicled latissimus dorsi muscle

or myocutaneous flap can be used for coverage of proximal forearm and elbow defects. Larger defects warrant the use of free tissue transfer for coverage. Either muscular free flaps (rectus abdominis, latissimus dorsi, gracilis) or fasciocutaneous free flaps (parascapular, scapular, lateral arm) can be used, depending on the soft tissue requirements (13).

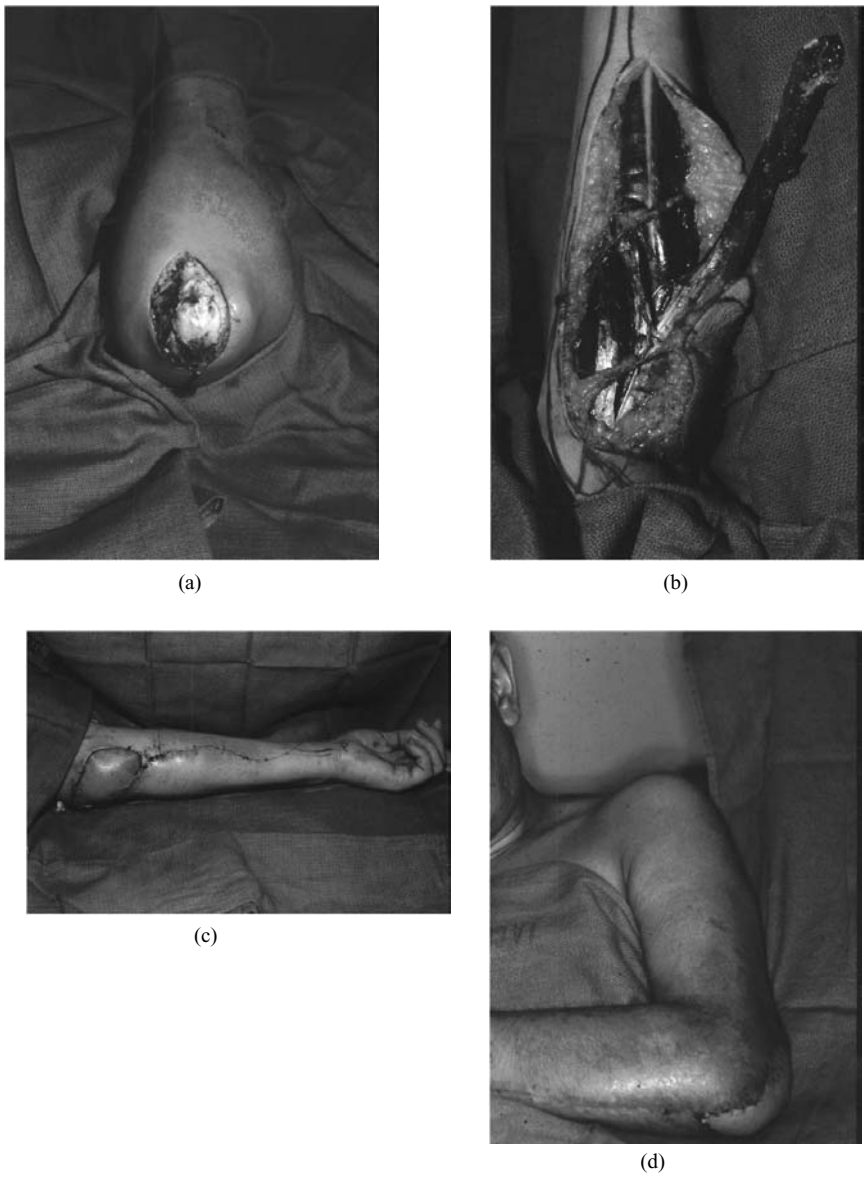
2. Elbow

Open wounds about the elbow require special attention because of the elasticity of the tissues normally found in the area and the wide range of motion required over the joint. Depending on the size of the defect, local, regional, or free flaps can be designed for wound coverage. The flexor carpi ulnaris muscle or myocutaneous flap (Fig. 1) based on the ulnar recurrent artery can be used to address defects in and about the olecranon as well as those in the antecubital fossa. The brachioradialis muscle is another reliable local flap for coverage around the elbow, especially for radial defects. Other local flaps include the radial forearm, ulnar artery, posterior interosseous, and lateral arm flaps.

The latissimus dorsi muscle or myocutaneous flap is the most frequently used pedicled flap for coverage of large composite wounds of the elbow. When islandized on its peclicle, the muscle flap can reach the proximal third of the forearm and can cover all composite defects of the olecranon or antecubital fossa. It can also be transferred as a functional unit to restore elbow flexion or extension as needed. Other pedicled flaps, which are very rarely used, include the serratus anterior muscle flap and the "distant pedicle two-stage flaps" such as the groin flap or other thoracoabdominal flap. Larger defects are more ideally covered with free tissue transfer of either muscle or skin and fascia. Depending on the size of the defect, we prefer to use the flexor carpi ulnaris locally, the latissimus dorsi muscle regionally, and the rectus abdominis muscle as a free tissue transfer. Functional restoration at the elbow can be achieved with either the latissimus dorsi or the gracilis (14).

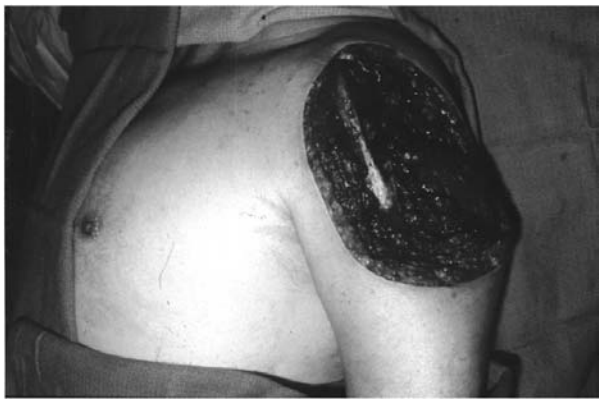
3. Upper arm and shoulder

Osteomyelitis of the humerus or shoulder joint is rare, and when vascularized soft tissue coverage is required, a pedicled latissimnus dorsi muscle or myocutaneous flap (Fig. 2) can be taken from the ipsilateral side. When the flap is isolated on its pedicle, both the origin and the insertion of the muscle can be released to allow coverage of the entire volar or dorsal surface of the upper arm, with extension of the muscle into the proximal forearm. The pectoralis major muscle or myocutaneous flap can also be used for these defects, but the arc of rotation is smaller and the donor site scar is more noticeable (15).



(a) (b) (c) (d)

Figure 1 (a) Recurrent, infected olecranon bursitis leading to ulnar osteomyelitis. (b) Flexor carpi ulnaris myocutaneous flap for coverage of the proximal ulna. (c) Full flap inset. (d) Flexor carpi ulnaris flap (different patient) well healed with range of motion preserved.



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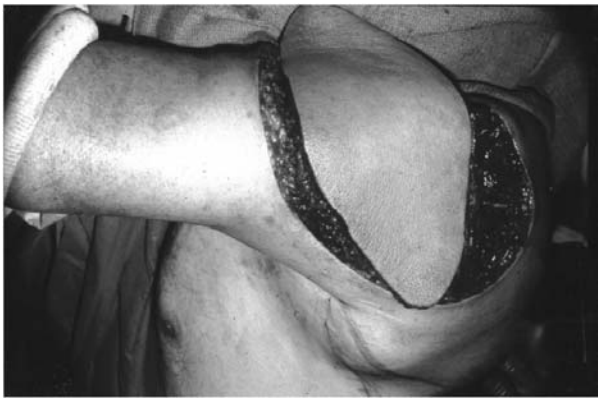

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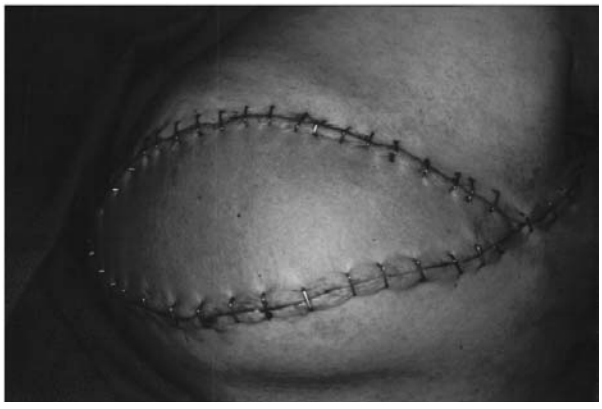


(c)

Figure 2 (a) Severe proximal humeral destruction with subsequent recurrent infection after resection. (b) Latissimus dorsi myocutaneous flap transposed for coverage. (c) Latissimus dorsi flap inset.

B. Lower Extremity

Most cases of osteomyelitis involve the tibia. Other sites of involvement include the tarsal bones, fibula, femur, and hip joint. Most cases are posttraumatic, but osteomyelitis can be seen postoperatively and from hematogenous seeding as a sequela of bacteremia from a primary source of infection elsewhere in the body. No matter what the cause, the treatment remains standard. The institution of intravenous antibiotics, débridement of infected, nonviable bone; and soft tissue and vascularized wound coverage are the basis for treatment of this disease process.

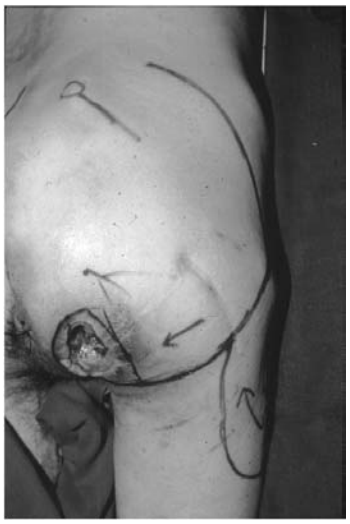
1. Pelvis

An unfortunate and extremely debilitating sequela to spinal cord paralysis, either paraplegia or tetraplegia, is decubitus ulceration, or pressure sores. If not addressed early, these pressure-induced skin breakdowns can rapidly progress to involve subcutaneous tissue, muscle, and bone. A basic understanding of the decubitus classification is mandatory for understanding of the progression of this disease process (Table 1).

Stage IV decubiti occur in three main areas: the sacrum, trochanter, and ischium. Other less frequent locations include the calcaneous and occiput. Once the bone is exposed, it must be treated in the same manner as any type of posttraumatic osteomyelitis (Fig. 3). Radical débridement of all involved bone with special attention to the removal of any bony prominences is the first priority. Culture-specific antibiotics must be started as soon as possible. This type of chemotherapy is an important adjunct to, but not a replacement for, aggressive surgical intervention. Once a clean wound is achieved, myocutaneous flap coverage can proceed. In nearly all circumstances, local flaps can be used to close these wounds. An overall strategy must be well thought out, given the recurring nature of pressure sores in this population. It is not unusual to encounter two or three recurrences of a specific decubitus over the life of an adult paraplegic

Table 1 Pressure Sore Staging

Pressure sores	Stages
Stage I	Erythema of affected skin, no ulceration
Stage II	Superficial ulceration, partial-thickness loss, no exposure of underlying structures
Stage III	Full-thickness skin loss, potential subcutaneous tissue involvement
Stage IV	All layers involved, including subtending muscle and bone, probable osteomyelitis



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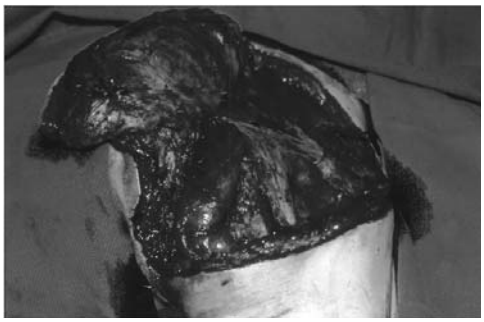

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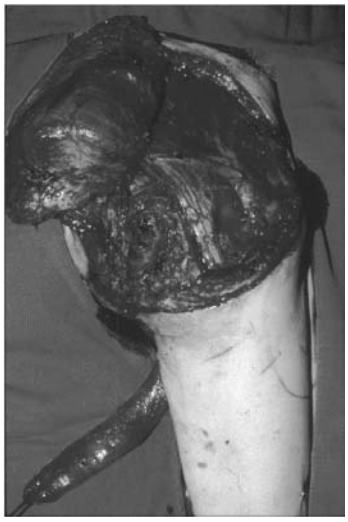

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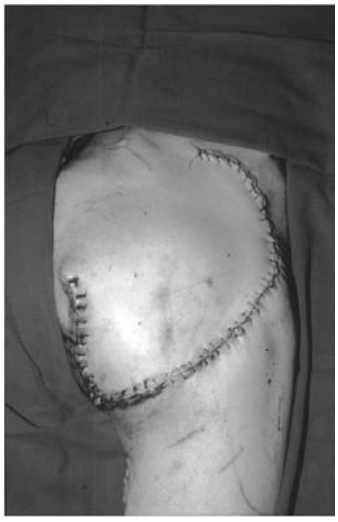


(d)

Figure 3 (a) Stage IV ischial pressure sore with loss of skin, subcutaneous tissue, and muscle and exposure of the bone with obvious osteomyelitis. (b) After radical débridement of all involved tissues, the gluteus maximus myocutaneous flap is raised on the superior gluteal artery. The gracilis muscle is also isolated. (c) The gracilis muscle is used to fill the deep dead space, while the gluteus is rotated to close the wound. (d) The appearance of the ischial area after completion of the transfers and wound closure.

patient. Table 2 summarizes various options for the three major pressure sore locations. The sacrum can be covered by numerous variations of the gluteus maximus myocutaneous flap, either rotated, transposed, or advanced. Other options include the distally based latissimus dorsi. The gluteus also works well as a rotation flap for pressure ulcers located in the trochanter region. The tensor fasciae latae is extremely reliable and can be reused in various circumstances. The vastus lateralis provides good muscle bulk but is a thicker dissection with a somewhat higher donor site morbidity incidence. The rectus abdominis muscle can be rotated down from the abdomen or the rectus femoris, in small lesions, from the anterior thigh. Ischium lesions are usually smaller in size but should not be underestimated in complexity. Options for closure of these defects include the gluteus, gracilis, and biceps femoris.

Ultimately, to be successful with these problem wounds, the surgeon must underscore to the patient the importance of patient education and compliance in pressure and shear stress avoidance.

Once reliable wound closure has been achieved through one of the preceding options, these patients enter a critical phase of their rehabilitation. The postoperative recovery period includes a prolonged phase (3 to 6 weeks) of direct pressure avoidance through the use of air fluidized beds. In addition, antispasmodics, such as baclofen, should be prescribed early to prevent tetanic contractures. Rehabilitation training must focus on pressure avoidance in all activities of daily living. Family and social support, often lacking in this population, must be investigated and maximized if possible. Recurrence after several years that is temporally related to an acute destabilization of the background social environment is not unusual.

Table 2 Pressure Sore Coverage Options

Location	Muscle flap option
Sacrum	Gluteus: rotation, advancement transposition
	Reversed latissimus dorsi
Trochanter	Gluteus
	Tensor fasciae latae (TFL)
	Vastus lateralis
	Rectus abdominus
	Rectus femoris
Ischium	Gluteus
	Graciles
	Biceps femoris

2. Hip and proximal/lateral thigh

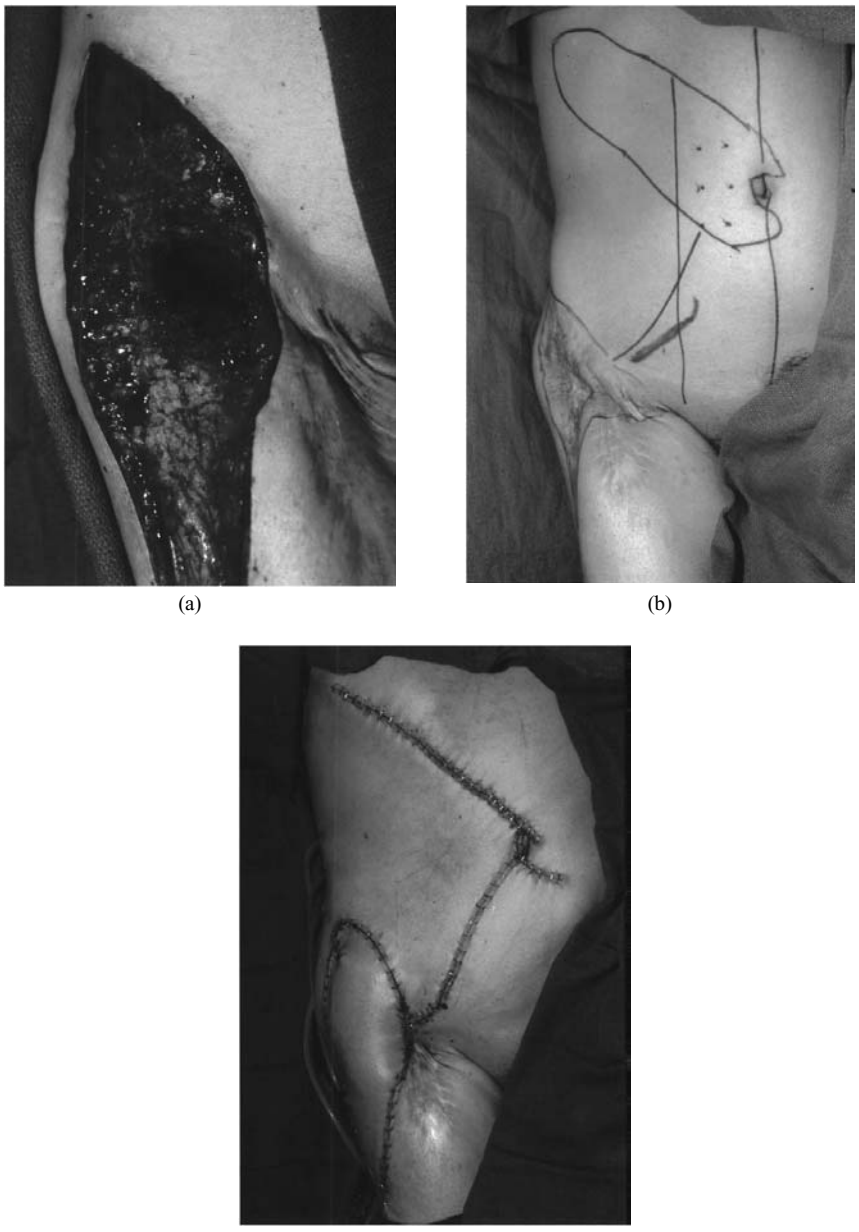
Hip and proximal/lateral thigh wounds usually result from complications in the management of hip fractures or arthroplasty, or from pressure necrosis over the greater trochanter or sacrum. Therefore, hip wounds often require vascularized coverage of exposed orthopedic hardware or obliteration of dead space after the removal of infected prostheses. Local lower extremity muscle or myocutaneous flap options include the tensor fasciae latae (TFL), vastus lateralis, and rectus femoris flaps, all of which are based on the lateral circumflex femoral artery. The vastus lateralis flap provides a larger bulk of muscle and can provide a skin paddle overlying its proximal half (16). This flap has the functional advantage of producing little or no effect on ambulation when mobilized and can reach most of the inferior and posterior pelvis. It is useful for large soft tissue defects and is commonly employed to fill the dead space created by Girdlestone resection of the femoral head. The rectus femoris flap is easily mobilized and has a fairly wide arc of rotation and can be elevated with a small skin paddle that allows primary closure of the donor site. It does not provide as much bulk as the vastus lateralis and is associated with some loss of strength in knee extension.

An excellent alternative for closure of large hip defects, particularly after explantation of an infected hip prosthesis, is the extended deep inferior epigastric (EDIE) flap. The EDIE flap is essentially a vertical rectus abdominis myocutaneous flap (Fig. 4), elevated with a random cutaneous extension adjacent to the paraumbilical perforators (17). Either a portion, or all, of the large cutaneous paddle may be deepithelialized for use in filling extensive soft tissue defects. Its arc of rotation may extend as far inferiorly as the knee. This versatile flap should be considered when local lower extremity muscle flaps are unavailable, inadequate in size, or considered to be unreliable because of vascular disease or prior radiation (18,19,20).

When the nature of the wound and/or potential donor sites precludes the use of pedicled flaps, free tissue transfer is indicated. The latissimus dorsi free flap (Fig. 5) is an obvious first choice since it provides the maximal possible soft tissue coverage and a donor site that is anatomically remote from the wound. A potential problem with microsurgical tissue transfer to this area is the availability of easily accessible, reliable recipient vessels.

3. Mid Thigh

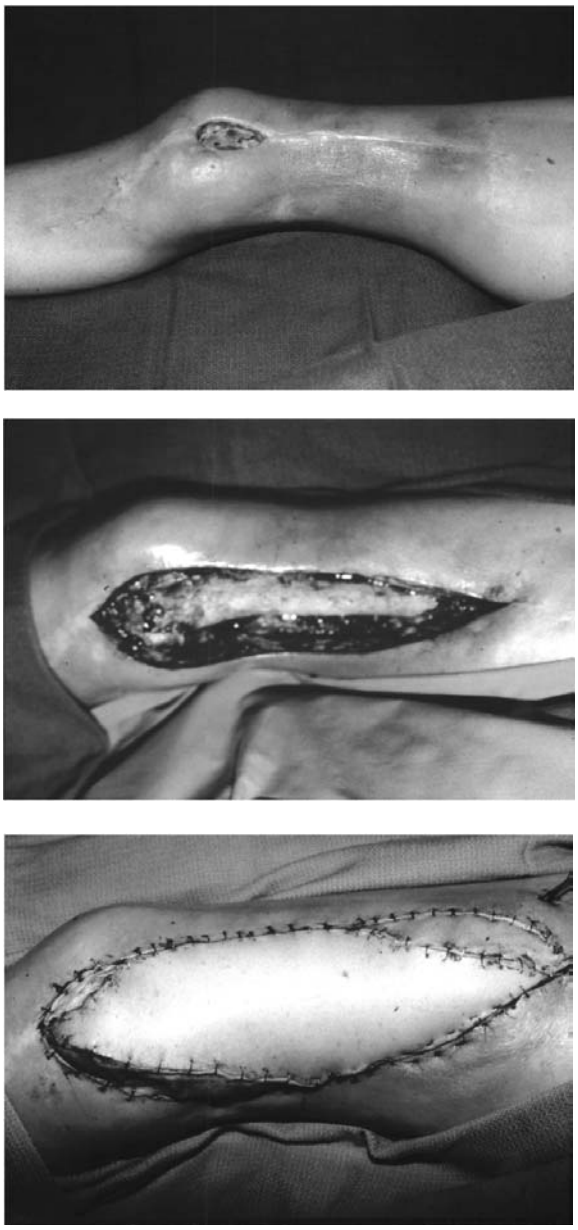
Wounds of the midthigh can often be closed with skin grafts or local fasciocutaneous flaps since a thick envelope of soft tissue protects the femur. Exposure of a femoral fracture or orthopedic hardware, however, requires well-vascularized muscle flap coverage. The TFL, vastus lateralis, and rectus femoris flaps may all be useful for midthigh wounds, if the lateral circumflex femoral pedicle is intact. The gracilis flap, based on the medical circumflex femoral artery, is available for



(a) (b)

(c)

Figure 4 (a) Deep space acetabular osteomyelitis. (b) Preoperative large skin and soft tissue deficiency as well as planned rectus abdominis myocutaneous flap. (c) Flap inset with donor site closure. Patient eventually had successful total hip replacement surgery.



(a)

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Figure 5 (a) Massively irradiated, infected distal femur with compromised soft tissue envelope after treatment of malignant fibrous histiocytoma. (b) After resection of involved tissues. (c) Latissimus dorsi myocutaneous free flap used for coverage.

coverage on the medial aspect of the thigh. Although it does not provide a great deal of muscle bulk, the gracilis can be "unfurled" by careful longitudinal dissection of intramuscular septae in order to cover broad defects. The vastus medialis muscle flap is supplied by perforators from the profunda femoris proximally and the superficial femoral artery distally and cannot be rotated on a vascular pedicle. However, it may be mobilized on its perforators and transposed medially for coverage of the femur. When left attached proximally, it may be used for reconstruction of the patellar tendon and restoration of knee extension (21,22). The rectus abdominis muscle and, more specifically, the EDIE flap are useful in circumstances involving extensive soft tissue loss. With recurrent infection of an underlying fracture requiring wide soft tissue débridement, free tissue transfer may be the best management option. As opposed to conditions in the hip area, in the thigh adequately sized and easily accessible vessels for inflow and outflow are usually available.

4. Knee

The femur flares distally into medial and lateral condyles, and the soft tissue envelope surrounding it tapers accordingly. This area is at or beyond the limit of the arc of rotation or the previously described rotation flaps. For coverage of exposed fractures and hardware at this level, an extended medial gastrocnemius muscle or myocutaneous flap is useful (Fig. 6). This flap incorporates a random fasciocutaneous extension of the usual gastrocnemius skin paddle and can effectively cover wounds at and just proximal to the level of the femoral condyles. In general, the skin paddle of the medial gastrocnemius flap is reliable up to 10 cm above the medial malleolus. In unusual circumstances, the skin paddle can be extended to within 5 cm above the malleolus by utilizing a delay procedure. This requires an additional procedure, usually 10 to 14 days before the actual flap rotation, in which the skin paddle is incised, then reapproximated, thus restricting skin vascularity to the subtending muscle.

5. Lower leg: proximal third tibia

Proximal tibial defects may usually be covered with a medial or lateral gastrocnemius muscle or myocutaneous flap, or a combination of the two. These muscles have a dominant proximal vascular pedicle, the medial and lateral sural arteries, respectively, and when completely islandized on their pedicles they may reach most wounds adjacent to the knee. These flaps are extremely reliable, and easily elevated and pose no functional deficiency if one muscle is mobilized. Perpendicular scoring of the fascial envelope of the gastrocnemius muscle, particularly on its undersurface, adds some length and width to the muscle belly. If both muscles are elevated as flaps, many patients demonstrate weakness in ankle plantar flexion. If the soleus muscle flap is used along with the medial or

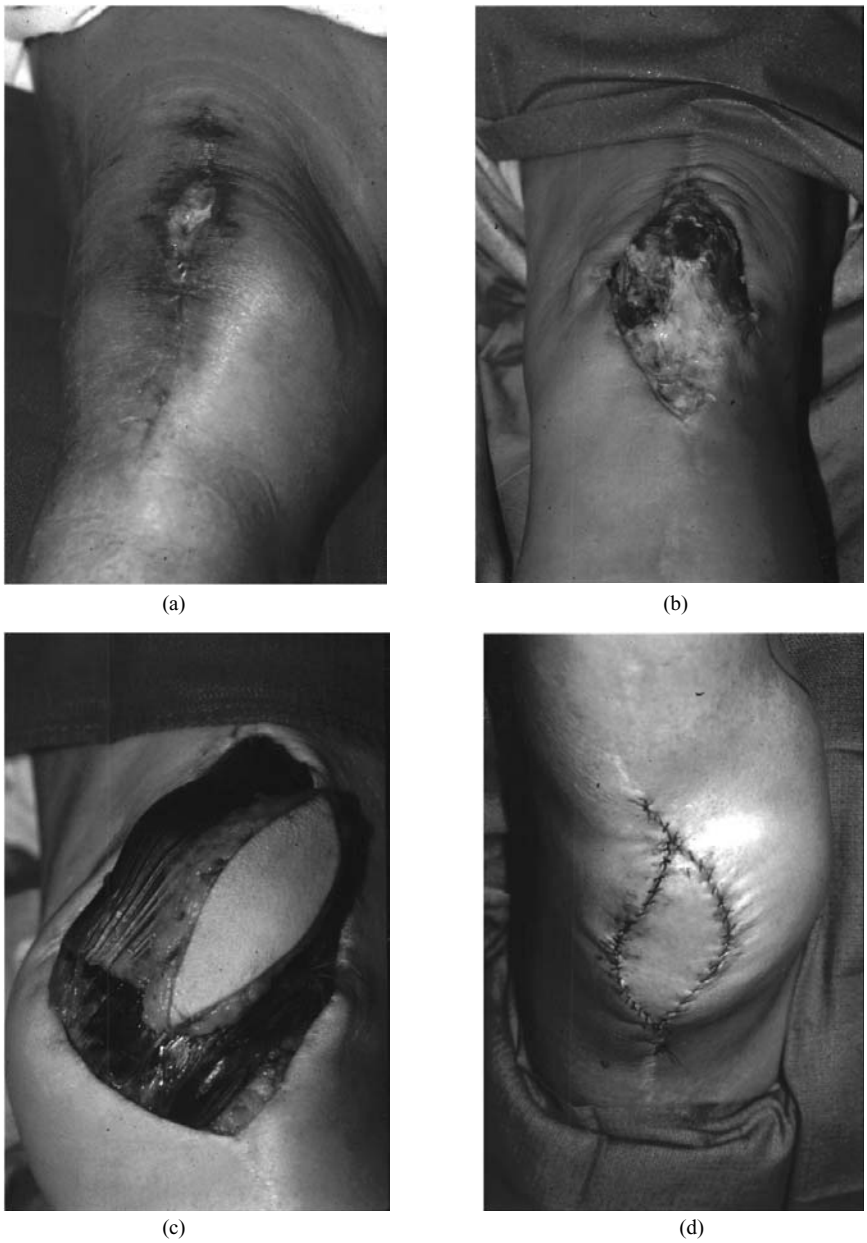


Figure 6 (a) Sinus tract from an infected total knee arthroplasty. (b) After resection and explantation with placement of an antibiotic spacer. (c) Transposition of gastrocnemius myocutaneous flap for coverage. (d) Completed inset.

lateral gastrocnemius flap for an extensive defect of the proximal to midtibia, a minimal to moderate functional defect results if one head of the gastrocnemius remains in situ. A cutaneous paddle can be raised with the muscle easily and may, in certain cases, obviate the need for skin grafting.

Other local muscle flaps have been described, such as a bipedicled tibialis anterior transposition flap; however, none has gained wide clinical use because of questionable reliability. A wide variety of fasciocutaneous flaps, based on superficial perforating vessels from the deep arterial system, such as the saphenous artery and sural artery flaps, have been reported. These flaps are less reliable than muscle flaps, may create unfavorable donor defects, and have a higher rate of complications (23). Proximal third tibia and knee defects that cannot be closed by using gastrocnemius flaps generally require free tissue transfer, most often a rectus abdominus or latissimus dorsi muscle flap with skin graft. Extremely large defects may require transfer of a free EDIE flap, which may allow recontouring of wounds with large skin and subcutaneous tissue defects, or a combined latissimus dorsi–serratus anterior flap, which can be transferred on a common pedicle.

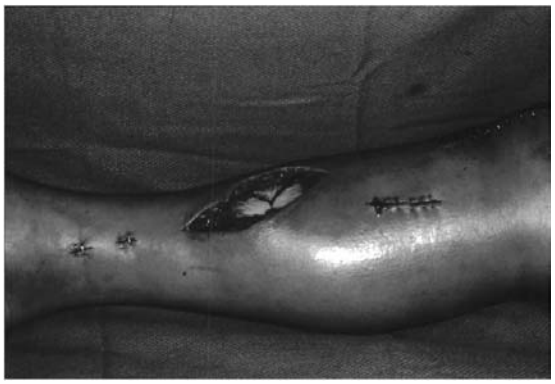
6. Lower leg: middle third tibia

The soleus flap (Fig. 7) can be raised only as a muscle flap and is the workhorse for coverage of middle third tibia defects. Like the gastrocnemius flap, the soleus flap is reliable and easily raised. Its bipennate morphological character allows the soleus to be split into a larger medial and a much smaller lateral hemisoleus flap (24). In our experience, however, there appears to be no advantage to bisecting the soleus in most situations. The soleus has a proximal dominant vascular supply from branches of the popliteal artery, and a secondary distal supply from branches of the posterior tibial artery.

A reversed soleus flap, based on the inferior circulation, for coverage of lower tibial and heel defects has been described (25); however, the reliability of this flap is questionable. As mentioned, large defects may require a combination of a soleus and a medial or lateral gastrocnemius flap. In these circumstances, it is usually more appropriate to choose free tissue transfer using either the rectus abdominus or latissimus dorsi muscles.

7. Lower leg: lower third tibia

Although distally based fasciocutaneous flaps may be adequate for small wounds of the distal third of the lower leg, most wounds involving significant tibial exposure and essentially all open tibial fractures require coverage by free tissue transfer. This is particularly true in the setting of osteomyelitis. Again, the rectus abdominus (Fig. 8) or latissimus dorsi free flaps are most commonly employed for large three-dimensional defects, especially when segmental tibial defects must be filled before formal osseus reconstruction. The gracilis flap is also readily



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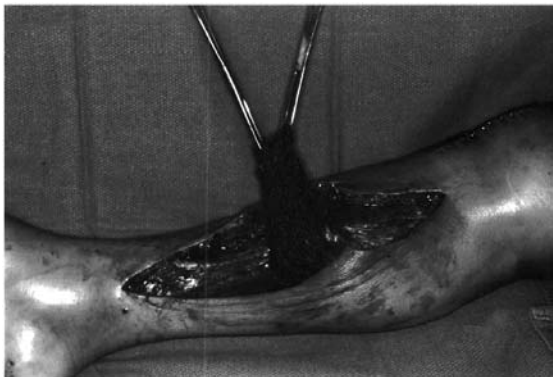

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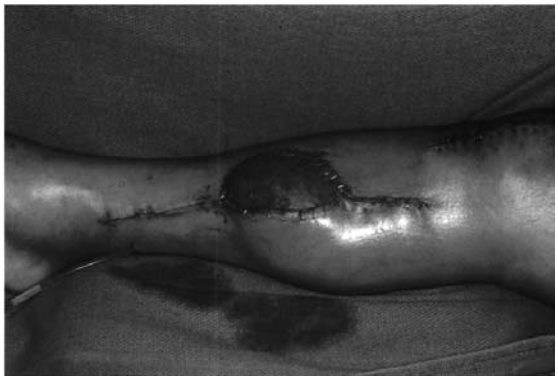


(c)

Figure 7 (a) Open type IIIB middle third tibial fracture after IM nailing. Notice devascularized butterfly fragment. (b) Elevation and rotation of soleus muscle for coverage. (c) After inset of soleus muscle and placement of a split-thickness skin graft.

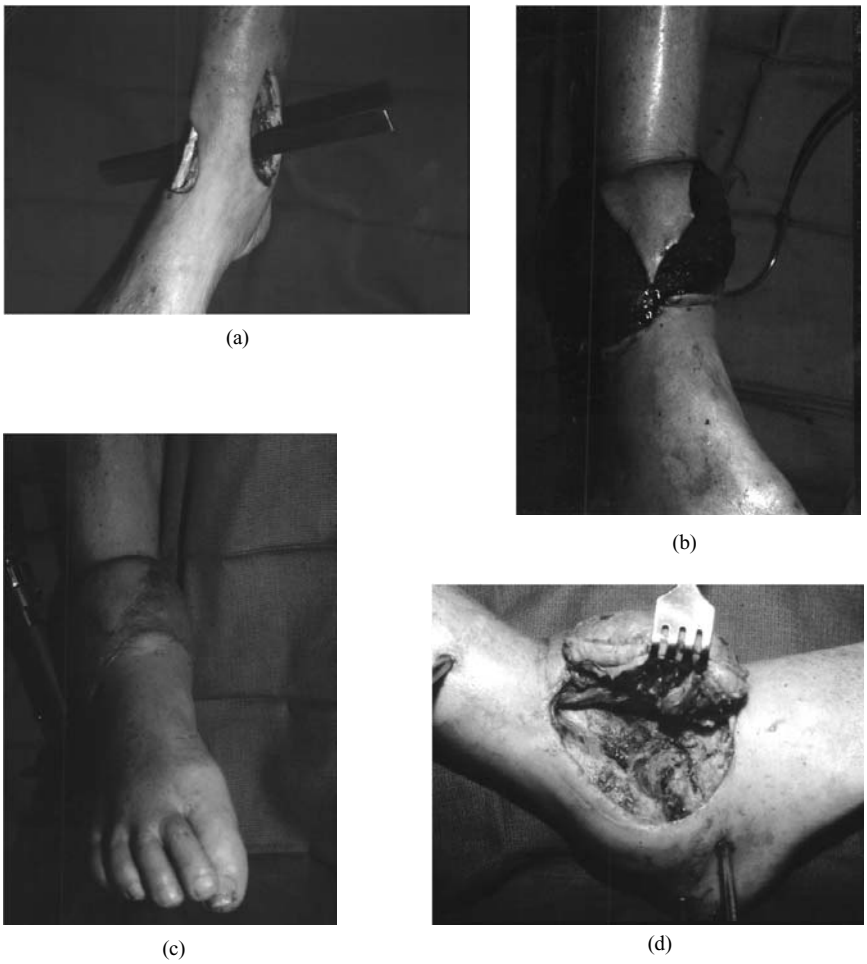


Figure 8 (a) Complex through-and-through deformity after radical resection of persistent osteomyelitis of a distal tibial articular fracture. (b) Rectus abdominis free flap split longitudinally for coverage and simultaneous obliteration of the deep dead space. (c) Healed flap. (d) Delayed elevation for bone graft placement. The deep muscle transplant component is removed at this time.

available, reliable, and useful for small, narrow defects. Less commonly used, the scapular or parascapular fasciocutaneous free flaps are equally effective. The widespread application of early wound closure by free tissue transfer in the setting of comminuted, open distal third tibia fractures has resulted in a dramatic decrease in the incidence of osteomyelitis and subsequent amputation.

If thinner soft tissue coverage is required for recontouring of defects in this area, the radial forearm and temporoparietal fascia free flaps are easily raised and reliable. The fasciocutaneous flaps described previously for smaller defects are essentially distally based reverse-flow flaps that are perfused by septocutaneous perforators from the tibial or peroneal vessels. Great care must be taken to preserve the tenuous inflow to these flaps during elevation, and flap design should be such that the flap length does not greatly exceed the width.

8. Foot

Hidalgo and Shaw (26) have developed a classification system for foot injuries that quantifies soft tissue deficits as well as associated osseus injuries and divides the foot into four separate areas for reconstruction. Type I injuries involve limited soft tissue loss only, type II injuries include major soft tissue deficits with or without distal amputation, and type III injuries are those with major soft tissue loss and accompanying open fracture(s) of the ankle, calcaneus, or bimalleolar area. The foot is divided anatomically into the Achilles and malleolar area, the heel and midplantar area, the distal plantar area, and the dorsum. For practical purposes, wounds resulting from débridement of infected tissue in the foot would be classified as type III wounds.

a. Achilles and Malleoli. Large type III wounds of the hindfoot, particularly those with exposed joints or fractures, require free muscle transfer for coverage. Paramount to the successful treatment of these injuries are adequate osseus débridement and stabilization. The gracilis muscle (Fig. 9) is especially well suited for this area because it is long and narrow, can be "unfurled" by dissection of the intramuscular septae to provide thin coverage, and can even be split transversely and transferred as two separate free flaps, by using a minor distal pedicle to revascularize the distal half of the muscle. The rectus abdominis (Fig. 10) and latissimus dorsi are also reliable and readily available.

b. Heel and Midplantar Area (Proximal Weight-Bearing Areas). Most defects require free tissue transfer, and in the case of the weight-bearing surface of the foot, free muscle flaps covered with split-thickness skin grafts may be more stable and functional than fasciocutaneous flaps. Although such flaps are initially insensate, neurotization along vascular channels with subtotal return of various sensory modalities has been widely reported in free tissue transfer, and it is possible that some degree of proprioception will return. May and colleagues (27) have reported on nine patients who underwent this technique of reconstruction for wounds of the weight-bearing heel or sole and noted plantar wound breakdown or ulceration in only one patient over an average follow-up interval of 19 months.

c. Distal Plantar Area and Forefoot. Most wounds of the distal plantar area require free tissue transfer for coverage. Plantar flaps cannot be sufficiently

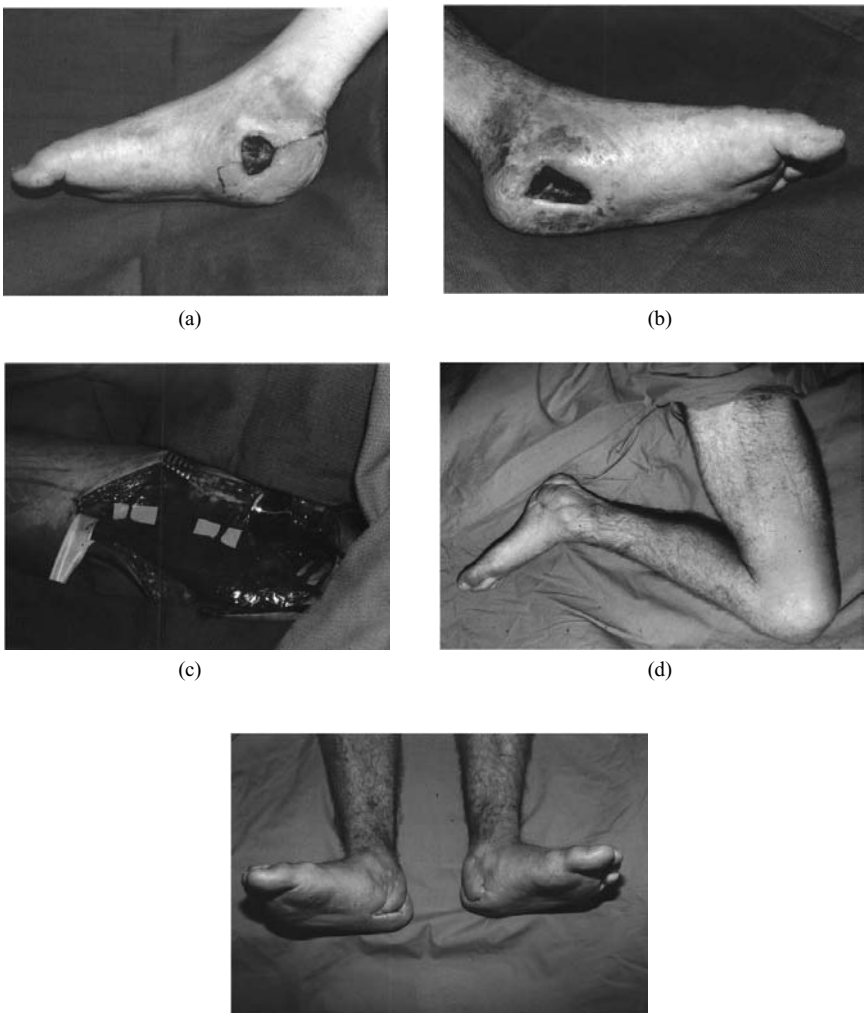


Figure 9 (a) Calcaneal osteomyelitis with overlying eschar after open reduction and internal fixation (ORIF). (b) Radiograph showing fracture with reduction and hardware. (c) After débridement. (d) Closed with small segment gracilis muscle flaps and full-thickness skin graft. (e) Healed wounds.

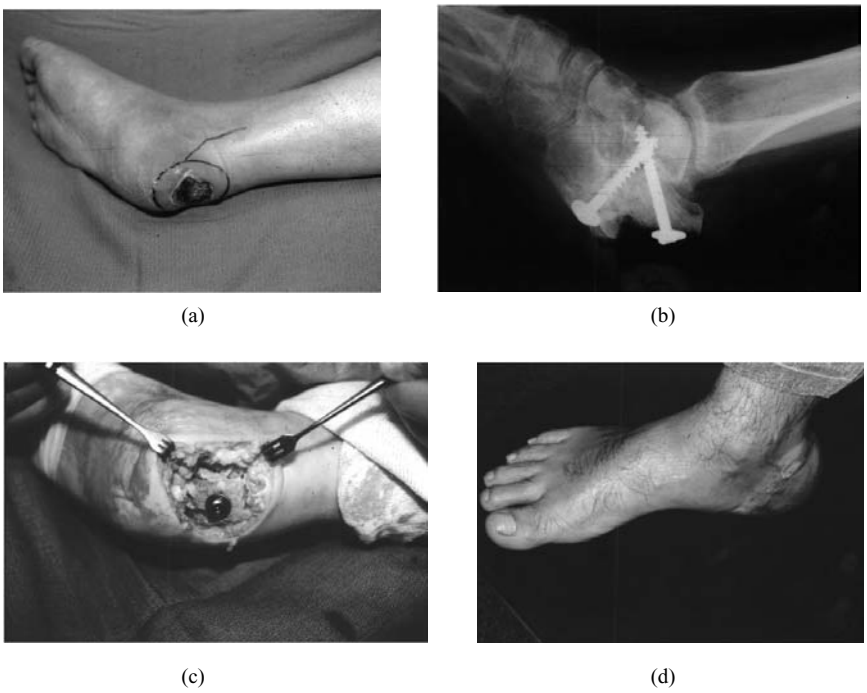
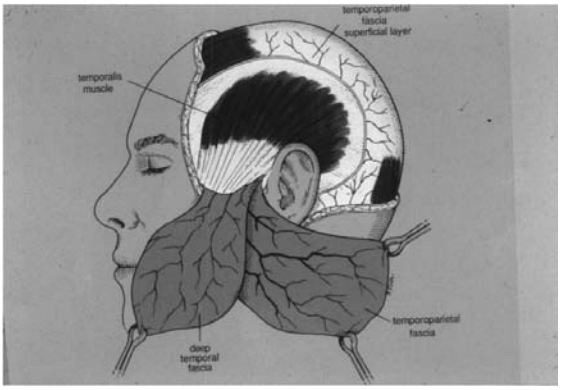


Figure 10 (a) Bilateral calcaneal osteomyelitis in a jumper (right foot shown). (b) Left foot. (c) Gracilis muscle showing major pedicle on right, minor pedicles middle and left. (d) Donor site of single donor for two recipient sites. Healed. Grafted hemigracilis shown on left hindfoot. (e) Bilateral healed recipients from a single gracilis muscle donor.

mobilized distally because of a tethering effect by the plantar nerves that innervate them. As for the proximal weight-bearing foot, free muscle flaps with split-thickness skin grafts appear to provide the more stable, durable coverage.

d. Dorsum. For deep wounds in the adult, thin fasciocutaneous flaps such as the temporoparietal fascia flap (TPF), radial forearm flap, or parascapular flap provide a more aesthetic reconstruction than muscle flaps with skin grafts. The TPF flap is ideally suited for those defects for which minimal bulk is required such as the dorsum of the foot or the malleolus, where vital structures such as tendon, bone, and nerve run just below the skin surface. The real advantage in this type of reconstruction is the retained ability of the patient to use normal footwear (Figs. 11 and 12). However, in cases of severe injuries associated with open fractures (type III), coverage with a muscle free flap may be prudent. Surprisingly, in young children, the latissimus is nearly ideal for reconstructing these subtypes.



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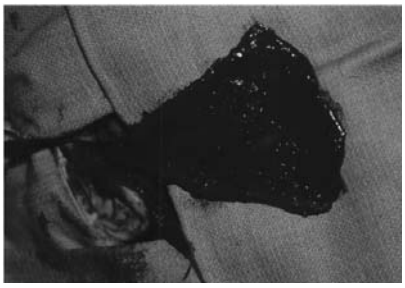

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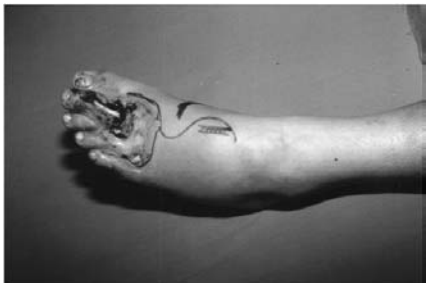

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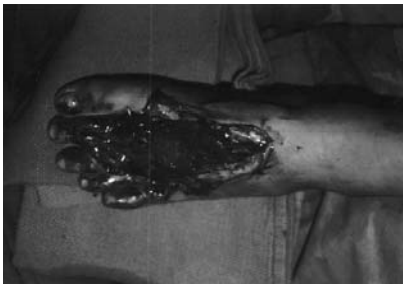

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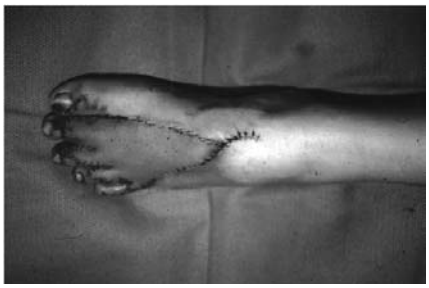
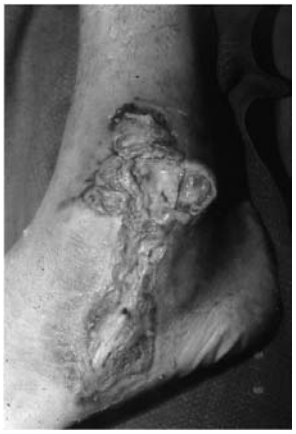


(e)

Figure 11 (a) Temporoparietal fascial flap (TPF) is an excellent donor when minimal bulk is desirable. If needed, the deep temporal fascia can be taken to develop a bilaminar construct. (b) TPF flap is dissected out. (c) Crushed, infected metatarsophalangeal (MTP) joint with surrounding soft tissue loss. (d) After débridement and placement of TPF flap. (e) Covered with a split-thickness skin graft maintaining normal contour.



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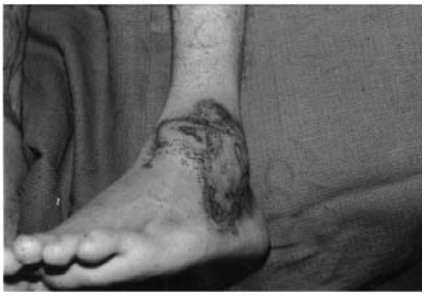

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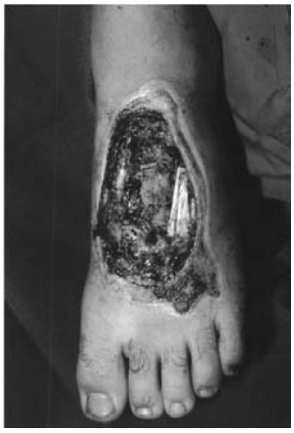

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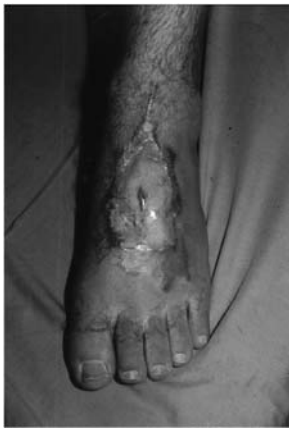
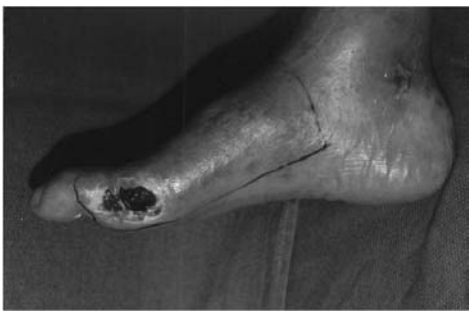


(i)

Figure 11 (f) Infected ankle joint. (g) Healed with TPF flap and a split-thickness skin graft. Notice normal contour, minimal bulk. (h) Dorsal composite wound with exposed tendons, bones, and joint. (i) Well-healed TPF flap with a split-thickness skin graft, producing no additional bulk.

IV. FLAP ELEVATION FOR SECONDARY ILIAC CREST BONE GRAFTING

After adequate wound coverage, antibiotic therapy is continued for a further 2 to 6 weeks. We have found 3 to 4 weeks of intravenous antibiotics to be adequate for most patients. Weiland and coworkers (28) stated the importance of increased



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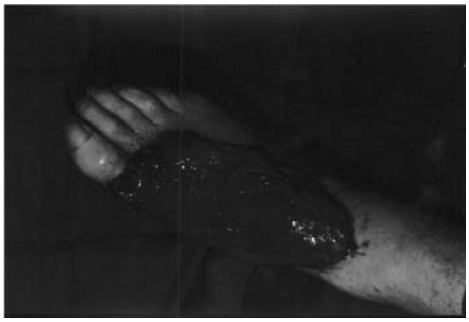

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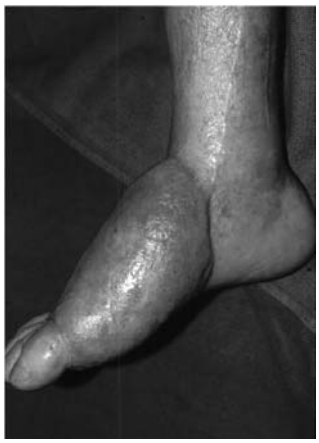

(c)

Figure 12 (a) Infected, irradiated, and exposed first metatarsophalangeal (MTP) joint and extensive surrounding soft tissue damage after treatment of melanoma. Patient also received regional chemotherapy perfusion with hyperthermia. (b) Radical débridement with placement of rectus abdominis muscle flap. (c) Healed and stable with a split-thickness skin graft. A modified shoe was built.

vascularity in the wound bed from the muscle flaps, which, in turn, aid in better incorporation of subsequent bone grafting. Before the advent of flap coverage for these types of injuries, the standard practice was to bone graft indirectly through a separate posterior approach. Posterior lateral bone grafting for the treatment of these large bony defects was hampered by the long delay in attempting to achieve closure of the primary wound by secondary intention and biomechanically by application of the bone graft in an area other than the direct diaphyseal shaft defect. The restoration of a vascularized soft tissue envelope has allowed the

orthopedic traumatologist to bone graft directly at the fracture site in a timely fashion. We wait approximately 6 weeks before performing bone grafting in cases with large bony defects. This interval permits control of infection as well as a decrease in the muscle edema.

Although simultaneous iliac crest bone grafting and vascularized wound closure with favorable results have been reported, the accepted standard of treatment at this time is early secondary iliac crest bone grafting 4 to 6 weeks after successful wound closure. The procedure is performed with both the orthopedist and plastic surgeon's participation. With the extremity under tourniquet control, the previously transferred flap can be elevated with care taken to maintain the vascular pedicle. Any muscle component that is used for the obliteration of the osseous dead space can then be directly excised. The iliac crest bone graft is then packed into the osseous defect directly, obliterating the diaphyseal defect completely. Wound cultures are taken to determine whether any persistent deep space infection is present; if so, this finding might then alter the postoperative antibiotic strategy. The flap is resutured under tourniquet control after placement of drains. Tourniquet release before wound closure after iliac crest bone grafting is not recommended because the rapid onset of flap swelling impairs wound closure and compromises the primary objective. Appropriate bulb suction drainage allows for the evacuation of any residual bleeding under the flap.

V. SUMMARY

In conclusion, high success rates (97%) can be achieved in the treatment of osteomyelitis via a team approach with the active participation of orthopedic surgeons, plastic surgeons, and infectious disease specialists. Successful results can be obtained by specific systemic antibiotic therapy, débridement of all nonviable tissues, stabilization of the fracture or nonunion with an external fixator, and local and free tissue transfers followed by autogenous bone grafting, when needed (29).

REFERENCES

1. JW May Jr, GG Gallico III, FN Lukash. Microvascular transfer of free tissue for closure of bone wounds of the distal lower extremity. N Engl J Med 306:253–257, 1982.
2. JW May Jr, GG Gallico III, J Jupiter, RC Savage. Free latissimus dorsi muscle flap with skin graft for treatment of traumatic chronic bony wounds. Plast Reconstr Surg 75:641–651, 1984.

3. JR Moore, AJ Weiland. Vascularized tissue transfer in the treatment of osteomyelitis. Clin Plast Surg 13:657–662, 1986.
4. R Ger, G Efron. New operative approach in the treatment of chronic osteomyelitis of the tibial diaphysis: a preliminary report. Clin Orthop 70:165–169, 1976.
5. WJ Stark. The use of pedicled muscle flaps in the surgical treatment of chronic osteomyelitis resulting from compound fractures. J Bone Joint Surg 28:343, 1946.
6. R Ger. Muscle transposition for treatment and prevention of chronic post-traumatic osteomyelitis of the tibia. J Bone Joint Surg 59A:784791, 1977.
7. N Chang, SJ Mathes. Comparison of the effect of bacterial inoculation in musculocutaneous and random pattern flaps. Plast Reconstr Surg 70:1–10, 1982.
8. L Feng, D Price, D Hohu, et al. Blood flow changes and leukocyte mobilization in infections: a comparison between ischemic and well-perfused skin. Surg Forum 34:603, 1983.
9. H Byrd, G Cierney, J Tebbetts. The management of open tibial fractures with associated soft tissue loss: External pin fixation with early flap coverage. Plast Reconstr Surg 68:73–79, 1981.
10. H Byrd, T Spicer, G Cierney. Management of open tibial fractures. Plast Reconstr Surg 76:719–728, 1985.
11. R Gustilo, J Anderson. Prevention of infection in the treatment of one thousand and twenty five open fractures of long bones. J Bone Joint Surg 58A:453–458, 1976.
12. RC Russell, WA Zamboni. Coverage of the elbow and forearm. Orthop Clin North Am 24:425–434, 1993.
13. PW Bray, MI Boyer, CVA Bowen. Complex injuries of the forearm. Hand Clin 13:263–278, 1997.
14. R Sherman. Soft tissue coverage for the elbow. Hand Clin 13:291–302, 1997.
15. HC Vasconez, S Oishi. Soft tissue coverage of the shoulder and brachium. Orthop Clin North Am 24:435–448, 1993.
16. R Dowden, J McCraw. The vastus lateralis muscle flap: technique and applications. Ann Plast Surg 4: 396–404, 1980.
17. DN Collins, KL Garvin, CL Nelson. The use of the vastus lateralis flap in patients with intractable infection after resection arthroplasty following the use of a hip implant. J Bone Joint Surg 69A(4):510–516, 1987.
18. G Taylor, R Corlett, J Boyd. The extended deep inferior epigastric flap: A clinical technique. Plast Reconstr Surg 72: 751–765, 1983.
19. M Gottleib, B Chandrasekhar, J Terz, R Sherman. Clinical applications of the extended deep inferior epigastric flap. Plast Reconstr Surg 78: 782–787, 1986.
20. T Wellisz, R Sherman, L Nichter, J Romano, J Lorant, B Chandrasekhar. The extended deep inferior epigastric flap for lower extremity reconstruction. Ann Plast Surg 30:405–410, 1993.
21. P Arnold, F Prunes-Carillo. Vastus medialis muscle flap for functional closure of the exposed knee joint. Plast Reconstr Surg 68:69–72, 1981.
22. G Tobin. Vastus medialis myocutaneous and myocutaneous-tendinous composite flaps. Plast Reconstr Surg 75: 677–684, 1985.
23. G Hallock. Complications of 100 consecutive fasciocutaneous flaps. Plast Reconstr Surg 88:264–268, 1991.

24. G Tobin. Hemisoleus and reversed hemisoleus flaps. Plast Reconstr Surg 76:87–96, 1985.
25. P Townsend. An inferiorly based soleus muscle flap. Br J Plast Surg 31:210–213, 1978.
26. D Hildago, W Shaw. Reconstruction of foot injuries. Clin Plast Surg 13:663–680, 1986.
27. JJ May, M Halls, S Simon. Free microvascular muscle flap with skin graft reconstruction of extensive defects of the foot: a clinical and gait analysis study. Plast Reconstr Surg 75: 627–639, 1985.
28. AJ Weiland, JR Moore, RK Daniel. The efficacy of free tissue transfer in the treatment of osteomyelitis. J Bone Joint Surg 66A:181–193, 1984.
29. MJ Patzakis, K. Abdollahi, R Sherman, PD Holtom, J Wilkins. Treatment of chronic osteomyelitis with muscle flaps. Orthop Clin North Am 24:505–509, 1993.

18

The Roles and Effectiveness of Adjunctive Therapy in the Management of Musculoskeletal Infections

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I. INTRODUCTION

Osteomyelitis is a difficult infection to treat effectively. Standard treatment includes radical local débridement and systemic antibiotics (1,2); bone grafts are performed secondary to fill bony defects. Bone grafts are invasive, and systemic antimicrobials are associated with potentially severe adverse effects. Failure of treatment or recurrence of disease often requires lower extremity amputation. Seabrook (3) demonstrated the limitations of systemic antibiotic treatment in diabetic foot infections. Antibiotics were not present in muscle tissue at surgical site in 14 of 26 diabetic patients given intravenous antibiotics 1 hour before débridement. Only 6 of 26 patients had therapeutic tissue levels of antibiotics in the foot.

One alternative method of systemic treatment is allowing higher therapeutic concentration of drugs that act locally and allow bone formation at the same time. In order to prevent toxicity and to minimize the need for long-term parenteral antibiotics, systems for local delivery of antibiotics have been used to

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overcome the limited penetration of systemic agents into poorly vascularized bone (4). Such systems include closed suction irrigation and antibiotic-impregnated materials such as plaster pellets, fibrin, collagen and porous calcium, hydroxyapatite, and synthetic polymers (5,6). There is broad application of the use of antibiotic-impregnated beads in the clinical treatment of bone and joint infections. This application may be further widened by optimizing antibiotics used in beads and loading dosages, as well as improving biodegradability of the carriers and attaining better control of the release rate of antibiotics.

In addition to bone infection and inflammation, poor mechanical integrity as a result of surgery is another complication. Despite the remarkable intrinsic capability of bone to regenerate and undergo repair, it often requires or benefits from an addition of an osteoinductive stimulus, traditionally in the form of autogenous bone grafts. In recent years, our understanding of bone regeneration and repair has greatly improved at both cellular and molecular levels. This is particularly true with respect to the molecular signalling responsible for regulating the recruitment, differentiation, and activity of molecules responsible for bone remodeling and osteogenic cells. Clinical applications of these factors combined with implants have shown promising results. Tissue-compatible biomaterial can help support cell proliferation by providing a suitable attachment substrate that can directly influence cellular differentiation into an osteogenic phenotype. Bone morphogenetic protein– (BMP)-impregnated implants play an increasingly important role in adjunctive therapy for long bone nonunions and spinal fusion.

The application of electrical stimulation for bone and soft tissue healing is another promising area. Numerous animal and human studies confirm that electrical stimulation of the proper charge, density, and total energy causes dramatic improvement in the healing of chronic wounds and nonunions. The antimicrobial effects of electrical stimulation have also been investigated by several methods. Currently, the Food and Drug Administration (FDA) has approved a variety of electric stimulation devices for clinical use in the United States. Continued technological improvement in all electrical stimulatory methods should broaden their usefulness and applicability.

The use of hyperbaric oxygen therapy for treatment is achieved when a patient breathes 100% oxygen in an environment of elevated atmospheric pressure. Physiologically, this technique produces a directly proportional increase in the plasma volume fraction of oxygen, which is directly available for cellular metabolism. Theoretically, a number of beneficial cellular and molecular effects can result from the use of hyperbaric oxygen as adjunctive therapy in orthopedic infection and injury. Clinically, careful staging of osteomyelitis helps identify potential candidates who can benefit from hyperbaric therapy.

II. BIOIMPLANTS

A. Bioimplants as Adjunctive Therapy in the Management of Chronic Osteomyelitis and Deep Soft Tissue Infections

1. Classification

Drug-impregnated implants are acknowledged as a safe method for delivering drugs specifically to musculoskeletal tissue. Currently, the materials frequently used as bioimplants include polymethylmethacrylate (PMMA), minerals (or inorganic material), fibrin, and synthetic polymers. These materials can be classified as either nonbiodegradable or biodegradable. The major representative of the nonbiodegradable implants is composed of PMMA. Examples of biodegradable implants include collagen, hydroxyapatite blocks, and synthetic polymers (Table 1).

2. Drug delivery

a.) Antibiotic-impregnated implants. Conventional treatment of osteomyelitis involves repeated surgical débridement of necrotic tissue coupled with prolonged systemic administration of antibiotics. In order to eradicate the bacterial infection, the antibiotic concentration must be many times higher than the minimal inhibitory concentrations of the pathogenic organisms. Parenteral administration of antibiotics for 4 to 6 weeks is usually recommended for the treatment of chronic osteomyelitis. However, the routine use of the standard dosage of systemic antibiotics is usually not adequate to eradicate bone infections (7) because of poor perfusion into diseased bone site and poor penetration into

Table 1 Classification of Biomaterial Commonly Used for Implants

	Nonbiodegradable	Biodegradable
Example	Polymethylmethacrylate (PMMA)	Collagen sponge
		Apatite-wollastonite glass ceramic block
		Hydroxyapatite block
		Synthetic polymers
Antibiotic release	High concentration	High concentration
Duration of release	4–6 Weeks (up to 8–9 weeks)	4 Months
Surgical removal	Yes	Not necessary
Release load	10%	60%

glycocalyx. When large dosages of antibiotics are administrated systemically over long periods of time, they may result in potentially severe nephrotoxicity, ototoxicity, or allergic reactions.

In the 1970s, Buchholz and Engelbrecht (8) introduced the concept of local antibacterial therapy in the form of antibiotic-impregnated bone cement to treat infected arthroplasties. Since then, antibiotic-impregnated beads have been developed to treat local infections of bone and soft tissue. The advantage of beads compared with parenteral therapy is that they fill dead space produced by débridement and deliver a high concentration of the antibacterial agent locally through diffusion, which is independent of vascular perfusion at the infected site. This is particularly important for patients with diabetes, who have a high prevalence of peripheral vascular disease. Use of antibiotic-impregnated beads prevents high systemic concentrations, thus precluding adverse effects that are often associated with parenteral antibacterial therapy. Antibiotic-impregnated cement has been used prophylatically for total arthroplasties (8) and as part of the treatment of total joint arthroplasty infection (9). Antibiotic beads have been used in the treatment of chronic osteomyelitis (10), and infected nonunion (11) and prophylatically when preparing open fractures (12). This modality has also been used in deep diabetic foot infections without osteomyelitis (13).

b.) Antibiotic selection. Antibiotic choice should be culture-directed whenever possible. A pharmaceutical grade antibiotic power should be used; the antibiotics must be heat-stable and water-soluble. For optimal success, the chosen antibiotic should be bactericidal and hypoallergenic (14).

The aminoglycosides and vancomycin are the best choices for use in antibiotic beads because of their broad spectrum of activity, low incidence of allergic reactions, heat stability, and extensive record of research experience. Gentamicin is the most widely studied antibiotic used in antibiotic-impregnated PMMA beads. However, in the United States, gentamicin is not available in a powder formulation, whereas tobramycin is. Thus, tobramycin is the aminoglycoside used most frequently. Other antibiotics used in PMMA beads and spacers include cephalosporins, β-lactams, macrolids, quinolones, and doxycycline (Table 2).

3. Materials

a.) Polymethylmethacrylate cement Bone cement consists of two components: antibiotics and monomer methyl methacrylate. On mixing, monomer methylmethacrylate undergoes an exothermic polymerization reaction that causes a local thermal necrosis in the bone tissues immediately adjacent to the cement. Theoretically, a suitable antibiotic for use in acrylic bone cement should be water-soluble and be able to resist degradation by the extreme temperature (up to 100°C) produced during the exothermic reaction.

Table 2 Selection of Antibiotics Used for Local Antibiotic-Impregnated Implants

Antibiotics	Mechanism of action	Heat stability
Aminoglycosides	Ribosome	Heat-stable
Penicillin	Cell wall	Labile
Vancomycin	Cell wall	Heat-stable
Cephalosporin	Cell wall	Labile
Quinolones	Deoxyribonucleic acid	Labile

The first use of PMMA for antibiotic delivery was in 1970, when Buchholz reported on the addition of penicillin, gentamicin, and erythromycin to total hip joint arthroplasties (112). Today, nonbiodegradable PMMA cement or beads have been extensively used for treatment and prophylaxis for bone infection. The PMMA antibiotic beads elute biomodally within the site of infection. An initial rapid release of 5% of the total amount of the antibiotic occurs within the first 24 hours (15). The initial release of drug is followed by a sustained elution that progressively diminishes over a period of a few weeks to months. In an isolated case, detectable antibiotic concentrations were reported 5 years after treatment. The elution of antibiotics from bioimplants is influenced by several factors, including composition and structural characteristics (size, shape, and surface topography). Other factors affecting elution are most often related to characteristics of the antibiotics, such as diffusion properties of individual antibiotics and antibiotic concentration in the beads. Finally, the turnover of the fluid in the local wound environment can also affect the elution rate of the antibiotics from the implant.

Negligible serum concentrations are reported after use of aminoglycoside-impregnated bone cement (16,17). This finding implies minimal risk of toxicity compared to that of systemic aminoglycoside therapy. These properties of lower toxicity and higher local antibiotic concentration with aminoglycoside-impregnated bone cement make it very useful as an effective alternative or addition to systemic therapy in deep bone infections (18,19). Calhoun and Mader (20) reported eradication of osteomyelits in 18 of 18 metatarsal head resections with antibiotic bead placement in the diabetic foot. One prospective, randomized study compared systemic prophylaxis with gentamicin PMMA alone for hip athroplasty (21). The gentamicin group had a reduction of deep postoperative infection from 1.6% to 0.4%. Walenkamp and associates (22) treated 100 osteomyelitis patients with débridement and gentamicin-PMMA beads and followed them for 5 (1–12) years. No systemic antibiotics were necessary except the local antibiotic treatment in 52 of the treatment periods. Healing was achieved in 92 patients.

Although the use of PMMA has many advantages over the use of intravenous infusion, the use of this nonbiodegradable polymer has its limitations,

including the following: (1) PMMA implants generally yield only 2 to 4 weeks of antibiotic elution above the minimal inhibition concentration for most common pathogenic organisms. The elution rate of most antibiotics is 10%–50%. Since adequate antibiotic elution from PMMA can be sustained for only 2 to 4 weeks, there is likelihood that organisms surviving the initial release of antibiotics may develop resistance to the antibiotic. (2) PMMA requires a second surgical procedure for removal (3) PMMA is quickly coated in host proteins such as fibrin, which provides an optimal environment for bacterial colonization. (4) The local immune response may be compromised by implantation of a medical device because of the foreign body reaction. (5) Local blood supply may be compromised when implants remain within the host for extended periods.

Biodegradable and biocompatible materials such as bioceramics and synthetic polymers have been developed as alternatives to PMMA (23). The major advantages of these implants are (1) steady and extended release, which provides longer and higher antimicrobial agent availability; (2) wider selection of antibiotics, including those that are thermolabile; (3) decreased morbidity, since surgical removal is not necessary; and (4) increased osteoconductivity and/or osteoinductivity.

b.) Hydroxyapatite. Self-setting apatite (24,25) is transformed into hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HAP), which has a high compatibility with natural bone tissue and sets within half an hour in situ. Hydroxyapatite can be derived from different sources such as calcium sulfate and coral. The advantages of HAP are that its chemical composition is similar to that of natural bone, it has a high affinity for hard tissue, and it is an ideal candidate for long-term use. These properties have prompted intensive efforts to investigate HAP musculoskeletal drug delivery systems for the administration of drugs such as antibiotics (26,27), growth hormones (28), and BMPs (29).

Shinto and colleagues (30) described the ability of gentamicin-impregnated calcium hydroxyapatite biodegradable beads to deliver five times the minimal inhibitory concentrations for *Staphylococcus* species for at least 12 weeks in vitro. Solberg and coworkers (31) showed that the gentamicin-impregnated hydroxyapatite cement is an effective treatment of osteomyelitis in an animal model. Yamashita and coworkers treated patients with osteomyelitis with good clinical results (32). Although the brittleness and poor strength of HAP have limited its use, HAP-coated metal implants with sufficient mechanical strength have been proposed as an alternative (33).

c.) Synthetic polymers. Biodegradable synthetic polymers such as polylactic acid (PLA) or polyglycolic acid (PLG) obviate the need for surgical removal and offer a potential advantage over PMMA and bone cement (34–37).

Calhoun and Mader (38) evaluated a polylactic acid and poly(DL-lactide):co-glycolide combined with vancomycin in a localized *Staphylococcus*

aureus osteomyelitic rabbit model. Bacterial colonies grown from the vancomycin-polymer group were approximately 100 times lower than those of control groups. Garvin and associates (39) showed that polyglycolide beads loaded with gentamicin resulted in the effective treatment of tibial *Staphylococcus aureus* osteomyelitis in a canine model.

d.) Fibrin sealant. Fibrin sealant consists of fibrinogen and thrombin solutions, which generate a crosslinked fibrin clot in a process that mimics the last stage of the physiological coagulation system. Fibrin sealants have been used widely for hemostasis in Europe in the past two decades. In the 1990s they were studied as a potential local delivery system for drugs such as antibiotics (40,41).

A fibrin sealant material impregnated with antibiotics may be better than PMMA beads or other biodegradable polymers and intravenous antibiotics in a variety of ways. First, fibrin is naturally present in damaged tissues, so a foreign body response is unlikely. Second, fibrin sealant crosslinks to tissue, so local delivery of antibiotics is ensured. Third, the fibrin material is reabsorbed by the host's natural fibrinolytic system and the soft tissue or bone defect gradually fills with tissue, making surgical removal and reconstructions unnecessary.

The delivery of antibiotics by fibrin is through either dissolution of the fibrin sealant or diffusion though the matrix, depending on the antibiotic-to-fibrin ratio and the antibiotic used. Although the release rate varies with the antibiotic used, several days of elution above the minimal inhibitory concentrations for the most common pathogens have been found (42). Redl and colleagues (43) found about 85% of the antibiotic content of fibrin seal clots was released within 72 hours. In a study of 46 patients treated with a cefotaxim-loaded fibrin sealant, Zilch and Lambiris (44) reported the serum cefotaxim concentrations were low and only identifiable for a period of 36 hours, and the wound drainage fluid contained very highly effective antibacterial concentrations over 3.5 days. The best clinical results were seen in cases of hematogenic osteomyelitis.

4. Safety

Serious adverse reactions including allergic reactions due to antibiotic-impregnated cement or beads have not been reported, and adverse reaction rates are lower than those among patients receiving systemic antibiotic treatment (45).

B. Bioimplants as Vehicles for Delivering Bone Morphogenetic Protein and Other Bioactive Factors in Bone and Soft Tissue Repair

Bone defects occur in clinical situations such as destruction by infection and after débridement surgery. The reconstruction of the defect, which provides mechanical integrity to the skeleton, is a critical step in the patient's rehabilitation. In

order to regain normal functional efficacy, the débrided tissue has to reproduce the structure, composition, and physicochemical properties of native tissue. The three components common to all tissue repair approaches are cells, bioactive factors, and scaffolds.

The following are potential strategies for repair and regeneration: (1) the scaffold alone can be implanted into a bone defect to direct and organize the extrinsic repair response, host mesenchymal cells have to repopulate and attach to the scaffold and differentiate into osteocytes; (2) delivery of bioactive factors with scaffolds, which can incorporate BMP arid other bioactive factors to encourage native cells to migrate into the defect area; (3) delivery of osteogenic cells with scaffolds by harvesting osteogenic cells from biopsy specimens, expanding them in culture, and attaching them to the scaffold before the implant is put into the defect.

Bone morphogenetic proteins (BMPs) elicit new bone formation in vivo and have great potential application in orthopedics to promote bone repair and reconstruction (46). BMP molecules can be successfully synthesized by means of deoxyribonucleic acid (DNA) recombination technology; a large amount of recombinant human bone morphogenetic proteins (rhBMPs) can now be prepared for clinical use as bone-graft substitutes. One major challenge is to define the optimal delivery system for BMPs. In combination with biomaterials, these proteins can be used in a clinical setting as bone-graft substitutes to promote bone repair.

In general, the ideal carrier materials for BMP should have several specific physical and biological properties. First, the materials should not be inflammatory or cytotoxic because an intense inflammatory reaction impedes bone formation by BMP. Second, they should be insoluble under physiological conditions in order to retain the BMP molecules. Third, they should be absorbable by host tissue so that they can be replaced by the newly forming bone in a few weeks after implantation.

Several delivery systems for BMP are under investigation. Collagen from animal sources has previously been the preferred carrier material in animal experiments and in clinical trials (47). Other materials such as porous hydroxyapatite, β-tricalcium phosphate, and, more recently, synthetic biodegradable polymers and fibrin have been tested as delivery vehicles for osteoinductive agents such as BMP.

1. Absorbable collagen sponges as recombinant human bone morphogenic protein carriers

Osteoinductive devices composed of biodegradable collagen scaffolds and rhBMPs are being actively studied for local bone induction in the clinical setting. An absorbable collagen sponge (ACS), reconstituted from bovine tendon and a

collagen-based matrix and derived from demineralised guanidine-extracted bovine bone, has been used for the delivery of rhBMP-2 and rhBMP-7, respectively (48,49).

The first prospective randomized clinical trial (50) on a member of the BMP family compared BMP-7 with fresh bone autograft in tibial nonunions. A total of 122 patients with 124 tilbia nonunions were recruited in 18 centers in the United States. The study showed that there was no statistically significant difference in outcome between the two groups.

The advantage of collagen is that it is a natural component of bone, whose degradation and degradation products can be mediated by physiological means. The disadvantages of collagen as a delivery system include potential risk of disease transfer and high immunogenic properties.

2. Ceramic for delivery of bone morphogenetic protein

The use of ceramics in bone repair applications is based on their structural similarity to the mineral phase of bone. The two most commonly investigated ceramics are β-tricalcium phosphate (β-TCP) and synthetic hydroxyapatite (HA). These materials are osteoconductive by providing an appropriate open cell porous structure on which osteoblasts can deposit bone.

3. Polymer delivery of bone morphogenetic protein

There are two characteristics that make polymers especially attractive for bone repair. First, there is great design flexibility because polymer composition and structure can be tailored to meet special needs. Second, the polymers are biodegradable. Polymers can undergo hydrolysis on exposure to the body's aqueous environment, and they also degrade by cellular or enzymatic pathways. The degradation rate is amenable to control by alteration in polymer properties such as hydrophobicity and crystallinity. The most frequently, investigated polymers, namely, poly(α-hydroxy esters), poly(lactic-co-glycolic acid) (PLLA), poly(glycolic acid) (PGA), and poly(lactic-co-glycolic acid) (PLGA), are approved for human use in the United States by the Food and Drug Administration.

These polymers can serve as scaffolds by providing an appropriate three-dimensional structure upon which osteoblasts grow and deposit bone extracellular matrix. The polymeric materials may also serve as carrier vehicles for the delivery of bioactive molecules.

Using a PLLA-PLGA delivery system, Johnson and coworkers (51) delivered allogenous BMP to treat four patients with distal tibial metaphyseal nonunions, all the patients were at the point of amputation as their next step in management. All the nonunions healed within 5 months after this treatment.

4. Fibrin delivery of bone morphogenetic protein

Human fibrin is relatively nonantigenic, angiotropic, and hemastatic and has osteoconductive properties, thus it may be an ideal candidate for a good biodegradable distributor and carrier for BMP (52). Fibrin stops intraoperative bleeding and can establish a BMP concentration gradient in the area of growing mesenchymal cells. Fibrin may stabilize BMP locally and improves contact between BMP and surrounding cells. The angiotrophic properties of fibrin stimulate sprouting of capillaries that accompany new bone formation. Fibrin enhances cell proliferation of undifferentiated mesenchymal cells or precondroblasts preceding new bone formation.

C. Bioimplants as Scaffolds and Vehicles for Osteogenic Cell Delivery

In addition to serving as a mechanical substrate, the bioimplant scaffold can interact with other elements in a dynamic, synergistic manner to direct and organize the process of regeneration. The transplantation of cultured autologous chondrocytes and mesenchymal cells into bone defects is currently being done. Alternatively, transplantation of a mixed biomaterial composed of chondrogenic and osteogenic cells selectively distributed within polymeric scaffolds is possible. Extensive evidence suggests that the three-dimensional synthetic polymers are ideal candidates for bioactive scaffolds in bone engineering applications (53).

D. Biodegradable Implant Devices for Fracture Fixation

Until recently, internal fixation of fractured bones and joints has often been managed by metal implants. The metallic implants often require removal through a second operation after fracture healing has occurred. An absorbable implant, lending sufficient strength and stiffness for support of the fracture during the healing period, then gradually decays and shifts acting forces over to the healing bone (54).

Extensive efforts have been made in the development of biodegradable implants for fixation in both animal and clinical studies. Today, bioabsorbable fixation devices have been in clinical use since the late 1980s, approximately 40 different biodegradable polymers, copolymers, and composites have been developed as substitutes for metal implants in internal fracture fixation (55). Repair of displaced malleolar fractures in 56 patients with ASIF screws and plates was compared with that with rods made of PLA-PGA. No major differences were observed during a 1-year follow-up period (56). Reporting their experience of more than 1000 operations using biodegradable materials, Peltoniemi and

associates (57) concluded that the degree of osteogenesis achieved with these materials is superior to that with metallic implants.

Bioabsorbable implants have many advantages: (1) Osteoporosis associated with metallic implants can be prevented; (2) obviation of the need for a second surgery to remove the implants results in financial as well as psychological advantages; (3) biodegradable materials produce no artifact on computed tomography (CT) or magnetic resonance imaging (MRI); (4) bioabsorbable implants can be impregnated with osteoinductive cytokines and BMP, which accelerate or facilitate tissue healing.

The main problem with biodegradable materials is that the mechanical strength may weaken before bone healing occurs. Bioabsorbable implants have only 50% of the tensile strength and about 15% of the rigidity of tempered steel implants; however, their bending strength is nearly the same. Biodegradable materials with better mechanical properties are currently under development (58). Another complication of biodegradable implant fixation is the development of sterile sinuses at the site of implantation.

III. ELECTRICAL STIMULATION

A. Background

Bone tissue has an electrically charged crystalline structure. In 1953, Fukada and Yasuda (59) first reported on the electrical properties of bone. They found that mechanically stressed bone generated an electrical potential and that areas of active bone growth and repair were electronegative when compared with less active areas. These observations led to the theory that electric currents help control the formation and repair of bone. Clinical and laboratory experience supports the theory that a relationship between bioelectricity and growth and repair of bone and cartilage exists (60–62). Extensive investigations are ongoing to delineate the relationship between bioelectricity and the cellular and molecular processes underlying bone growth, remodeling, and wound repair.

Today, the Food and Drug Administration has approved a variety of electric stimulation devices for clinical use in the United States. These devices are categorized into three different types: (1) constant direct current stimulation using percutaneous or implanted electrodes (invasive); (2) inductive coupling produced by a magnetic field (noninvasive), and (3) capacitive coupling (noninvasive).

1. Direct current

Direct current is applied through electrodes implanted in the area to be stimulated. The percutaneous direct current bone growth stimulator is partially invasive, allows patient mobility, can be used with magnetic fixation devices, and

can be monitored for proper function. However, it requires surgical placement, cannot be used in the presence of infection, and is subject to breakage. The implantable direct current bone growth stimulator is similar but is totally invasive.

2. Inductive coupling

Inductive coupling consists of applying a magnetic field across the area to be stimulated by means of external coils. The magnetic field induces an electrical field in the tissue between the coils. Inductive coupling is often referred to as *pulsed electromagnetic fields* (PEMFs).

3. Capacitive coupling

Capacitive coupling is achieved by applying capacitor plates to the area to be stimulated. As the plates become charged, they induce an electrical field in the target tissues. This type of external stimulator is noninvasive and can be used in the presence of infection, but it requires long, exact patient compliance.

B. Mechanisms of Action

Interest in the role of electrical interactions as epigenetic regulators of bone and wound healing arose in the 1970s, but the mechanisms of action are still not fully understood. Many studies have evaluated the effects on cellular behavior of exposure to an electrical field. These investigations show that the application of an electrical field can promote some important components of the wound healing process, including angiogenesis, fibroblastic proliferation, collagen synthesis, and epithelial cell migration (63,64). Studies using animals have demonstrated that electrical stimulation increases both perfusion and healing rates of skin wounds (65). The antimicrobial effects of electrical stimulation have been investigated by several methods (66–68). Natural epithelial-derived sodium currents have been discovered in the wounds of invertebrates and mammals. The messenger ribonucleic acid (mRNA) for BMP-2 (68) and BMP-4 (69) is unregulated on electrical stimulation. Differentiation of osteoblast and mineralization are enhanced by electrical stimulation (70). These findings are summarized in Table 3.

C. Clinical Applications

Bone stimulation has evolved with indications for use in a variety of pathological bone conditions. Today, bone stimulators have been used to augment open reduction with internal and external fixation. Additionally, the osteogenicity of bone grafts has been assisted by the use of electrical stimulation. Bone stimulation also assists in the healing of failed arthrodesis. More recently, the use of bone

Table 3 Mechanisms of Electrical Stimulation[a]

Improvement in tissue perfusion
Increase in DNA synthesis
Upregulation of mRNA for BMP-2 and BMP-4
Upregulation of growth factor TGF, IGF-2
Oseoblast differentiation
Acceleration of biomineralization
Enhancement of angiogenesis
Promotion of fibroblastic proliferation
Increase in collagen synthesis
Promotion of epithelial cell migration
Inhibition of bacterial growth

[a]DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; BMP, bone morphogenetic protein; TGF, transforming growth factor; IGF-2, insulin-like growth factor-2.

stimulators has shown promise in the treatment of osteoarthritis, osteonecrosis, and neuropathic arthropathy.

1. Nonunion fractures

In the United States, approximately 5% to 10% of the 5.6 million fractures occurring annually show some signs of delayed or impaired healing. This results in an annual incidence of 150,000 to 200,000 nonunions in predisposed bones.

Management of nonunions requires careful and critical assessment of the true biological status of the fracture. Using a direct current stainless steel electrode, Friedenberg and associates (71) reported the first successful use of electric treatment for a human nonunion fracture in 1971. The effectiveness of electrical and PEMF stimulation for enhancement of bone healing has since been reported by many authors. It is noninvasive, cost-effective, and free of complications. Success rates of up to 80% compare well with those of open surgical repair (72,73). The long-term follow-up of fracture nonunions treated with PEMF stimulation is superior to that of placebo (74). Percutaneous direct current electrostimulation also proved to be a reliable and effective method of managing the most common nonunions of the tibia or distal femur. It appears to be less satisfactory for more proximal femoral fractures and fractures of the humerus.

2. Lumbar spinal fusion

The first clinical study on the efficacy of electrical stimulation as an adjunct to lumbar spinal function was reported by Dwyer and Wickham (75) in 1974. Since then, electrical stimulation has gained acceptance as a postoperative adjunct to increase the rate of fusion for various lumbar spine disorders. A randomized double-blind prospective study of pulsed electromagnetic fields for lumbar interbody fusions was performed on 195 subjects (76). There was a 92% success rate in the active group; the control group had a 65% success rate.

3. Cartilage repair

Certain electromagnetic fields have been shown to stimulate chondrocytes to proliferate and/or increase synthesis of proteoglycans (77,78). Hyaline cartilage, when stimulated with certain PEMFs, may elevate glycosaminoglycan content and suppress degradation of existing glycosaminoglycan (79). Low-energy alternating and direct current magnetic fields stimulate the metabolism of articular cartilage, as measured by radiolabeled sulfate incorporation, coincidental to calcium ion uptake by the cells (80). Extremely low frequencies (i.e., < 60 Hz) affect cell behavior through increased transcription (81) and enhanced DNA synthesis (82).

4. Wound healing

Living tissues possess direct current surface electropotentials that regulate, at least in part, the healing process. After tissue damage, a current of injury is generated that is thought to trigger biological repair. In addition, exogenous electrical stimuli have been shown to enhance the healing of wounds in both human subjects and animal models.

A randomized, double blind multicenter study compared the healing of chronic dermal ulcers treated with pulsed electrical stimulation with the healing of similar wounds treated with sham electrical stimulation (83). After 4 weeks, wounds in the treatment and control groups were 44% and 67% of their initial size, respectively. The healing rates per week for the treatment and control groups were 14% and 8.25%, respectively.

Gardner and colleagues (84) performed meta-analysis to quantify the effect of electrical stimulation on chronic wound healing. Electrical stimulation was most effective on pressure ulcers (net effect = 13%). Findings regarding the relative effectiveness of different types of electrical stimulation devices were inconclusive. Although electrical stimulation produces a substantial improvement in the healing of chronic wounds, further research is needed to identify which electrical stimulation devices are most effective and which wounds respond best to this treatment.

5. Pain and arthritis

Constant magnetic stimulation may influence small C fibers and may preferentially desensitize sensory neurons by modifying membrane potentials (85,86). Transcutaneous electric nerve stimulation was developed in the early 1970s and has since become a useful physical therapy tool for acute and subacute pain. A 1998 pilot study supported the use of magnetic footpads for painful diabetic peripheral neuropathy (87), but larger studies are needed for validation of this finding (88).

The application of PEMF stimulation for the amelioration of osteoarthritis pain is a relatively new area, which has been supported by several trials (89,90). In a randomized trial, Zizic and associates (91) studied a pulsed electric device used to treat 78 patients with chronic knee osteoarthritis. The treatment was superior to placebo in reducing pain.

D. Safety

Most investigators believe that exposures to the low energy of magnets and brief exposure to medical PEMF devices are safe. A 10-year, long-term follow-up showed no evidence of adverse effects (92). Additionally, there was no evidence that electromagnetic fields from power lines caused cancer (93).

Contraindications to the use of electrical stimulation include use of cardiac pacemakers and concomitant use of metal-containing solutions, such as mercurochrome. PEMF treatment should be avoided by patients known to have cancer and pregnant women. Other contraindications include a gap greater than half of the diameter of the bone. Direct current is contraindicated in active infection.

E. Limitations

Electrical stimulation does not alter limb length and alignment, and it does not eliminate the need for stabilization of the nonunions or the ultimate need for bone.

Continued technological improvement in all electrical stimulatory methods should broaden their usefulness and applicability. However, critical evaluation and clarification of indications are essential.

The healing status of the fracture and the processes by which each fracture responds must be carefully assessed to appreciate what is being affected by electrical stimulation.

IV. HYPERBARIC OXYGEN THERAPY

Hyperbaric oxygen (*HBO*) *therapy* is defined as a mode of medical treatment in which the patient is breathing 100% oxygen intermittently at a pressure greater

than 1 atmosphere. Treatment can be carried out in either a monoplace or a multiplace chamber. The monoplace chamber accommodates a single patient and the entire chamber is pressurized with 100% oxygen that the patient breathes directly. The multiplace chamber holds two or more people (patients and support personnel). The chamber is pressurized with compressed air while the patients breathe 100% oxygen via a mask, head tent, or endotracheal tube.

A. Principles and Mechanisms

The blood transports oxygen in two different ways: chemically bound to hemoglobin in erythrocytes and physically dissolved in plasma according to Henry's law. At normal atmospheric pressure, the oxygen in arterial blood is almost entirely bound to hemoglobin, breathing 100% oxygen at 2 or 3 atmospheres absolute, a significant proportion of arterial oxygen is in dissolved form. An increased PO_2 has a negligible impact on total hemoglobin oxygen content; however, it does result in an increase in the amount of oxygen dissolved directly into plasma. With 100% inspired oxygen, the amount of plasma oxygen increases to 2.09% vol%; at 3 atmospheres absolute (ATA) the plasma contains 6.8% oxygen.

Since the 1980s we have seen a clarification of its mechanism of action and a greater understanding of its potential benefit. The potential mechanisms are listed in Table 4.

B. Indications

There are only 19 indications for HBO use approved by the Undersea and Hyperbaric Medical Society (UHMS) (94,95). In the field of orthopedics, HBO alone or as adjunctive therapy has proved useful for refractory osteomyelitis, infected and noninfected pseudoarthroses, slow bone healing or nonunion after limb lengthening, and high-risk fractures. HBO therapy is also indicated in the management of chronic limb ischemia, diabetic foot ulcers, and acute osteomyelitis in critical locations such as the skull or sternum. Furthermore, there is an indication to apply HBO to radiation-induced tissue injury (osteoradionecrosis, soft tissue ulceration, fibrosis), crush injury, compartment syndrome, and other acute traumatic ischemia. Finally, compromised skin, bone graft, or flaps and excessive blood loss are also frequently treated with hyperbaric oxygen (Table 5).

These clinical indications were evaluated in a Consensus Conference of the Undersea and Hyperbaric Medical Society that has classified its application according to its efficiency. Indications were classified as strongly recommended (positively affects the patient's survival) recommended (does not influence the patient's survival/but is important for the prevention of serious disorders), and optional (regarded as an additional treatment modality) (94).

Table 4 Potential Mechanisms of Hyperbaric Oxygen Therapy in the Treatment of Musculoskeletal Infection and Its Complications

Antimicrobial
Increased killing of leukocytes
Lethal effects to certain anaerobic bacteria, e.g., *Clostridium perfringens*
Inhibition of exotoxin production of alpha toxin and detoxification of oxygen-labile extoxins of theta toxin of *Clostridium perfringens*
Potentiation of bactericidal activity of aminoglycosides and vancomycin
Tissue protection and healing promotion
Reduction of tissue edema
Preservation of intracellular adenosine triphosphate
Increase in flexibility of red blood cells
Enhancement of neovascularization
Stimulation of fibroblast growth
Increase in collagen formation
Promotion of more rapid growth of capillaries
Termination of lipid peroxidation
Promotion of wound healing in compromised wound
Prevention of adherence of polymorphonuclear leukocytes (PMNs) to damaged endothelial cells
Osteogenesis
Acceleration of activity and rate of osteoinduction by recombinant human bone morphogenetic protein-2 (rhBMP-2)
Enhancement of osteoclastic activity to remove bony debris
Enhancement of osteogensis and neovascularization to fill dead space with vasculary or structurally sound bony tissue

Table 5 Indications for Hyperbaric Oxygen Therapy

Refractory osteomyelitis
Nonhealing wounds, diabetic foot ulcer
Osteoradionecrosis and radiation-induced soft tissue injury
Necrotizing fasciitis
Clostridial myonecrosis (gas gangrene)
Comprised transplants of bone or soft tissue (skin graft and flaps)
Excessive blood losss
Crush injury
Compartment syndrome and other acute traumatic ischemia

C. Clinical Indications

1. Osteomyelitis

The term *refractory osteomyelitis* refers to lack of response despite adequate surgical and antibiotic therapy. Factors including systemic and/or local compromised host status are frequently associated with refractory osteomyelitis. Hyperbaric oxygen can be used as an adjunctive treatment in chronic refractory osteomyelitis along with appropriate antibiotics, surgical treatment, and nutritional support.

The mechanisms of action of HBO in treatment of osteomyelitis are as follows: (1) HBO raises the tissue oxygen tension in hypoxic tissue by providing adequate oxygen tension that enhances the leukocyte killing mechanisms that are oxygen-dependent through hydrogen peroxide and superoxide production. In animals, the oxygen tension of infected bone increased from 23 mmHg to 104 mmHg in response to HBO at 2 ATA (96). Since the bactericidal activity of leukocytes in vitro is directly related to local oxygen tension, transient reversal of hypoxia may increase clearance of bacteria. (2) HBO enhances osteoclastic activity to remove bony lesions. Optimal wound P_{O_2} can also enhance osteogenesis or neovascularization to fill the dead space with vascularly or structurally sound bone tissues. (3) HBO potentiates the action of aminoglycosides and vancomycin in the killing of susceptible bacteria. Hyperbaric oxygen therapy has been shown to enhance the activity of tobramycin in the eradiation of *Pseudomonas aeruginosa* from infected bone (97).

The Cierny-Mader system (98) (Table 6) can be used as a guide to determine the types of osteomyelitis that may benefit from adjunctive hyperbaric therapy. The patients are classified according to factors that may compromise their healing, such as "A," a normal host, or "B," a compromised host (Table 6). Adjunctive HBO is generally reserved for treatment of advanced stages of osteomyelitis (3B and 4B) (99,100). Patients are generally treated at 2.0 to 2.5 ATA abs for 90–120 minutes per day and receive 20–40 treatments.

The results of multiple open clinical trials suggest a beneficial effect of the addition of adjunctive hyperbaric oxygen to usual osteomyelitis treatment regimens, whereas other clinical studies (101) have not demonstrated such a benefit. Chen and associates (102) present the preliminary results of adjunctive hyperbaric oxygen therapy for patients with refractory osteomyelitis. Fifteen patients who were diagnosed with refractory tibia osteomyelitis were treated prospectively with adjunctive hyperbaric oxygen therapy, aggressive surgical débridement, and parenteral antibiotic treatment. Successful treatment was achieved in 13 patients (86%) during an average follow-up of 17.2 months. Davis and coworkers (103) studied 38 patients with chronic nonhematogenous osteomyelitis treated by local débridements of the wound, parenteral administration of antibiotics, and daily treatments with hyperbaric oxygen. Hyperbaric

Table 6 Cierny and Mader Classification System of Osteomyelitis[a]

Anatomical class	
Stage 1 Medullary	
Stage 2 Superficial	
Stage 3 Localized	
Stage 4 Diffuse	
Physiological class	
A Host: Normal host	
B Host: Systemic compromise (Bs); local compromise (Bl)	
C Host: Treatment worse than disease	
Systemic or local factors that affect immune surveillance, metabolism, and local vascularity	
Systemic (Bs)	
1Bs.	Malnutrition
2Bs.	Renal, liver failure
3Bs.	Diabetes mellitus
4Bs.	Chronic hypoxia
5Bs.	Malignancy
6Bs.	Extremes of age
7Bs.	Immune disease
8Bs.	Immunosuppression or immune deficiency
9Bs.	Asplenic patients—functional asplenia and sickle cell disease
10Bs.	HIV/AIDS
11Bs.	IVDA
12Bs.	ETOH
13Bs.	Tobacco abuse
Local (Bl)	
1Bl.	Chronic lymphedema
2Bl.	Venous stasis
3Bl.	Major vessel compromise
4Bl.	Arteritis
5Bl.	Extensive scarring
6Bl.	Radiation fibrosis
7Bl.	Small vessel disease
8Bl.	Neuropathy

[a]HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IVDA, intravenals drug abuse; ETOH, alcohol abuse

oxygen appeared to prolong the infection-free interval of patients with chronic, nonhematogenous osteomyelitis.

Regrettably, there have been no randomized, prospective double-blind studies of patients with chronic refractory osteomyelitis. The many clinical

variables involved in osteomyelitis make clinical studies difficult to design and evaluate. Significant variables include different infected bone sites, different organism, and different antibiotics. Additional variables include the routes of antibiotic administration, duration of antibiotic treatment, amount of bone penetration by the antibiotic(s), type of surgery, adequacy and timing of débridement, dead space management, and status of adjacent soft tissue. Clearly, more clinical research is needed to address this question, despite the research design problems inherent in the osteomyelitis population.

2. Wound healing

Problem wounds are the most frequent entity treated with hyperbaric oxygen therapy in United States. Problem wounds are those that do not respond to established medical and surgical management. These wounds usually develop in compromised hosts with multiple local and systemic factors contributing to inhibition of tissue repair. These include diabetic foot ulcers, compromised amputation sites, nonhealing traumatic wounds, and vascular insufficiency ulcers.

Common causes of the nonhealing of diabetic foot ulcers are infection and/or ischemia. In a hypoxic environment, wound healing is halted by decreased collagen production, capillary angiogenesis, and impaired oxygen-dependent intracellular leukocyte killing. Physiologically, HBO appears to have the potential to enhance wound healing. HBO increases oxygen diffusion and reverses tissue hypoxia. It appears to promote neovascularization and increase granulation tissue formation. In addition, HBO can modify the cellular functions of the activated neutrophil, resulting in increased oxidative microbial killing and decreased neutrophil-endothelial adhesion. HBO also upregulates platelet-derived growth factor receptor messenger RNA activity. All of these physiological activities may help optimize wound healing.

The heterogeneity of diabetic foot ulcers contributes to the confusing role of HBO as a treatment modality. Neuropathic foot ulcers with adequate blood supply can be healed relatively easily with appropriate wound care and off-loading without the need for HBO. Ischemic ulcer healing, however, may be enhanced by HBO. In particular, patients with nonhealing ischemic ulcers with vascular lesions not amenable to angioplasty or vascular surgery who wish to avoid amputation may benefit from HBO. Transcutaneous oxygen tension assessment of the involved extremity may help identify appropriate candidates for HBO by documenting low oxygen tensions in the area of the ulcer.

Multiple anecdotal reports and retrospective studies of HBO therapy in diabetic patients suggest that HBO can be an effective adjunct in the management of diabetic wounds. Prospective studies also show the beneficial effects of HBO. Of the seven published studies pertaining to the diabetic foot, only two were randomized, controlled clinical trials. One of the prospective, randomized,

controlled studies reported significantly fewer major amputations for the HBO group, but only among patients with Wagner grade IV lesions (104). There was no statistical difference in minor amputations between the HBO and control groups; nor was there a difference in major amputation among the less severe Wagner ulcer classification groups. The second prospective, randomized, controlled study reported significantly fewer major amputations in the HBO group than in the standard treatment control group (105). There was no difference in length of hospitalization or the number of minor amputations between the groups.

The Fourth Consensus Conference of the European Committee in Hyperbaric Medicine concluded, "Further controlled studies should be carried out to obtain more precise data on HBO before widely implementing this therapy in patients with diabetes." Given the limited evidence of positive results in select groups of patients with severe wounds, additional randomized clinical trials are warranted. In the clinical setting, HBO treatment is considered inpatient therapy for Wagner III–V lesions that do not respond to conventional treatment (106). Patients are generally treated at 2.0 to 2.5 ATA abs for 90–120 minutes per day and receive 20–30 treatments.

3. Necrotizing fasciitis

Necrotizing fasciitis is a severe, fulminant infection most commonly encountered in patients with diabetes mellitus, alcohol abuse, and intravenous drug abuse. The infection can spread, unrecognized, along fascial planes beneath seemingly normal skin. The relatively benign appearance of the extremity is misleading and often results in a delay in diagnosis and increased morbidity or death. Necrotizing fasciitis is rapidly progressing synergistic bacterial infection with a reported mortality rate of 38% (107). The progressing necrosis is usually associated with edema and an occlusive arteritis. Immediate aggressive surgical débridement in combination with antibiotic therapy is necessary for control of these limb- and life-threatening soft tissue infections. HBO is frequently used as adjunctive therapy.

Oxygen, at increased pressures, augments tissue oxygen partial pressure, allowing increased bacterial killing by providing substrate for the formation of oxygen free radicals and augmenting the respiratory burst. During the healing process, hyperoxia causes increased formation of capillaries for oxygen, nutrients, and antibiotic delivery, leading to increased efficacy of some antibiotics in the high-oxygen environment and possibly more rapid overall wound healing. Although there are no randomized trials of HBO in these infections, in vitro data and meta-analysis of clinical cases strongly support the use of HBO.

Riseman and colleagues (108) described 29 patients with necrotizing fasciitis; 12 received surgical treatment and antibiotics only and the other 17

patients received HBO in addition to débridement surgery and antibiotics. The groups were similar in age, sex, microbiological characteristics, and antibiotic treatment. However, the HBO group was more severely ill, having more perineal involvement (53% versus 12%), more shock (29% versus 8%), and more diabetes (47% versus 33%). Mortality rate was 23% in the HBO group versus 66% in the non-HBO group.

Patients generally received 5 to 30 treatments at 2.0–2.5 ATA abs for 90–120 minutes.

4. Gas gangrene

Gas gangrene, or clostridial myonecrosis, is commonly encountered in extremity wounds that involve devitalized or necrotic soft tissues. Infection with *Clostridium perfringens* in devitalized tissue is the most common cause of infectious myonecrosis. Clostridial microorganisms are anaerobes that produce local and systemic toxins. Wide surgical débridement and appropriate antibiotic therapy remain the standard of care. However, the addition of hyperbaric oxygen therapy to standard management has been shown to have a synergistic effect in reducing morbidity and mortality rates in both canine and murine models. HBO induces high oxygen partial pressure in all tissues, but it is possible to achieve levels high enough to be lethal to some anaerobic bacteria such as *Clostridium perfringens*. HBO also has an antiedema effect, causes activation of fibroblasts and macrophages, and stimulates angioneogenesis. Although no prospective human data are available, retrospective data indicate that concomitant hyperbaric oxygen therapy has resulted in a twofold reduction in mortality rate (109).

D. Side Effects

Hyperbaric oxygen therapy is generally safe and well tolerated. Table 7 lists the most common side effects associated with hyperbaric oxygen therapy. Most side

Table 7 Common Side Effects of Hyperbaric Oxygen Therapy

Barotrauma
Middle ear
Sinus squeeze
Oxygen toxicity
Pulmonary symptoms
Neurological symptoms
Miscellaneous
Claustrophobia
Myopia
Cataract

effects are mild and reversible, but some severe consequences can occur in rare cases.

Middle ear barotrauma is the most common side effect of hyperbaric therapy. A review of 14,446 patients with 31,599 exposures showed an incidence of barotrauma of approximately 2% (110). It can be prevented in most patients by teaching autoinflation techniques or by use of typanostomy tubes for those who cannot autoinflate their middle ear compartment. Patients with a history of eustachian tube dysfunction may have serious otitis media.

The second most common complication of hyperbaric therapy is sinus squeeze. This occurs less frequently than middle ear barotraumas and usually occurs in patients with upper respiratory tract infections or allergic rhinitis.

Claustrophobia, which appears to be present in about 2% of the general population, may cause some degree of confinement anxiety, even in a multiplace chamber. Mild sedation is often initially required for these patients to continue with daily hyperbaric oxygen treatment.

Progressive myopia has been observed in some patients undergoing prolonged periods of daily hyperbaric treatment. Although the exact mechanism remains obscure, it is apparently lenticular in origin and usually reverses completely within a few days to several weeks after the last therapy. Development of cataracts has been reported in patients receiving more than 150 treatments.

Pulmonary and neurological manifestations of oxygen toxicity are often cited as major concerns. Seizures are seen in 1.3 per 10,000 patient treatments.

Hyperbaric oxygen treatment may contribute to oxygen toxicity seen in critically ill patients who receive high concentrations of inspirited oxygen between hyperbaric treatments. Pneumothorax is a rare complication of hyperbaric treatment, usually occurring only in patients with severe lung disease. Air embolism, which presumably results from a small tear in the pulmonary vasculature, is also a rare complication. No evidence of tumorigenic effects has been found with hyperbaric oxygen therapy.

Untreated pneumothorax is an absolute contraindication to hyperbaric therapy. Concurrent therapy with doxorubicin, cisplatinum, and disulfiram is also contraindicated. Other conditions such as low seizure threshold, high fevers, emphysema with CO_2 retention, upper respiratory infections, and congenital spherocytosis are considered relative contraindications for HBO therapy. These relative contraindications can be mitigated with medications.

V. SUMMARY

Musculoskeletal infections are of considerable clinical importance. Definitive therapy requires a combination of a wide range of multidisciplinary interventions including medical, surgical, and adjunctive therapies.

Extensive investigations have been done to develop a biodegradable implant impregnated with antibiotics as an adjunct to current therapy for musculoskeletal infections. Findings from case reports and recent clinical trials suggest that interventions that combine conventional approaches and bioimplants have a clinically significant impact in reducing complications and improving outcomes for musculoskeletal infections or their complications such as chronic osteomyelitis. Recently developed biodegradable polymers with a slow degradation process and longer stability are increasingly used and have shown lower complication rates. These new materials are playing an increasingly important role as an adjunctive therapy for musculoskeletal infections.

Electrical stimulation is a proven effective modality for delayed or nonunion fractures, spinal fusions, cartilage repair, and wound healing with potential clinical application for osteoarthritis, osteonecrosis of bone, and osteoporosis. Static magnets may provide temporary pain relief under certain circumstances. On the basis of clinical studies, electrical stimulation appears to be a promising adjunctive treatment for bone and joint disorders.

Hyperbaric oxygen therapy has shown its beneficial effects in several areas of musculoskeletal disorders, including refractory osteomyelitis, chronic limb ischemia, diabetic foot ulcers, radiation-induced tissue injury, crush injuries, compartment syndromes and other acute traumatic ischemia, compromised skin, bone grafts and flaps, and excessive blood loss. Although numerous clinical reports and trials demonstrate the effectiveness of hyperbaric oxygen therapy, more clinical research and better controlled trials are needed to delineate the clinical effectiveness and benefits of hyperbaric oxygen therapy in each individual disease entity. HBO therapy should be used in conjunction with an aggressive multidisciplinary protocol and should not be substitutive, but additional, to other therapeutic procedures.

REFERENCES

1. FA Waldvogel, G Medoff, MN Swartz. Treatment of osteomyelitis. N Engl J Med 283(15):822, 1970.
2. JT Mader, ME Shirtliff, SC Bergquist, JH Calhoun. Antimicrobial treatment of chronic osteomyelitis. Clin Orthop 360:47–65, 1999.
3. GR Seabrook, CE Edmiston, DD Schmitt, C Krepel, DF Bandyk, JB Towne. Comparison of serum and tissue antibiotic levels in diabetes-related foot infections. Surgery 110(4):671–676, 1991.
4. SL Henry, KP Galloway. Local antibacterial therapy for the management of orthopaedic infections. Pharmacokinetic considerations. Clin Pharmacokinet 29(1):36–45, 1995.
5. JH Calhoun, JT Mader. Antibiotic beads in the management of surgical infections. Am J Surg 157(4):443–449, 1989.

6. AK Jain, R Panchagnula. Skeletal drug delivery systems. Int J Pharm 206(1–2): 1–12, 2000.
7. J Ciampolini, KG Harding. Pathophysiology of chronic bacterial osteomyelitis. Why do antibiotics fail so often? Postgrad Med 76(898):479–483, 2000.
8. HW Buchholz, H Engelbrecht. Depot effects of various antibiotics mixed with Palacos resins. Chirurg 41(11):511–515, 1970.
9. HW Buchholz, RA Elson, E Engelbrecht, H Lodenkamper, J Rottger, A Siegel. Management of deep infection of total hip replacement. J Bone Joint Surg Br 63B(3):342–353, 1981.
10. B Roeder, CC Van Gils, S Maling. Antibiotic beads in the treatment of diabetic pedal osteomyelitis. J Foot Ankle Surg 39(2):124–130, 2000.
11. JH Calhoun, SL Henry, DM Anger, JA Cobos, JT Mader. The treatment of infected nonunions with gentamicin-polymethylmethacrylate antibiotic beads. Clin Orthop 295:23–27, 1993.
12. PA Ostermann, D Seligson, SL Henry. Local antibiotic therapy for severe open fractures: a review of 1085 consecutive cases. J Bone Joint Surg Br 77B(1):93–97, 1995.
13. DE Stabile, AM Jacobs. Local antibiotic treatment of soft tissue and bone infections of the foot. J Am Podiatr Med Assoc 80(7):345–353, 1990.
14. GJ Popham, P Mangino, D Seligson, SL Henry. Antibiotic-impregnated beads. Factors in antibiotic selection. Orthop Rev 20(4):331–337, 1991.
15. K Adams, L Couch, G Cierny, J Calhoun, JT Mader. In vitro and in vivo evaluation of antibiotic diffusion from antibiotic-impregnated polymethylmethacrylate beads. Clin Orthop 278:244–252, 1992.
16. JB Eckman, SL Henry, PD Manino, D Seligson. Wound and serum levels of tobramycin with the prophylactic use of tobramycin impregnated polymethylmethacrylate beads in compund fractures. Clin Orthop 237: 213–215, 1988.
17. RP Evans, CL Nelson. Gentamicin-impregnated polymethylmethacrylate beads compared with systemic antibiotic therapy in the treatment of chronic osteomyelitis. Clin Orthop 295:37–42, 1993.
18. GS Heard, LM Oloff, DA Wolfe, MD Little, DD Prins. PMMA bead versus parenteral treatment of Staphylococcus aureus osteomyelitis. J Am Podiatr Med Assoc 87(4):153–164, 1997.
19. JD Blaha, CL Nelson, LF Frevert, SL Henry, D Seligson, JL Esterhai Jr, RB Heppenstal, J Calhoun, J Cobos, J Mader. The use of septopal (polymethylmethacrylate beads with gentamicin) in the treatment of chronic osteomyelitis. Instr Course Lect 39:509–514, 1990.
20. JH Calhoun, JT Mader. Treatment of osteomyelitis with a biodegradable antibiotic implant. Clin Orthop 341:206–214, 1997.
21. G Josefsson, L Lindberg, B Wiklander. Systemic antibiotics and gentamicin-containing bone cement in the prophylaxis of postoperative infections in total hip arthroplasty. Clin Orthop 159:194–200, 1981.
22. GH Walenkamp, LL Kleijn, M de Leeuw. Osteomyelitis treated with gentamicin-PMMA beads: 100 patients followed for 1–12 years. Acta Orthop Scand 69(5):518–522, 1998.

23. K Kanellakopoulou, EJ Giamarellos-Bourboulis. Carrier systems for the local delivery of antibiotics in bone infections. Drugs 59(6):1223–1232, 2000.
24. Y Takezawa, Y Doi, S Shibata, K Uno, T Horiguchi, N Wakamatsu, H Kamemizu, T Gyotoku, M Adachi, Y Moriwaki. Self-setting apatite cement. 6. Possibility as bone substitute. Jpn J Oral Biol 31(3):240–247, 1989.
25. LC Chow, WE Brown. A physicochemical bench-scale caries model. J Dent Res 63(6):868–873, 1984.
26. M Otsuka, Y Matsuda, D Yu, J Wong, JL Fox, WI Higuchi. A novel skeletal drug delivery system for anti-bacterial drugs using self-setting hydroxyapatite cement. Chem Pharm Bull (Tokyo) 38(12):3500–3502, 1990.
27. S Sasaki, Y Ishii. Apatite cement containing antibiotics: efficacy in treating experimental osteomyelitis. J Orthop Sci 4(5):361–369, 1999.
28. J Guicheux, G Grimandi, M Trecant, A Faivre, S Takahashi, G Daculsi. Apatite as carrier for growth hormone: in vitro characterization of loading and release. J Biomed Mater Res 34(2):165–170, 1997.
29. A Kamegai, N Shimamura, K Naitou, K Nagahara, N Kanematsu, M Mori. Bone formation under the influence of bone morphogenetic protein/self-setting apatite cement composite as a delivery system. Biomed Mater Eng 4(4):291–307, 1994.
30. Y Shinto, A Uchida, F Korkusuz, N Araki, K Ono. Calcium hydroxyapatite ceramic used as a delivery system for antibiotics. J Bone Joint Surg Br 74B(4):660–664, 1992.
31. BD Solberg, AP Gutow, MR Baumgaertner. Efficacy of gentamycin-impregnated resorbable hydroxyapatite cement in treating osteomyelitis in a rat model. J Orthop Trauma 13(2):102–106, 1999.
32. Y Yamashita, A Uchida, I Yamakawa, Y Shinto, N Araki, K Kato. Treatment of chronic osteomyelitis using calcium hydroxyapatite ceramic implants impregnated with antibiotic. Int Orthop 22(4):247–251, 1998.
33. JA Jansen, JP van de Waerden, JG Wolke, K de Groot. Histologic evaluation of the osseous adaptation to titanium and hydroxyapatite-coated titanium implants. J Biomed Mater Res 25(8):973–989, 1991.
34. G Wei, Y Kotoura, M Oka, T Yamamuro, R Wada, SH Hyon, Y Ikada. A bioabsorbable delivery system for antibiotic treatment of osteomyelitis: The use of lactic acid oligomer as a carrier. J Bone Joint Surg Br 73B(2):246–252, 1991.
35. W Amass, A Amass, B Tighe. A review of biodegradable polymers: uses, current developments in the synthesis and characterization of biodegradable polyesters, blends of biodegradable polymers and recent advances in biodegradation studies. Polym Int 47:89, 1998.
36. J B Turesin, I Gursel, V Hasirci. Biodegradable polyhydroxyalkanoate implants for osteomyelitis therapy: in vitro antibiotic release. J Biomater Sci Polym Ed 12(2):195–207, 2001.
37. JD Meyer, RF Falk, RM Kelly, JE Shively, SJ Withrow, WS Dernell, DJ Kroll, TW Randolph, MC Manning. Preparation and in vitro characterization of gentamycin-impregnated biodegradable beads suitable for treatment of osteomyelitis. J Pharm Sci 87(9):1149–1154, 1998.

38. JH Calhoun, JT Mader. Treatment of osteomyelitis with a biodegradable antibiotic implant. Clin Orthop 341:206–214, 1997.
39. KL Garvin, JA Miyano, D Robinson, D Giger, J Novak, S Radio. Polylactide/polyglycolide antibiotic implants in the treatment of osteomyelitis: a canine model. J Bone Joint Surg Am 76A(10):1500–1506, 1994.
40. ST Boyce, IA Holder, AP Supp, GD Warden, DC Greenhalgh. Delivery and activity of antimicrobial drugs released from human fibrin sealant. J Burn Care Rehabil 15(3):251–255, 1994.
41. DF Thompson, TW Davis. The addition of antibiotics to fibrin glue. South Med J 90(7):681–684, 1997.
42. MS Park, YB Kim. Sustained release of antibiotic from a fibrin-gelatin-antibiotic mixture. Laryngoscope 107(10):1378–1381, 1997.
43. H Redl, G Schlag, G Stanek, A Hirschl, T Seelich. In vitro properties of mixtures of fibrin seal and antibiotics. Biomaterials 4(1):29–32, 1983.
44. H Zilch, E Lambiris. The sustained release of cefotaxim from a fibrin-cefotaxim compound in treatment of osteitis: pharmacokinetic study and clinical results. Arch Orthop Trauma Surg 106(1):36–41, 1986.
45. JD Blaha, JH Calhoun, CL Nelson, SL Henry, D Seligson, JL Esterhai Jr, RB Heppenstall, J Mader, RP Evans, J Wilkins. Comparison of the clinical efficacy and tolerance of gentamicin PMMA beads on surgical wire versus combined and systemic therapy for osteomyelitis. Clin Orthop (295):8–12, 1993.
46. JM Wozney, V Rosen, AJ Celeste, LM Mitsock, MJ Whitters, RW Kriz, RM Hewick, EA Wang. Novel regulators of bone formation: molecular clones and activities. Science 242(4885): 1528–1534, 1988.
47. W Friess, H Uludag, S Foskett, R Biron, C Sargeant. Characterization of absorbable collagen sponges as recombinant human bone morphogenetic protein-2 carriers. Int J Pharm 185(1):51–60, 1999.
48. GE Riedel, A Valentin-Opran. Clinical evaluation of rhBMP–2/ACS in orthopedic trauma: a progress report. Orthopedics 22(7):663–665, 1999.
49. MW Chapman, R Bucholz, C Cornell. Treatment of acute fractures with a collagen-calcium phosphate graft material. A randomized clinical trial. J Bone Joint Surg Am 79A(4):495–502, 1997.
50. GE Friedlaender, CR Perry, JD Cole, SD Cook, G Cierny, GF Muschler, GA Zych, JH Calhoun, AJ LaForte, S Yin. Osteogenic protein-1 (bone morphogenetic protein-7) in the treatment of tibial nonunions. J Bone Joint Surg Am 83A(suppl 1 pt 2):S151–S158, 2001.
51. EE Johnson, MR Urist, GA Finerman. Repair of segmental defects of the tibia with cancellous bone grafts augmented with human bone morphogenetic protein: a preliminary report. Clin Orthop 236:249–257, 1988.
52. M Kawamura, MR Urist. Human fibrin is a physiologic delivery system for bone morphogenetic protein. Clin Orthop 235:302–310, 1988.
53. EJ Caterson, LJ Nesti, WJ Li, KG Danielson, TJ Albert, AR Vaccaro, RS Tuan. Three-dimensional cartilage formation by bone marrow-derived cells seeded in polylactide/alginate amalgam. J Biomed Mater Res 57(3):394–403, 2001.

54. P Rokkanen, O Bostman, S Vainionpaa, K Vihtonen, P Tormala, J Laiho, J Kilpikari, M Tamminmaki. Biodegradable implants in fracture fixation: early results of treatment of fractures of the ankle. Lancet 1(8443):1422–1424, 1985.
55. PU Rokkanen. Bioabsorbable fixation devices in orthopaedics and traumatology. Ann Chir Gynaecol 87(1):13–20, 1998.
56. O Bostman, S Vainionpaa, E Hirvensalo, A Makela, K Vihtonen, P Tormala, P Rokkanen. Biodegradable internal fixation for malleolar fractures: a prospective randomised trial. J Bone Joint Surg Br 69B(4):615–619, 1987.
57. HH Peltoniemi, RM Tulamo, T Toivonen, D Hallikainen, P Tormala, T Waris. Biodegradable semirigid plate and miniscrew fixation compared with rigid titanium fixation in experimental calvarial osteotomy. J Neurosurg 90(5):910–917, 1999.
58. T Yamamuro, Matsusue Y, Uchida A, Shimada K, Shimozaki E, Kitaoka K. Bioabsorbable osteosynthetic implants of ultra high strength poly-L-lactide: a clinical study. Int Orthop 18(6):332–340, 1994.
59. I Yasuda. Fundamental aspects of fracture treatment. J Kyoto Med Soc 4:395–406, 1953.
60. F Benazzo, M Mosconi, G Beccarisi, U Galli. Use of capacitive coupled electric fields in stress fractures in athletes. Clin Orthop 310:145–149, 1995.
61. V Cane, P Botti, S Soana. Pulsed magnetic fields improve osteoblast activity during the repair of an experimental osseous defect. J Orthop Res 11:664–670, 1993.
62. KL Grace, WJ Revell, M Brookes. The effects of pulsed electromagnetism on fresh fracture healing: osteochondral repair in the rat femoral groove. Orthopedics 21:297–302, 1998.
63. JG Fleischli, TJ Laughlin. Electrical stimulation in wound healing. J Foot Ankle Surg 36(6):457–461, 1997.
64. OM Alvarez, PM Mertz, RV Smerbeck, WH Eaglstein. The healing of superficial skin wounds is stimulated by external electrical current. J Invest Dermatol 81(2):144–148, 1983.
65. M Brown, MK McDonnell, DN Menton. Polarity effects on wound healing using electric stimulation in rabbits. Arch Phys Med Rehabil 70(8):624–627, 1989.
66. L Bolton, B Foleno, B Means, S Petrucelli. Direct-current bactericidal effect on intact skin. Antimicrob Agents Chemother 18(1):137–141, 1980.
66a. K Tamura. Some effects of weak direct current and silver ions on experimental osteomyelitis and their clinical application. Nippon Seikeigeka Gakkai Zasshi 57(2):187–197, 1983.
67. BA Rouley, J Mckenna, G Chase. The influence of electrical current on an infecting organism in wounds. Ann N Y Acad Sci 238:543–551, 1974.
68. T Bodamyali, B Bhatt, FJ Hughes, VR Winrow, JM Kanczler, B Simon, J Abbott, DR Blake, CR Stevens. Pulsed electromagnetic fields simultaneously induce osteogenesis and upregulate transcription of bone morphogenetic protein 2 and 4 in rat osteoblasts in vitro. Biochem Biophys Res Commun 250:458–461, 1998.
69. A Yajima, M Ochi, Y Hirose, 0 Nakade, Y Abiko, T Kaku, K Sakaguchi. Effects of pulsing electromagnetic fields on gene expression of bone morphogenetic proteins in human osteoblastic cell line in vitro (Abstract T326). J Bone Miner Res 11(suppl 1):S381, 1996.

70. H Wiesmann, M Hartig, U Stratmann, U Meyer, U Joos. Electrical stimulation influences mineral formation of osteoblast-like cells in vitro. Biochim Biophys Acta 1538(1):28–37, 2001.
71. ZB Friedenberg, MC Harlow, CT Brighton. Healing of nonunion of the medial malleolus by means of direct current: a case report. J Trauma 11(10):883–885, 1971.
72. HR Gossling, RA Bernstein, J Abbott. Review: treatment of ununited tibial fracture: a comparison of surgery and PEMF. Orthopedics 15(6):711–719, 1992.
73. G Scott, JB King. A prospective, double-blind trial of electrical capacitive coupling in the treatment of non-union of long bones. J Bone Joint Surg Am 76A:820–826, 1994.
74. DE Garland, B Moses, W Salyer. Long term follow up of fracture non-unions treated with PEMF. Contemp Orthop 22(3):295–302, 1991.
75. AF Dwyer, GG Wickham. Direct current stimulation in spinal fusion. Med J Aust 1(3):73–75, 1974.
76. V Mooney. A randomized double-blind prospective study of the efficacy of pulsed electromagnetic fields for interbody lumbar fusions. Spine 15(7):708–712, 1990.
77. RK Aaron, DM Ciombor, G Jolly. Stimulation of experimental endochondral ossification by low-energy pulsing electromagnetic fields. J Bone Miner Res 4:227–233, 1989.
78. B Baker, J Spadaro, A Marino, RO Becker. Electrical stimulation of articular cartilage regeneration. Ann N Y Acad Sci 238:491–499, 1974.
79. H Liu, J Abbott, JA Bee. Pulsed electromagnetic fields influence hyaline cartilage extracellular matrix composition without affecting molecular structure. Osteoarthritis Cartilage 4:63–76, 1996.
80. DA Grande, FP Magee, AM Weinstein, BR McLeod. The effect of low-energy combined AC and DC magnetic fields on articular cartilage metabolism. Ann NY Acad Sci 635:404–407, 1991.
81. R Goodman, CA Bassett, AS Henderson. PEMF induced cellular transcription. Science 220:1283–1285, 1983.
82. AR Liboff, T Williams, DM Strong, R Wistar Jr. Time varying magnetic fields: effect on DNA synthesis. Science 223:818–819, 1984.
83. J Feedar, L Kloth, G Gentzkow. Chronic dermal ulcer healing enhanced with monophasic pulsed electrical stimulation. Phys Ther 72(7):539, 1992.
84. SE Gardner, RA Frantz, FL Schmidt. Effect of electrical stimulation on chronic wound healing: a meta-analysis. Wound Repair Regen 7(6):495–503, 1999.
85. RK Olney, YT So, DS Goodin. A comparison of magnetic and electrical stimulation of peripheral nerves. Muscle Nerve 13:957–963, 1990.
86. LL Lednev. Possible mechanisms of weak magnetic fields on biological systems. Bioelectromagnetics 12:71–75, 1991.
87. MI Weintraub. Chronic submaximal magnetic stimulation in peripheral neuropathy. Am J Pain Manag 8:12–16, 1998.
88. A Weinberger, A Nyska, S Giler. Treatment of experimental inflammatory synovitis with continuous magnetic field. Isr J Med Sci 32:1197–1201, 1996.
89. DH Trock, AJ Bollet, R Markoll. The effect of PEMF in the treatment of OA of the knee and cervical spine. J Rheumatol 21:1903–1911, 1994.

90. DH Trock, AJ Bollet, RH Dyer, LP Fielding, WK Miner, R Markoll. A double-blind trial of the clinical effects of PEMF in osteoarthritis. J Rheumatol 20(3):456–460, 1993.
91. TM Zizic, KC Hoffman, PA Holt, DS Hungerford, JR O'Dell, MA Jacobs, CG Lewis, CL Deal, JR Caldwell, JG Cholewczynski. The treatment of osteoarthritis of the knee with pulsed electrical stimulation. J Rheumatol 22(9):1757–1761,1995.
92. PJ Cundy, DC Paterson. A ten-year review of treatment of delayed union and nonunion with an implanted bone growth stimulator. Clin Orthop 259:216–222, 1990.
93. WJ Broad. Cancer fear is unfounded, physicists say: power line concern is called needless. The New York Times, May 14, 1995.
94. EM Camporesi, ed. Hyperbaric Oxygen Therapy Committee Report. Kensington, MD: Undersea and Hyperbaric Medical Society, 1996.
95. JC Davis, JM Dunn, RD Heimbach. Indications for hyperbaric oxygen therapy. Tex Med 76(8):44–47, 1980.
96. JT Mader, GL Brown, JC Guckian, CH Wells, JA Reinarz. A mechanism for the amelioration by hyperbaric oxygen of experimental staphylococcal osteomyelitis in rabbits. J Infect Dis 142(6):915–922, 1980.
97. JT Mader, CA Hicks, J Calhoun. Bacterial osteomyelitis: adjunctive hyperbaric oxygen therapy. Orthop Rev 18(5):581–585, 1989.
98. G Cierny, JT Mader, HA Pennick. Clinical staging system of adult osteomyelitis. Contemp Orthop 10:17–37, 1985.
99. JH Calhoun, JA Cobos, JT Mader. Does hyperbaric oxygen have a place in the treatment of osteomyelitis? Orthop Clin North Am 22(3):467–471, 1991.
100. JT Mader, KR Adams, WR Wallace, JH Calhoun. Hyperbaric oxygen as adjunctive therapy for osteomyelitis. Infect Dis Clin North Am 4(3):433–440, 1990.
101. JL Esterhai Jr, J Pisarello, CT Brighton, RB Heppenstall, H Gellman, G Goldstein. Adjunctive hyperbaric oxygen therapy in the treatment of chronic refractory osteomyelitis. J Trauma 27(7):763–768, 1987.
102. CY Chen, SS Lee, YS Chan, CY Yen, EK Chao, SW Ueng. Chronic refractory tibia osteomyelitis treated with adjuvent hyperbaric oxygen: a preliminary report. Chang gengYi Xue Za Zhi 21(2):165–171, 1998.
103. JC Davis, JD Heckman, JC DeLee, FJ Buckwold. Chronic non-hematogenous osteomyelitis treated with adjuvant hyperbaric oxygen. J Bone Joint Surg Am 68A(8):1210–1217, 1986.
104. E Faglia, F Favales, A Aldeghi, P Calia, A Quarantiello, G Oriani, M Michael, P Campagnoli, A Morabito. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. Diabetes Care 19(12):1338–1343, 1996.
105. N Doctor, S Pandya, A Supe. Hyperbaric oxygen therapy in diabetic foot. Postgrad Med 38(3):111, 112–114, 1992.
106. MR Hamilton-Farrel. Fourth Consensus Conference of the European Committee on Hyperbaric Medicine. Diabetes Nutr Metab 12(1):47–48, 1999.

107. ME Sutherland , AA Meyer. Necrotizing soft tissue infections. Surg CIin North Am 74:591–607, 1994.
108. JA Riseman, WA Zamboni, A Curtis, DR Graham, HR Konrad, DS Ross. Hyperbaric oxygen therapy for necrotizing fasciitis reduces mortality and the need for débridements. Surgery 108(5):847–850, 1990.
109. GB Hart, RC Lamb, MB Strauss. Gas gangrene. J Trauma 23(11):991–1000, 1983.
110. C Plafki, P Peters, M Almeling, W Welslau, R Busch. Complications and side effects of hyperbaric oxygen therapy. Aviat Space Environ Med 71(2):119–124, 2000.
111. HW Buchholz, H Engelbrecht. Uber die deportwirkung einiger antibiotica bei vermischung mit dem Kunstharz palacos. Chirug 41:511–515, 1970.

19

Gene Therapy in Musculoskeletal Repair

State of the Art

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I. INTRODUCTION

Management of bone defects and chronic wounds resulting from musculoskeletal infection can be very challenging. Bone defects, caused by open fractures or destruction through chronic osteomyelitis, frequently require multiple-stage surgical procedures to achieve adequate union. Traditional methods used to repair bone defects are mechanical stabilization, medical treatment, bone grafting with autogenous cancellous bone, and use of alloplastic/synthetic devices. Every year, 450,000 surgical bone grafts are performed in the United States alone; 5% to 10% of these result in delayed or impaired healing (1). Various problems are associated with these procedures, including donor site morbidity, loss of function, and a limited blood supply (2). Chronic nonhealing wounds also present a challenge to the orthopedic physician. It is estimated that at any given time, approximately 1.5% of the population has a chronic wound that requires treatment (3). Chronic wounds are often complications of chronic illness such as diabetes, connective tissue disease, vascular insufficiency, or peripheral neuropathy. More than 4% of the population, or 16

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million people, in the United States have diabetes. Among them, in 15% a foot ulcer will develop at some point of their lifetime. The social and economic burden and effect on the individual patient's quality of life are enormous.

Normal wound repair requires both promotion of the healing process and proper regulatory controls to prevent aberrant wound healing (4,5). Normal wound healing initially consists of the accumulation of fibrin and platelet degranulation; the latter process results in the release of large quantities of platelet-derived growth factor (PDGF), transforming growth factor β (TGF-β), epidermal growth factor (EGF), and insulin-like growth factor-1(IGF-1) into the wound environment. Additionally, neutrophils and macrophages accumulate during the inflammatory phase of wound healing; the latter cell type secretes more TGF-β, basic fibroblast growth factor, and vascular endothelial growth factor (VEGF). These growth factors stimulate proliferation of fibroblasts and endothelial cells. Fibroblasts and other representative cells accumulate at the injury site and contribute to synthesis and secretion of extracellular matrix (ECM) components. The process of early repair in normal wound healing results from the transient expression of growth factors from different cell types. If the production of these growth factors by resident and migrating cells into the wound site remains in balance, normal tissue repair ensues. This early tissue repair process is normally followed by the production and activation of protease, decreased synthesis of protease inhibitors, tissue maturation, remodeling, and reorganization.

The normal response to injury is a timely and orderly process that results in the restoration of anatomical and functional integrity (6). In chronic wounds and nonunions, the healing process is prolonged and incomplete, proceeding in an uncoordinated manner and resulting in a poor anatomical and functional outcome (7). Lack of cellular and molecular signals required for the normal wound repair process, such as resolution of inflammation, angiogenesis, deposition of extracellular matrix, contraction, epithelialization, and remodeling, are major contributing factors to poor wound healing and nonunion. Cytokines, especially growth factors, provide many of the cellular and molecular signals necessary for tissue repair and healing.

This is an exciting time for clinicians interested in treating patients with bone defects and chronic nonhealing wounds. In the past 10 years, in addition to current treatment modalities (including surgical débridement, meticulous wound care, hyperbaric oxygen, and electrical stimulation), several novel biotechnology-based treatment modalities (in vivo delivery of growth factors/cytokines or the replacement of damaged tissue by transplantation of in vitro expansion of endogenous cells) have been shown to improve outcomes of nonhealing wounds and defects. In 1999, the United States Food and Drug Administration (FDA) approved recombinant human platelet–derived growth factor (rhPDGF)

(8) and a skin substitute (Graftskin) (9) for the treatment of diabetic foot ulcers and chronic wounds. In recent years, the effort has involved the use of a gene therapy approach. We can now intervene in wound and bone healing at the deoxyribonucleic acid (DNA) level. This chapter reviews the advances in musculoskeletal tissue repair at the nongene level (biologically based) and at the gene level (gene therapy).

II. BIOLOGICAL (NON-GENE-BASED) APPROACH TO WOUND REPAIR

Fetal tissue injury is healed by tissue regeneration, whereas the adult repair process is guided by inflammation-induced scar formation. Knowledge of the cellular and molecular events associated with bone and soft tissue healing has led to efforts to seek biological alternatives to synthetic materials, notably, seeding wounds or bridging bone gaps with in vitro expanded cells or the addition of growth factors involved in tissue repair and regeneration.

A. Local Delivery of Growth Factors

1. Osteoinduction with bone morphogenetic proteins

In 1965, Urist (10) first showed that the demineralized matrix of a bone graft was capable of induction of de novo bone formation. Since then, there has been an ongoing effort to develop an ideal osteoinductive bone graft substitute. In purifying the active component of the demineralized bone graft, researchers discovered a family of regulatory molecules known as *bone morphogenetic proteins* (BMPs). Fifteen BMPs have been identified since the early 1990s (11) (Table 1). These proteins have been produced in highly purified form through the use of recombinant DNA technology.

The mechanisms of BMP regulation of growth and differentiation are currently under extensive investigation (12,13). BMPs, together with other cytokines and matrix components, induce a cascade of chemotaxis, migration, proliferation, and differentiation of mesenchymal stem cells. Undifferentiated mesenchymal cells migrate to the implanted site by chemotaxis, undergo mitosis, and are condensed in regions. Chondroblasts derived from mesenchymal cells secrete extracellular matrix to form a cartilaginous template. The hypertrophied cartilage and the extracellular matrix are vasculized by hematopoietic and endothelial cells. Osteoblasts and osteoclasts appear locally and cartilage is reabsorbed and replaced by bone.

Local application of these growth factors to fractures or to the sites of segmental bone defects may stimulate fracture repair and minimize the rate of nonunion. Delivering BMPs to the fracture site with a carrier matrix such as

Table 1 Bone Morphogenetic Proteins and Their Potential Biological Function

Bone morphogenetic proteins (BMPs)	Potential function
BMP-1	Metalloproteases/procollagen C proteinase
BMP-2 (BMP-2A)	Cartilage and bone morphogenesis, inhibiting effects of myogenic effects of other factors
BMP-4 (BMP-2B)	Cartilage and bone morphogenesis
BMP-3	Bone formation
BMP-3B (GDF-10)	Bone membrane
BMP-5	Bone morphogenesis, initiation of formation of particular skeletal elements
BMP-6	Cartilage hypertrophy, bone induction in rats, regulation of differentiation of primary skin keratinocytes, possible neurotropic factor
BMP-7 (osteogenic protein 1)	Bone differentiation, neurogenesis, tubulogenesis
BMP-8 (osteogenic protein 2)	Bone formation
BMP-9	Bone induction in rats, possible regulatory role in hepatic growth and function
BMP-10	Bone induction in rats
BMP-11 (GDF-10)	Bone induction in rats
BMP-12	Inhibition of terminal myoblast
BMP-13	Ectopical induction of tendon and ligament in rats, inhibition of terminal myoblast
BMP-14	Ectopical induction of tendon and ligament in rats

(GDF-10): growth/differentiation factor-10

collagen or hypdoxyapatite matrix stimulated new bone formation and accelerated bone formation and fracture union in an animal model (14–18). Numerous human studies, with encouraging results, involving spinal fusion, long bone defects, selected fracture repair, craniomaxillofacial disease, and periodental and dental disease, have also been reported.

In 1988, Johnson and associates (19) used endogenous human BMP to supplement autogeneic cancellous grafts in the successful healing of six traumatic segmental 3 to 17-cm-long tibial defects in humans. Geesink and colleagues (20) performed a prospective, randomized double-blind study of 24 patients undergoing high tibia osteotomy evaluating the effectiveness of rhBMP-7/type I collagen carrier composite in a critical size fibula defect.

There was no significant new bone formation in the collagen-alone group, whereas in the rhBMP-7/type I collagen group, all patients except one showed new bone formation after 6 weeks.

2. Growth factors and wound healing

Several lines of evidence suggest that growth factors such as PDGF, EGF, fibroblast growth factor (FGF), and TGF, which are found in abundance in injured or inflamed skin, play a critical role in bone and soft tissue healing (Table 2). These growth factors promote cell proliferation, differentiation, angiogenesis, and matrix synthesis by smooth muscle cells, fibroblast cells, chondrocytes, and osteoblasts. The first two cell types and second two are largely responsible for wound repair and formation of fracture callus, respectively. Wound fluid studies have shown decreased levels of growth factor concentration in chronic wounds (21). Circulating levels of growth factors as well as bone mineral density are decreased with age. Administering growth factors increases bone turnover in patients with low mineral density (22). On the basis of the demonstrated

Table 2 Growth Factors and Wound Healing

Growth factor	Cell source	Biological function
TGF-α	Platelets, macrophages, keratinocytes	Activation of neutrophils, fibroblast mitogen, stimulation of angiogenesis
TGF-β	Platelets, macrophages, lymphocytes	Stimulation of fibroplasia and angiogenesis; induction of proliferation of many different cells
PDGF	Platelets, macrophages, keratinocytes, endothelial cells	Induction of proliferation, chemotaxis, matrix synthesis for smooth muscle cells and fibroblasts
FGF	Macrophages, neural tissue, nearly ubiquitous	Stimulation of endothelial cell growth, mitogen for mesodermal- and neuroectodermal-derived cells
KGF	Keratinocytes, fibroblasts	Epithelialization
EGF	Platelets, keratinocytes, salivary gland	Mitogen for keratinocytes, endothelial cells, and fibroblasts
IGF	Liver	Stimulation of fibroblasts and smooth muscle cells, lymphocytes, chondrocytes
NGF	Neuron	Keratinocyte proliferation and vascular neoangiogenesis

[a]TGF, transforming growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; KGF, keratinocyte growth factor; EGF, epidermal growth factor; IGF, insulin-like growth factor; NGF, neuronal growth factor.

deficiency of growth factors in chronic wounds and the successful reversal of impaired healing in many animal models by application of various growth factors, a series of clinical trials evaluating healing has been performed using exogenous application of growth factors in an attempt to accelerate wound healing. Currently, only recombinant growth factor PDGF has been approved by the FDA for use in the treatment of diabetic foot ulcers and chronic nonhealing wounds (23–25). Clinical trials of other growth factors such as FGFβ and keratinocyte growth factor (KGF) in wound healing are ongoing in order to establish appropriate dosages and vehicles and to ascertain which cytokines alone or in combination will optimize the wound healing process.

B. Cell Transplantation

1. Mesenchymal stem cell–based implants for bone defect repair

Multipotential marrow stromal cells (MSCs) were discovered by Friedenstein and colleagues in 1966 (26). They established that cells that are adherent, clonogenic, nonphagocytic, and fibroblastic can give rise, under appropriate experimental conditions, to a broad spectrum of fully differentiated connective tissues, V including cartilage, bone, adipose tissue, fibrous tissue, and myelosupportive stroma. MSCs from mice, rats, rabbits, and humans readily differentiate into colonies of osteoblasts, chondrocytes, and adipocytes in response to dexamethasone, 1,25-dihydroxyvitamin D_3, or cytokines such as BMP-2 (27).

Because MSCs are thought to be the source of osteoblastic cells during the process of normal bone growth, remodeling, and fracture repair, an approach was developed to transplant MSCs directly into the site in need of bone augmentation. Locally injected MSCs were shown to promote repair of surgical incisions in the knee cartilage of rabbits, and MSCs in ceramic beads were shown to promote bone healing in an animal model (28–34). This approach is particularly attractive for patients who have fractures that are difficult to heal or patients experiencing a decline in their repository of MSCs as a result of age, diabetes, or other pathological conditions (35,36).

Several investigators have reported their results in human studies (37,38). The combination of MSCs with a porous hydroxyapatite–tricalcium phosphate implant material appears to be an effective strategy for healing of large osseous defects (39). Alternatively, growth factors such as BMP, TGF, or IGF-1 may be coadministered with MSC-based implants (40). Composite implants of bone marrow cells with endogenous and recombinant BMPs have been shown to augment bone healing over bone marrow cells or BMPs alone in calvarial defects in dogs (41), rats (42), and critical-sized femoral defects in rats (43).

2. Autologous cell approach to wound healing

Ideal skeletal reconstruction depends on the regeneration of normal tissue that results from initiation of progenitor cell activity. Practical methods are currently being investigated to amplify in vitro cultivation of the appropriate autologous cells to aid skeletal healing and repair. Current cell therapy procedures include the use of tissue cultured skin cells (4) for the treatment of nonhealing ulcers. The application of autologous fibroblasts and autologous keratinocytes is being investigated.

The FDA has approved graftskin for the treatment of diabetic foot and nonhealing ulcers. Graftskin (Apligraft) is a bilayered skin substitute, prepared by an organotypic culture of skin derived from human neonatal keratinocytes layered over human neonatal epidermal and dermal fibroblasts embedded in a collagen matrix (9). Graftskin was found to integrate rapidly with mouse tissue containing living normal cells (45). In an open-label, multicenter study of 112 patients with diabetic plantar neuropathic ulcers, 56% had complete healing achieved within 12 weeks (9).

III. GENE-BASED THERAPY IN MUSCULOSKELETAL REPAIR

A. Overview

Local application of exogenous cytokines, such as PDGF, IGF, TGF, and BPMs, has been shown to modulate wound and bone healing in both animal studies and human clinical trials (46). However, routine clinical use of topically applied cytokines can be limited by a short half-life, inefficient delivery to target cells, need for repeated application to achieve a therapeutic effect, and high manufacturing cost of pure proteins.

Direct introduction of growth factors to cells in the bone repair site by gene therapy (47,48) is another area undergoing extensive investigation. The basic concept of gene therapy is to reprogram wound repair cells by introducing a therapeutic gene whose expression can lead to a transient advantage for tissue growth and regeneration. Gene therapy of musculoskeletal defects is usually achieved by delivery of a gene into those cells involved in the healing process. It should be possible to engineer the synthesis and delivery of a specific therapeutic protein into the wound or surgical site and to achieve therapeutic levels of growth factors and cytokines locally at physiological levels for a sustained period. This process may enhance the therapeutic benefit of wound-healing agents and create environments that shift the balance from tissue destruction to tissue repair and facilitate a more significant healing response. Moreover, these delivery systems

may deliver their products in a more biologically active form than that achieved by the exogenous application of recombinant proteins.

B. Gene Delivery

Gene therapy can be accomplished by an in vivo or ex vivo approach. Ex vivo gene therapy can be used to target cytokine expression to a specific cell type by genetically modifying cells grown from a biopsy specimen in culture. These cells can subsequently be transplanted to wounds as grafts or as components of composite cultured cell replacement. Although time-consuming, the ex vivo approach has several advantages over in vivo gene delivery. For example, if autologous cells are used, the graft can persist for years after transplantation and allow for extended expression of the transfected gene. In addition, the expression of transfected genes can be assayed before transplantation of the modified cells and the number and location of the modified cells can be more tightly regulated than by the in vivo approach.

Alternatively, an in vivo approach delivers the DNA encoding a particular cytokine directly to the wound, fracture, or other desired site by either injection or topical application methods. Compared with other tissues, the musculoskeletal system is easily accessible for in vivo gene therapy. The advantage of this approach is simplicity, allowing localized exposure of the target tissue and a reduced risk of systemic side effects. In addition, harvesting and reimplantation are not necessary.

The extent to which gene therapy is effective on musculoskeletal disease is the direct result of several key factors: (1) selection of the appropriate target cell or tissue for gene delivery, (2) high efficiency of the gene delivery system, and (3) appropriate expression, regulation, and stability of the gene therapy product(s).

In a successful gene therapy, the expression of a transferred gene has to reach and sustain a certain level of activity to achieve its therapeutic purpose. The level and timing of the gene's expression within target cells should be reversibly controlled, by a pharmacological agent, for example. The therapeutic dosage can be finely tuned as the disease or tissue repair evolves and stopped when it is no longer needed.

C. Vector System

A vector is the vehicle used to introduce the gene into the target cells. There are a number of viral and nonviral vectors available for transferring genes to surgical injury or wound sites. Low-virulence viruses are usually used because of their high efficiency in transferring nucleic acid. Several types of viruses, including retroviruses, adenoviruses, adeno-associated virus (AAV), and herpesvirus, have been modified in the laboratory for use in gene therapy application in musculo-

skeletal disorders (49–53). Nonviral vectors, based on plasmid DNA produced in bacteria and often complexed with lipids, are also being used (54–57). The properties of commonly used vectors are summarized in Table 3.

1. Viral vectors

a.) Retroviruses Retroviruses are single-stranded ribonucleic acid (RNA) viruses that consist of 5′ and 3′ long-terminal repeat sequences and structural genes. When the recombinant virus infects a target cell, it integrates into the host genome and expresses viral genes as well as the transgene. It offers a means for stable transformation and can potentially provide long-term expression of a therapeutic gene within tranfected cells. Defective retroviral vectors cannot undergo subsequent replication. The advantage of these vectors is that genetic construction is not complex, and they elicit little host immune response. Disadvantages include low target-cell selectivity and integration only into actively dividing cells. Because of their ability to integrate into chromosomes in a random fashion, they can potentially induce insertional mutagenesis and potentially transform target cells, although the probabilities are quite low. Currently, approximately 37% of gene therapy clinical studies are based on retrovirally mediated gene transfer.

b.) Adenoviruses. Adenoviruses contain a double-stranded DNA core protein complex surrounded by a protein capsid. The adenoviral genome is transcribed in two major stages. The early phase precedes DNA replication and the late phase starts 6–8 hours later. Adenoviral vectors are constructed with deletion of the El genes that render the virus replication-deficient and thus eliminate the possibility of transforming host cells. The E1-deleted adenoviral vector is propagated in 293 cells that contain a stably integrated segment of the adenoviral genome that provides El function. Adenoviral vectors have advantages, including high efficiency of transfection of both dividing and nondividing cells and larger package capacity. The viral genome does not integrate into host chromosome and remains episomal. Adenoviral vectors may be engineered to

Table 3 Characteristics of Commonly Used Viral Vectors in Human Gene Therapy[a]

Vector	Genome	Packing size	Duration	Comments
Retrovirus	ssRNA	8–10 kb	Extended	Requirement for dividing cells
Adenovirus	dsDNA	7–8 kb	Transient	Transduction of wide range of cells
HSV	dsDNA	35 kb	Extended	Neurotoxicity
AAV	ssDNA	4–5 kb	Extended	Excellent duration in some tissues

[a]ssRNA, single-stranded ribonucleic acid; ds, double-stranded deoxyribonucleic acid; HSV, herpes simplex virus; AAV, adeno-associated virus.

infect specific cells. Adenoviral vectors are very effective for both in vivo and ex vivo gene transfer. They are especially effective for in vivo gene transfer to skin wounds, and high levels (up to microgram quantities) of therapeutic protein can be achieved in the wound microenvironment. Adenoviral vectors account for 20% of human gene therapy trials. The major disadvantage of adenoviral vectors is that they induce antiviral immune responses, which often limit gene expression in vivo. Attempts at rechallenging an immunocompetent host with an adenoviral vector may result in diminished transgene expression.

c.) Adeno-associated viral vector. Adeno-associated virus (AAV) vector is a nonpathogenic virus that infects approximately 80% of the human population. It is a single-stranded DNA virus with a genome size of 4.7 kb. AAV particles are physically stable and small (2025 nm), implying that vector particles can transverse tissue barriers with relative ease. Given AAV's broad spectrum of host cells, including both dividing and nondividing cells, and its site-specific integration on human chromosome 19q13.3, it can achieve long-term gene expression. Deletion of the AAV coding sequences from a rAAV vector prevents the generation of wild-type help virus and eliminates the possibility of an immune response to viral gene products. In initial attempts, the administration of rAAV into human subjects appears safe, with no evidence of germline transmission, local tissue toxicity, or immune system perturbation. The major disadvantages of AAV vectors is their limited packing capacity (<4.5 kb).

d.) Herpes simplex virus. Herpes simplex virus (HSV) is a double-stranded DNA virus that infects neurons and many epithelial cell types. HSV undergoes cytopathic replication or a latency life cycle characterized by almost no viral replications. Up to 30 kb of foreign DNA may be packaged in recombinant HSV vectors. A major limitation of the clinical use of HSV is the potential for neural toxicity.

Additional viruses, including lentiviruses, papilloma virus, simian virus 40, polyoma, vaccinia, picornavirus, and Epstein-Barr virus, are also under investigation as possible future vectors for gene therapy.

2. Nonviral methods

Genes can also be delivered to tissue by using nonviral methods, such as gene gun, liposome-mediated methods, topical application, direct injection into muscle or subcutaneous tissue, and gene-activated matrix (GAM) (see Table 4).

a.) Plasmid deoxyribonucleic acid. Plasmid DNA is a circular construct of naked DNA that was identified because of its ability to transmit antibiotic resistance to bacteria. DNA-encoding therapeutic gene products can be incorporated into these plasmids, then transferred to cells. The advantages of plasmids are the virtually unrestricted size of genes that can be introduced and the relative

Table 4 Nonviral Gene Transfer Methods

Delivery method[a]	Transfection efficiency	Integration efficiency
Electroporation	Low	Low
Topical application	Low	Low
Microinjection	High	Low
Direct injection (intramuscular, intradermal)	Low	Low
Gene gun	High	Low
GAM	Low	Low
Naked DNA	Low	Low

[a]GAM, gene-activated matrix; DNA, deoxyribonucleic acid.

lack of toxicity. Plasmids are inherently stable and flexible and can be manufactured by using simple protocols that would be expected to yield kilogram amounts of sterile clinical grade material on a routine basis at significantly less cost than typical bulk protein reagents. Another advantage of naked plasmid DNA is the minimal inflammatory cell and neutralizing antibody response produced when compared to that of adenovirus vector.

Plasmid DNA generally is not considered the optimal vector for gene therapy, in part because of the presumed inefficiency in cellular transfection and relatively shorter term of expression. However, gene expression that decreases over a period of days or weeks may be desirable in skeletal repair, whose primary goal is to regulate wound healing until a stable repair process is established. Short-term expression may be amenable to clinical scenarios in which postoperative injections are titrated to the clinical response.

Plasmid-mediated transfer of vascular endothelial growth factor (VEGF) to induce new blood vessel growth in ischemic limbs was studied in a clinical trial by Baumgartner and coworkers (58). Naked plasmid DNA encoding the isoform of human VEGF was injected directly into the muscle of the ischemic limbs. Increased serum VEGF level was documented, the ankle-brachial index improved significantly, and newly visible collateral blood vessels were shown by contrast angiography in 7 of 10 limbs. Magnetic resonance angiography showed evidence of improved distal blood flow in 8 of 10 limbs.

b.) Particle-mediated gene transfer. Particle-mediated gene transfer methods employ a physical force to penetrate the cellular membrane of target cells and to deliver DNA that is adhered to microscopic gold particles of 1–2 μm in diameter. In the wound environment, where significant amounts of nuclease activity is likely to be present, the gene gun method of delivery of DNA may be the preferred method because of its ability to deliver DNA to target cells and avoid degradation. The gene gun method to introduce the epidermal growth factor

gene into wound keratinocytes leading to accelerated wound repair of pig skin has been demonstrated (59).

c.) Electroporation. Electroporation involves the application of pulsed electric fields to cells to enhance cell permeability, resulting in exogenous polynucleide transit across the cytoplasmic membrane. Electrically mediated in vivo gene transfer has been performed only in animal models to date. Electroporation is a means of targeting expression to the cells of interest. The use of plasmid DNA simplifies gene preparation and the physical nature of electroporation makes this type of delivery applicable especially to skin and surgical wounds.

d.) Liposomes. Liposomes are synthetically prepared vesicles consisting of positively charged lipids such as dioleoyl phosphatidylethanolamine. Through an electrostatic interaction, cationic liposomes can effectively form a complex with negatively charged DNA molecules. The resulting liposome -DNA complex interacts with the cell membranes of transfected cells, allowing introduction of DNA molecules into the cells, presumably through endocytosis. The efficiency of cationic liposome-mediated gene transfer in vitro can vary greatly and ranges from 5% to 18% for nonpermissive cells and up to 90% for other cell lines. The major advantage of liposomal vectors is their low immunogenicity, which allows repetitive in vivo administration. A disadvantage of current liposomal vectors is their low transfection efficiency in vivo, likely due to serum inactivation. Successful gene transfer to a wound with a growth factor–encoding plasmid/liposome complex has been reported. Studies showed that the topical application of liposome-acidic FGF–encoding plasmid to excisional wounds in diabetic mice for 3 consecutive days accelerated wound closure comparably to that achieved with recombinant aFGF applied for 15 days (60).

e.) Gene-activated matrix. Plasmids have been incorporated onto three-dimensional structure matrices called *gene-activated polymer matrices* (GAMs) (61). The method targets granulation tissue fibroblasts for plasmid gene transfer. These fibroblasts normally originate in viable tissue surrounding injury, where they proliferate and migrate into GAMs along with an appropriate vasculature. Once in GAMs, the fibroblasts encounter, take up, and transiently express plasmid DNA. The GAM has two functions: it holds plasmid DNA in the wound site and it also acts as a scaffold that promotes cell ingrowth and accumulation of fibroblasts near DNA. While in the matrix, transfected fibroblasts act as bioreactors, producing plasmid-encoding proteins that stimulate tissue repair and bone regeneration. Fang and colleagues used GAM to enhance fracture healing in rat and canine models (62). Implantation of a GAM containing either a BMP-4 plasmid or a parathyroid hormone 1–34 (PTH) 1–34) plasmid results in a biological response of new bone filling the gap. Implantation of two-plasmid

GAM (BMP-4 plus PTH 1–34, which act synergistically) causes new bone to form faster than does either factor alone.

f.) Target cells for gene therapy for musculoskeletal repair. The treatment of musculoskeletal disorders with systemic or local gene delivery requires the development of techniques for delivery of genes into bone, cartilage, tendon, ligament, muscle, or synovial tissue. The optimal target cells that deliver DNA to the musculoskeletal system remain undetermined. The ideal cell candidate should reside in tissue for which a biopsy specimen is easily obtained, and in vitro cell isolation, transfection, and expression should be reliable and efficient.

In recognition of their broad growth and differentiation potential, bone marrow mesenchymal stromal cells have been explored as vehicles for both cell therapy and gene therapy (63,64). These cells are relatively easy to isolate from a small aspiration of bone marrow that can be obtained under local anesthesia. They are also relatively easy to expand in culture and transfect with exogenous genes. BMPs and growth factors have been introduced into marrow mesenchymal stromal cells for segmental bone gap filling, maxillary bone defect repair, and spinal fusion (65–68).

Other cells investigated for target cells include periosteal-derived cells, synovial cells, fibroblasts, chondrocytes, myoblasts, endothelial cells, and smooth muscle cells (69). Ready accessibility makes the skin extremely attractive for therapeutic gene transfer. Successful ex vivo and in vivo gene delivery into skin keratinocytes has been reported (70).

IV. APPLICATION OF GENE THERAPY TO MUSCULOSKELETAL REPAIR

A. Strategies

A number of experimental animal models have been developed in gene therapy paradigms for musculoskeletal disease states, including trauma, fracture, ischemia, nonhealing wounds, and osteomyelitis.

One consequence of the complexity of tissue repair is the multifactorial influence of malnutrition, immunocompromised status, and therapeutic intervention with corticosteroids and immunosuppressant agents. The molecular basis of chronic nonhealing wounds is unclear. One hypothesis is that growth factor activity in the wound is insufficient in the wound environment (21). Growth factors may be "trapped" within extracellular matrix molecules or may be degraded by increased protease activity found in chronic nonhealing wounds. In contrast, an overproduction of growth factors leads to hypertrophic scars and keloids. It has been hypothesized that the defect may reside in the balance of

synthesis and degradation of the extracellular matrix. Therapeutic strategies for musculoskeletal repair have three basic modalities:

1. Provide general support to promoting factors such as cytokines, growth factors or their receptors, and hormones: Wound healing growth factors, which stimulate cell proliferation and synthesis of extracellular matrix, are obvious candidates for tissue repair gene transfer. Since a compromised blood supply is frequently responsible for inhibiting bone healing, VEGF, a potent stimulator of angiogenesis, is a prudent candidate. Other candidate genes include protease inhibitors to protect growth factor actions and receptor antagonists or inhibitors, which can be applied to either ex vivo or in vivo gene therapy.
2. Deliver antisense RNA, or ribozymes, to block the translation of those growth factors involved in overfibrosis and scar formation: For instance, delayed union or nonunion may involve excessive local production of osteoclastic mediators (71) such as interleukin-1 (IL-1) and IL-6. Overexpression of TGF-β may cause excessive scarring and loss of tissue function (72). In, such cases, local delivery of antisense RNA of these genes, or genes encoding the appropriate cytokine antagonist molecules, would, theoretically, be helpful. The functional knockout of a specific growth factor in the wound environment can also be achieved by gene transfer of soluble growth factors receptors or antisense RNA.
3. Treatment for skeletal disorders by use of bone-specific promoters or molecular conjugates (DNA molecule attached to cell-specific ligands) to restrict expression of therapeutic genes to distinct populations of cells in the skeleton: Transcription factors and intranuclear targeting of transcription factors provide options for directing the therapeutic gene expression to specific transcriptionally active subnuclear sites (73–75). Investigators have also shown the feasibility of constructing vectors that regulate the elements that can direct the gene to be expressed only under specific conditions (e.g., the presence of tetracycline).

B. Gene Therapy and Chronic, Nonhealing Wounds

Gene therapy is a promising new modality for nonhealing wounds (76,77). This therapeutic approach modifies the host's cells to express a therapeutic protein by transfer of genetic material through a variety of techniques, including viral and nonviral agents. Genes can be delivered through in vivo or in vitro methods.

Tyrone and associates (78) tested the wound healing effects of topically applied platelet-derived growth factor (PDGF)-A or -B chain DNA plasmids embedded within a collagen lattice. PDGF-B DNA increased new granulation

tissue formation by up to 52% and epithelialization by 34% when compared with controls. Wound closure was increased up to threefold (78). Andree and colleagues (79) showed that the expression of exogenous epidermal growth factor in the skin increased wound healing by 20%. Liechty demonstrated that adenovirus-mediated gene transfer of platelet-derived growth factor-B overcame the ischemic defect in wound healing (80).

Baumgartner and colleagues (58) used a method of direct injection of a VEGF plasmid into the leg muscles of patients with ischemic limbs, nonhealing ulcers, and rest pain. The treatment prompted a significant improvement in indices of ankle-brachial pressure, and contrast angiography showed collateral blood vessel formation in 7 of 10 limbs. The chronic ulcers either healed or improved substantially in four of seven limbs and successful limb salvage proved possible in three patients who had been advised to undergo a below-knee amputation.

Another area of recent interest, which may lead to future treatment modalities, is the modulation of TGF levels in preventing scarring and fibrosis during wound healing.

C. Gene Therapy and Bone Defects

A large number of cytokines that control the cellular events associated with bone formation and repair have been identified. The most promising BMP fractions, BMP-2, BMP-4, and BMP-7(OP-1), have been evaluated in various experimental models (81–87).

Different methods of gene transfer are currently being investigated for the purpose of enhancing bone formation, including in vivo nonviral delivery of plasmid DNA by a three-dimensional matrix.

D. Gene Therapy of Osteoarthritis

Osteoarthritis is a common, debilitating, costly, incurable, and, in many cases, treatment-resistant disease process. Novel approaches to therapy are clearly required. Because osteoarthritis affects a limited number of weight-bearing joints and lacks an important systemic component, the local treatment of individual diseased joints is the preferred approach to gene therapy. Genes whose products stimulate chondrogenesis or inhibit breakdown of the cartilaginous matrix are obviously candidates for therapeutic use (88–90). These genes may be transferred to the synovium or cartilage of affected joints by in vivo or ex vivo means by using a variety of vectors. Transfer of such genes to chondroprogenitor cells is a particularly attractive approach.

E. Gene Therapy of Tendon Repair or Injuries to Ligaments

Injuries to ligaments and tendons are common, and many of the most frequently injured tissues, such as the cruciate ligaments and articular cartilage, have very limited capabilities for spontaneous repair. They also respond poorly to surgical and nonsurgical intervention. Subtle genetic differences between individuals may account for those who appear to be injury-prone. Studies suggest that gene transfer could improve the management of such injuries (91–93), particularly when used as vehicles for the targeted delivery of growth factors. The concept of gene therapy in orthopedic sports medicine can be extended to include disorders that are manifested as laxity or mechanical weakness of ligaments. In these cases, it is likely that genes encoding the structural macromo1ecules of the matrix are defective. Local gene supplementation in such cases could be useful in the future.

In vitro and in vivo studies have shown that PDGF, TGF-β, and EGF have the potential to improve ligament healing. Extensive studies have been designed to investigate the feasibility of three different gene therapy approaches (direct-, fibroblast-, and myoblast-mediated gene transfer) to the ligaments and tendons (94,95), such as the anterior cruciate ligament.

F. Gene Therapy for the Prevention of Musculoskeletal Infection

Despite the use of antibiotics and improved sterile techniques, infection remains one of the most frequent complications of wound healing. One of the goals of wound management is to keep the wound organism count as low as possible. The development and widespread use of vaccines against infectious agents have been a great triumph of medical science. A new form of vaccination (96), using DNA that contains the gene for the antigen of interest, is under intensive investigation because it can engender both humoral and cellular immune responses. The plasmid encoding for methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin binding protein (PBP2a′) (97), *Pseudomonas aeruginosa* (PsA) outmembrane protein F (OPRF) (98), and extoxin A (99) expressing plasmids have been introduced into animals and have demonstrated an antibacterial effect to these organisms. Other DNA vaccines against *Streptococcus* sp. (100), tuberculosis (101), and fungi such as coccidioidomycosis (102) also show promising results in animal experiments. The potential of prophylaxis against common organisms found in musculoskeletal infections, MRSA, PsA, and *Streptococcus* sp., by DNA vaccine is encouraging.

V. FUTURE DIRECTIONS

With the advance in molecular biology, gene therapy will likely become an increasingly important tool in wound healing and bone defect repair. The main

limitation of gene therapy for musculoskeletal defect repair is the lack of animal models that truly reflect the clinical conditions associated with poor healing and nonunion. More basic research needs to be done to increase our understanding of underlying mechanisms of wound healing and nonunion, and the roles that the growth factors and their receptors play in these processes. These studies will eventually accelerate the use of gene therapy in musculoskeletal repair. Currently, little attention has been paid to the biological component of the healing process other than growth factors. However, there are numerous other necessary components without which the growth factors would be ineffective. Cellular receptors for these growth factors are one example. Because these factors are typically transmembrane proteins, their exogenous application is not likely to restore biological responsiveness. In contrast, transfer of the genes encoding the receptors should accomplish the restoration because the endogenously synthesized molecules can be inserted into the plasma membranes in the normal fashion.

The success of gene therapy in bone and tissue repair relies on the ability of gene delivery systems to deliver therapeutic genes selectively to a sufficient number of target cells to yield expression levels that impact healing. This can be achieved through physical targeting and molecular biological targeting (103). Physical targeting relies on the attachment to the delivery vehicle by ligands that bind to cell surface receptors unique to the target cells. *Molecular biological targeting* refers to selective expression of the therapeutic gene by the target cell through the use of selective promoters (104,105). Selective expression can be further achieved by the use of expression systems controlled by extrinsic induction molecules. Various gene therapy approaches will require the development of methods to determine the most appropriate dosage and methods of in vivo control and the most effective methods and timing for delivery of the gene. The regulated delivery of growth factors in the wound environment would maximize their biological effect and decrease the potential toxicity resulting from overexpression. Potential variation of gene therapy methods includes inducible or controllable tissue-specific promoters To date, four major inducible systems have been developed: the tetracycline inducible system (106), the ecdysone (an insect steroid) inducible system (107), the RU486/antiprogestin mifepristone inducible system (108), and the rapamycin inducible system (109).

The effects of potential synergistic combinations of factors and the sequential delivery of different factors have not been studied. The availability and function of various growth factors in normal wound healing appear to be sequential. Wound fluid evaluations suggest that, normally, the various cytokines are present in the wound at different periods (110,111). No single growth factor has been shown to be uniformly efficacious in clinical trials so far. Multiple growth factor gene therapy and/or a combination of delivery of genes encoding

for growth factors and their specific receptors might be more effective than single growth factor therapy alone. A combination of several gene therapies may be a logical extension of the current single-gene therapy system.

Finally, depending on the types of vectors used, the safety of this approach remains a key concern and will require extensive study before clinical application, particularly in self-limited conditions such as normal bone and wound healing. Important safety parameters include the interaction between the gene therapy and tissue at the delivery site, vector persistence and bioavailability, interaction between gene therapy and the immune system, and pharmacokinetics and pharmacodynamics of vector-encoded proteins, both at the site of delivery and systemwide.

VI. SUMMARY

Recent advances in the fields of biotechnology and molecular biology offer the orthopedic surgeon exciting avenues for repair or regeneration of skeletal tissue lost to injury, infection, tumor, or aging. Growth factors, which are key elements in wound repair and bone healing, control cell proliferation, cell migration, and formation and accumulation of extracellular components. The ability of growth factors to enhance human bone formation and wound healing substantially has been clearly documented in preclinical testing. The development of isolation and culture techniques for mesenchymal progenitor cells from various tissues has promoted interest in the use of these cells for repair and regeneration of musculoskeletal tissues. A combination of implantation of bone-forming cells with osteoinductive growth factors is also under active investigation.

Local and, potentially, systemic bone and soft tissue engineering using gene therapy may prove to be the next major advance in molecular modulation of musculoskeletal tissue. We define gene therapy as the transfer of genetic materials to achieve a therapeutic effect on tissue repair. The focus of gene therapy is to place therapeutic agents at the injury or wound site at safe levels to prevent toxicity, yet have the desired therapeutic effect. Gene therapy largely involves the transfer of gene-encoding growth factors and cytokines, which regulate cell proliferation, migration, and syntheses of ECM components. Several different approaches have been used to transfer growth factors into cells and tissues. Tissue-specific promoters and specific inducible promoters are used to aid in localizing the production of factors to certain cell types and ensure that their expression takes place at the right time and in a controllable fashion. Use of gene therapy to enhance tissue repair is still in an early stage of development, but it has the potential to revolutionize the practice of orthopedic surgery. The era of "clinical orthopedic gene therapy" may soon be a reality.

REFERENCES

1. MP Bostrom, KJ Saleh, TA Einhorn. Osteoinductive growth factors in preclinical fracture and long bone defects models. Orthop Clin North Am 30(4):647–658, 1999.
2. JC Banwart, MA Asher, RS Hassanein. Iliac crest bone graft harvest donor site morbidity: a statistical evaluation. Spine 20:1055–1060, 1995.
3. TJ Phillips. Chronic cutaneous ulcers: etiology and epidemiology. J Invest Dermatol 102(6):38S–41S, 1994.
4. NT Bennett, GS Schultz. Growth factors and wound healing:, II. Role in normal and chronic wound healing. Am J Surg 166(l):74–81, 1993.
5. DL Steed. The role of growth factors in wound healing. Surg Clin North Am 77(3):575–586, 1997.
6. GS Lazarus, DM Cooper, DR Knighton, DJ Margolis, RE Pecoraro, U Rodeheaver, MC Robson. Definitions and guidelines for assessment of wounds and evaluation of healing. Arch Dermatol 130(4):489–493, 1994.
7. BC Nwomeh, DR Yager, IK Cohen. Physiology of the chronic wound. Clin Plast Surg 25(3):341–356, 1998.
8. JM Smiell, TJ Wieman, DL Steed, BH Perry, AR Sampson, BH Schwab. Efficacy and safety of becaplermin (recombinant human platelet-derived growth factor-BB) in patients with nonhealing, lower extremity diabetic ulcers: a combined analysis of four randomized studies. Wound Repair Regen 7(5):335–346, 1999.
9. A Veves, V Falanga, DG Armstrong, ML Sabolinski. Graftskin, a human skin equivalent, is effective in the management of noninfected neuropathic diabetic foot ulcers: a prospective randomized multicenter clinical trial. Diabetes Care 24(2):290–295, 2001.
10. MR Urist. Bone: formation by autoinduction. Science 150(698):893–899, 1965.
11. JM Wozney, V Rosen. Bone morphogenetic protein and bone morphogenetic protein gene family in bone formation and repair. Clin Orthop 346:26–37, 1998.
12. AH Reddi. Initiation of fracture repair by bone morphogenetic proteins. Clin Orthop 355(suppl):S66–S72, 1998.
13. JM Wozney. The bone morphogenetic protein family and osteogenesis. Mol Reprod Dev 32(2):160–167, 1992.
14. AW Yasko, JM Lane, EJ Fellinger, V Rosen, JM Wozney, EA Wang. The healing of segmental bone defects, induced by recombinant human bone morphogenetic protein (rhBMP–2): a radiographic, histological, and biomechanical study in rats. J Bone Joint Surg Am 74:659–670, 1992.
15. TN Gerhart, CA Kirker-Head, MJ Kriz, ME Holtrop, GE Hennig, J Hipp, SH Schelling, E Wang. Healing segmental femoral defects in sheep using recombinant human bone morphogenetic protein. Clin Orthop 293:317–326, 1993.
16. M Bostrom, JM Lane, E Tomin, M Browne, W Berberian, T Turek, J Smith, J Wozney, T Schildhauer. Use of bone morphogenetic protein-2 in the rabbit ulnar nonunion model. Clin Orthop 327:272–282, 1996.
17. SD Cook, MW Wolfe, SL Salkeld, DC Rueger. Effect of recombinant human osteogenic protein–1 on healing of segmental defects in non-human primates. J Bone Joint Surg Am 77:734–750, 1995.

18. SD Cook, GC Baffes, MW Wolfe, TK Sampath, DC Rueger. Recombinant human bone morphogenetic protein-7 induces healing in a canine long-bone segmental defect model. Clin Orthop 301:302–312, 1994.
19. EE Johnson, MR Urist, GA Finerman. Repair of segmental defects of the tibia with cancellous bone grafts augmented with human bone morphogenetic protein: a preliminary report. Clin Orthop 236:249–257, 1988.
20. RG Geesink, NH Hoefnagels, 8K Bulstra. Osteogenic activity of OP-1 bone morphogenetic protein (BMP-7) in a human fibular defect. J Bone Joint Surg Br 8l(4):710–718, 1999.
21. DM Cooper, EZ Yu, P Hennessey, F Ko, MC Robson. Determination of endogenous cytokines in chronic wounds. Ann Surg 219(6):688–691, 1994.
22. GF Pierce, JE Tarpley, J Tseng, J Bready, D Chang, WC Kenney, R Rudolph, MC Robson, J Van de Berg, P Reid. Detection of platelet-derived growth factor (PDGF)-AA in actively healing human wounds treated with recombinant PDGF-BB and absence of PDGF in chronic nonhealing wounds. J Clin Invest 96(3):1336–1350, 1995.
23. MC Robson, LG Phillips, A Thomason, LE Robson, GF Pierce. Platelet-derived growth factor BB for the treatment of chronic pressure ulcers. Lancet 339(8784):23–25, 1992.
24. MC Robson, LG Phillips, WT Lawrence, JB Bishop, IS Youngerman, PG Hayward, LD Broemeling, JP Heggers. The safety and effect of topically applied recombinant basic fibroblast growth factor on the healing of chronic pressure sores. Ann Surg 216(4):401–406, 406–408, 1992.
25. GL Brown, L Curtsinger, MJ Jurkiewicz, F Nahai, G Schultz. Stimulation of healing of chronic wounds by epidermal growth factor. Plast Reconstr Surg 88(2):189–194, 1991.
26. AJ Friedenstein, II Shapiro-Piatetzky, KV Petrakova. Osteogenesis in transplants of bone marrow cells. J Embryol Exp Morphol 16:381–390, 1966.
27. JJ Rogers, HE Young, LR Adkison, PA Lucas, AC Black Jr. Differentiation factors induce expression of muscle, fat, cartilage, and bone in a clone of mouse pluripotent mesenchymal stem cells. Am Surg 61(3):231–236, 1995.
28. SP Bruder, DJ Fink, AL Caplan. Mesenchymal stem cells in bone development, bone repair, and skeletal regeneration therapy. J Cell Biochem 56(3):283–294, 1994.
29. M Richards, BA Huibregtse, AL Caplan, JA Goulet, SA Goldstein. Marrow-derived progenitor cell injections enhance new bone formation during distraction. J Orthop Res 17(6):900–908, 1999.
30. SP Bruder, AA Kurth, M Shea, WC Hayes, N Jaiswal, S Kadiyala. Bone regeneration by implantation of purified, culture-expanded human mesenchymal stem cells, J Orthop Res 16(2):155–162, 1998.
31. BD Boyan, AI Caplan, ID Heckman, DP Lennon, W Ehler, Z Schwartz. Osteochondral progenitor cells in acute and chronic canine nonunions. J Orthop Res l7(2):246–255, 1999.
32. SP Bruder, KH Kraus, VM Goldberg, S Kadiyala. The effect of implants loaded with autologous mesenchymal stem cells on the healing of canine segmental bone defects. J Bone Joint Surg Am 80(7):985–996, 1998.

33. HA Awad, DL Butler, GP Boivin, FN Smith, P Malaviya, B Huibregtse, AI Caplan. Autologous mesenchymal stem cell-mediated repair of tendon. Tissue Eng 5(3):267–277, 1999.
34. JU Yoo, TS Barthel, K Nishimura, L Solchaga, AI Caplan, VM Goldberg, B Johnstone. The chondrogenic potential of human bone-marrow-derived mesenchymal progenitor cells. J Bone Joint Surg Am 80(12):1745–1757, 1998.
35. SM Mueller, J Glowacki. Age-related decline in the osteogenic potential of human bone marrow cells cultured in three-dimensional collagen sponges. J Cell Biochem 82(4):583–590, 2001.
36. JP Rodriguez, S Garat, H Gajardo, AM Pino, G Seitz. Abnormal osteogenesis in osteoporotic patients is reflected by altered mesenchymal stem cells dynamics. J Cell Biochem 75(3):414–423, 1999.
37. R Quarto, M Mastrogiacomo, R Cancedda, SM Kutepov, V Mukhachev, A Lavroukov, E Kon, M Marcacci. Repair of large bone defects with the use of autologous bone marrow stromal cells. N Engl J Med 344(5):385–386, 2001.
38. PH Krebsbach, MH Mankani, K Satomura, SA Kuznetsov, PG Robey. Repair of craniotomy defects using bone marrow stromal cells. Transplantation 66(10):1272–1278, 1998.
39. T Noshi, T Yoshikawa, M Ikeuchi, Y Dohi, H Ohgushi, K Horiuchi, M Sugimura, K Ichijima, K Yonemasu. Enhancement of the in vivo osteogenic potential of marrow/hydroxyapatite composites by bovine bone morphogenetic protein. J Biomed Mater Res 52(4):621–630, 2000.
40. GB Stark, M Volgt, C Andree, DJ Schaefer, H Bannasch. Cell transplantation in surgery—reality and prospects for tissue engineering. Schweiz Rundsch Med Prax 89(43):1737–1740, 2000.
41. K Sato, MR Urist. Induced regeneration of calvaria by bone morphogenetic protein (BMP) in dogs. Clin Orthop 197:301–311, 1985.
42. DC Covey, JA Albright. Clinical induction of bone repair with demineralized bone matrix or a bone morphogenetic protein. Orthop Rev 18(8):857–863, 1989.
43. JM Lane, AW Yasko, E Tomin, BJ Cole, S Waller, M Browne, T Turek, J Gross. Bone marrow and recombinant human bone morphogenetic protein-2 in osseous repair. Clin Orthop 361:216–227, 1999.
44. VV Terskikh. AV Vasiliev. Cultivation and transplantation of epidermal keratinocytes. Int Rev Cytol 188:41–72, 1999.
45. CJ Nolte, MA Oleson, JF Hansbrough, J Morgan, G Greenleaf, L Wilkins. Ultrastructural features of composite skin cultures grafted onto athymic mice. J Anat 185(pt 2):325–333, 1994.
46. DL Steed. Modifying the wound healing response with exogenous growth factors. Clin Plast Surg 25(3):397–405, 1998.
47. WF Anderson. Human gene therapy. Nature 392(6679 suppl): 25–30, 1998.
48. J Bonadio. Tissue engineering via local gene delivery: update and future prospects for enhancing the technology. Adv Drug Deliv Rev 44(2–3):185–194, 2000.
49. WS Hu, VK Pathak. Design of retroviral vectors and helper cells for gene therapy. Pharmacol Rev 52(4):493–511, 2000.

50. TJ Oligino, Q Yao, SC Ghivizzani, P Robbins. Vector systems for gene transfer to joints. Clin Orthop 379(suppl):S17–S30, 2000.
51. AR Davis, NA Wivel, JL Palladino, L Tao, JM Wilson. Construction of adenoviral vectors. Mol Biotechnol 18(1):63–70, 2001.
52. TM Crombleholme. Adenoviral-mediated gene transfer in wound healing. Wound Repair Regen 8(6):460–472, 2000.
53. WH Gunzburg, B Salmons. Virus vector design in gene therapy. Mol Med Today 1(9):410–4l7, 1997.
54. C Ropert. Liposomes as a gene delivery system. Braz J Med Biol Res 32(2):163–169, 1999.
55. PL Felgner. Nonviral strategies for gene therapy. Sci Am 276(6):102–106, 1997.
56. S Li, L Huang. Nonviral gene therapy: promises and challenges. Gene Ther 7(l):31–34, 2000.
57. JM Davidson, T Krieg, SA Eming. Particle-mediated gene therapy of wounds. Wound Repair Regen 8(6):452–459, 2000.
58. JM Isner, I Baumgartner, G Rauh, R Schainfeld, R Blair, O Manor, S Razvi, JF Symes. Treatment of thromboangiitis obliterans (Buerger's disease) by intramuscular gene transfer of vascular endothelial growth factor: preliminary clinical results. J Vasc Surg 28(6):964–973, 1998.
59. C Andree, WF Swain, CP Page, MD Macklin, J Slama, D Hatzis, B Eriksson. In vivo transfer and expression of a human epidermal growth factor gene accelerates wound repair. Proc Natl Acad Sci USA 91(25):12188–12192, 1994.
60. L Sun, L Xu, H Chang, FA Henry, RM Miller, JM Harmon, TB Nielsen. Transfection with aFGF cDNA improves wound healing. J Invest Dermatol 108(3):313–318, 1997.
61. J Bonadio. Tissue engineering via local gene delivery: update and future prospects for enhancing the technology. Adv Drug Deliv Rev 44(2–3):185–194, 2000.
62. J Fang, YY Zhu, E Smiley, J Bonadio, JP Rouleau, SA Goldstein, LK McCauley, BL Davidson, BJ Roessler. Stimulation of new bone formation by direct transfer of osteogenic plasmid genes. Proc Natl Acad Sci USA 93:5753–5758, 1996.
63. JD Mosca, JK Hendricks, D Buyaner, J Davis-Sproul, LC Chuang, MK Majumdar, R Chopra, F Barry, M Murphy, MA Thiede, U Junker, RJ Rigg, SP Forestell, E Bohnlein, R Storb, BM Sandmaier. Mesenchymal stem cells as vehicles for gene delivery. Clin Orthop 379(suppl):S7l–S90, 2000.
64. P Bianco, P Gehron Robey. Marrow stromal stem cells. J Clin Invest 105(12): 1663–1668, 2000.
65. D Gazit, G Turgeman, P Kelley, E Wang, M Jalenak, Y Zilberman, I Moutsatos. Engineered pluripotent mesenchymal cells integrate and differentiate in regenerating bone: a novel cell-mediated gene therapy. J Gene Med 1:121–133, 1999.
66. J Lou, F Xu, K Merkel, P Manske. Gene therapy: adenovirus-mediated human bone morphogenetic protein-2 gene transfer induces mesenchymal progenitor cell proliferation and differentiation in vitro and bone formation in vivo. J Orthop Res 17(1):43–50, 1999.

67. TD Alden, EJ Beres, JS Laurent, JA Engh, S Das, SD London, JA Jane Jr, SB Hudson, GA Helm. The use of bone morphogenetic protein gene therapy in craniofacial bone repair. J Craniofac Surg 11(l):24–30, 2000.
68. JR Lieberman, LQ Le, L Wu, GA Finerman, A Berk, ON Witte, S Stevenson. Regional gene therapy with a BMP-2-producing murine stromal cell line induces heterotopic and orthotopic bone formation in rodents. J Orthop Res 16:330–339, 1998.
69. DS Musgrave, P Bosch, JY Lee, D Pelinkovic, SC Ghivizzani, J Whalen, C Niyibizi, J Huard. Ex vivo gene therapy to produce bone using different cell types. Clin Orthop 378:290–305, 2000.
70. M Meuli, Y Liu, D Liggitt, M Kashani-Sabet, S Knauer, C Meuli-Simmen, MR Harrison, NS Adzick, TD Heath, RJ Debs. Efficient gene expression in skin wound sites following local plasmid injection. J Invest Dermatol 116(1):131–135, 2001.
71. WB van den Berg. Anti-cytokine therapy in chronic destructive arthritis. Arthritis Res 3(1):18–26, 2001.
72. MF Cordeiro, SS Bhattacharya, GS Schultz, PT Khaw. TGF-betal, -beta2, and -beta3 in vitro: biphasic effects on Tenon's fibroblast contraction, proliferation, and migration. Invest Ophthalmol Vis Sci 41(3):756–763, 2000.
73. Z Hou, Q Nguyen, B Frenkel, SK Nilsson, M Milne, AJ van Wijnen, JL Stein, P Quesenberry, JB Lian, GS Stein. Osteoblast-specific gene expression after transplantation of marrow cells: implications for skeletal gene therapy. Proc Natl Acad Sci USA 96(13):7294–7299, 1999.
74. JB Lian, GS Stein, JL Stein, AJ van Wijnen. Marrow transplantation sand targeted gene therapy to the skeleton. Clin Orthop 379(suppl):S146–S155, 2000.
75. GS Stein, JB Lian, JL Stein, AJ van Wijnen. Bone tissue specific transcriptional control: options for targeting gene therapy to the skeleton. Cancer 88(suppl 12):2899–2902, 2000.
76. JM Davidson, JS Whitsitt, B Pennington, CB Ballas, S Eming, SI Benn. Gene therapy of wounds with growth factors. Curr Top Pathol 93:111–121, 1999.
77. AH Trainer, MY Alexander. Gene delivery to the epidermis. Hum Mol Genet 6(10): 1761–1767, 1997.
78. JW Tyrone, JE Mogford, LA Chandler, C Ma, Y Xia, GF Pierce, TA Mustoe. Collagen-embedded platelet-derived growth factor DNA plasmid promotes wound healing in a dermal ulcer model. J Surg Res 93(2):239–236, 2000.
79. C Andree, WF Swain, CP Page, MD Macklin, J Slama, D Hatzis, E Eriksson. In vivo transfer and expression of a human epidermal growth factor gene accelerates wound repair. Proc Natl Acad Sci USA 91(25):12188–12192, 1994.
80. KW Liechty, M Nesbit, M Herlyn, A Radu, NS Adzick, TM Crombleholme. Adenoviral-mediated overexpression of platelet-derived growth factor-B corrects ischemic impaired wound healing. J Invest Dermatol 113(3):375–383, 1999.
81. JY Lee, D Musgrave, D Pelinkovic, K Fukushima, J Cummins, A Usas, P Robbins, FH Fu, J Huard. Effect of bone morphogenetic protein-2-expressing muscle-derived cells on healing of critical-sized bone defects in mice. J Bone Joint Surg Am 83(7):1032–1039, 2001.

82. Y Okubo, K Bessho, K Fujimura, T Iizuka, SI Miyatake. In vitro and in vivo studies of a bone morphogenetic protein-2 expressing adenoviral vector. J Bone Joint Surg Am 83(suppl 1, pt 2):S99–S104, 2001.
83. GA Helm, TD Alden, EJ Beres, SB Hudson, S Das, JA Engh, DD Pittman, KM Kerns, DF Kallmes. Use of bone morphogenetic protein-9 gene therapy to induce spinal arthrodesis in the rodent. J Neurosurg 92(2 suppl):191–196, 2000.
84. TD Alden, DD Pittman, EJ Beres, GR Hankins, DF Kallmes, BM Wisotsky, KM Kerns, GA Helm. Percutaneous spinal fusion using bone morphogenetic protein-2 gene therapy. J Neurosurg 90(suppl 1):109–l14, 1999.
85. DS Musgrave, P Bosch, S Ghivizzani, PD Robbins, CH Evans, J Huard. Adenovirus-mediated direct gene therapy with bone morphogenetic protein-2 produces bone. Bone 24(6): 541–547, 1999.
86. AS Breitbart, DA Grande, JM Mason, M Barcia, T James, RT Grant. Gene-enhanced tissue engineering: applications for bone healing using cultured periosteal cells transduced retrovirally with the BMP-7 gene. Ann Plast Surg 42(5):488–495, 1999.
87. JR Lieberman, LQ Le, L Wu, GA Finerman, A Berk, ON Witte, S Stevenson. Regional gene therapy with a BMP-2-producing murine stromal cell line induces heterotopic and orthotopic bone formation in rodents. J Orthop Res 16(3):330–339, 1998.
88. CH Evans, PD Robbins, SC Ghivizzani, JH Herndon, R Kang, AB Bahnson, JA Barranger, EM Elders, S Gay, MM Tomaino, MC Wasko, SC Watkins, TL Whiteside, JC Glorioso, MT Lotze, TM Wright. Clinical trial to assess the safety, feasibility, and efficacy of transferring a potentially anti-arthritic cytokine gene to human joints with rheumatoid arthritis. Hum Gene Ther 7(10):1261–1280, 1996.
89. K Otani, I Nita, W Macaulay, HI Georgescu, PD Robbins, CH Evans. Suppression of antigen-induced arthritis in rabbits by ex vivo gene therapy. J Immunol 156(9):3558–3562, 1996.
90. GL Hung, J Galea-Lauri, GM Mueller, HI Georgescu, LA Larkin, MK Suchanek, MH Tindal, PD Robbins, CH Evans. Suppression of intra-articular responses to interleukin-1 by transfer of the interleukin-l receptor antagonist gene to synovium. Gene Ther 1(l):64–69, 1994.
91. TG Gerich, R Kang, FH Fu, PD Robbins, CH Evans. Gene transfer to the patellar tendon. Knee Surg Sports Traumatol Arthrosc 5(2):118–123, 1997.
92. DA Hart, CH Evans. Orthopaedic gene therapy: ligament and tendon. Clin Orthop 379 (suppl):S260–S26l, 2000.
93. J Menetrey, C Kasemkijwattana, CS Day, P Bosch, FH Fu, MS Moreland, J Huard. Direct- fibroblast- and myoblast-mediated gene transfer to the anterior cruciate ligament. Tissue Eng 5(5):435–442, 1999.
94. I Ozkan, K Shino, N Nakamura, T Natsuume, N Matsumoto, S Horibe, T Tomita, Y Kaneda, T Ochi. Direct in vivo gene transfer to healing rat patellar ligament by intra-arterial delivery of haemagglutinating virus of Japan liposomes. Eur J Clin Invest 29(l):63–67, 1999.

95. CS Day, C Kasemkijwattana, J Menetrey, SS Floyd Jr, D Booth, MS Moreland, FH Fu, J Huard. Myoblast-mediated gene transfer to the joint. J Orthop Res 15(6):894–903, 1997.
96. CJ Pachuk, DE McCallus, DB Weiner, C Satishchandran. DNA vaccines—challenges in delivery. Curr Opin Mol Ther 2(2):188–198, 2000.
97. A Ohwada, M Sekiya, H Hanaki, KK Arai, I Nagaoka, S Hori, S Tominaga, K Hiramatsu, Y Fukuchi. DNA vaccination by mecA sequence evokes an antibacterial immune response against methicillin-resistant *Staphylococcus aureus*. J Antimicrob Chemother 44(6):767–774, 1999.
98. J Gabelsberger, B Knapp, S Bauersachs, UI Enz, BU von Specht, H Domdey. A hybrid outer membrane protein antigen for vaccination against *Pseudomonas aeruginosa*. Behring Inst Mitt (98):302–314, 1997.
99. KS Denis-Mize, BM Price, NR Baker, DR Galloway. Analysis of immunization with DNA encoding *Pseudomonas aeruginosa* exotoxin A. FEMS Immunol Med Microbiol 27(2):147–154, 2000.
100. H Bercovier, C Ghittino, A Eldar. Immunization with bacterial antigens: infections with streptococci and related organisms. Dev Biol Stand 90:153–160, 1997.
101. DP Fonseca, B Benaissa-Trouw, M van Engelen, CA Kraaijeveld, H Snippe, AF Verheul. Induction of cell-mediated immunity against *Mycobacterium tuberculosis* using DNA vaccines encoding cytotoxic and helper T-cell epitopes of the 38-kilodalton protein. Infect Immun 69(8):4839–4845, 2001.
102. K Li, JJ Yu, CY Hung, PF Lehmann, GT Cole. Recombinant urease and urease DNA of *Coccidioides immitis* elicit an immunoprotective response against coccidioidomycosis in mice. Infect Immun 69(5):2878–2887, 2001.
103. KW Peng. Strategies for targeting therapeutic gene delivery. Mol Med Today 5(10):448–453, 1999.
104. W Walther, U Stein. Cell type specific and inducible promoters for vectors in gene therapy as an approach for cell targeting. J Mol Med 74(7):379–392, 1996.
105. RT Franceschi. The developmental control of osteoblast-specific gene expression: role of specific transcription factors and the extracellular matrix environment. Crit Rev Oral Biol Med 10(1):40–57, 1999.
106. M Gossen, H Bujard. Tight control of gene expression in mammalian cells by tetracycline-responsive promoters. Proc Natl Acad Sci USA 89(12):5547–5551, 1992.
107. D No, TP Yao, RM Evans. Ecdysone-inducible gene expression in mammalian cells and transgenic mice. Proc Natl Acad Sci USA 93(8):3346–3351, 1996.
108. Y Wang, BM O'Malley Jr, SY Tasai, BM O'Malley. A regulatory system for use in gene therapy. Proc Natl Acad USA 91:8180–8184, 1994.
109. VM Rivera, T Clackson, S Natesan, R Pollock, JF Amara, T Keenan, SR Magari, T Phillips, NL Courage, F Cerasoli Jr, DA Holt, M Gilman. A humanized system for pharmacologic control of gene expression. Nat Med 2(9):1028–1032, 1996.
110. J Matsuoka, GR Grotendorst. Two peptides related to platelet-derived growth factor are present in human wound fluid. Proc Natl Acad Sci USA 86(12):4416–4420, 1989.
111. VM Dvonch, RJ Murphey, J Matsuoka, GR Grotendorst. Changes in growth factor levels in human wound fluid. Surgery 112(1):18–23, 1992.

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