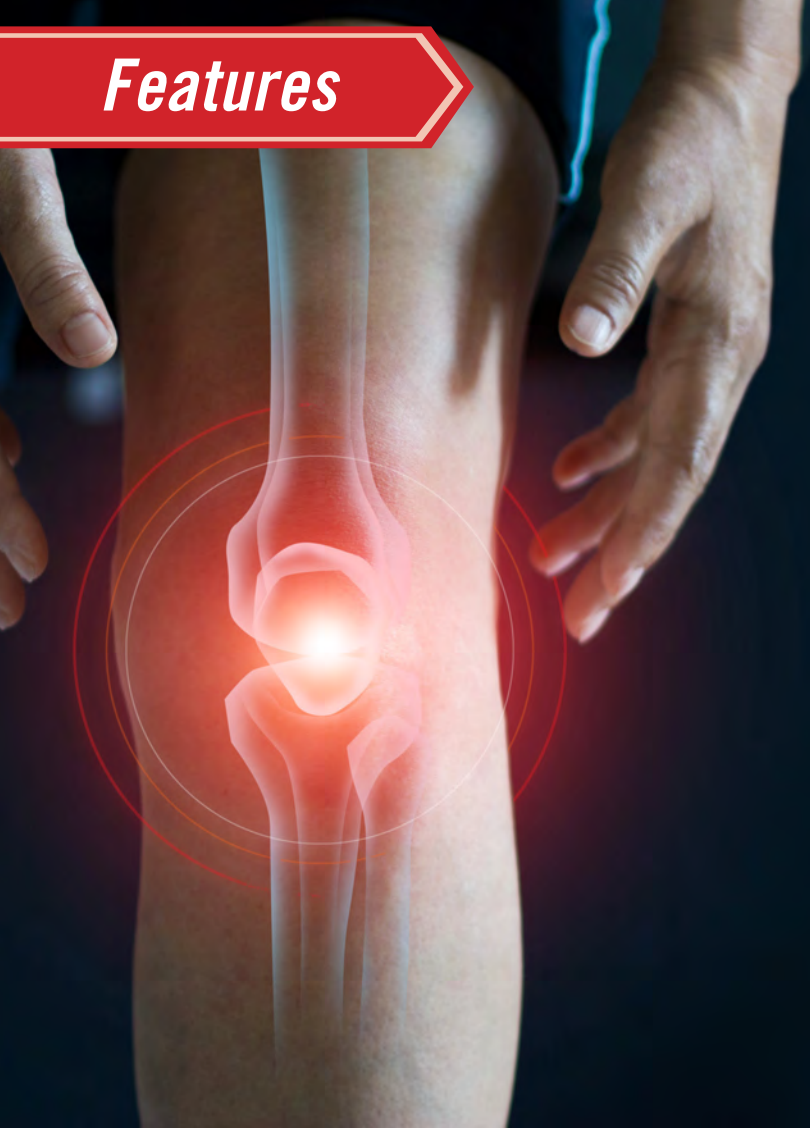

ID Corner
Pain in the Patella: Updates in the Management of Osteomyelitis

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Osteomyelitis (OM), acute or chronic inflammation of the bone and marrow caused by infectious pathogens, is widely regarded as a challenging infection to treat.[1-3] OM is associated with substantial morbidity, including amputation and loss of mobility, and high healthcare costs.[1,4,5] The introduction of pathogens into bone tissue leads to an inflammatory state that causes progressive bone necrosis, and ultimately formation of devitalized bone, or sequestrum.[4] The development of biofilm, an organized matrix of bacteria adherent to a surface, often contributes to the chronicity and high recurrence rate of OM.[3,6] Infection typically arises from one of three sources: (1) hematogenous seeding, (2) contiguous spread from adjacent infected structures, or (3) direct inoculation during surgery or trauma.[3,4] Patients with diabetes, vascular insufficiency, obesity, smoking, and intravenous (IV) drug use are at highest risk.[4] Hematogenous OM is typically monomicrobial, while contiguous OM is more commonly polymicrobial.[3,4] *Staphylococcus* species are the most commonly causative pathogens in all subtypes of OM, comprising more than 50% of cases.[1-3] Other aerobic Gram-positive cocci, Gram-negative bacilli, and anaerobic organisms may play a role, particularly in polymicrobial OM.[2,3] The identification rate of Gram-negative bacilli such as *Pseudomonas aeruginosa* and Gram-negative anaerobes in OM varies by etiology and geographic region, with estimates for *Pseudomonas aeruginosa* ranging from 3.5-17% and anaerobes from 9-11%.[2,7,8] Alternative methods of bacterial identification, such as rRNA gene sequencing, identify anaerobes more commonly than is appreciated with traditional bone culture, with one report suggesting higher than 85% incidence.[9,10] Organizations such as the International Working Group on the Diabetic Foot (IWGDF), however, caution against the use of molecular methods to direct antimicrobial therapy, as the pathogenic role of obligate anaerobes in infection hasn't been confirmed by these studies.[11]

General Treatment Principles

Clinical practice guidelines for the treatment of OM have been published (Table 1), although it should be noted that the Infectious Diseases Society of America (IDSA) guidelines were published between 2012-2015, and there are notable gaps in the disease states addressed, such as non-vertebral OM originating from trauma or pressure ulcers.[11-13] Source control, including debridement of infected tissue and amputation, is a critical adjuvant to antimicrobial therapy in most subtypes of OM.[2,3,5] In stable patients without concomitant skin and skin structure infection, it is preferable to wait for cultures of the infected bone or blood to initiate pathogen-directed therapy when possible.[2,3,6] Unfortunately, randomized clinical trials of pharmacotherapy for OM are limited in number, and there are no

TABLE 1. Clinical Practice Guidelines that Address Management of Osteomyelitis

Organization	*Title*	*Year*	*Comments*
Infectious Diseases Society of America (IDSA) www.idsociety.org	Clinical Practice Guidelines for the Diagnosis and Treatment of Native Vertebral Osteomyelitis in Adults	2015 (current)	
Infectious Diseases Society of America (IDSA) www.idsociety.org	Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections	2012 (archived)	Question VIII addresses OM of the foot
International Working Group on the Diabetic Foot (IWGDF) https://iwgdfguidelines.org	Practical Guidelines on the Prevention and Management of Diabetic Foot Disease	2019	Authors primarily from Europe and Australia, addresses OM of the foot

OM = Osteomyelitis

identified regimens that are clearly superior for treatment.[13-16]

Although the use of parenteral antibiotics with adequate bone penetration for 4-6 weeks is a common teaching among practitioners and is endorsed by expert consensus, the data in support of this practice for osteoarticular infections are actually limited.[2,16,17] The rationale for parenteral therapy derives partially from concerns about penetration into bone, particularly for antimicrobials with low bone concentrations relative to serum, such as beta-lactams.[15,16] However, it should be noted that studies of bone penetration are often limited by methodology and the bone concentrations must be interpreted in the context of the pathogen's minimum inhibitory concentration (MIC).[16] The role of oral therapies for OM is thus evolving, with both guidelines and individual experts advocating for specific oral agents.[14,15] The IDSA native vertebral OM guidelines currently list the oral agents linezolid and levofloxacin plus rifampin as alternative options for *Staphylococcus aureus* and ciprofloxacin for Enterobacteriaceae.[12] IWGDF recommendations for diabetic foot OM endorse a switch to an oral antibiotic "that has high bioavailability after perhaps five to seven days," assuming identified pathogens have *in vitro* susceptibility.[11] Since publication of these existing guidelines, new data have been published regarding the use of oral antibiotics and long acting lipoglycopeptides.

Oral Antibiotics in the Treatment of OM

Oral antibiotics with a pharmacokinetic profile similar to parenteral therapy, such as fluoroquinolones and linezolid, should theoretically yield similar clinical outcomes. Cohort studies have demonstrated that this efficacy may also extend to oral antibiotics with moderate-high bioavailability, regardless of the regimen's approximation of parenteral serum levels; sulfamethoxazole-trimethoprim, clindamycin, amoxicillin-clavulanate, and first generation cephalosporins have all been studied.[14,16,20] Fluroquinolones remain the most commonly studied oral antibiotic class for chronic OM, with most studies reporting cure rates of 60-80% and most reported failures occurring primarily in patients with *Pseudomonas aeruginosa* or *Staphylococcus aureus*.[15] Rifampin is particularly well-suited for staphylococcal infections given that organism's propensity for biofilm formation; it is one of the few antimicrobials with high intracellular activity and bactericidal killing of stationary-phase staphylococci in biofilm.[2,3,20] Table 2 summarizes potential oral agents for OM.

The most compelling clinical data for the use of oral therapy in the treatment of adults with bone and joint infections is the recently published multi-center randomized controlled non-inferiority trial Oral Versus Intravenous Antibiotics for Bone and Joint Infection (OVIVA), which assigned over 1000 patients at 26 centers in the United Kingdom with bacterial OM or joint infection to receive oral or parenteral therapy for 6 weeks.[8] Antibiotic selection was at the discretion of infection specialists, but switch to oral therapy was required within one week of surgical debridement or the beginning of IV therapy for nonoperative management. The primary endpoint was treatment failure within one year, defined as the presence of at least one clinical, microbiologic, or histologic criterion of failure. The cohort was primarily comprised of patients with hardware-related infection (60.6%). Oral antibiotic therapy was non-inferior to parenteral therapy in terms of treatment failure, with 13.2% versus 14.6% incidence (95% CI -5.6-2.9% difference with a prespecified noninferiority margin of 7.5%). Early discontinuations occurred more frequently in the IV group (18.9% vs 12.8%, p= 0.006). Length of stay, treatment costs, and vascular line complications were also lower in the oral treatment group.

The majority of patients received a surgical source control procedure, including debridement for OM (30.6%), debridement and implant retention for prosthetic joint infection (23.4%), and removal of orthopedic device or joint implant (28.6%). Only 7.6% of patients were treated without surgical intervention. The most common organisms identified were *Staphylococcus aureus* and coagulase-negative staphylococci (CONS), representing over 60% of isolated pathogens. In the parenteral group, the most commonly prescribed antibiotics were glycopeptides (41.1%) and cephalosporins (33.2%). In the oral group, fluoroquinolones (36.5%, primarily ciprofloxacin), penicillins (15.9%), and macrolides (13.0%) were the most

TABLE 2. Oral Antibiotics in the Context of Osteomyelitis

	Agent	Bioavailability	Bone-Serum Ratio	Notes
Most studied agents	Ciprofloxacin[14,15,18-20]	75-85%	27-100%	Caution against monotherapy with staphylococcal infections given potential selection of resistant mutants.
	Levofloxacin[2,6,18 15,19,20]	> 95%	38-99%	Generally lower MICs for Gram-positive pathogens compared to ciprofloxacin. Combination therapy with rifampin for staphylococcal OM is advised.
	Trimethoprim-sulfamethoxazole[3,14,15,18]	90-100%	50/15% (TMP/SMX)	Studied in combination with rifampin. Higher dosing (2DS tabs twice daily with normal renal function) proposed by some experts.
	Rifampin[3,15,20]	70-90%	> 100%	Not recommended as monotherapy. Several drug-drug interactions via CYP3A4 induction and p-glycoprotein.
	Metronidazole[15,18]	> 95%	80-100%	
	Clindamycin[15,18,20]	60-90%	40-67%	D-test positive staphylococcal isolates are likely to develop resistance.
	Linezolid[2,3,15,18,20]	>95%	37-51%	Long-term therapy limited by pancytopenia, peripheral neuropathy, optic neuritis.
Less studied agents	Amoxicillin[21]	74-92%	3-31%	Modeling indicates the max MIC allowing target attainment in serum is 1 mg/L with 1000 mg q8h dosing.
	Amoxicillin-clavulanate[18]	75%	3-31%/1-14%	
	Cephalexin[21]	90-100%	18%	Modeling indicates the max MIC allowing target attainment in serum is 4 mg/L with 1000 mg q6h dosing.
	Doxycycline[15,16,18,20]	>95%	2%–6% orthopedic, 86% mandible	

MIC = minimum inhibitory concentration, OM = osteomyelitis; TMP/SMX = Trimethoprimsulfamethoxazole; DS = double strength; q = every; h = hour

commonly utilized regimens. More than half of patients in the oral group and 40% in the parenteral group received combination therapy with rifampin for at least a portion of the treatment period. Most patients received antibiotic therapy beyond the required 6-week timeframe.

Although the pragmatic study design of OVIVA improves its overall generalizability, the heterogeneity of antimicrobial regimens, pathogens, and disease states in the study limits clinicians' ability to draw conclusions about specific subpopulations and regimens. This may be particularly important for patients without surgical source control and for oral beta-lactam regimens, which seemed to have a non-statistically significant higher risk of failure in subgroup analyses that were underpowered.[8] Given concerns about the inferior oral bioavailability and bone penetration of beta-lactams compared to other available oral antibiotic classes, this finding should be investigated in future studies before widespread adoption of oral beta-lactam therapy. OVIVA was not blinded and, although a blinded endpoint committee reviewed potential treatment failures, bias may still be a concern for what is arguably a subjective primary endpoint.[22,23]

Lipoglycopeptides for OM

The long-acting lipoglycopeptides dalbavancin and oritavancin have also been proposed as a potential treatment option for osteoarticular infections in light of their more convenient administration schedule, *in vitro* activity in biofilm models, and activity against many pertinent Gram-positive pathogens including methicillin resistant *Staphylococcus aureus* (MRSA) and CONS.[2] Surveillance studies have demonstrated that dalbavancin MICs are at least eight-fold lower than comparator agents such as vancomycin, linezolid, and daptomycin for *S. aureus* isolates obtained from patients with bone and joint infections.[24] Dalbavancin has accrued the most clinical data of the lipoglycopeptides in the treatment of OM and joint infection, notably with the publication of a randomized clinical trial that investigated the efficacy and safety of a two-dose dalbavancin regimen for the treatment of first-episode OM in adult patients at a tertiary care hospital in Ukraine.[25] Eighty patients were randomized 7:1 to dalbavancin 1500 mg IV on days 1 and 8 or standard of care (SOC) for 4-6 weeks. The dosing regimen was based on a phase I pharmacokinetic study demonstrating sustained tissue exposure above the dalbavancin $MIC_{99.9}$ of 0.12 mcg/mL for *S. aureus* for eight weeks.[26] Patients were excluded if they had received more than 24 hours of IV antibiotics within 96 hours of randomization, had prosthetic material at the infection site, or had infection associated with a sacral decubitus ulcer, among others. The majority of patients had lower extremity OM, with methicillin-susceptible *S. aureus* being the most common causative pathogen. Greater than 70% of all patients underwent surgical debridement, and very few (6% dalbavancin, 10% SOC) presented with concomitant bacteremia. The primary efficacy outcome, clinical cure at day 42, was achieved by 97% in dalbavancin group (95% CI 89.6 – 99.6%) and 88% in SOC group (95% CI 47.3 – 99.7%), and this was sustained through one year of followup. The primary safety outcome,

treatment-emergent adverse events, was observed in 14.3% of the dalbavancin group and 0% in SOC group, but only one adverse event was assessed as being related to dalbavancin.

The study's clinical success rate in both treatment arms was high, likely reflecting the relatively uncomplicated patient population of patients without hardware, bacteremia, or pressure ulcer-related OM.[26] Although these results have been largely reflected in subsequent retrospective cohort studies, it should also be noted that failures have been reported in the context of incomplete administration of dalbavancin as continuation therapy after receipt of vancomycin and incomplete source control for OM.[27-29]

Conclusion

The approach to treating bone and joint infections has historically consisted of prolonged antimicrobial therapy with parenteral antibiotics. While efficacious, this standard is often inconvenient, costly, and incurs risks associated with long-term vascular catheters. Data to support long-acting lipoglycopeptides and oral routes of antimicrobial therapy are emerging. Pharmacists can play an important role in interpreting these data and making recommendations about which patients may be candidates for these more convenient treatment modalities. Key considerations include completeness of surgical source control, presence of hardware, virulence and persistence of identified pathogens, immunocompetence of the host, need for biofilm-active antimicrobials such as rifampin, and host factors that may predispose a patient to recurrence or poor outcomes. Osteoarticular infections may be a pain in the patella, but clinicians should appreciate that therapeutic strategies are evolving.

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