

Medical Management of Osteomyelitis

It's important to use
the right antibiotic to achieve
maximum efficacy.

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Objectives

- 1) Define osteomyelitis and briefly describe clinical presentation and diagnostics
- 2) Identify causative microbes based on osteomyelitis etiology
- 3) Interpret literature evaluating medical management of osteomyelitis, with a focus on oral antimicrobial therapy
- 4) Analyze factors affecting therapy choice and treatment duration

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Following this article, an answer sheet and full set of instructions are provided (pg. 144).—Editor

Definitions

Osteomyelitis (OM) is defined as an infection of the cancellous or cortical bone caused by any of three general etiologies—hematogenous seeding, spread of contiguous infection, or association with vascular insufficiency [Glaudemans 2019, Bevilacqua 2007]. Hematogenous seeding of the bone is often seen in pediatric and geriatric patients [Lew 2004]. Contiguous spread includes infections secondary to an adjacent soft tissue, joint infection, or external source—including trauma, fracture, or surgery [Bevilacqua 2007,

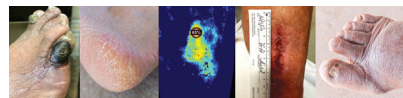
Hematogenous seeding is generally considered the most common etiology of osteomyelitis in the pediatric patient.

Glaudemans 2019, Lew 2004].

Patients with uncontrolled diabetes often present with lower extremity ulcers secondary to peripheral neuropathy and vascular insufficiency [Lew 2004]. Ulcerations and persistent hyperglycemia allow bacteria to colonize and infect the

bone [Glaudemans 2019, Bevilacqua 2007]. Patients with poorly managed diabetic foot infection (DFI) can experience progression to osteomyelitis [Bevilacqua 2007, Lew 2004]. OM can be characterized as acute or chronic [Lew 2004].

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Signs, Symptoms, and Presentation

The immune response to the infection leads to inflammation, bone destruction, and clinical signs associated with osteomyelitis [Bevilacqua 2007, Lew 2004]. Signs and symptoms

organisms may be pathogenic in OM secondary to DFI [Lipsky 2012].

Increasing healthcare exposure and antimicrobial overuse has led to the propagation of antibiotic resistance in the healthcare and community settings. Methicillin-resistance among *S. aureus* isolates (MRSA) has

oral options exist for treatment of Gram-negative infection and rising resistance rates to first-line agents increase relapse risk [Framow 2009]. Fluoroquinolones and TMP-SMX are mainstays in therapy against Enterobacteriaceae. Ciprofloxacin is considered more active against Gram-negatives, including *P. aeruginosa*, compared to levofloxacin and moxifloxacin, which have greater efficacy against *S. aureus* [Framow 2009, Kim 2014]. Clindamycin, metronidazole, beta-lactam/beta-lactamase inhibitor combinations, and moxifloxacin are effective against most anaerobic pathogens. Empiric treatment should, however, be based on institutional antibiograms and treatment pathways.

Staphylococci most commonly causes community-acquired osteomyelitis in adults.

of infection include fever, malaise, and pain [Bevilacqua 2007]. Chronic infection and inflammation can lead to bone necrosis and sequestrum or sinus tract formation [Lew 2004].

Diagnosis

Diagnostics of osteomyelitis includes clinical examination, plain radiography, magnetic resonance imaging (MRI), three-phase bone scan, white blood cell scans, and probe-to-bone test. Although MRI can reveal edema and inflammation, bone histology and culture are required for definitive diagnosis [Bevilacqua 2007]. Blood cultures are also recommended in patients with suspicion of hematogenous spread or systemic infection.

Monitoring laboratory parameters trends may aid in OM diagnosis and management. A study performed at our institution delineated C-reactive protein (CRP) greater than 3.2 and erythrocyte sedimentation rate (ESR) greater than 76 to be attributable to OM.

Microbiology

The two most common pathogenic organisms in OM are *Staphylococcus aureus* followed by *Streptococcus* spp. *S. aureus* is hardy and particularly difficult to treat due to its ability to form biofilm and predilection to intracellular persistence [Lew 2004]. Post-traumatic and post-surgical infections may be polymicrobial or due to nosocomial Gram-positive or Gram-negative bacteria [Lew 2004]. Vertebral OM may be caused by either Gram-positive or Gram-negative species or *M. tuberculosis* [Barbari 2015, Lew 2004]. Various Gram-positive, Gram-negative, or anaerobic

risen dramatically. Rates of community-acquired MRSA (CA-MRSA) infection have increased recently and it is often considered more virulent than healthcare-acquired species (HA-MRSA). Nevertheless, CA-MRSA is generally more sensitive to common antimicrobials, including doxycycline, clindamycin, and trimethoprim-sulfamethoxazole

Other Potential Causative Pathogens

Coagulase-negative *Staphylococci* (CoNS), including *S. epidermidis*, beta-hemolytic *Streptococci*, *Enterococci*, and *Cutibacterium* (Propion-

Treatment Options—General

Management of OM in adults often includes surgical intervention and antimicrobial therapy. Debridement and drainage of abscesses should be performed to ensure source control and pharmacotherapy success. Management of OM traditionally required long-term intravenous antimicrobials followed by highly bioavailable oral suppressive

Bone histology and culture in addition to clinical judgment, are needed for a definitive diagnosis of osteomyelitis.

ibacterium) *acnes* are also potential causative pathogens. *S. epidermidis* is increasingly resistant to methicillin (MRSE) and other common empiric antimicrobials, including fluoroquinolones and TMP-SMX [Lew 2004]. Penicillins and narrow-spectrum cephalosporins are first-line against *Streptococci* with linezolid and clindamycin considered alternatives. Oral treatment options against *Enterococci*, including vancomycin-resistant strains, include linezolid, tedizolid, and tetracyclines [Framow 2009].

Gram-negative or polymicrobial infections may be encountered in susceptible patients, such as those with recent healthcare exposure, diabetes, trauma, or surgery. Limited

therapy upon symptomatic improvement and availability of culture and sensitivity reports [Lipsky 2012, Khan 2012]. An increasing body of literature questions the lengthy duration of intravenous drug administration and supports even earlier transition to oral therapy [Li 2019].

In the recently published OVIVA study, patients in the oral treatment arm had reduced hospital length of stay compared to IV treatment (14 vs. 11 days; $p < 0.001$) [Li 2019]. Treatment with oral medications increases patient convenience, decreases economic burden, and prevents potential complications of long-term venous access, including catheter occlusion

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and infection, found to occur in up to 9% of patients [Li 2019, Khan 2012].

Treatment Options—Oral

Drug-specific factors affecting oral antimicrobial choice include: protein binding, bioavailability, volume of distribution, lipophilicity, molecular weight, charge, and bone penetration. As Fraimow and colleagues highlight, interpretation of standard minimum inhibitory concentration

TMP-SMX

TMP-SMX is a combination bactericidal antimicrobial that synergistically and sequentially inhibits bacterial folic acid biosynthesis [Khan 2012]. Spectrum of activity includes MSSA, CA-MRSA, and certain Gram-negative pathogens, including *E. coli*, *Klebsiella* spp., *Enterobacter* spp., and *Proteus mirabilis* [Fraimow 2009]. Treatment success rates in studies using TMP-SMX with or without rifampin approach 90% [Euba 2009, Nguyen 2009, Spellberg 2012].

topoisomerase IV and DNA gyrase, leading to disruption of DNA processing. Commonly employed agents in the class include ciprofloxacin, levofloxacin, and moxifloxacin. Spectrum of activity includes MSSA, Streptococci, *E. coli*, *K. pneumoniae*, *S. marcescens*, *Enterobacter* spp., and *P. aeruginosa*. The widespread use of fluoroquinolones in infectious diseases practice has led to promulgation of resistance to these agents. Monotherapy may be considered against susceptible Gram-positive and Gram-negative isolates. Co-administration with rifampin is recommended to curb resistance development and enhance bactericidal activity against Gram-positive pathogens. High doses of each oral agent are recommended for management of OM, such as ciprofloxacin 500 mg–750 mg every 12 hours, levofloxacin 750 mg once daily, and moxifloxacin 400 mg once daily. Clinicians should monitor for musculoskeletal (tendonitis, muscle weakness), central nervous system (hallucinations, agitation), and cardiac (QT-prolongation) toxicities.

Half-life does not greatly impact choice of oral antimicrobial in treatment of osteomyelitis.

(MIC) results is based on achievable serum concentrations and may not be reliable depending on active, free drug concentrations in the bone [Fraimow 2009]. A review by Thabit, et al. provides cortical and cancellous bone concentrations compared to MIC breakpoints of commonly encountered pathogens in OM [Thabit 2019]. Drug distribution to the bone often may be unpredictable. Infected and inflamed bone may lead to hyperemia and increased drug presence. However, avascular and necrotic bone, presence of foreign material, and biofilm prevent adequate penetration to site of infection due to lack of blood flow and distribution [Lew 2004, Kim 2014].

Highly bioavailable oral antimicrobials should be utilized in management of OM [Lipsky 2012]. The dose and frequency should be adapted to maximize pharmacokinetic and pharmacodynamic parameters of each agent. Potential drug-specific adverse drug reactions (ADRs), including *C. difficile* infection, also affect treatment choice, especially at the high doses needed to effectively treat OM [Khan 2012, Fraimow 2009]. Lastly, it is imperative to determine whether monotherapy or combination therapy should be used. Especially in the cases of foreign-material associated bone and joint infection due to MRSA, monotherapy was associated with treatment failure [Kim 2014, Lew 2004].

The pharmacodynamic parameter associated with efficacy is time above MIC; however, achieving an adequate C_{max} above MIC is vital. Oral TMP-SMX is not effective against *P. aeruginosa*.

Dosing for management of MRSA OM ranges from 4–7 mg TMP/kg/dose every 12 hours orally. Higher doses of up to 10 mg/kg TMP (approximately 2 TMP-SMX double-strength tablets (160 mg TMP/800 mg SMX) twice daily) may increase bone penetration and monotherapy treatment success [Kim 2014]. These doses, however, are likely to predispose patients to ADRs, including hyperkalemia, hemolysis in patients with G6PD deficiency, pancytopenia, nephrotoxicity, and gastrointestinal distress. Severe dermatologic reactions, including Stevens-Johnson syndrome may also occur with this agent. Plasma protein binding is estimated at 44% for TMP and 70% for sulfamethoxazole. Oral TMP-SMX is considered highly bioavailable—IV to oral dose conversion is 1:1 [Klepser 1996]. TMP-SMX distributes extensively into body tissues, making it an appealing choice in treatment of OM. Bone penetration is 50% and 15% of serum concentrations for TMP and SMX, respectively [Spellberg 2012].

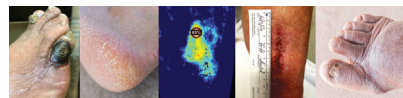
Fluoroquinolones

Fluoroquinolones are bactericidal agents that inhibit bacterial

Potentially significant drug interactions exist with cations and antiarrhythmic drugs [Khan 2012]. Ciprofloxacin and levofloxacin protein binding range from 20 to 40% in plasma. The pharmacodynamic parameters associated with efficacy are C_{max} and AUC to MIC ratio. *aeruginosa* Rapid absorption from the GI tract and high volumes of distribution allow appreciable drug concentration in deep tissues, including bone [Khan 2012]. Mean bone to serum ratios range from 27–120% for oral ciprofloxacin and 43–105% for oral moxifloxacin, generally exceeding the Staphylococci MIC₉₀ [Spellberg 2012, Kim 2014, Landersdorfer 2009]. These agents are especially enticing for use against *S. aureus* due to their ability to penetrate osteoblasts where this pathogen often persists [Landersdorfer 2009].

Fluoroquinolone treatment success rates in OM trials have ranged from 50–77% [Greenberg 2000, Gentry 1990, Khan 2012, Zimmerli 1998, Spellberg 2012]. Delafloxacin was recently approved by the US Food and

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Drug Administration (FDA). This agent demonstrates *in vitro* activity against MRSA, in addition to the previously noted pathogens. Delafloxacin is approved for treatment of acute

vancomycin-resistant isolates), and is indicated for treatment of ABSSSI, nosocomial pneumonia, and VRE infections. Oral and intravenous dosing are equivalent (100% bioavailability) at 600 mg every 12 hours. Bone to serum ratio of linezolid ranges

available regarding tedizolid's bone penetration [Si 2017]. Labeled dosing is 200 mg once daily.

Metronidazole

Metronidazole is a bactericidal agent that inhibits nucleic acid synthesis by binding to DNA and electron-transport proteins. This agent possesses activity against a myriad of anaerobic pathogens, including *Bacteroides* and *Clostridium* spp. Metronidazole is indicated for treatment of many anaerobic infections, including bone and joint infections caused by *Bacteroides* spp. Possible adverse reactions include convulsive seizures, peripheral neuropathy, dysgeusia, neutropenia, and a disulfiram-like reaction. The pharmacodynamic parameter associated with efficacy is C_{max} above MIC. Plasma protein binding is minimal and dosing is equivalent for IV and oral (1:1) at 500 mg every 8 hours due to high bioavailability. Metronidazole bone concentration is similar to serum concentrations, making it an attractive option for oral treatment of anaerobic OM [Spellberg 2012].

Tetracyclines

Tetracyclines are bacteriostatic agents that inhibit bacterial protein

Rifampin demonstrates greatest efficacy against biofilms and foreign material-associated osteomyelitis.

bacterial skin and skin structure infections (ABSSSI). Its role in management of OM remains to be elucidated.

Clindamycin

Clindamycin is a bacteriostatic lincosamide that acts on the 50S ribosomal subunit inhibiting bacterial protein synthesis. Its spectrum of activity includes CA-MRSA, *Streptococcus* spp., and anaerobes, including *Peptostreptococcus* spp. and *Prevotella* spp. Clindamycin has shown efficacy in treatment of pediatric and adult OM. Oral doses in treatment of OM range from 300–450 mg every 6 hours to 600 mg every 8 hours, with higher doses preferred, if tolerated. Adverse reactions associated with clindamycin include gastrointestinal distress, elevated liver function values, and dermatologic reactions. Clindamycin demonstrates greater than 90% plasma protein binding and a bioavailability of 90%. The pharmacodynamic parameter associated with efficacy is AUC to MIC. Of note, *S. aureus* may display inducible clindamycin-resistance that should be tested for using the erythromycin D-test [Framow 2009]. Traditionally, clindamycin bone penetration ranges were estimated at 40 to 70% of serum concentrations, though recent literature suggest ratios closer to 21–45% [Spellberg 2012, Landersdorfer 2009].

Oxazolidinones

Oxazolidinones inhibit bacterial protein synthesis by binding to the 23S ribosomal subunit. Linezolid is the most commonly employed agent in this class. Its spectrum of activity includes MRSA, *Streptococcus* spp., and *Enterococci* (including

from 37–51%, with bone concentrations exceeding *Staphylococci* MIC₉₀ [Spellberg 2012, Kim 2014, Landersdorfer 2009]. Treatment success rates range from 55 to 100% in Gram-positive OM and are comparable to ampicillin-sulbactam for DFI [Nguyen 2009, Lipsky 2004, Kim 2014].

Linezolid has generally poor activity against biofilm and should be combined with a biofilm-active agent, such as rifampin, if indicated. ADRs associated with linezolid include myelosuppression (anemia, thrombocytopenia), peripheral and optic neuropathy, and hypoglycemia. One study reported side effects in over 50% of patients, especially in those with treatment duration greater

than two weeks. Treatment discontinuation rates were up to 30% [Seneville 2006].

Linezolid's inhibition of monoamine oxidase can lead to drug-drug interactions with antipsychotics, anti-depressives, and anxiolytic agents. Plasma protein binding of linezolid is approximately 30%, and volume of distribution is 0.65 L/kg. The pharmacodynamic parameter associated with efficacy is time above MIC. The FDA recently approved a novel agent in this class, tedizolid, with reportedly lower incidences of ADRs. Increasing data demonstrate potential utility as oral treatment of OM [Park 2016, Launer 2018]. Limited information is

synthesis through 30S ribosomal subunit binding. Oral tetracyclines, including doxycycline and minocycline, are commonly employed in management of OM. These agents are active against CA-MRSA and are indicated in a variety of infections. *Staphylococci* generally have greater sensitivity to minocycline compared to doxycycline, although many isolates are sensitive to both [Framow 2009]. These agents have greater than 90% bioavailability allowing for equivalent IV to PO conversion. Both agents are highly protein-bound (greater than 90%) and each dosed at 100 mg every 12 hours. Tetracyclines' extremely high volumes

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of distribution make them effective in OM. The pharmacodynamic parameter associated with efficacy is AUC to MIC. Doxycycline's bone to serum concentration ranges from 2–86% and depends on the site of infection [Spellberg 2012].

Rifampin

Rifampin, a commonly employed agent in the rifamycin class, inhibits bacterial-specific DNA-dependent RNA polymerase. This agent is commonly an adjunct in managing OM due to its activity against MRSA, ability to penetrate biofilm, and retention of activity against stationary phase Gram-positive organisms [Kim 2014]. Resistance to rifampin can develop rapidly through polymerase mutations and, hence, should not be used as monotherapy. Co-administration of rifampin with another agent, such as a fluoroquinolone or tetracycline, can increase treatment success rates and prevent emergence of resistance to either agent [Fraitow 2009, Zimmerli 1998]. Combination treatment with rifampin achieved treatment success rates of greater than 80%, including foreign material-associated infections. Rifampin has the potential for a myriad of drug-drug interactions due to its induction of drug metabolism and transport enzymes.

Notable side-effects include flu-like symptoms, red-orange discoloration of body fluids, rash, and hematologic and hepatic toxicity [Khan 2012]. Rifampin bioavailability can vary depending on the duration of therapy. Single dose pharmacokinetic studies demonstrate a bioavailability of greater than 90% [Kim 2014, Agrawal 2005]. However, auto-induction of metabolizing enzymes decrease bioavailability to approximately 70% over time [Agrawal 2005]. The optimal dose of rifampin in managing OM is generally cited as 600 mg daily, although 450 mg every 12 hours has also been reported [Fantoni 2019]. Rifampin demonstrates a large volume of distribution, including penetration into bone and central nervous system [Khan 2012]. Rifampin's bone to serum concentration ratio range from 20–57% accord-

ing to some studies and approximate its serum levels in others [Spellberg 2012, Landersdorfer 2009].

Beta-lactams

The beta-lactam class, including penicillins, cephalosporins, carbapenems, and monobactams, are among the most effective and commonly prescribed anti-infectives. They exert bactericidal activity by inhibiting cell wall transpeptidation [Khan 2012]. Spectrum of activity varies with inter- and intra-class. Of note, no oral beta-lactam in the U.S. possesses clinically relevant activity against MRSA or *P. aeruginosa*. Beta-lactam bioavailability is lower than previously reviewed antimicro-

Miscellaneous Agents

Data exist regarding utility of other oral antimicrobials, including fosfomycin, fusidic acid, and pristinamycin in treatment of Gram-positive OM. However, these agents were not reviewed due to limited or conflicting data or lack of availability in the U.S.

Combination Therapy

A variable amount of data exists for combination oral treatment of complex bone infections. Examples primarily include: fluoroquinolones, linezolid, TMP-SMX, clindamycin, fusidic acid, and tetracyclines each in combination with rifampin [Kim 2014, Lew 2004]. Please see individual sections above.

Oral TMP-SMX is not effective against *P. aeruginosa*.

bials, emphasizing the need to optimize pharmacokinetic and pharmacodynamic parameters. Commonly employed oral beta-lactams include amoxicillin, amoxicillin-clavulanate, (di)cloxacillin, and cephalixin. The pharmacodynamic parameter associated with efficacy is time above MIC.

Plasma protein binding and bioavailability vary greatly depending on the agent. For example, bioavailability for ampicillin ranges from 37–39% compared to 80% for amoxicillin. Bone penetration of these agents relative to serum concentrations are estimated at 10–20% [Fraitow 2009].

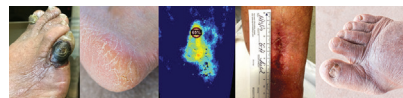
Amoxicillin may achieve up to 30% of its serum concentration in the bone (range: <10–31%) compared to 14% for clavulanate [Landersdorfer 2009]. Cephalixin and cefpodoxime achieve 18 and up to 30%, respectively. Maximally tolerated doses should be employed to ensure consistent bone concentrations above the MIC of the target pathogen. For example, amoxicillin 500mg every 8 hours, or amoxicillin-clavulanate 1g every 8 hours to 2g every 12 hours, may be used [Fantoni 2019]. More data are available indicating beta-lactam efficacy in pediatric, hematogenous OM compared to adult, chronic OM [Kim 2014].

Treatment Duration

Antimicrobial treatment duration is often dependent on outcome of surgical intervention. Intravenous therapy for 4–6 weeks is commonly recommended to ensure adequate serum and bone concentrations during the period of bone revascularization after surgery [Kim 2014, Lew 2004, Mouzopolous 2011]. Current data, however, suggest initial, short-course intravenous therapy (1–2 weeks) during the period of highest bacterial burden followed by oral therapy is appropriate even in the setting of foreign material, assuming adequate surgical intervention [Li 2019, Mouzopolous 2011, Daver 2007]. Success rates of less than 2 weeks intravenous therapy before switching, 2–4 weeks, 4–6 weeks, and greater than 6 weeks were 83%, 72%, 75%, and 66%, respectively ($p=0.68$) [Daver 2007].

The Infectious Diseases Society of America (IDSA) recommends the following treatment durations: if infected soft tissue remain, continue treatment for 2–4 weeks. If infected bone remains or surgery is not performed, treatment for 6 weeks to greater than 3 months is recommended [Lipsky 2012, Bevilacqua 2007]. OM secondary to MRSA often necessitates

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treatment for 8 weeks or longer. Suppression therapy for months after initial management may also be required, especially in the setting of infected hardware or prostheses. In practice, treatment duration often depends on clinical response and correction of laboratory abnormalities, including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR).

Conclusion

Medical management of OM is a constantly evolving landscape. An increasing body of data supports early conversion to oral antimicrobial treatment of osteomyelitis. Choice of agent should take in account patient, drug, and pathogen-specific factors. Optimization of pharmacokinetic and pharmacodynamic parameters may increase probability of treatment success. **PM**

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The duration of intravenous antimicrobial treatment of acute osteomyelitis should be based on patient-specific risk factors, clinical response, laboratory parameter normalization, and evaluation of collateral impact of long-term venous access.

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CME EXAMINATION

SEE ANSWER SHEET ON PAGE 145.

1) What is generally considered the most common etiology of osteomyelitis in the pediatric patient?

- A) Vascular insufficiency
- B) Hematogenous seeding
- C) Contiguous—adjacent soft tissue infection
- D) Contiguous—trauma

2) Which of the following pathogens most commonly causes community-acquired osteomyelitis in adults?

- A) Staphylococci
- B) Enterobacteriaceae
- C) *Cutibacterium (Propionibacterium) acnes*
- D) *Pseudomonas aeruginosa*

3) Which of the following diagnostic tests, in addition to clinical judgment, are needed for a definitive diagnosis of osteomyelitis?

- A) Plain radiograph
- B) Magnetic resonance imaging
- C) Bone histology and culture
- D) Positive blood cultures

4) Which of the following are potential complications of long-term venous access?

- A) Access site infection
- B) Mechanical or thrombotic occlusion
- C) Increased cost
- D) All of the above

5) Which of the following drug-specific characteristics do NOT greatly impact choice of oral antimicrobial in treatment of osteomyelitis?

- A) Bioavailability
- B) Bone penetration
- C) Half-life
- D) Volume of distribution

6) Potential adverse drug reactions secondary to long-term linezolid therapy include which of the following?

- A) Optic neuropathy
- B) Myelosuppression
- C) Nephrotoxicity
- D) A + B

Continued on page 144

7) Which of the following agents demonstrates greatest efficacy against biofilms and foreign material-associated osteomyelitis?

- A) Cephalexin
- B) Doxycycline
- C) Linezolid
- D) Rifampin

8) No oral beta-lactam in the U.S. possesses clinically relevant activity against_____.

- A) MRSA or *P. aeruginosa*
- B) Streptococcus
- C) Staphylococcus
- D) Clostridium

9) Against which of the following pathogens would oral TMP-SMX NOT be effective?

- A) *E. coli*
- B) *P. aeruginosa*
- C) MSSA
- D) CA-MRSA

10) Duration of intravenous antimicrobial treatment of acute osteomyelitis should be:

- A) At least 6–8 weeks, irrespective of the pathogen
- B) Based on patient-specific risk factors, clinical response, laboratory parameter normalization, and evaluation of collateral impact of long-term venous access
- C) Contingent solely on normalization of CRP and ESR
- D) Length of hospital stay

SEE ANSWER SHEET ON PAGE 145.

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EXAM # 10/20
Medical Management of Osteomyelitis
(Caputo and Raja)

Circle:

- | | |
|------------|-------------|
| 1. A B C D | 6. A B C D |
| 2. A B C D | 7. A B C D |
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A B C D
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