

Diagnosis and Management of Chronic Infection

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Abstract

High-energy penetrating extremity injuries are often associated with severe open fractures that have varying degrees of soft-tissue contamination and tenuous soft-tissue coverage. The result is a relatively high prevalence of chronic osteomyelitis compared with that in civilian trauma patients. Diagnosing chronic osteomyelitis requires a careful history and thorough physical and radiographic examinations. Cross-sectional imaging can help delineate the extent of bony involvement, and scintigraphy can be used as a diagnostic tool and to gauge response to treatment. Clinical staging also directs surgical management. Adequacy of débridement remains the most important clinical predictor of success; thus, adopting an oncologic approach to complete (ie, wide) excision is important. Reconstruction can be safely performed by a variety of methods; however, proper staging and patient selection remain critical to a successful outcome. Although systemic and depot delivery of antibiotics plays a supporting role in the treatment of chronic osteomyelitis, the ideal dosing regimens, and the duration of treatment, remain controversial.

Most commonly, the term chronic infection in combat-related extremity trauma connotes osteomyelitis. The cause is usually multifactorial but stems from the high-energy nature of the initial injury. Severe open fractures, with varying degrees of gross contamination and tenuous soft-tissue envelopes, are commonplace. Throughout the phases of treatment, considerable efforts are directed toward limb salvage or preservation of residual limb length. Despite the judicious use of internal and external fixation in these patients, the prevalence of osteomyelitis, chronic or otherwise, is relatively high compared with that in civilian trauma patients.¹⁻³

Chronic infection negatively affects several aspects of recovery in this

predominately young, active patient population. Severe open fractures, already predisposed to delayed union and nonunion in the absence of complication, become extremely difficult to treat, particularly in the presence of infected internal fixation.^{2,4} Weight-bearing restrictions affect ambulatory status, functional mobility, and independence. In addition, serial débridement procedures, prolonged hospitalization, and long-term antibiotic therapy are associated with considerable expense, delays in rehabilitation, and loss of productivity.⁵ Chronic osteomyelitis deserves many of the same clinical considerations as malignant tumors. For example, an accurate tissue (albeit microbiologic) diagnosis guides treatment;^{6,7} staging carries prognostic value⁸ and guides treatment;⁶ and

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the treatment often involves complete (ie, wide) excision of the involved bone,^{6,9} followed by complex bony and soft-tissue reconstruction.¹⁰

Diagnosis

Diagnosing chronic osteomyelitis requires a thorough evaluation. A comprehensive physical examination is necessary to identify any systemic manifestations of infection, although these findings are rare. Focused physical examination of the extremities should also be performed, with an emphasis on the condition of the soft tissues overlying the area of interest. Neurologic and vascular function should be assessed and any deformities (including limb length discrepancies) noted. A thorough social, past medical, and surgical history should be taken to identify any comorbid conditions for the purpose of “describing the host”⁸ and assigning an accurate physiologic class (A through C).¹¹

Imaging remains the cornerstone of the evaluation process.⁹ Radiographs provide useful information in terms of bone loss, deformity, and the type and number of implants. Cross-sectional imaging can help identify the presence of an abscess or sequestrum, as well as delineate the extent of medullary edema and, perhaps more importantly, the extent of cortical involvement. Contrast MRI studies should be obtained whenever possible, although these studies demonstrate signal degradation in the presence of internal and/or external fixation, particularly

when intramedullary implants are present. For this reason, CT should be considered in this setting. Indium 111–labeled white blood cell scintigraphy is more specific than three-phase technetium-99m bone scan in identifying infection¹² and thus is routinely used, not only to help diagnose and localize focal areas of osteomyelitis but also to evaluate response to treatment and, ultimately, the eradication of infection.

Laboratory evaluation, with the exception of microbiologic testing, is often nonspecific. Leukocyte count with differential is usually normal.⁷ The erythrocyte sedimentation rate, in contrast, is typically elevated but lacks specificity necessary to diagnose extremity infections. C-reactive protein, procalcitonin and other inflammatory cytokine levels are reliably elevated in the setting of acute, posttraumatic extremity infections^{13,14} but have not been fully evaluated in the setting of chronic osteomyelitis. Liver and kidney function as well as the patient’s human immunodeficiency virus status should be assessed. An accurate microbiologic assessment should be performed in all cases and include tissue and fluid cultures for aerobic, anaerobic acid-fast bacilli, and fungal organisms. Gram stain results at the time of initial débridement/biopsy should also be recorded.

Classification

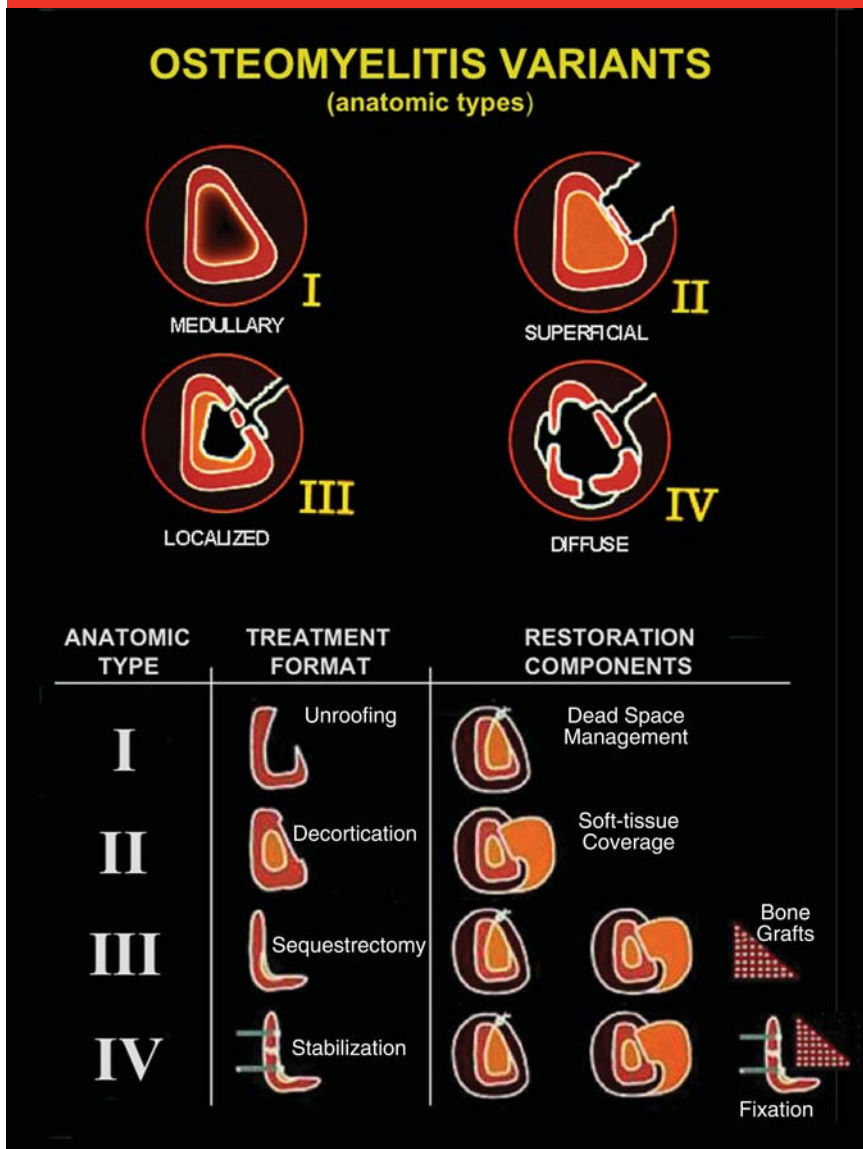
Chronic osteomyelitis is a biofilm infection caused by complex colonies

of phenotypically diverse microorganisms propagating freely within a microbial-based, polysaccharide matrix that provides an immunity to host defenses and systemic concentrations of antimicrobial agents.^{15,16} Once the biofilm bacteria establish macromolecular attachments to exposed, nonviable surfaces within the wound (ie, tissue, implants, foreign bodies), there is no way to eradicate the disease shy of either killing the host or physically removing the inflammatory nidus, including the colony and all substrate attachments.¹⁷ Thorough surgical débridement, a competent host response, and pathogen-specific antimicrobial coverage are, therefore, the essential components of treatment protocols: the débridement removes the biofilm burden while antibiotics rid the host of residual bacterial phenotypes, leaving the host free to heal a live, clean, manageable wound.

Published in 1985, the Cierny-Mader classification of adult osteomyelitis¹¹ is the first system to articulate treatment with the natural history of the disease.^{6,18} In this system, the biofilm nidus is characterized by one of four anatomic types whose complexity and associated risk for treatment failure escalate numerically (Figure 1). In type I, medullary osteomyelitis (Figure 2), the nidus is endosteal whereas, in type II, superficial osteomyelitis (Figure 3), it is confined to an outer surface of bone that remains exposed, usually unprotected by a refractory, soft-tissue deficit. Localized osteomyeli-

Dr. Cierny or an immediate family member has stock or stock options held in Royer Biomedical and serves as a board member, owner, officer, or committee member of the Limb Lengthening and Reconstruction Society and the Musculoskeletal Infection Society. Dr. Webb or an immediate family member is a member of a speakers’ bureau or has made paid presentations on behalf of the Musculoskeletal Transplant Foundation; serves as a paid consultant to Zimmer; has received nonincome support (such as equipment or services), commercially derived honoraria, or other non-research–related funding (such as paid travel) from Synthes, Smith & Nephew, Stryker, and Kinetic Concepts; and serves as a board member, owner, officer, or committee member of the Orthopaedic Trauma Association Southeastern Fracture Consortium. Neither of the following authors or any immediate family member has received anything of value from or owns stock in a commercial company or institution related directly or indirectly to the subject of this article: Dr. Forsberg and Dr. Potter.

Figure 1



A graphic depiction of the four anatomic types of osteomyelitis, matched with their respective treatment formats and components of their reconstruction. (Adapted from Cierny G III: Chronic osteomyelitis: Results of treatment. *Instr Course Lect* 1990;39:495-508.)

infected fracture-union following medullary stabilization; type II, full-thickness wounds resulting from pressure or venous stasis ulcers, an infected fracture-union with a soft-tissue deficit, or nonhealing Papineau grafts;¹⁹ type III, infected fracture-union with butterfly-fragment sequestration or previous plate fixation; and type IV, periprosthetic infections, chronic septic arthritis, or infected nonunions.

In this same system, the patient-host is stratified with regard to his or her physiologic capacity to detour infection, withstand treatment, and/or benefit from cure. A hosts are healthy patients; B hosts are patients who possess comorbidities known to have a detrimental effect on wound healing. The effect can be local (BL), systemic (BS), or combined (BL/S), depending on the circulatory, hematopoietic, metabolic, immunologic, and nutritional status of the patient. Finally, a C host is a patient, compromised or otherwise healthy, who qualifies only for palliative, not curative, treatment (eg, patients who derive no quality-of-life improvement with cure, the morbidity of treatment is excessive, the prognosis is poor, and/or the patient's cooperation is lacking). By combining the anatomic type with the host classification, a clinical stage is designated. For example, a diabetic patient (BS/L host) with an infected nonunion of the distal tibia (type IV osteomyelitis) is designated as a stage IV BS/L osteomyelitis.

Deriving an accurate clinical stage is important for many reasons. It aids in planning the course of treatment, identifies progressive stages of the disease,⁶ and serves as a prognostic indicator.¹⁸ In addition, determination of an accurate clinical stage guides the nature of the surgical procedure²⁰ and is reproducible, so it can be used to compare outcomes in patient and treatment cohorts.^{8,21}

tis, type III, is a well-margined sequestration of an attached or floating fragment of bone (Figure 4), often combining the features of both types I and II osteomyelitis. In localized osteomyelitis, the entire nidus can be excised with a wide margin without causing the osseous segment to become unstable. In type IV lesions, diffuse osteomyelitis, the pro-

cess is permeative and involves a segment of bone and/or an entire joint (Figure 5), and it often exhibits characteristics of types I, II and III. Type IV lesions are mechanically unstable either before and/or after a complete and thorough débridement.

Examples for each anatomic type include the following: type I, hematogenous osteomyelitis, or an

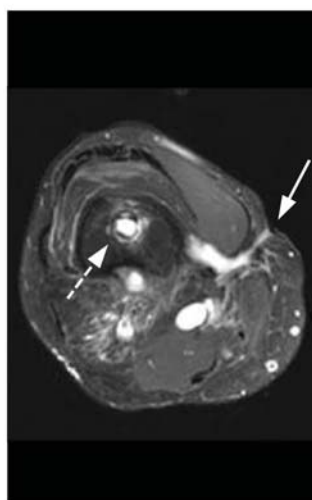
Figure 2



A



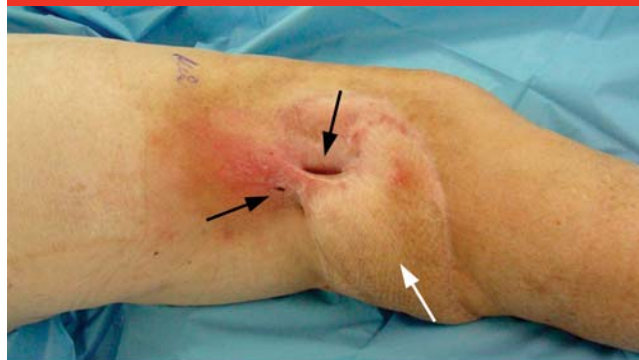
B



C

Type I osteomyelitis of the distal femur. **A**, Clinical photograph demonstrating draining fistula (arrow) at the medial knee in a man with an open fracture. He had undergone intramedullary fixation of the femur more than 20 years previously. **B**, Lateral radiograph demonstrating the healed fracture (white arrow) and possible sequestra distally (black arrows). **C**, Axial T1-weighted postcontrast magnetic resonance image of the distal femur. The solid arrow indicates the medial sinus. The dashed arrow indicates the medullary nidus.

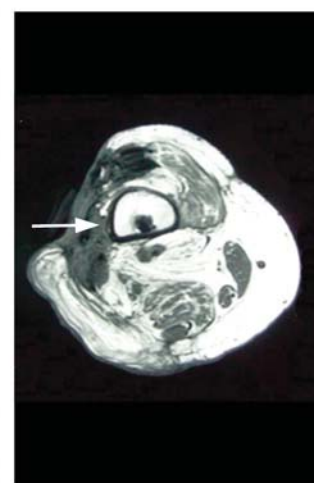
Figure 3



A



B



C

Type II osteomyelitis of the distal femur. **A**, Clinical photograph showing two sinus tracts (black arrows) at the lateral knee, near the tip of a partially failed free flap (white arrow), 2 years after resection and postoperative radiation done for liposarcoma. **B**, AP radiograph with periosteal new bone formation seen along the lateral femur (arrow). **C**, A T1-weighted magnetic resonance image depicting no involvement of the medullary contents (arrow), consistent with superficial (type II) osteomyelitis.

Management

Clinical staging begins with a review of the patient's medical and surgical history and ends with assignment of the treatment format (Table 1). To justify the morbidity and risk of limb salvage, the expected outcome must offer a distinct advantage over amputation or observation alone. If treatment for cure is contraindicated or deemed to be excessive, the pa-

tient is classified as a C host, and he or she is offered palliation (eg, incision/drainage, oral antibiotics, ambulatory aides, pain medication). Amputation is indicated when limb salvage and palliation are neither safe nor feasible.

Amenable comorbidities are reversed and/or minimized (host optimization) before surgical intervention. Thereafter, soft tissues are resected to supple, well-perfused margins. Bone is tangentially excised

until exposed surfaces bleed in a uniform, haversian (cortical) or sinusoidal (cancellous) pattern (ie, the paprika sign).⁴⁰ All foreign bodies and surgical implants are removed, the wound is lavaged of debris, and the surgical field is prepared for closure (double setup).

Multiple tissue samples, not wound swabs, are collected from deep wound surfaces (eg, loculated fluids, reactive granulations, foreign bodies), and specimens are set up for



Figure 4
 Type III osteomyelitis of the distal tibia. **A**, Scar contracture, soft-tissue loss, and a draining sinus (arrow) in the distal leg of a 39-year-old diabetic who sustained an open tibial fracture 13 years before presentation. **B**, AP radiograph demonstrating healed fractures, a distal cortical defect (white arrow), and medullary sequestration proximally (black arrow). **C**, An inversion recovery magnetic resonance scan depicting the cloaca (white arrow), a medullary nidus (dashed arrow), and a cortical sequestrum (asterisk).

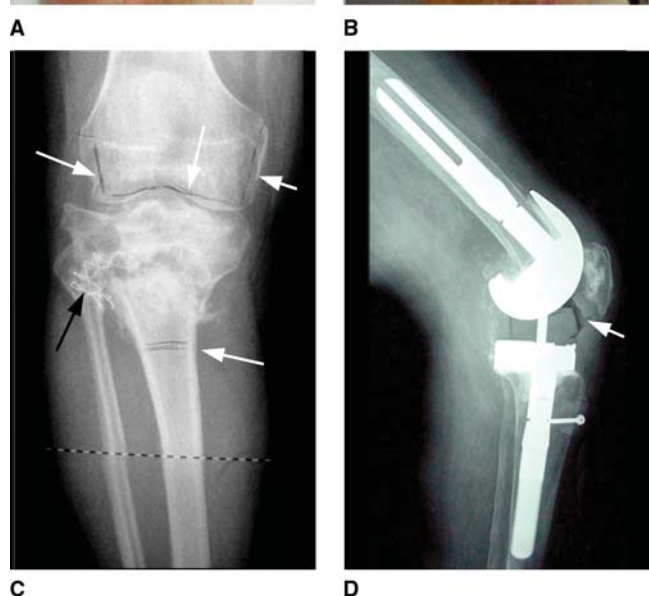


Figure 5
 Type IV osteomyelitis of the distal femur, knee joint, and proximal tibia. **A** and **B**, Two different patients, who each presented with a soft-tissue deficit (white arrows) at the knee and/or proximal leg associated with an underlying, diffuse osteomyelitis. **C**, AP radiograph illustrating deformity with nonunion of a tibial plateau fracture, antibiotic beads (black arrow), and clinician markings at the sites of intended resection (white arrows). **D**, Lateral radiograph of the second patient showing air within the joint (white arrow) containing a well-fixed, long-stemmed revision total knee prosthesis.

culture and sensitivity testing for aerobic and anaerobic bacteria. When orthopaedic implants, foreign bodies, and/or sequestra are retrieved, quantitative cultures following sonication sequencing²³ and/or quantitative polymerase chain reaction pyrosequencing²⁴ are performed to identify the microbial populations within the biofilm colony. Frozen-

section biopsies confirm the presence of inflammation, validate the need for fungal and/or mycobacterial culture setups in the laboratory, and usually rule out the presence of pathologic states mimicking infection (eg, neoplasms, pseudotumors, autoimmune disorders, dysplasias).

Following débridement, each reconstruction must take into consideration

(1) the advantages and disadvantages of attempting to supplement the existing soft-tissue envelope, (2) the mechanical integrity of the remaining bony segments, and (3) how best to manage residual dead space (Table 1: VI, A, 2; VI, B, 4; VIII, A, 3; and XI). Wound closure by any means is imperative when vital structures (eg, vessels, nerves, tendons) are exposed and/or

when the reconstruction of choice (ie, surgical implants, allografts) requires a clean surgical field to succeed. Closure is safeguarded by the systemic administration of pathogen-specific antibiotics and the elimination of dead space by either the apposition of viable tissues (eg, soft-tissue transpositions and/or transfers; acute limb shortening) or the implantation of an antibiotic depot (eg, antibiotic beads, sponges, or spacers). In a closed wound, the high concentrations of antibiotics created by a space-filling, high-dose antibiotic depot will eliminate all remaining phenotypes from the biofilm colony. Furthermore, antibiotic-impregnated polymethylmethacrylate (PMMA) beads and/or spacers will maintain any workable dead space needed for future use (known as the spacer effect).⁴¹ Following wound healing and patient resuscitation, the depot is removed, the “space” reclaimed, and reconstruction performed as a clean surgical procedure.^{21,31} When flaps fail and/or circumstances preclude their use, bone transport,³²⁻³⁴ combined methods of limb shortening/lengthening,²⁵ and negative pressure-assisted closures are valuable tools.⁴²

A live, clean wound will heal by secondary intention and thereby circumvent the need for restoration of the soft-tissue envelope. For these reasons, open reconstruction techniques, such as open cancellous bone grafting,¹⁹ acute limb shortening,²⁵ vascularized bone flaps, and open methods of bone transport,⁴³ can be used, but they have several potential disadvantages. The components used in the reconstruction must also be live (Table 1: VI, A, 2 and XI); the open wound has a prolonged exposure to contamination and/or superinfection; external devices are the fixation of choice; and the surface area for bone grafting is limited. Nevertheless, despite these limitations, open techniques can be useful in carefully selected patients, particu-

larly when a salvage solution is needed.

Depot and Systemic Delivery of Antibiotics

Local depot delivery of antibiotics to infected wounds has become a critical component of musculoskeletal infection management in the last two decades. By this method, one can achieve local antibiotic concentrations several-fold greater than both bacterial minimum inhibitory concentrations and the levels safely attainable with systemic administration, with negligible systemic toxicity. The elution rates and ultimate local concentrations of antibiotics are dependent on the delivery vehicle, surface area of the delivery vehicle, type and concentration of antibiotics, fluid presence and fluid turnover rate, time in vivo, and permanence or bioabsorbable nature of the vehicle.⁴⁴ Antibiotic-impregnated PMMA is versatile and can be used to make spacers for prosthetic joint resections or segmental bone defects and beads to increase surface area and resultant elution rate of antibiotics, as well as to coat intramedullary implants when needed to simultaneously treat osteomyelitis and bony instability. These techniques have been widely adopted and have proven utility in the management of a variety of deep, fracture- and implant-related infections.⁴⁴⁻⁴⁶ Sustained suprathereapeutic local antimicrobial concentrations exceeding 6 weeks in duration are routinely achievable with these delivery methods.⁴⁷ The so-called membrane technique of PMMA spacer placement, followed by subsequent spacer removal and bone grafting, has demonstrated both good clinical success and the bioactivity of the biologic and osteoinductive layer that forms around such spacers.⁴⁶

More recently, several bioabsorbable delivery vehicles have become available with favorable elution characteristics and putatively similar efficacy. These delivery vehicles have the added benefits of obviating the need for removal and, in many cases, of being osteoconductive and/or osteoinductive.^{26,48,49} Direct and minimal carrier application of local antibiotics is now being investigated via several modalities, although the duration of effect persistence will ostensibly be decreased.⁵⁰⁻⁵⁴ Local adjuvants therefore represent an increasingly critical component of the physician's armamentarium in the fight against chronic musculoskeletal infections. As increasingly biocompatible and bioabsorbable technologies continue to develop and greater supporting evidence becomes available, a shift away from PMMA-based therapy appears both inevitable and advisable in the absence of planned secondary procedures for reinstrumentation, bone grafting, or soft-tissue reconstruction. As infection eradication rates improve, additional focus may be warranted in assessing and minimizing local tissue toxicity because of suprathereapeutic antibiotic concentrations in search of the optimal balance between infection eradication and osseous union or soft-tissue healing.^{55,56}

There is now evidence that local depot antibiotic delivery has equivalent or better efficacy with regard to infection prevention or eradication than does systemic therapy.⁵⁷ However, the efficacy of combining these antibiotic treatment modalities appears to be additive, if not synergistic;⁴⁵ particularly in the setting of chronic infection, primary treatment success rates are not yet high enough, and long-term recidivism is too frequent, to routinely eschew systemic in favor of local therapy. A general guideline for the duration of systemic antimicrobial therapy is 6

Table 1

Treatment of Adult Chronic Osteomyelitis^a

I	Patient evaluation
II	Preoperative testing <ul style="list-style-type: none"> A. Laboratory testing: full metabolic panel, CBC with differential, coagulation panel, UA, ESR, CRP level, colonization testing²² B. Diagnostics: vascular indices, ultrasonography, oxygen tensions (tc PO₂) C. Radiography: plain radiography, MRI, CT, nuclear scan, PET, angiography D. Tissue specimens: cultures, histology sections, PCR pyrosequencing^{23,24}
III	Clinical staging <ul style="list-style-type: none"> A. Anatomic type: I, medullary; II, superficial; III, localized; IV, diffuse B. Physiologic class: A host, B host, C host
IV	Treatment format <ul style="list-style-type: none"> A. Limb salvage; amputation; palliation: C hosts; no treatment for cure
V	Host optimization <ul style="list-style-type: none"> A. Reverse amenable comorbidities
VI	First surgery <ul style="list-style-type: none"> A. One-stage treatment <ul style="list-style-type: none"> 1. Débridement, cultures, biopsy, antibiotics (all treatment formats) 2. Dead space management (limb salvage, amputation) <ul style="list-style-type: none"> a. Wound: secondary intention, primary vs delayed closure b. Bone: vascularized bone flaps, acute shortening²⁵ c. Fixation: orthoses, external fixators d. Depots: antibiotic beads²⁶⁻³⁰ B. First stage of multistage treatments <ul style="list-style-type: none"> 1. Débridement, cultures, biopsy, systemic antibiotics 2. Double setup: change instruments; re-prep and redrape; new gowns, gloves^{21,31} 3. Temporary fixation: external fixation, antibiotic-coated devices 4. Dead space management (limb salvage, amputation) <ul style="list-style-type: none"> a. Wound: secondary intention, primary vs delayed closure b. Bone: bone transport,³²⁻³⁸ vascularized bone flaps c. Fixation: orthoses, external fixators, devices (coated)^{b 36-38} d. Depots: antibiotic beads, antibiotic spacers^{38,39}
VII	Outpatient follow-up <ul style="list-style-type: none"> A. Wound surveillance; laboratory values: ESR, CRP; physical rehabilitation
VIII	Second surgery (second stage) <ul style="list-style-type: none"> A. Definitive reconstruction <ul style="list-style-type: none"> 1. Prophylactic antibiotics, device removal, débridement, cultures (frozen biopsy negative—no inflammation) 2. Double setup: change instruments; re-prep and redrape; new gowns, gloves 3. Reconstruction <ul style="list-style-type: none"> a. Wound: primary closure b. Bone: bone grafts, vascularized bone flaps, prosthetic joints c. Fixation: orthoses, external or internal fixation, prosthetic joints d. Depots: antibiotic beads, permanent spacers,^{18,36} devices (coated)^b B. Staged reconstruction no. 2 <ul style="list-style-type: none"> 1. Prophylactic antibiotics, device removal, débridement, cultures (frozen biopsy positive—acute inflammation) 2. VI B treatments vs amputation
IX	Outpatient follow-up <ul style="list-style-type: none"> A. Wound surveillance; laboratory values: ESR, CRP; physical rehabilitation

Table 1 (continued)**Treatment of Adult Chronic Osteomyelitis^a**

X	Third surgery (third stage) A. Definitive reconstruction (frozen biopsy negative—no inflammation) 1. VIII A treatments B. Staged reconstruction no. 3 (frozen biopsy positive—acute inflammation) 1. VI B treatments vs amputation
XI	Fourth surgery (fourth stage) A. Biologic reconstructions ^c 1. No devices, no foreign bodies
XII	Outpatient follow-up A. Wound surveillance, laboratory values: ESR, CRP; physical rehabilitation

CBC = complete blood count, CRP = C-reactive protein, ESR = erythrocyte sedimentation rate, PCR = polymerase chain reaction, PET = positron emission tomography, UA = urinalysis

^a In the San Diego treatment algorithm for chronic osteomyelitis, patients entering a palliation protocol and/or not requiring reconstruction following débridement exit after the initial surgery (VI, A, 2). Osseous reconstructions and the use of surgical implants are staged to follow intervals of local and systemic antibiotic therapy.

^b Devices (coated): a medullary rod, cortical plate or prosthesis coated with antibiotic-impregnated bone cement

^c Biologic reconstructions—eg, bypass synostosis, acute shortening/fusion, bone transport, resection arthroplasty.

Adapted from Cierny G III, DiPasquale D: Adult osteomyelitis, in Cierny G III, McLaren AC, Wongworawat MD, eds: *Orthopaedic Knowledge Update: Musculoskeletal Infection*. Rosemont, IL, American Academy of Orthopaedic Surgeons, 2009, pp 135-153.

weeks for most patients, with extension to 3 months for patients with retained infected implants,⁵⁸ although extended suppressive therapy to fracture union, followed by subsequent implant removal, has been advocated.⁵⁹

High-volume, low-pressure irrigation remains a critical component of the débridement process. Intermediate- and high-pressure lavage systems are readily available and widely used, but they decrease wound bioburden and contamination at the expense of host tissue damage, which may be responsible for the reported bacterial rebound phenomenon observed following their use.⁶⁰ The addition of detergents, antiseptics, or antimicrobials to irrigant solutions has not consistently been demonstrated to improve outcomes.⁶¹

Negative-pressure wound therapy with reticulated open-cell foam dressings (NPWT/ROCF) is an important wound adjunct that increases patient comfort and care convenience while improving local circulation, accelerating granulation

tissue formation, and increasing edema clearance, but it only variably affects bacterial bioburden and may be more effective at preventing than treating infections.⁶² Silver nanoparticulate-impregnated ROCF and infusion of antiseptics have recently become commonplace supplements to NPWT, but to date, clinical evidence of efficacy is limited.

Future Directions

Part of the reason for the current difficulty with antibiotic resistance is attributable to our misunderstanding of what an antibiotic is and what it imposes on the bacterial genome. This is exemplified by the declaration credited to the surgeon general William Stewart in 1967: “The time has come to close the book on infectious diseases. We have basically wiped out infection in the United States.”⁶³ Antibiotics came to be (and, at the time of this writing, continue to be) used as a feed additive in subtherapeutic doses in the dairy and livestock industries. In fact, 70% of

all antibiotics used in the United States are administered in this fashion.⁶⁴ What has been little appreciated is the resilience and adaptability of the bacterial genome, which were, from an evolutionary viewpoint, minimally thwarted by the widespread use of antibiotics. Currently, penicillin is as effective against acute hematogenous osteomyelitis as is a placebo, whereas, shortly after its introduction in World War II, penicillin was nearly 100% curative of this disease.⁶⁵ As Nobel laureate Christian de Duve points out, “Given an adequate supply of nutrients, a single bacterial cell can generate 280,000 billion individuals (‘generations’) in a single day.”⁶⁶ This rapid duplication and exchange of bacterial genetic material represents a continuous probing of the environment by the bacterial genome for selective advantage by spontaneous mutations. In 70 years, penicillin has gone from wonder drug to placebo. The message is clear: indiscriminate use of antibiotics facilitates the emergence of resistance.

To compound matters, the devel-

opment of new antibiotics by the pharmaceutical industry has been slow. No fundamentally new class of antibiotics has been brought to market since the 1970s. Thus, clinicians need to be resourceful in the use of the tools available. Buchholz and Engelbrecht⁶⁷ as well as Klemm²⁷ were early proponents of local antibiotic elution from impregnated PMMA. Theoretically, when the local antibiotic concentration is kept high (ie, levels well above minimal bacterial concentration levels of relevant pathogens), bacterial growth can be eliminated; low systemic concentrations associated with this strategy minimize the likelihood of adverse systemic effects.²⁸ The concept has been successfully employed and incorporated in several treatment regimens.⁶⁸ One problem is the permanence of methylmethacrylate as a carrier. Frequently, this warrants additional surgery for removal. Hence, the use of a resorbable carrier has appeal. Recent clinical reports of calcium sulfate, polylactic acid, and calcium phosphate, as well as other bioabsorbable “carrier” materials,⁶⁹⁻⁷² are encouraging but limited. One study involved the use of tobramycin with calcium sulfate carrier pellets in 25 patients with chronic osteomyelitis following débridement, with eradication reported in 92%.²⁶ A second study on the use of either vancomycin or tobramycin in calcium sulfate carrier pellets in six patients with chronic osteomyelitis following débridement showed no infection and progressive bony healing in five of the six at a mean follow-up of 28 months.⁷³

Another aspect of musculoskeletal infection that has prompted research includes bacterial adhesion. This feature is thought to be pivotal to the chronicity of osteomyelitis as well as the “foreign body effect.” Elek and Conen⁷⁴ elegantly demonstrated a 10,000-fold enhancement of the

“minimal pustule forming dose” of staphylococcus in human skin by the presence of a single silk suture. Gibbons and Socransky⁷⁵ elucidated the complex affinity of *Streptococcus mutans* for the enamel of the human tooth by identifying specific enzymes that break down sucrose and polymerize the component glucose into insoluble glucan. The specific affinity of glucan for the enamel of the tooth provides the “glue” that binds that surface to bacterial microcolonies (ie, plaque) acting as a syncytium. Bacterial metabolism generates the acid responsible for enamel dissolution and formation of dental caries. By understanding the complex relationships between glucan, the bacteria, plaque formation, and acid generation, the pathophysiology of dental caries and gum disease was elucidated, and appropriate therapies were designed to greatly lower their incidence and severity. Paralleling these insights, Gristina and Costerton⁷⁶ and others²⁸ have shown the role of the glycocalyx and biofilm in adhesion to dead bone and implants and its pivotal role in the production of and persistence of musculoskeletal infection.

One of the major obstacles to basic research in this area is the fact that standard bacterial culture (eg, Columbia blood agar plate) selects for bacteria devoid of glycocalyceal coats. The free-floating, “naked” bacteria seen in pure laboratory cultures are not the same as their glycocalyceal-coated cousins adhering to bone or implant in an area of osteomyelitic focus. Hence, new bacterial culture techniques that select for and preserve the glycocalyx and, therefore, the bacteria in their adherent mode, need to be developed, standardized, and used as a system for assessing the effectiveness of therapeutic agents.⁷⁷

New concepts of bacterial syncytia and quorum sensing may help pro-

vide a way of averting the elaboration of virulent factors characteristic of fulminance.⁷⁸ That is, by preventing the ability of resident bacteria to “sense a quorum,” it may be possible to keep the resident bacteria in their peaceful commensal state and thereby avoid the confrontation with host white cells and the elaboration of tissue-destructive lysosomal enzymes and free radicals, which characterize a full-blown local tissue infection. Investigation of quorum-sensing signal molecules or their receptors, and understanding their interactions, may provide novel strategies for treatment and prevention.^{78,79} The development of appropriate models to enable standardization and assessment of these parameters is in its infancy.⁸⁰

Other insights into musculoskeletal infection include those of Hudson et al,⁸¹ who demonstrated the intracellular presence of staphylococci in osteoblasts. Later work demonstrated that the intracellular staphylococci were potentially viable and “re-infective,” given their “passage” through their host osteoblast.⁸² Additionally, it was shown that antibiotic “pressure” caused an adaptive change in intracellular staphylococci—that is, the elaboration of an extracellular capsule.⁸³ Pillai et al⁸⁴ have used nanotechnologic methodologies to couple the antibiotic nafcillin to poly(lactic-co-glycolic acid) and thereby facilitate its ability to penetrate the cell membrane of the osteoblast. Using this Trojan horse strategy, they have reported clearance of intracellular staphylococci.

Other aspects of microbial pathophysiology that provide potentially fertile areas for research are bacterial viruses, or bacteriophages. One of the largest centers investigating this approach is the Eliava Institute of Bacteriophage, Microbiology and Virology in Tbilisi, Georgia. Currently, treatment using bacteriophages is not

approved in countries other than Georgia. The FDA obstacles against the use of the methodology are significant. Although employing bacteriophages is theoretically appealing, the level of evidence for efficacious treatment of chronic infection using this approach has been low. One compelling and potentially promising line of inquiry is the multidisciplinary approach combining phage research with nanotechnology.⁸⁵ Phage is species- and strain-specific; tying that specificity to a drug is appealing and at least theoretically offers the potential for a unique class of therapeutic drugs.

Understanding the fundamental aspects of the pathophysiology of microbial musculoskeletal infection is necessary for the development of efficacious treatment strategies. Despite new and exciting lines of inquiry, it is still very early in this process.

Summary

The treatment of chronic, posttraumatic osteomyelitis in the extremity is challenging and often requires a commitment by both the patient and the treating surgeon toward complete (ie, wide) resection of the involved bone. Reconstruction can be safely performed by a variety of methods; however, proper staging and patient selection remain critical to a successful outcome. Consensus regarding the use of depot-delivered antibiotics, as well as the timing and duration of systemic antibiotics, is lacking and deserving of further study.

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