Review Article

Osteomyelitis: Recent advances in pathophysiology and therapeutic strategies

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ARTICLE INFO

Article history:

Received 26 September 2016

Accepted 13 October 2016

Available online 26 October 2016

Keywords:

Osteomyelitis

Bone infection

Antibiotic

Arthroplasty

Fracture

ABSTRACT

This review article summarizes the recent advances in pathogenic mechanisms and novel therapeutic strategies for osteomyelitis, covering both periprosthetic joint infections and fracture-associated bone infections. A better understanding of the pathophysiology including the mechanisms for biofilm formation has led to new therapeutic strategies for this devastating disease. Research on novel local delivery materials with appropriate mechanical properties, lower exothermicity, controlled release of antibiotics, and absorbable scaffolding for bone regeneration is progressing rapidly. Emerging strategies for prevention, early diagnosis of low-grade infections, and innovative treatments of osteomyelitis such as biofilm disruptors and immunotherapy are highlighted in this review.

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1. Introduction

Musculoskeletal infections, specifically osteomyelitis, create a substantial burden to the patient, treating physician and the health care system as a whole.¹ The definition of osteomyelitis is generally accepted as an inflammatory process of bone and bone marrow caused by an infectious organism(s) which results in local bone destruction, necrosis and apposition of new bone. The term osteomyelitis implies bone or joint infection.^{2–4}

The occurrence and economic burden of osteomyelitis is staggering. The incidence of joint infection following arthroplasty (joint replacement) ranged from 0.3% to 2.4% for total hip arthroplasties (THA) and 1.0% to 3.0% for total knee arthroplasties (TKA), depending on the study series. The incidence of osteomyelitis is higher in cemented than in cementless arthroplasties.^{5–8} The mortality after septic revision (18%) was six times higher than that of aseptic revision (3%).⁹ A recent Nationwide Inpatient Sample (NIS) study with 235,857 revision THA (RTHA) and 301,718 RTKA procedures demonstrated that joint infection was the most common reason (25%) for RTKA and the third most common reason (accounted for 15.4%) for RTHA in the United States (U.S.). Average individual hospitalization costs associated with periprosthetic infection were \$25,692 for RTKA and \$31,753 for RTHA in the U.S.

hospitals.¹⁰ Accumulative costs for the individuals with bilateral joint infections or multi-stage revisions would be much higher.

The incidence of fracture-associated bone infection varies from 1.8% to 27% depending on the bone involved and the grade/type of fracture. Closed and Gustilo type-I open fractures have lowest rate of infection (1.8%), while severe high energy lower extremity open fractures have highest occurrence of infection (27%), with the tibia being the most commonly affected.^{11–15} The overall incidence of bone infection may continue to rise due to multiple factors including improved diagnosis, increasing patient risk factors (*i.e.* diabetes), and increased needs for arthroplasties.^{16,17}

A better understanding of pathophysiology of osteomyelitis is a key factor for development of better therapeutic strategies for this devastating disease. In this review article, we will focus on the recent advances in pathophysiology and novel therapeutic strategies for joint infection following arthroplasty and post-traumatic (fracture-associated) bone infections resulting from contaminated open fractures or open treatment of closed fractures. The information is derived from both clinical and experimental studies.

2. Pathophysiology of osteomyelitis

2.1. General pathophysiology

Osteomyelitis encompasses a broad spectrum of disease mechanisms with three generally accepted categories: hematogenous (blood borne) spread, contiguous contamination and vascular

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or neurologic insufficiency associated infection.¹⁸ The characteristics of each category can be summarized as follows: (1) Primary hematogenous spread of bacteria mainly afflicts the metaphysis of skeletally immature patients or vertebral bodies at all ages, although infection at other locations may occur.^{19,20} (2) Contiguous infection is usually spread from a contaminated site, most commonly seen with direct contamination of bacteria in open fractures or joint replacement surgery with an orthopedic implant.³ (3) Vascular or neurologic insufficiency associated osteomyelitis results from poor blood supply, diabetic wounds, loss of protective sensation and altered immune defenses, commonly affecting the lower extremity (Fig. 1).^{3,21,22}

Although all types of organisms, including bacteria, viruses, parasites, and fungi may cause osteomyelitis, bone infections are commonly caused by certain pyogenic bacteria and mycobacteria (in some countries). *Staphylococcus aureus* (*S. aureus*) is responsible for 80% to 90% of the cases of pyogenic osteomyelitis, while *Staphylococcus epidermidis* (*S. epidermidis*) is the most abundant skin flora which seems to predominately infect medical devices, including orthopedic hardware implants and catheters.^{23,24} More recently, Benito et al. reported a five-fold increase in the yearly occurrence of polymicrobial infections from 2004 to 2010, and an equally alarming increase in the yearly proportion of infections caused by gram-negative bacteria. Of these, Enterobacteriaceae are challenging because they resist a wide range of antibiotics.^{25–27}

When bone tissue is infected, the bacteria induce an acute inflammatory reaction. The bacteria and inflammation affect the periosteum and spread within the bone causing bone necrosis. In children, the periosteum is loosely attached to the cortex, allowing for the formation of sizable subperiosteal abscesses along the bone surface. Lifting of the periosteum further impairs the blood supply to the affected bone causing segmental bone necrosis known as a

sequestrum.³ In the chronic stage, numerous inflammatory cells and their release of cytokines stimulate osteoclastic bone resorption, ingrowth of fibrous tissue, and the deposition of reactive new bone in the periphery. When the newly deposited bone forms a sleeve of living tissue around the segment of devitalized infected bone, it is known as an *involucrum*. Rupture of a subperiosteal abscess may lead to a soft-tissue abscess and the eventual formation of a *draining sinus*.³

2.2. Pathophysiology of periprosthetic joint infection

Periprosthetic joint infection (PJI) can occur at different times throughout the lifetime of an orthopedic implant, which can be classified into early (<3 months), delayed (3 months–2 years), and late (>2 years).²⁸ Early infections occur as a result of direct perioperative inoculation. Delayed infections can be caused by perioperative inoculation of a less virulent bacterium, or a hematogenous source. Late onset infections are more commonly caused by a remote infection that leads to hematogenous seeding of the implant surface or joint space by harmful bacteria. Poor host conditions could worsen this process.^{25,28} Patients with a history of PJI had a greater risk of developing PJI in a subsequent THA or TKA.²⁹

In 2011, the Musculoskeletal Infection Society proposed a unique set of PJI criteria, which were later revised at the International Consensus Meeting (ICM) on PJI. The diagnosis of PJI can be established if one of the following three major criteria occurs: two positive periprosthetic cultures with identical organisms; a sinus tract communicating with the joint; having three of the following minor criteria: (a) elevated serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR), (b) elevated synovial fluid white blood cell (WBC) count, (c) elevated synovial

Fig. 1. A diagram showing three categories of osteomyelitis. (A and B) Primary hematogenous (blood borne) spread of bacteria mainly afflicts the vertebral bodies at all ages or the metaphysis of skeletally immature patients. (C and D) Contiguous bone infection is most commonly seen with direct contamination of bacteria in open fractures or joint replacement surgery with prosthetic implants. (E) Vascular or neurologic disease associated osteomyelitis most commonly affects the lower extremity.

fluid polymorphonuclear neutrophil percentage, (d) positive histological analysis of periprosthetic tissue, and (e) a single positive culture of periprosthetic tissue or fluid.^{30,31} Clinically, however, PJI may be present without meeting all these criteria. Some revisions labeled as “aseptic loosening” may instead be undiagnosed septic loosening caused by low-grade or less virulent organisms.^{32,33}

PJI is usually initiated by bacterial adherence and subsequent biofilm formation, which is a key mechanism of action for Staph-related infection.^{34,35} Infective organisms create a microenvironment to promote growth and sequestration from host defense mechanisms. Once placed within the body, the implant quickly becomes coated with host adhesins (e.g. fibronectin, fibrin, fibrinogen etc.) within the host extracellular fluid. Fibronectin is particularly important with Staph adhesion, as fibronectin binding proteins promote adherence of Staph species to substratum.³⁶ The implant coated with these proteins provides a large surface biofilm to which free floating bacteria can attach.³⁷ This adherence has recently been termed polysaccharide intercellular adhesion (PIA) and has been found to be a requirement for bacterial biofilm formation in Staph species.³⁸ The extracellular polymeric substance of biofilms is largely composed of polysaccharides that encapsulate bacterial colonies, filter antimicrobial chemicals, prevent antibiotic perfusion, and limit pharmaceutical efficacy.³⁹ Using genomic analyses, Li et al. found that dead cells in the biofilms could act as donors of a chromosomally encoded antibiotic resistance determinant.⁴⁰

Quickly following the initial adherence, a thin layer of slime produced by the affecting organism induces inflammation from host defenses.³⁷ Biofilm formation and slime production are the prominent processes by which these organisms can evade host defense systems. Staph can bind and colonize muco-cutaneous surfaces and *S. aureus* have been known to invade and persist within host cells.⁴¹ Ironically, Staph has also been found to invade and colonize immune cells such as macrophages and neutrophils.⁴¹ It is unclear how the organisms are internalized and remain resistant to lysosomes within the host cell causing minimal virulence over long periods of time.⁴² Additionally, Staph can produce so called small colony variants (SCVs) which may result in an altered virulence and antibiotic resistance profile.^{43,44} These traits further result in difficulty eradicating infections.

Studies using specialized techniques, including sonication to remove adherent bacteria and direct detection using various forms of microscopy, have confirmed that bacteria are present in many culture-negative cases. This led to the suggestion that at least some cases of failed orthopedic implants being considered aseptic loosening based on the failure to isolate bacteria may actually have an infectious etiology. In addition to biofilms, false-negative culture results include the failure to recognize small colony variants induced during growth *in vivo* and the presence of bacteria inside host cells including osteoblasts. Importantly, bacteria persisting as small colony variants within biofilms and/or inside osteoblasts also may be an explanation for the recurrent nature of musculoskeletal infection.³³

2.3. Pathophysiology of post-traumatic osteomyelitis

The term “post-traumatic osteomyelitis” usually implies bone infections following open fracture or open treatment of closed fractures with intramedullary nailing or plating for fracture stabilization. The pathophysiology of traumatic osteomyelitis varies greatly depending on bones involved, characteristic of the initial injury, and patient conditions.

Unlike the PJI which initiates in the affected joint cavity or periprosthetic bone marrow, open fractures are at high risk of transcutaneous contamination of bacteria and non-union compared

to closed fractures. Infection may directly affect soft tissue, cortical bone, and bone marrow around the fracture site. When the bone tissue is involved, the bacteria proliferate and induce an acute inflammatory reaction resulting in necrosis of the entrapped bone. The bacteria and inflammation spread within the shaft of the bone and may percolate throughout the Haversian systems and periosteum, which compromise the formation of callus and result in an infected non-union of fracture.^{3,45,46}

A number of animal models have been developed to mimic fracture-associated bone infection seen in humans. Clinically, damages to the bone seen in open fractures vary from patient to patient depending on the fracture characteristics. It is technically difficult to exactly model open fractures seen in human patients. Many investigators have utilized an osteotomy or bone defect model to mimic fracture-associated bone infection in order to further elucidate the pathological changes during the progression of osteomyelitis at the fracture sites. Either *S. aureus* or *S. epidermidis* contamination has been used for creation of infected non-union animal models of osteomyelitis.^{46,47}

In a rat model of *S. aureus* induced bone infection after tibial osteotomy, cytokine and chemokine analyses of bone tissue homogenates showed that the infected bone had increased concentrations of proinflammatory mediators including interleukin-1 β (IL-1 β) and macrophage inflammatory protein-2 (MIP-2) etc. as early as day 1 after infection. The data also revealed increased amounts of IL-10, a prototype of a Th2 anti-inflammatory cytokine, in all infected animals. Histologically, accumulations of immunocompetent cells or granulocytes were found at the osteotomy sites. Tartrate-resistant acid phosphatase (TRAP)-positive cells were rarely seen on post-operative day 1 but more frequently on day 42, which were predominantly located in the areas with bone impairment and bone resorption processes. Periosteal reaction, cortical thickening, myeloid hyperplasia, polymorphonuclear cells in the granulation tissue were observed.^{46,47} These findings suggest that both pro- and anti-inflammatory reactions are present during the progression of post-traumatic osteomyelitis.

3. Therapeutic strategies

Treatment of bone infection remains a clinical challenge, although many methods have achieved widespread use. Treatment options are mainly depending on the initial causes and local pathological changes of patients with bone infection. Treatment modalities for PJI following arthroplasty and post-traumatic osteomyelitis are discussed below.

3.1. Treatment of PJI

When a primary orthopedic implant fails from PJI, surgeons are generally challenged by limited options for intervention. Bacteria are difficult to eradicate from synovial joints due to their exceptionally diverse taxonomy, complex attachment mechanisms, and tendency to evolve antibiotic resistance. The standard treatment involves systemic antibiotic administration and options to retain or remove the infected prosthesis. Bedair et al.⁴⁸ summarized the three commonly used surgical treatment options for controlling PJI as follows: (1) open irrigation and debridement with component retention; (2) a one-stage exchange (revision) in which the infected prosthetic components are all removed following irrigation and debridement, and then replaced with new components; and (3) a two-stage revision (considered by many to be the gold standard treatment for an infected arthroplasty) whereby the prosthetic components are all removed, an antibiotic-loaded cement spacer is placed, and then at a later date prosthetic components are reinserted once the infection has been controlled.

The standard of local antibiotic delivery has progressed to include the use of poly-methylmethacrylate (PMMA) bone cement mixed with a combination of heat stable and soluble antibiotics. The most commonly used antibiotics include Vancomycin, Gentamycin and Tobramycin. Many studies have displayed the efficacy of these antibiotic cements in the treatment of bone infections.^{49–51} The antibiotic impregnated PMMA cement can provide structural supports following the removal of prostheses and fill a large bone defect that otherwise would create a poorly vascularized environment favorable for bacterial growth. Additionally, PMMA with antibiotics can elute high concentrations of medication locally with minimal systemic effects.^{52,53} An intraoperatively produced custom made PMMA cement spacer loaded with antibiotics has been developed for a two-stage revision of infected arthroplasties, which may retain the joint space and allow for the motion of the joint.^{54,55}

Although PMMA bone cements have been used to successfully anchor prostheses, limitations and problems associated with PMMA have been identified. The potential issues include the high exothermic property of PMMA that allows only limited number of heat stable antibiotics to be used for treatment, limited antibiotic elution from the superficial area of PMMA that does not achieve full release of the included antibiotics,^{56,57} poor osteointegration with host bone⁵⁸ and leachable MMA monomer which may cause local tissue toxicity and systemic effects such as blood pressure lability, hypoxia and mental confusion.^{59,60} Many efforts have been made to develop an alternative to PMMA bone cement. A BisGMA-TEGDMA based bone cement, Cortoss™, has been cleared by the U.S. Food and Drug Administration (FDA) for vertebral augmentation with the goal to replace current cement products. The Cortoss™ bone cement exhibited less exothermic reaction, reduced shrinkage, and comparable mechanical properties to other PMMA products. However, there are still many concerns regarding its leachable monomers and the biocompatibility.^{61–63} Recently developed silorane cements displayed low exothermicity (approximately 26 °C). *In vitro* and animal studies have demonstrated the ability of the silorane cement to impregnate with heat sensitive and chemically sensitive antibiotics with no toxicity.⁶⁴

Another important problem with PMMA bone cements is the need for removal as this material is non-absorbable *in vivo*. This subjects the patient to have repeated anesthesia and operative procedures resulting in increased risks of wound infections as well as significant health care costs. In addition, PMMA does not provide scaffolding for eventual bone regeneration. PMMA has also been shown to provide a surface for which bacteria can bind and become a 2nd nidus for infection.^{65,66} Considerable efforts have been taken to develop more effective local antibiotic delivery vehicles using degradable materials as alternatives to PMMA. Collagen sponge is a widely used natural, biodegradable polymer. However, studies have shown rapid antibiotic release rates and conflicting results for its use as a carrier of antibiotics. Consequently, there has been interest in developing biodegradable polymer carrier materials with longer-lasting release rates. Several synthetic biodegradable polymers, such as polylactic acid (PLA), polyglycolic acid (PGA), and their copolymers polylactic-co-glycolic acid (PLGA), have been proven to be biocompatible and controllable antibiotic release carrier materials. Both *in vitro* and *in vivo* elution studies demonstrated that polycaprolactone (PCL) delivered significantly higher concentrations of Tobramycin than PMMA over 8-week experiments.^{67–70}

Inorganic materials that are compatible with bone and promote bone formation have also been studied as alternative carrier materials. Calcium sulfate (CaSO₄) and calcium phosphate biomaterials such as beta-tricalcium phosphate (β-TCP, Ca₃(PO₄)₂) and hydroxyapatite (HA, Ca₁₀(PO₄)₆(OH)₂) have been used as biodegradable ceramic carrier materials for treatment of osteomyelitis in animal models and clinical studies.^{49,69,70}

Silver has been used as a coating for orthopedic implants to minimize infectious risk. A recent case–control study showed that silver-treated implants were particularly useful in two-stage revisions for infection and in those patients with incidental positive cultures at the time of implantation of the prosthesis. Debridement with antibiotic treatment and retention of the implant appeared to be more successful with silver-coated implants.⁷¹ Silver-hydroxyapatite (Ag-HA)-coated implants may enhance the intrinsic osteoconductive property of the implant and the improve patients' activities of daily living without causing adverse reactions attributable to silver in the human body.⁷²

More recently, a novel technique has been developed by utilizing bioactive glass which can elute antibiotics and has the unique ability to provide bone scaffolding for bone ingrowth. The antibacterial activity of bioactive glasses has been investigated via three approaches: (1) specially formulated bioactive glasses can change the local physiological conditions to produce a bactericidal effect; (2) bioactive glasses manufactured with trace quantities of elements such as Ag that are known for their antibacterial activity and, as the glass degrades, those elements are released at a clinically desirable rate; (3) bioactive glasses in conjunction with antibiotics act either as a high-surface-area carrier for the antibiotics or as a bioactive filler in an antibiotic-loaded biodegradable matrix. The greatest advantage of bioactive glass-based carrier systems is that they can potentially provide a system for simultaneously eradicating infection and regenerating bone, thereby eliminating the need for subsequent bone grafting.^{73–75} Many animal models have confirmed the antibiotic properties of the bioactive glass and its ability to support bone regeneration as the bioglass degrades. Preliminary human studies have demonstrated promising results.^{76–79}

The current understanding of the differences in biological properties between non-absorbable PMMA and absorbable biomaterials for treatment of PJI is summarized in Fig. 2.

3.2. Treatment of post-traumatic osteomyelitis

Managing infections in fractures is an ongoing challenge. Although antibacterial treatment and surgical debridement, irrigation, and drainage are well established procedures for infected fractures, orthopaedists sometimes in a dilemma to determine whether the hardware should be retained or removed. It is generally accepted that deep infections cannot be cured in the presence of hardware. However, removing hardware in the presence of an unhealed fracture greatly complicates fracture management; external fixation is usually required to stabilize the unhealed fracture.^{15,80,81} Rightmire et al. evaluated the effectiveness of treating bone infections with retained hardware. Patients achieving successful union with original hardware in place were considered having successful results and patients who required hardware removal before healing were considered having failed results. Forty-seven of 69 cases (68%) were successful and 22 (32%) were unsuccessful. The results were more disappointing if success is defined as union with no infection. Eighteen of the 47 successful cases had hardware removed eventually for persistent infection after union.⁸¹ The data suggest that it is possible to achieve bone healing for infected fractures with original hardware in place, but the success rate is less than widely believed. Orthopaedic Trauma Association (OTA) type-C fractures are at high risk for infection. Performing a fasciotomy also increases the risk of infection.⁸² Early aggressive debridement coupled with broad-spectrum antibiotic cement-coated plate insertion may provide fracture stability and help eradicate the infection with one surgical procedure.⁸³

Chan et al. reported a therapeutic modality for infected tibia fractures. All patients were treated with a two-stage protocol. In the first stage, antibiotic-impregnated PMMA bead chains were

Fig. 2. A diagram summarizing the major differences between non-absorbable PMMA and absorbable biomaterial for a severely infected arthroplasty. When severe periprosthetic infection occurs, the prosthetic components are all removed, an antibiotic-loaded PMMA cement spacer releasing antibiotics is placed, then PMMA is removed once the infection has been controlled, bone grafting is performed to reconstruct the bone defect, and at a later date prosthetic components are reinserted. In contrast, when the infection is treated with an absorbable biomaterial scaffold releasing both antibiotics and osteogenic growth factors, bone grafting is not required. This shortens the time needed for bone reconstruction and reduces the total cost for a two-stage revision.

used to obliterate the debrided osseous defects (ranged from 2 to 4 cm). In the second stage, the beads were removed and the defects were reconstructed with antibiotic impregnated autogenous cancellous bone graft. Wound healing and bony union were achieved in all patients. The infection arrest rate was 94.4%. Minor pin tract infection of the external fixation was seen in two patients. A 3–5 years of follow-up showed that this treatment protocol provided rapid recovery from post-traumatic osteomyelitis.⁸⁴ The same group also utilized antibiotic-impregnated autogenous cancellous bone graft for infected tibial non-unions. Wound healing and bony union were achieved in all 46 patients, with recurrent infections in 2 patients.⁸⁵

The importance of host condition for treatment modality has been recognized. Diabetes, arteriosclerosis, alcoholism, obesity, smoking, and aging are considered host condition-related risk factors for bone infection.^{80–82} Cierny et al. reported comprehensive treatment modalities for different types of osteomyelitis including infected fracture nonunions.⁸⁶ They developed a clinical staging system (Cierny-Mader Staging System) for adult osteomyelitis, which combines four anatomic types (medullary, superficial, localized and diffuse) of osteomyelitis with three physiologic classes (host conditions) to define 12 clinical stages.⁸⁶ The authors stated that the treatment of adult osteomyelitis is influenced by four factors: the condition of the host, the functional impairment

Table 1

Treatment modalities for different types of osteomyelitis.

Anatomic type	Description	Treatment
I. Medullary	Endosteal nidus: Infection is confined to medullary space; treatment likely does not require bone grafting.	Small unroofing of cortex, curettage of medullary space, medullary reaming
II. Superficial	Bone surface nidus: Infection is confined to outer surface of bone with soft tissue compromise. Treatment will not destabilize bone and thus will not require hardware fixation.	Superficial decortication Soft tissue coverage - Pedicle tissue flap - Free tissue flap
III. Localized	Localized bone necrosis: Focalized sequestration of cortical bone. Excision may require fixation if there is a destabilized bone structure.	Sequestrectomy, medullary decompression, scar excision, superficial decortication, stabilization if necessary
IV. Diffuse	Extensive bone destruction: Involvement of permeated destruction of cortical bone causes unstable bone structure.	Stabilization and soft tissue coverage are required; external fixation is the safest and most versatile technique.
All four types of osteomyelitis require antibiotic coverage systemically with possible adjuvant local treatment:		
- Antibiotic laden beads.		
- Antibiotic cement spacers.		
- Antibiotic intramedullary nail.		
- Local antibiotic powders.		

caused by the disease, the site of involvement, and the extent of bony necrosis. The description and treatment options for the four anatomical types of osteomyelitis are summarized in Table 1, in which the information is mainly derived from three publications.^{86–88}

4. Future perspectives

Biofilm formation and slime production are the prominent processes by which bacteria are protected from host defense mechanisms and from antimicrobial agents. Antibiotic resistance poses a serious obstacle to the treatment of bone infection. Recent studies identified that a cholesterol biosynthesis inhibitor could block *S. aureus* virulence and that specific low molecular weight compounds inhibited *S. aureus* virulence gene expression and biofilm formation in *in vitro* and in murine infection models.^{89–91} An *in vitro* anti-biofilm study revealed that a chlorhexidine gluconate scrub (antiseptic detergent) was the most effective in eradicating Methicillin-resistant *Staphylococcus aureus* (MRSA) from implants compared to castile soap, iodine, saline, and saline with bacitracin.⁹² Further studies are needed to assess the efficacy of new biofilm disruptors and other therapeutic agents in large animals and clinical trials.

Enhancing the host immune system to attract immune cells to a site of bone infection is another promising direction. Macrophage infiltration is an important component of the host innate immune system, thereby killing bacteria at the very early stage prior to the destructive bone changes. Coating implants with monocyte chemoattractant protein-1 (MCP-1) has been found to reduce *S. aureus* infection in a rat model of open fracture.⁹³ Innate defense regulator peptide-1018 (IDR-1018) is a synthetic peptide which may possess intrinsic antimicrobial effects by promoting immune cell immigration, directly killing *S. aureus*, recruiting macrophages to the infection site, and minimizing the negative effects that infection has on osseous integration in a murine model.⁹⁴ These novel results from rodent models warrant further validation in large animals and in humans.

The increase in the infections caused by polymicrobes, less virulent organisms, and gram-negative bacteria is an additional challenge because many of them resist a wide range of antibiotics.^{25–27} This requires more sensitive diagnostic techniques for microbial detection. Less virulent organisms may not be detected by routine microbiology methods. When a low virulence microbial infection is suspected the incubation time of the culture sample should be extended.⁹⁵ Sonication of joint tissue explants has been shown to increase the positive rate of pathogen detection.⁹⁶ Synovial fluid biomarkers and synovial tissue culture

enhance the sensitivity of bacterial detection for PJI.^{97,98} Additional studies are required to further improve the sensitivity and specificity of the newly developed methods of diagnosis.

Local use of high doses of sensitive antibiotics or customized therapeutic strategies for each patient, joint, and prosthetic component could prove more effective for those infections caused by antibiotic-resistant and polymicrobial infections while minimizing the risks of systemic toxicity associated with traditional methods of intravenous delivery of antibiotics. A recent study by Lehar et al. introduced a novel therapeutic that effectively kills intracellular *S. aureus* by using an anti-*S. aureus* antibody-antibiotic conjugate.⁹⁹ Further advancements are needed before these new approaches can be widely accepted.

More effective delivery materials will need to be further optimized to meet the clinical needs. An ideal system(s) for local delivery of antibiotics and osteogenic factors should have appropriate mechanical properties to support physiological loading with lower exothermic reaction, provide controlled and sustainable release of high-concentration effective antibiotics to the site of infection, and serve as a gradually absorbable scaffold for promoting bone regeneration.

5. Conclusion

Recent advances in experimental and clinical studies on osteomyelitis have significantly improved our understanding of pathophysiology of osteomyelitis, including the mechanisms of bacterial adherence, biofilm formation, intracellular infection, and bone destruction. A better understanding of the pathophysiology has led to the development of new therapeutic strategies for this devastating disease. A remarkable advancement in treatment of osteomyelitis is the local delivery of antibiotics, which improves therapeutic outcomes and minimizes the side effects of systemic administration of high-dose antibiotics. However, none of the materials currently used for local delivery of antibiotics fully meet the clinical needs. Research on new delivery materials with appropriate mechanical properties, lower exothermic reaction, controlled release of antibiotics, and absorbable scaffolding for promoting bone regeneration is progressing rapidly. Development of more effective strategies for prevention, early diagnosis, and innovative treatments of osteomyelitis such as biofilm disruptors and immunotherapy is underway through joint efforts by both clinicians and scientists.

Conflicts of interest

The authors have none to declare.

Acknowledgments

This work was supported in part by the U.S. National Institutes of Health (NIH) under Award Number R01 DE018713 (to J. Wang), the Mary A. & Paul R. Harrington Distinguished Professorship Endowment, the Asher Orthopedic Research Endowment, and the Orthopedic Department at the University of Kansas Medical Center. The authors thank Dr. Jennifer McEllin and Mr. Brian Egan for their graphic and editorial assistance.

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