

Skin and Soft Tissue Infections and Bone and Joint Infections

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Learning Objectives

- Assess advantages and disadvantages of pharmacotherapies for bone and joint infections and skin and soft tissue infections, including antimicrobial spectrum of activity, pharmacokinetics, and pharmacodynamics.
- Select the most appropriate pharmacotherapeutic plan and monitoring based on patient- and disease-specific information, antibiogram data, and best available evidence.
- Recommend modifications of patient-specific pharmacotherapeutic plans based on efficacy and adverse effects.
- Interpret signs, symptoms, and laboratory and other relevant diagnostic test results.
- Identify drug-related problems associated with the therapeutic plan.
- Describe the etiology, diagnosis, and treatment of acute bacterial osteomyelitis and septic arthritis in pediatric patients.



Skin and Soft Tissue Infections: Types of Infections

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Segment 1

HA is a 34-year-old woman who presents to her PCP for evaluation of an abscess in her groin region. She reports a subjective fever at home. Her PCP examines the abscess, performs I&D, and sends a sample for culture and susceptibility testing. HA has a medical history of polycystic ovarian syndrome (PCOS) and has no known allergies.
Tmax 100.8 °F, HR 82 bpm, BP 118/78, RR 20/min

Question 1: What would be the most appropriate empiric therapy?

- A. No empiric antimicrobial therapy is indicated at this time
- B. Clindamycin 300 mg by mouth every 6 hours for 5 days
- C. Trimethoprim/sulfamethoxazole 1 DS tablet every 12 hours for 14 days
- D. Doxycycline 100 mg by mouth twice daily for 10 days

I&D: Incision and drainage, PCOS: polycystic ovarian syndrome



Patient HA (continued): The PC decides to initiate trimethoprim/sulfamethoxazole and follow up with the culture result to adjust antimicrobial therapy, if necessary. Three days later, the final I&D culture result is available.

Question 2: What is the most appropriate treatment decision after reviewing the culture result?

| Wound Culture Report | |
|--------------------------------------|-------------|
| Staphylococcus aureus, mecA positive | |
| Interpretation | |
| Oxacillin | Resistant |
| Clindamycin | Resistant |
| Doxycycline | Susceptible |
| TMP/SMX | Susceptible |
| Vancomycin | Susceptible |
| Linezolid | Susceptible |

- A. Change to oral linezolid for 7 more days
- B. Continue trimethoprim/sulfamethoxazole for 7 more days
- C. Change to doxycycline for 10 more days
- D. Continue trimethoprim/sulfamethoxazole for 10 more days

TMP/SMX: trimethoprim/sulfamethoxazole



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Guidance for Questions 1&2

- IDSA Skin and Soft Tissue Infections
– Stevens D et al. *Clin Infect Dis.* 2014; 59:e10-52

| Question 1 | Question 2 |
|--|---|
| A. Fever warrants antimicrobial treatment | A. Expensive |
| B. Appropriate per IDSA guidelines, but high community resistance among MRSA | B. Best answer choice |
| C. Exceeds recommended treatment duration | C. Exceeds recommended treatment duration |
| D. Best answer choice | D. Exceeds recommended treatment duration |

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Types of Skin Infections

Primary Infections

- Cutaneous abscess
- Folliculitis
- Furuncles and carbuncles
- Impetigo
- Erysipelas
- Cellulitis (purulent vs non-purulent)
- Necrotizing fasciitis

Typically Mild

S
E
V
E
R
E

Severe and Potentially life-threatening

Stevens D et al. *Clin Infect Dis.* 2014; 59:e10-52.

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Sample of Unique Pathogens

| Type of Infection | Unique Pathogens |
|---------------------------------|---|
| Diabetic Foot Infections | <i>Staphylococcus aureus</i> (MSSA or MRSA) <i>Streptococcus pyogenes</i> , Group B <i>Streptococcus</i> Consider gram-negative bacilli or anaerobic pathogens |
| Animal Bites | <i>Staphylococcus aureus</i> (MSSA or MRSA) <i>Streptococcus</i> sp. <i>Pasteurella canis</i> , <i>Pasteurella multocida</i> |
| Human Bites | <i>Staphylococcus aureus</i> (MSSA or MRSA) <i>Streptococcus</i> sp., particularly Viridans Group Oral flora: <i>Eikenella corrodens</i> , <i>Peptostreptococcus</i> sp., <i>Peptococcus</i> sp., <i>Corynebacterium</i> sp., |

The accompanying workbook lists many more bacterial, fungal, viral, and parasitic pathogens that can be associated with skin and soft tissue infections

Stevens D et al. *Clin Infect Dis.* 2014; 59:e10-52.

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Additional Notes

- Use of steroids
- Recurrent infection (including MRSA decolonization)
- Immunocompromised patients
- Adjunctive clindamycin

MRSA: methicillin-resistant *Staphylococcus aureus*

Stevens D et al. *Clin Infect Dis.* 2014; 59:e10-52.

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Segment 2

Skin and Soft Tissue Infections: Surgical Site Infections

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Patient Case

G.R., a 66-year old, 137-kg patient with uncontrolled diabetes mellitus is in the operating room for a left total hip arthroplasty. The surgeon calls the pharmacy for preoperative antimicrobial recommendations after noticing a penicillin allergy on the patient's profile. The allergic reaction is listed as nausea and vomiting, and the patient has healthy renal function.

Question 3: What is the most appropriate regimen for preoperative surgical prophylaxis in this patient?

A. Vancomycin 25 mg/kg IV
B. Cefazolin 3 g IV
C. Cefazolin 2 g IV + metronidazole 500 mg IV
D. Clindamycin 600 mg IV

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2013 Surgical Prophylaxis Guidelines

- Interprofessional Guidelines: ASHP, IDSA, SIS, SHEA
- Summary of recommendations
 - Antimicrobial selection by type of surgery and alternatives for patients with β -lactam allergy
 - Cefazolin remains the first-line agent for most types of surgery
 - Preoperative timing: 60 min prior to incision, 120 min for vancomycin and fluoroquinolones
 - Weight-based dosing in obesity (cefazolin 3 g >120 kg)
 - Intraoperative repeat administration: length of procedure, obesity, significant blood loss
 - Duration of prophylaxis (up to 24 hr)
 - Topical administration of vancomycin and gentamicin requires further research
 - Preoperative MRSA screening and decolonization
- Additional studies are needed in areas with increased antimicrobial resistance patterns

ASHP: American Society of Health-System Pharmacists
IDSA: Infectious Disease Society of America
SIS: Surgical Infection Society
SHEA: The Society for Healthcare Epidemiology of America
MRSA: Methicillin-resistant *Staphylococcus aureus*

Bratzler DW et al. *Am J Health-Syst Pharm*. 2013; 70:195-283.

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Patient Case G.R. (continued)

10 days post-implantation, G.R. presents to the clinic with purulence and erythema at surgical incision. A CT Hip shows superficial edema, and no evidence of fluid collection. Tmax 99.3°F, WBC 8.9 x10³ cells/mm³. There is <5 cm surrounding erythema noted on physical exam.

Question 4: Which surgical or pharmacotherapeutic plan is most appropriate for Patient GR in this situation?

A. Incision and drainage only
B. Incision and drainage, plus vancomycin IV x 48 hr
C. Cephalexin x 7 days without incision and drainage
D. Incision and drainage, plus vancomycin IV for 48 hr, then switch to linezolid orally to complete 7 days of antibiotic therapy

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Surgical Site Infections (SSI)

| | Superficial Incisional | Deep Incisional | Organ/Space |
|------------------------|---|---|---|
| Time Frame | ≤ 30 days after surgery | ≤ 90 days after surgery | ≤ 90 days after surgery |
| Anatomical Involvement | Only skin and subcutaneous tissue | Deep soft tissues of incision (fascial and muscle layers) | Any area deeper than fascial/muscle layers that was opened during the procedure |
| Criteria | At least one of the following: <ul style="list-style-type: none"> • Purulent drainage • Pathogen obtained from aseptically-obtained specimen • Pain, tenderness, localized swelling, erythema, or heat • Diagnosis by surgeon or attending physician | At least one of the following: <ul style="list-style-type: none"> • Purulent drainage • Spontaneous dehiscence, or is deliberately opened, and at least one: fever, localized pain, and tenderness • Abscess involving incision detected by imaging or histopathology | At least one of the following: <ul style="list-style-type: none"> • Purulent drainage via drain • Pathogen obtained from aseptically-obtained fluid or tissue • Abscess involving organ/space detected by imaging or histopathology |

Stevens D et al. *Clin Infect Dis*. 2014; 59:e10-52.
Centers for Disease Control and Prevention, National Healthcare Safety Network.
Surgical site infection procedure-associated module. January 2018.

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Treatment of Surgical Site Infections

| Infection Criteria | Recommendation |
|--|--|
| No evidence of systemic response | <ul style="list-style-type: none"> • Suture removal plus incision and drainage (strong, low) • Antimicrobial therapy is likely unnecessary (weak, low) |
| Evidence of systemic response, defined as the presence of at least one of the following: <ol style="list-style-type: none"> 1. T >38.5°C (101.3°F) 2. WBC >12 x10³ cells/mm³ 3. HR > 110 bpm 4. >5 cm extending erythema or induration | <ul style="list-style-type: none"> • Suture removal plus incision and drainage (strong, low) • Short course antimicrobial therapy (24-48 hours) may be beneficial (weak, low), especially trunk, head and neck, and extremities (strong, low) • Empiric therapy options: (strong, low) <ul style="list-style-type: none"> • MSSA: 1st generation cephalosporin or antistaphylococcal penicillin • MRSA: vancomycin, daptomycin, linezolid, telavancin, ceftaroline • Gram-negative rods: cephalosporin or fluoroquinolone plus metronidazole |

MSSA: methicillin-susceptible *Staphylococcus aureus*

Stevens D et al. *Clin Infect Dis*. 2014; 59:e10-52.

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Segment 3

Bone and Joint Tissue Infections: Prosthetic Joint Infections

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Prosthetic Joint Infection (PJI)

- 2-5% of procedures
- Multiple joint locations
 - Knee -> Hip -> Shoulder -> Ankle
- Characteristics of infection
 - Biofilm formation
 - Can be both contiguous and hematogenous
- Risk factors
 - Obesity, diabetes mellitus, rheumatoid arthritis, immune suppression, cancer, procedure duration, postop complications, prior arthroplasty or septic arthritis

Osmon D et al. Clin Infect Dis. 2013; 56:1-25.
Tande AJ et al. Clin Microbiol Rev. 2014;27:302-45.
Berrios-Torres SI et al. JAMA Surg. 2017; 152:784-91 and associated supplemental materials.

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Question 5: Two months post-implantation during a follow-up clinic visit, a draining sinus tract was noted along the surgical incision. Which of the following diagnostic criteria for prosthetic joint infection (PJI) is most strongly supported by IDSA guidelines?

- Presence of an actively draining sinus tract that communicates with the prosthesis
- Elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)
- A single positive tissue or bone culture collected intra-operatively
- Radiographic, CT, or MRI imaging suggestive of diagnosis

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| Prosthetic Joint Infection: Diagnostic Criteria | | Level of Evidence |
|---|---|-------------------|
| Clinical Symptoms | Actively draining sinus tract or purulence that communicates with the prosthesis | B-III |
| | Acute onset of painful prosthesis | B-III |
| | Chronic painful prosthesis | B-III |
| Laboratory | CRP and ESR in combination may be useful when diagnosis is not clinically evident | A-III |
| Microbiology | Preoperative synovial fluid for aerobic and anaerobic culture | A-III |
| | Withhold antimicrobial therapy at least 2 weeks prior to culture collection | A-II |
| | ≥ 2 intraoperative cultures that yield the same organism | B-III |
| | Blood culture if febrile, acute onset, or concern for hematogenous seeding | B-III |
| Synovial Fluid Analysis (especially in acute infection) | Total cell count | A-III |
| | Neutrophil % | A-III |
| | Withhold antibiotics for 2 weeks before obtaining a sample if stable | B-III |
| Imaging | Radiograph | A-III |
| | Not for routine use: bone scans, MRI, CT | B-III |
| Histopathology | Intraoperative sampling | B-II |

Osmon D et al. Clin Infect Dis. 2013; 56:1-25.

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Stages of Prosthetic Joint Infection

| | Early | Delayed | Late |
|------------|---|--|--|
| Time Frame | 1 to 3 months after implantation | >3 months to 1-2 years after implantation | >1 to 2 years after implantation |
| Etiology | During implantation (more common) Hematogenous (less common) | During implantation | Hematogenous |
| Symptoms | Acute | Chronic pain or loosening prosthesis | Acute septic arthritis syndrome |
| Pathogens | <i>Staphylococcus aureus</i> Coagulase-negative <i>Staphylococcus</i> Aerobic gram-negative bacilli <i>Enterococcus</i> sp. Polymicrobial infection | <i>Staphylococcus aureus</i> Coagulase-negative <i>Staphylococcus</i> <i>Streptococcus</i> sp. Culture negative | <i>Staphylococcus aureus</i> Coagulase-negative <i>Staphylococcus</i> <i>Streptococcus</i> sp. Culture negative |

Osmon D et al. Clin Infect Dis. 2013; 56:1-25.
Tande AJ et al. Clin Microbiol Rev. 2014; 27:302-45.

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Question 6: Which of the following statements about antibiotic treatment for prosthetic joint infections is correct?

- Antimicrobial doses for long-term suppressive therapy should be 25-50% of the full initial treatment dose
- Oral therapy is an option for *Staphylococcus* infections in patients undergoing 2-stage exchange procedures
- If hardware cannot be removed, 6 months of therapy is recommended regardless of the pathogen
- A longer duration of therapy is required for infections caused by multidrug-resistant gram-negative pathogens rather than susceptible pathogens

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PJI Treatment and Hardware Intervention

| Retain | Replace | Remove |
|---|--|---|
| <ul style="list-style-type: none"> Debridement and Implant Retention (DAIR) Includes inner liner exchange | <ul style="list-style-type: none"> 1-Stage Exchange* 2-Stage Exchange* | <ul style="list-style-type: none"> Permanent Resection Amputation |
| Treatment Duration Months -> Indefinite | Treatment Duration Weeks -> Indefinite | Treatment Duration None or Weeks |

* 1-Stage: In a single surgical procedure, all hardware is removed, and new hardware is inserted.
 * 2-Stage: Two surgeries are required, typically ≥8 weeks. First, all hardware is removed and a spacer is inserted into the joint. In a subsequent surgery, a new prosthesis is inserted. This creates a hardware-free period during infection treatment.

Osmon D et al. *Clin Infect Dis.* 2013; 56:1-25.

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Staphylococcus Treatment

| Type of Surgery | Level of Evidence | Initial Treatment Phase | Long Term Suppression Phase |
|---------------------|-------------------|--|-------------------------------------|
| DAIR | A-Ia | 2-6 weeks intravenous (4-6 weeks if no Rifampin) Rifampin Oral 6 months total (knee) 3 months total (hips, shoulder, ankle) | Indefinite oral suppression (B-III) |
| 1-Stage Exchange | C-II | 2-6 weeks intravenous (4-6 weeks if no Rifampin) Rifampin Oral 3 months total regardless of joint site | Indefinite oral suppression (B-III) |
| 2-Stage Exchange | A-II | 4-6 weeks intravenous or High bioavailability oral | |
| Permanent Resection | A-II | 4-6 weeks intravenous or High bioavailability oral | |
| Amputation | C-III | 24-48 hours after amputation | |

Osmon D et al. *Clin Infect Dis.* 2013; 56:1-25.
Tande AJ et al. *Clin Microbiol Rev.* 2014; 27:302-45.

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Non-Staphylococcus Treatment

| Type of Surgery | Level of Evidence | Initial Treatment Phase | Long Term Suppression Phase |
|---------------------|-------------------|--|-------------------------------------|
| DAIR | B-II | 4-6 weeks intravenous or High bioavailability oral | Indefinite oral suppression (B-III) |
| 1-Stage Exchange | A-II | 4-6 weeks intravenous or High bioavailability oral | Indefinite oral suppression (B-III) |
| 2-Stage Exchange | A-II | 4-6 weeks intravenous or High bioavailability oral | |
| Permanent Resection | A-II | 4-6 weeks intravenous or High bioavailability oral | |
| Amputation | C-III | 24-48 hours after amputation | |

Note the differences for DAIR and 1-Stage Exchange:

- Shorter duration
- Route of administration can be either IV or PO
- No rifampin

Osmon D et al. *Clin Infect Dis.* 2013; 56:1-25.
Tande AJ et al. *Clin Microbiol Rev.* 2014; 27:302-45.

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PJI Intravenous Antimicrobial Selection

| Pathogen | Preferred Agent | Alternative Agent |
|--|--|--|
| MSSA | Nafcillin, cefazolin, ceftriaxone PLUS rifampin (hardware-retained) | Vancomycin, daptomycin, linezolid PLUS rifampin (hardware-retained) |
| MRSA | Vancomycin PLUS rifampin (hardware-retained) | Daptomycin, linezolid PLUS rifampin (hardware-retained) |
| <i>Streptococcus</i> sp (mostly Group B) | Penicillin, ceftriaxone | Vancomycin |
| <i>Enterococcus</i> sp | Penicillin, ampicillin | Vancomycin, daptomycin, linezolid |
| <i>Enterobacteriaceae</i> | IV β-lactam, ciprofloxacin | |
| <i>Enterobacter</i> sp | Cefepime, ertapenem | Ciprofloxacin |
| <i>Pseudomonas aeruginosa</i> | Cefepime, meropenem | Ciprofloxacin, ceftazidime |
| <i>Propionibacterium acnes</i> | Penicillin, ceftriaxone | Clindamycin, vancomycin |

Osmon D et al. *Clin Infect Dis.* 2013; 56:1-25.

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PJI Oral Antimicrobial Selection

| Antimicrobial | Oral Bioavailability | Recommended Adult Dosage |
|-----------------------|----------------------|---|
| Cephalexin (C-III) | 90% | 1-4 g oral daily, divided every 6-8 hours |
| Dicloxacillin (C-III) | 37% | 500 mg oral every 6 hours |
| Minocycline (B/C-III) | 95% | 100 mg oral twice daily |
| Doxycycline (B/C-III) | 90% | 100 mg oral twice daily |
| TMP/SMX (A-II) | 85% | 2 DS tablets oral twice daily |
| Ciprofloxacin (A-I) | 70% | 750 mg oral twice daily |
| Levofloxacin (A-I) | 99% | 750 mg oral daily |

TMP/SMX: Trimethoprim/sulfamethoxazole

Osmon D et al. *Clin Infect Dis.* 2013; 56:1-25.
Sanford Guide Web Edition (accessed on 1/21/18).
Clinical Pharmacology. <https://www.clinicalkey.com/pharmacology> (accessed on 1/21/18).

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Bone Penetration of Antimicrobials

- Challenges
 - Bone is not a homogenous tissue
 - Variation in collection technique
 - Unclear concentration to efficacy relationship
 - Impact of diseased bone

| Antimicrobial | Bone Penetration (%) |
|---------------|----------------------|
| Cefazolin | 11 – 18 |
| Ceftriaxone | 7 – 19 |
| Clindamycin | 21 – 67 |
| Daptomycin | 7 |
| Doxycycline | 2 – 86 |
| Levofloxacin | 38 – 99 |
| Linezolid | 37 – 51 |
| Rifampin | 57 – 100 |
| TMP/SMX | 15/50 |
| Vancomycin | 10 – 27 |

Landersdorfer C et al. *Clin Pharmacokinet.* 2009; 48:89-124.
Spellberg B et al. *Clin Infect Dis.* 2012; 54:393-407.

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Role of Antimicrobial Agents in Bone Cement

- Common agents: vancomycin and aminoglycosides
- Controversial issues
 - Lack of FDA approval regarding antimicrobial use
 - Lack of randomized controlled trials and product standardization
 - Future implications for antimicrobial stewardship programs
 - Safety concerns with aminoglycosides

Athans V et al. *Pharmacotherapy*. 2017; 37:1565-77.
 Iarikov D et al. *Clin Infect Dis*. 2012; 55:1474-80.
 Noto M et al. *Clin Infect Dis*. 2014; 58:1783-4.
 Sterling GJ et al. *J Bone Joint Surg Br*. 2003; 85:646-9.

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Role of Rifampin in PJI and Osteomyelitis

- Staphylococcus* infections (biofilm)
- Cannot be used as monotherapy
- Controversies:

| Appropriate Dosage (Oral) | Use Beyond Foreign-Device Osteomyelitis | Use with other Pathogens | Optimal Combinations | Drug Interactions |
|--|---|---|---|--|
| <ul style="list-style-type: none"> 300-450mg twice daily 600-900mg daily | <ul style="list-style-type: none"> Non-operable osteomyelitis Diabetic foot | <ul style="list-style-type: none"> <i>Streptococcus</i>? | <ul style="list-style-type: none"> RIF + Fluoroquinolone RIF + Vancomycin RIF + other agents | <ul style="list-style-type: none"> Linezolid TMP/SMX Fusidic acid |

Spellberg B, et al. *Clin Infect Dis*. 2012; 54(7):959-607.
 Spellberg B, et al. *Clin Infect Dis*. 2012; 54(3):395-407.
 Forrest G, et al. *Clin Microbiol Rev*. 2010; 23(1):14-34.
 Lora-Tamayo J, et al. *Clin Infect Dis*. 2017; 64(12):1742-52.
 Kim BK, et al. *J Antimicrob Chemother*. 2016; 60:309-322.
 Forrest G, et al. *Clin Microbiol Rev*. 2010; 23(1):14-34.
 Kim BK, et al. *J Antimicrob Chemother*. 2016; 60:309-322.
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 Gandermaier K, et al. *J Clin Pharmacol*. 2011; 51:229-236.
 Pushkin E, et al. *Clin Infect Dis*. 2016; 63(12):1595-604.
 Tomero E, et al. *J Antimicrob Chemother*. 2016; 71:1395-401.

Senneville E et al. *Clin Infect Dis*. 2011; 53:334-40.
 Lora-Tamayo J et al. *Clin Infect Dis*. 2013; 56:182-94.

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Role of Long-Term Suppressive Antimicrobial Therapy

- IDSA guideline panel was not unanimous
- Controversies:

| Antimicrobial selection | Appropriate Dose | Pathogen-specific benefits | Impact on Antimicrobial Resistance | Safety | Appropriate Duration |
|--|--|---|---|--|--|
| <ul style="list-style-type: none"> FQ +/- RIF Doxycycline TMP/SMX | <ul style="list-style-type: none"> Prolonged full treatment dose versus lower doses | <ul style="list-style-type: none"> Worse outcomes when MRSA than other pathogens | <ul style="list-style-type: none"> Low development of resistance | <ul style="list-style-type: none"> <i>C. difficile</i> Other adverse effects | <ul style="list-style-type: none"> Is longer better? Or does it postpone the inevitable? |

Byren I et al. *J Antimicrob Chemother*. 2009; 63:1254-71; Keller SC et al. *Open Forum Infect Dis*. 2016; 3(4):ofw176;
 Pradier M et al. *Infection*. 2018; 46:39-47; Segreti J et al. *Clin Infect Dis*. 1998; 27:711-3;
 Prendki V et al. *Eur J Clin Microbiol Infect Dis*. 2017; 36:1577-85; Wouthuyzen-Bakker M et al. *J Bone Jt Infect*. 2017; 2:77-83;
 Pradier M et al. *Int J Antimicrob Agents*. 2017; 50:447-52; Siqueira MB et al. *J Bone Joint Surg Am*. 2015; 97:1220-32;
 Prendki V et al. *Int J Infect Dis*. 2017; 60:57-60; Nowak M et al. *Am J Health-Syst Pharm*. 2015; 72(suppl 3):S150-5.

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Segment 4

**Skin and Soft Tissue Infections
 Bone and Joint Tissue Infections:
 Vancomycin Therapeutic Drug Monitoring**

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Vancomycin Pharmacodynamics

- Bactericidal
- AUC/MIC ≥ 400
- Cell Wall Synthesis Inhibitor

MIC: Minimum inhibitory concentration

Rybak M et al. *Am J Health-Syst Pharm*. 2009; 66:82-98.
 Rybak M. *Clin Infect Dis*. 2006; 42:535-9.

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Vancomycin Susceptibility Reporting

Staphylococcus aureus
2006 CLSI Susceptibility Breakpoints (MIC)

MIC Value (mg/L)

0.5 1 1.5 - 2

| | |
|--------------|-----------|
| Susceptible | ≤ 2 mg/L |
| Intermediate | 4-8 mg/L |
| Resistant | ≥ 16 mg/L |

Nadarajah R. *Am J Clin Pathol.* 2010; 133:844-8.
 Prakash V et al. *Antimicrob Agents Chemother.* 2008; 52:4528.
 Sader H et al. *Antimicrob Agents Chemother.* 2009; 53:3162-5.
 Rybak M et al. *Am J Health-Syst Pharm.* 2020;77:835-864.

CLSI: Clinical & Laboratory Standards Institute

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Staphylococcus Resistance to Vancomycin

| | VRSA | VISA | hVISA |
|-------------------|---|--|---|
| Definition | Vancomycin Resistant <i>Staphylococcus aureus</i> | Vancomycin Intermediate <i>Staphylococcus aureus</i> | Heteroresistant VISA |
| MIC (mg/L) | ≥ 16 | 4 to 8 | 1 to 2 |
| Mechanism | Transfer of resistant genes from <i>Enterococcus</i> (plasmid transfer) | Overproduction of D-alanine D-alanine (Cell wall thickening) | Subpopulations with intermediate resistance |
| Prevalence | Rare (13 cases reported in 2010 in U.S.) | Uncommon | Common |

Rybak M et al. *Am J Health-Syst Pharm.* 2009; 66:82-98; Maor Y et al. *Clin Infect Dis.* 2009;199:619-24;
 Derenski S. *J Infect Dis.* 2009; 199:605-9; Centers for Disease Control and Prevention.
https://www.cdc.gov/hai/settings/lab/vrsa_lab_search_containment.html [last updated May 13, 2014].

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Question 7: Vancomycin 1500 mg IV every 12 hr + oral rifampin 300 mg twice daily are initiated for Patient GR's hip PJI based on intraoperative cultures that were positive for MRSA. A vancomycin serum trough concentration collected immediately before the fifth dose is 13.7 mg/L. Which of the following goal serum trough levels and actions are appropriate for Patient GR, who is 137-kg and 72-in tall with a SCr of 0.7 mg/dL?

A. Goal 10-20 mg/L, with no modifications to current regimen
 B. Goal 15-20 mg/L, with increase the dose to 1750 mg IV every 12 hr
 C. Goal AUC 400-600 mg*h/L, with perhaps no modifications to current regimen
 D. Goal 20-25 mg/L, with increase the dose to 1250 mg IV every 8 hr

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2009 Guideline Consensus Vancomycin Dosing Recommendations

- Loading Dose: 25-30 mg/kg IV x1 dose, seriously ill patients (B-III)
- Maintenance Dose: 15-20 mg/kg IV every 8-12 hr (A-III)
 - Actual body weight should be used (II-A)
 - Consider maximum daily dose of 4.5 g
- Intermittent dosing is preferred over continuous infusion (A-II)
- If MIC ≥ 2 mg/L, alternative therapies should be considered (B-III)

Rybak M et al. *Am J Health-Syst Pharm.* 2009; 66:82-98.
 Meng L et al. *Pharmacotherapy* 2017; 37:1415-31.

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2009 Guideline Consensus Vancomycin Monitoring Recommendations

- Trough serum concentrations: "most predictable and accurate surrogate markers of AUC" (II-B)
 - ≥ 10 mg/L, all infection types to prevent emergence of resistance (B-III)
 - 15 to 20 mg/L: complicated infections (osteomyelitis) (B-III)
- Peak levels do **not** need to be measured
- Adverse Effects:
 - Related to vancomycin exposure: nephrotoxicity
 - Related to infusion: red-man syndrome, extend infusion time 1 g/hr (B-III)

Rybak M et al. *Am J Health-Syst Pharm.* 2009; 66:82-98.
 Rybak M et al. *Am J Health-Syst Pharm.* 2020;77:835-864.
 Aljefri DM et al. *Clin Infect Dis.* 2019;69(11):1881-7.

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Vancomycin Knowledge Gaps

- Dosing and Monitoring
 - Pediatrics
 - Obesity
 - Renal dysfunction including renal replacement therapies
- Utility of prolonged or continuous infusion
- Safety
 - Impact of higher serum concentrations (15 to 20 mg/L) and higher doses (> 3 grams/day)

Rybak M et al. *Am J Health-Syst Pharm.* 2020;77:835-864.

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2020 Vancomycin Guideline Consensus

- Serious MRSA infections (bacteremia)
 - Loading Dose 20-35 mg/kg not to exceed 3 grams (B-II)
 - AUC Goal 400-600 mg*h/L within the first 24-28 hours (A-II)
 - Multiple methodologies to calculate an AUC (software versus calculators)
 - Trough only monitoring is no longer recommended (A-II)
 - Data lacking in meningitis, osteomyelitis, endocarditis, pneumonia
- Mild infections (UTI, SSTI): No change to dosing or monitoring
- Efficacy data lacking for AUC < 400 mg*h/L

Rybak M et al. Am J Health-Syst Pharm. 2020;77:835-864.

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2020 Vancomycin Guideline Consensus

- Additional Discussions
 - Disease state recommendation gaps
 - Obesity
 - Continuous infusion
 - Intermittent hemodialysis
 - Continuous renal replacement therapies
 - Pediatrics
 - Insufficient data to support loading doses
 - Dosing recommendations for neonates, children, and adolescents
 - Obesity considerations

Rybak M et al. Am J Health-Syst Pharm. 2020;77:835-864.

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Segment 5

Skin and Soft Tissue Infections Bone and Joint Tissue Infections: Outpatient Parenteral Therapy

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Question 8: Patient GR does not qualify for acute rehab and is being discharged home. He states, "I cannot give myself this medication."

What alternative to vancomycin can you recommend for OPAT?

- Weight-based daptomycin 6 mg/kg IV once daily
- Fixed dose telavancin 750 mg IV once daily
- Ceftaroline 1200 mg IV once daily
- Tigecycline 100 mg IV once daily

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Daptomycin

| Skin | Bone/Joint | Infusion Time | |
|---|--|--------------------------------|---|
| Adults: 4 mg/kg IV every 24 hr *Actual Body Weight (BW) | Adults: 6-10 mg/kg IV every 24 hr • Actual BW | 30 min 2-min IV push | Bone & Joint Dosing <ul style="list-style-type: none"> • PJI Study 6 mg/kg vs. 8 mg/kg: no significant difference • Emergence of resistance during therapy • Higher doses of 8-10 mg/kg +/- rifampin • No therapeutic drug monitoring Adverse Events <ul style="list-style-type: none"> • Generally well tolerated • Rare muscle toxicity or rhabdomyolysis: reversible elevation in creatinine kinase Cost <ul style="list-style-type: none"> • Generic formulation available • Don't confuse IV formulation products (Cubicin vs Cubicin RF) |
| Pediatrics: weight-based dosing | Pediatrics: See Table 5 PIDS/IDSA AHO Guidelines | | |

Byren I et al. Antimicrob Agents Chemother. 2012; 56:5626-32; Lora-Tamayo J et al. Diagn Microbiol Infect Dis. 2014; 80:66-71; Kullar R et al. Pharmacotherapy. 2011; 31:527-36; Cubicin RF (daptomycin) prescribing information. Whitehouse Station, NJ: Merck & Co.; 2017 Mar.



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Ceftaroline

| Skin | Bone/Joint | Infusion Time | |
|--|---|--------------------|---|
| <p>Adults: 600 mg IV every 12 hours</p> <p>Pediatrics: weight-based dosing</p> | <p>Adults 600 mg IV every 8 to 12 hours</p> <p>Pediatrics: See Table 5 PIDS/IDSA AHO Guidelines</p> | <p>5 to 30 min</p> | <p>Bone & Joint Studies</p> <ul style="list-style-type: none"> • Every 8 hours vs. every 12 hours dosing: not well established <p>Adverse Events</p> <ul style="list-style-type: none"> • Hematologic (anemia, leukopenia/neutropenia), 4-25% • Rash, 10-16% • GI-related (nausea) <2% <p>Cost</p> <ul style="list-style-type: none"> • Generic not available <p>Stability</p> <ul style="list-style-type: none"> • 6 hours at room temp, therefore 24-hr continuous infusion not feasible |

[Athanas V et al. J Antimicrob Chemother. 2016; 71:3568-74;](#)
[Jain R et al. Pharmacotherapy. 2014; 34:758-63;](#)
[Turner RB et al. J Antimicrob Chemother. 2018; 73:772-8;](#)
[Corey G et al. Clin Infect Dis. 2010; 51:641-50;](#)
[Castaño A et al. Antimicrob Agents Chemother. 2016; 58:2541-546;](#)
[Johnny et al. ID Week 2016 Poster 26](#)

|   | | | |
|--|---|----------------|--|
| Skin | Bone/Joint | Infection Time | |
| Adults: 10 mg/kg IV once daily | Adults: 10 mg/kg IV once daily Bone penetration data lacking in humans Small case series with clinical success | 1 hour | Dosing Updates <ul style="list-style-type: none"> • Weight-based versus 750 mg fixed dose • No therapeutic drug monitoring Adverse Events <ul style="list-style-type: none"> • NIOSH drug (adverse reproductive effects) • Nephrotoxicity • Infusion-related reactions: rigors, chills, red-man syndrome • QT-prolongation • Interference with anticoagulant monitoring: aPTT and INR Cost <ul style="list-style-type: none"> • Generic not available |



Linezolid

| Skin | Bone/Joint | Infusion Time | |
|---|--|-------------------|---|
| <p>Adults: 600 mg IV/PO every 12 hours</p> <p>Pediatrics: Weight-based dosing</p> | <p>Adults: 600 mg IV/PO every 12 hours</p> <p>Pediatrics: See Table 5 PIDS/IDSA AHO Guidelines</p> | <p>30-120 min</p> | <p>Advantages</p> <ul style="list-style-type: none"> Excellent oral bioavailability, 99% Excellent tissue and bone penetration <p>Adverse Events & Drug Interactions</p> <ul style="list-style-type: none"> Bone marrow suppression (>3-4 weeks of therapy) Neuropathies (peripheral, optical) Risk of serotonin syndrome with serotonergic agents GI intolerance Rare lactic acidosis and hepatotoxicity <p>Cost</p> <ul style="list-style-type: none"> Generic products are available |

Stevens D et al. *Clin Infect Dis*. 2014; 59:e10-52.

Osmon D et al. *Clin Infect Dis*. 2013; 56:1-25.

Morata L et al. *Infect Dis Ther*. 2014; 3:235-43.

Woytowich M, et al. *Ann Pharmacother*. 2013; 47:388-97.





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Segment 6

Skin and Soft Tissue Infections: Clinical Trial Design and New Agents for Acute Bacterial Skin and Skin Structure Infections


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The logo for the American College of Clinical Pharmacy (ACCP) and the American Society of Hospital Pharmacists (ASHP) is located in the bottom right corner. It features the text "accp" in a large, bold, blue font, with "American College of Clinical Pharmacy" in smaller text below it. To the right of this is the "ashp" logo in a stylized blue font, with "Certification Resources" in a smaller blue font below it.



ABSSI Clinical Trial Design Update

- 2010 – 2012 FDA guidance draft & expert opinion recommendations
 - Addition of reduction of $\geq 20\%$ lesion size to primary endpoint
 - Removal of fever requirement
 - End of therapy (EOT) should remain as a secondary endpoint
 - Management of early non-responders
 - Timing and limitation of antipyretic and analgesic drugs
- 2014: three new antimicrobials FDA approved




Tedizolid

| Skin | Bone/Joint | Infusion Time | |
|--|----------------------|---------------|---|
| 200 mg IV/PO once daily ESTABLISH-1 ESTABLISH-2 Trials | Dose not established | 1 hr | Advantages <ul style="list-style-type: none"> Excellent oral bioavailability, 91% Excellent tissue and bone penetration Once-daily dosing Shorter duration of therapy (6 days) vs. linezolid (10 days) Fewer adverse effects and serotonergic interactions compared with linezolid Adverse Events & Drug Interactions <ul style="list-style-type: none"> Similar to linezolid Stability (intravenous) <ul style="list-style-type: none"> Not more than 24 hours, even if refrigerated |

Prokocimer P et al. *JAMA*. 2013; 309:559-69.
 Moran G et al. *Lancet Infect Dis*. 2014; 14:696-705.
 Burdette S et al. *Clin Infect Dis*. 2015; 61:1315-21.

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Newer Lipoglycopeptides

| Agent | Skin | Bone/ Joint | Infusion Time | |
|-------------|---|----------------------|---------------|--|
| Oritavancin | Adults: 1200 mg IV x1 dose | Dose not established | 3 hours | Bone & Joint <ul style="list-style-type: none"> Osteomyelitis package insert warning Adverse Effects & Potential Drug Interactions <ul style="list-style-type: none"> GI (10%), headache (7%), AST/ALT elevations (2%) Injection site reactions (2%); limb/subcutaneous abscess Interference with anticoagulant monitoring: aPTT and INR Weak CYP3A4/2D6 inducer, Weak 2C9/2C19 inhibitor |
| Dalbavancin | Adults: 1500 mg IV x1 dose or 1000 mg IV x1 dose, then 500 mg IV on Day 8 | Dose not established | 30 min | Bone & Joint <ul style="list-style-type: none"> Enhanced biofilm activity with rifampin and no drug interactions Adverse Effects <ul style="list-style-type: none"> Mostly GI + headache (5%), rash (2%) Other <ul style="list-style-type: none"> Renal dosage adjustment when CrCl <30 mL/min New 2021: Pediatric ABSSSI FDA approval |

Roberts K et al. *Pharmacotherapy*. 2015; 35:935-48; Delaportas D et al. *Pharmacotherapy*. 2017; 37:e90-2;
 Schulz L et al. *Pharmacotherapy*. 2018; 38:152-9; Corey G et al. *N Engl J Med*. 2014; 370:2180-90;
 Dunne M et al. *Clin Infect Dis*. 2016; 62:545-51; Bouza E et al. *Int J Antimicrob Agents*. 2018; 51:571-7.

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Delafloxacin

| | |
|-------------------------------------|--|
| FDA Approved Indication (June 2017) | <ul style="list-style-type: none"> ABSSSI: versus vancomycin/aztreonam, duration of therapy 5-14 days <ul style="list-style-type: none"> Optional IV to PO switch at Day 4 Ongoing studies for community-acquired pneumonia and UTI |
| Antimicrobial Spectrum ¹ | <ul style="list-style-type: none"> <i>Staphylococcus</i> including MRSA, <i>Streptococcus</i> sp, <i>Enterococcus faecalis</i> Enteric gram-negative rods including <i>Pseudomonas</i> |
| ABSSSI Dosing | <ul style="list-style-type: none"> IV 300 mg every 12 hr over 60 minutes, renal dosage adjustment eGFR² <30 mL/min PO 450 mg every 12 hr, no renal dosage adjustment, oral bioavailability 58% |
| Adverse Effects | <ul style="list-style-type: none"> Warnings (class effects): tendonitis and tendon rupture, peripheral neuropathy, central nervous system effects, exacerbation of myasthenia gravis, <i>Clostridium difficile</i> infections, hypersensitivity GI-related: nausea/diarrhea (8%) Lack of QT prolongation and photosensitivity |
| Drug Interactions | <ul style="list-style-type: none"> Chelation with cations: antacids, vitamins, enteral feedings, nutritional supplements |

¹ Only spectrum of activity for ABSSSI is listed. Pullman J et al. *J Antimicrob Chemother*. 2017; 72:3471-80.
² eGFR: estimated glomerular filtration rate as calculated by the MDRD equation. O'Riordan W et al. *Clin Infect Dis*. 2018; 67:657-66.

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Omadacycline


| | |
|--|--|
| FDA Approved Indication (October 2018) | <ul style="list-style-type: none"> ABSSSI: versus linezolid, duration of therapy 7-14 days |
| Antimicrobial Spectrum ¹ | <ul style="list-style-type: none"> <i>Staphylococcus</i> including MRSA, <i>Streptococcus</i> sp, <i>Enterococcus faecalis</i> Enteric gram-negative rods including <i>Enterobacter</i> and <i>Klebsiella</i> |
| ABSSSI Dosing | <ul style="list-style-type: none"> IV 200 mg on Day 1, then 100 mg once daily (optional 100 mg IV every 12h on Day 1) PO 450 mg on Day 1 and 2 once daily, then 300 mg once daily |
| Adverse Effects | <ul style="list-style-type: none"> Warnings (class effects): tooth discoloration and inhibition of bone growth in pregnancy, infancy, and childhood <8 years of age, <i>Clostridium difficile</i> infections, hypersensitivity GI-related: nausea (21.9%) and vomiting (11.4%) Infusion site reactions, liver function test elevations, headache, insomnia |
| Drug Interactions | <ul style="list-style-type: none"> Chelation with food, dairy and other cations: antacids, vitamins, enteral feedings, nutritional supplements Anticoagulation doses may require a downward adjustment |

¹ Only spectrum of activity for ABSSSI is listed. Nuzyna (omadacycline) [package insert]. Boston, MA: Paratek Pharmaceuticals; 2018.

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Segment 7

Skin and Soft Tissue Infections Bone and Joint Tissue Infections: Diabetic Foot Infections

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Diabetic Foot Infections (DFI)

- Non-healing ulcer
- Disease state complications
 - Glycemic control impacts immunity
 - Neuropathy
 - Vascular disease
- 30 million diabetics
 - Hospitalizations and amputations

Stevens D et al. *Clin Infect Dis*. 2014; 59:e10-52.
Lipsky B et al. *Clin Infect Dis* 2012; 54:e132-73.
Centers for Disease Control and Prevention. 2017 National Diabetes Statistics Report.

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Patient Case

Patient JJ, a 46 year-old, 87-kg male patient with diabetes mellitus (A1C 14.6%) presents to the clinic for follow-up regarding a left foot ulcer not improving with wound care interventions over the past 2 months. Symptoms noted on physical exam include 4 cm of surrounding erythema, warmth, and purulence.

Tmax 98.6°F, WBC 7.5 x10³ cells/mm³, RR 18/min, HR 83 bpm

Allergies: sulfa (rash)

PMH: diabetes mellitus, peripheral vascular disease, hypertension, 1.5 PPD smoker, depression

Surgical history: Right foot transmetatarsal amputation (1 year ago)

Antimicrobial History:

- Cephalexin 500 mg orally every 6 hours x 7 days completed 4 weeks ago
- Amoxicillin/clavulanic acid 875 mg orally twice daily x 7 days completed 3 days ago

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Question 9: What is the severity of infection and an appropriate antimicrobial recommendation for this patient?

A. Mild; outpatient treatment with clindamycin orally x 10 days

B. Moderate; outpatient treatment with levofloxacin orally x 10 days

C. Moderate; hospital admission for vancomycin, ceftriaxone, and metronidazole IV

D. Severe; hospital admission for tigecycline IV

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Severity, Etiology, and Treatment of DFI

| IDSA Severity | Criteria | Likely Pathogens | Recommended Route of Therapy |
|---------------|---|---|------------------------------|
| Uninfected | No symptoms or signs of infection | None | No treatment |
| Mild | Local infection involving skin and subcutaneous tissue • ≤ 2 cm surrounding erythema | <i>Staphylococcus aureus</i> β-hemolytic streptococci | Oral |
| Moderate | Local infection involving deeper tissues (abscess, osteomyelitis, fasciitis) • > 2 cm surrounding erythema • < 2 systemic signs (below) | <i>Staphylococcus aureus</i> β-hemolytic streptococci Aerobic gram negative bacilli Anaerobes | Intravenous or Oral |
| Severe | Local infection involving deeper tissues (same as above) • ≥ 2 signs of systemic inflammatory response syndrome (SIRS); Temperature >38°C or <36°C, HR >90 bpm, RR >20/min or PaCO ₂ <32 mm Hg, WBC >12 x10 ³ cells/mm ³ or <4 x10 ³ cells/mm ³ | <i>Staphylococcus aureus</i> β-hemolytic streptococci Aerobic gram negative bacilli including <i>Pseudomonas</i> Anaerobes | Intravenous |

Lipsky B et al. *Clin Infect Dis*. 2012; 54:e132-73.

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DFI Antimicrobial Treatment

| Severity | Pathogen | Preferred Antimicrobial Agents |
|---------------------------------|--|--|
| Mild ¹ | MSSA and β-hemolytic Streptococci | Dicloxacillin, cephalexin, clindamycin, amoxicillin/clavulanic acid |
| | MRSA ¹ | Clindamycin, doxycycline, minocycline, TMP/SMX, linezolid |
| Moderate to Severe ² | MSSA β-hemolytic Streptococci Aerobic gram negative bacilli Anaerobes | Ampicillin/sulbactam, ceftriaxone, cefoxitin, cefotetan, ertapenem, levofloxacin, moxifloxacin |
| | Additional MRSA coverage ³ | Vancomycin, daptomycin, linezolid, ceftaroline, TMP/SMX, doxycycline, minocycline, tigecycline |
| | Additional <i>Pseudomonas</i> coverage | Piperacillin/tazobactam, meropenem, imipenem/cilastatin Ciprofloxacin, cefepime, ceftazidime, or aztreonam +/- metronidazole or clindamycin |

¹Antimicrobial spectrum can be narrowed based on infecting pathogen. Example: amoxicillin or penicillin VK can be used if *Streptococcus* only

²Antimicrobial spectrum can be narrowed based on infecting pathogen. Example: cefazolin, nafcillin, or oxacillin can be used if MSSA only

³Clinical trial data are lacking for newer anti-MRSA agents: tedizolid, delamanid, telavancin, oritavancin, dalbavancin

Lipsky B et al. *Clin Infect Dis*. 2012; 54:e132-73.
Lipsky BA et al. *Diabetes Metab Res Rev*. 2015; 31:395-401.

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The Pharmacist's Role

- Antimicrobial Stewardship
 - Encourage quality microbiology sampling (swab versus tissue/bone) and interpret results
 - Route and duration of therapy: SSTI (1-3 weeks) versus osteomyelitis (4-6 weeks)
 - Narrowing spectrum: empiric versus pathogen-directed therapy
- Interprofessional involvement
 - Wound Care, Podiatry, Internal Medicine/Endocrinology, Vascular, Plastics, Orthopedics, Infectious Disease
- Prevention
 - Diabetes education and management
 - Daily foot inspection and hygiene, trim toenails, lotion to prevent callouses/cracking, annual foot exams, protective footwear
 - Appropriate antimicrobial surgical prophylaxis before, during, and immediately after surgery

Lipsky B et al. *Clin Infect Dis*. 2012; 54:e132-73.

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Segment 8

Skin and Soft Tissue Infections Bone and Joint Tissue Infections: Vertebral Osteomyelitis

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Native Vertebral Osteomyelitis

- Infection of the vertebra that extends to the vertebral disc space
- IDSA Guideline limitation: native vertebral infection only (NVO)
- Characteristics of infection
 - Mostly hematogenous and monomicrobial
 - *Staphylococcus aureus* is the most common pathogen
 - Incidence is increasing among intravenous drug users
- New or worsening back or neck pain, PLUS one of the following:
 - Fever
 - Increased ESR or CRP
 - Concurrent or recent (<3 months) bloodstream infection or endocarditis, particularly with *Staphylococcus aureus*

Berbari E et al. Clin Infect Dis. 2015; 61:26-46.

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Native Vertebral Osteomyelitis (cont.)

- MRI is the image of choice, and can be useful for identifying abscess
- Blood culture should be obtained
 - Biopsy may not be necessary if concurrent or recent (< 3 months) *Staphylococcus aureus*, *Staphylococcus lugdunensis*, or *Brucella* bloodstream infection
- Definitive therapy should be based on culture and susceptibility
- Treatment (most bacteria): 6 weeks IV or oral agent with high bioavailability

Berbari E et al. Clin Infect Dis. 2015; 61:26-46.

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NVO Treatment Considerations

| | |
|---|--|
| Concurrent <i>Staphylococcus aureus</i> bacteremia | • Oral treatment is currently not recommended |
| Concurrent endocarditis | • Oral treatment is currently not recommended |
| Instrumentation | <ul style="list-style-type: none"> • Use of adjunctive rifampin for <i>Staphylococcus aureus</i> hardware-associated VO is described in the literature. • Duration of therapy for hardware-associated infections |
| Concurrent epidural abscess | <ul style="list-style-type: none"> • Oral treatment is currently not recommended • In addition to treatment of VO, only antimicrobials that also have adequate central nervous system penetration should be used |
| MRSA infection | • Future studies are needed to clarify treatment duration and optimize therapy |

Park KH et al. Clin Infect Dis. 2016; 62:1262-9.
Park KH et al. Clin Infect Dis. 2015; 60:1330-8.
Derouiche R. N Engl J Med. 2006; 355:2012-20.

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Additional Topics (See Table 27 in workbook)

- Skin, bone, and joint complications in intravenous drug users
- Penicillin allergy
- Septic arthritis
- Oral versus intravenous therapy for bone & joint infections
- Management of sacral decubitus ulcers
- Studies evaluating shorter durations of therapy for skin infections or osteomyelitis (including prosthetic joint infection)
- Tickborne diseases

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Conclusions

- Various factors are taken into consideration in devising a strategy to prevent or treat SSIs, ABSSSIs, PJIs, and DFIs
- Pharmacists play an important role in devising these strategies

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Segment 9

Skin and Soft Tissue Infections and Bone and Joint Infections: Musculoskeletal Infections in Pediatric Patients

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Case Introduction: LL

- LL is a 6-year-old male with no significant PMH who presents to the emergency department with right arm pain extending between his right shoulder and elbow
- He fell off his scooter a couple of days ago and hit his head and right side of his body on the concrete
- He came in with right knee pain, fever, and vomiting the day of the fall and was diagnosed with gastroenteritis and sent home
- Use of ibuprofen alternating with acetaminophen at home with no relief in pain
- T_{max} 39°C, WBC 23 x 10³/mm³, all other labs pending

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Pediatric Musculoskeletal Infections

- Mostly bacterial infections invading bone and/or joint
 - Acute bacterial osteomyelitis or septic arthritis
 - **New in 2021:** PIDS/IDSA Acute Hematogenous Osteomyelitis (AHO) Guidelines
 - **In progress:** PIDS/IDSA Management of Bacterial Arthritis in Children
 - Within 4 weeks of onset (usually within 1 week)
 - Rare: chronic osteomyelitis in the USA
- Mostly hematogenous spread to a damaged anatomical site
 - Bacteremia may be transient or persistent
- Peak age: 2-6 years
 - Age range: 1 month -> 18 years of age; guidance excludes neonates

Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844

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Clinical presentation

- History of recent injury in ~20%
- Acute osteomyelitis: most cases = a single (95%), long bone (75%)
- Signs & Symptoms
 - **Fever** or other abnormal vital signs (if sepsis)
 - **Pain**, redness, swelling
 - Musculoskeletal function: refusal to bear weight
 - Skin trauma
- If sepsis, caution rapidly progressing infection

Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844

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Imaging

- Step 1: Conventional radiographs in all cases (*strong/mod*)
- Step 2: Ultrasound (joint) or MRI (osteomyelitis) (*conditional/low*)
- Alternative Imaging
 - Bone scan if multifocal disease is suspected
 - End of treatment re-imaging: not necessary unless physis involvement (growth plates) or complicated (defined later in duration of therapy)

Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844

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Laboratory Testing

- Microbiology
 - Blood culture, prior to antimicrobials if possible (*strong/mod*)
 - 30-50% positivity rate; highest with *S. aureus*
 - Joint aspirate or bone biopsy (*conditional/mod*)
 - OK to hold antimicrobials 48-72h if clinically stable
 - PCR or other molecular testing should not replace culture processing
- CRP: at presentation and sequentially (*conditional/low*)
- Complete blood count with differential
- Not recommended: procalcitonin (*conditional/low*)

Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844

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Surgical Management

- Septic arthritis
 - Joint drainage and irrigation, needle aspiration
 - Surgical drainage (arthroscopy or arthrotomy)
- Osteomyelitis
 - Irrigation and debridement, especially if acute, sepsis, presence of abscess (*strong/mod*)
 - IDSA/PIDS discourages use of local surgical antimicrobials (cement, irrigation, other implants) (*strong/low*)


Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844.

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Infants < 3 month
Staphylococcus aureus
Escherichia coli and other Gram-negative bacteria
Group B *Streptococcus*
Neisseria gonorrhoeae (newborns)



3 month to 5 years
Staphylococcus aureus
Kingella kingae
Group A *Streptococcus*
Streptococcus pneumoniae
Haemophilus Influenzae type b
Salmonella



≥ 5 years
Staphylococcus aureus
Group A *Streptococcus*
Neisseria gonorrhoeae (Sexually active adolescents)

Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844
Saavedra-Lozano J et al. Pediatr Infect Dis J. 2017; 36:788-99.

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Review of Systems: LL

- General appearance
 - Well appearing with no obvious signs of illness
- Musculoskeletal
 - Right Upper Extremity: Tender at the site of concern with limited range of motion (ROM). R elbow held in 30 degrees of flexion at rest, active ROM from 30° to 80°, tender over proximal humerus, edema medially proximal to the elbow joint
 - Right Lower Extremity: Tender at the site of concern with limited ROM. Refuses to move right lower extremity on exam.

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Question 10: Which of the following organisms is most likely to be identified as the etiology of LL's osteomyelitis and septic arthritis?

- Streptococcus pyogenes*
- Staphylococcus aureus* (methicillin susceptible [MSSA] or resistant [MRSA])
- Escherichia coli*
- Streptococcus pneumoniae*

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Pharmacologic Management

- Empiric therapy directed against *S. aureus* (*strong/mod*)
 - Include MRSA coverage when CA-MRSA prevalence ≥ 10%–15%
- Additional coverage if:
 - K. kingae*: age < 4 years (septic arthritis is more common than OM¹)
 - Salmonella* spp.: sickle cell patients
 - S. pneumoniae* and *H. influenzae*: unvaccinated
 - Enteric gram-negative coverage: neonates and young infants

¹OM: osteomyelitis
Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844
Saavedra-Lozano J et al. Pediatr Infect Dis J. 2017; 36:788-99

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Empiric Therapy Acute Osteomyelitis (≥ 3 months)

| | |
|----------|--|
| Stable | <ul style="list-style-type: none"> If ≤ 10% CA-MRSA locally: nafcillin, oxacillin or cefazolin If > 10% CA-MRSA & clindamycin resistance ≤ 10-20% locally: Clindamycin* If > 10% CA-MRSA & clindamycin resistance > 10-20% locally: Vancomycin* |
| Unstable | <ul style="list-style-type: none"> If ≤ 10% CA-MRSA locally: Nafcillin, oxacillin or cefazolin If > 10% CA-MRSA locally: Vancomycin* |

* If *K. kingae* concern, add cefazolin, ceftriaxone, ampicillin, or BL/BL-Inhibitor combination
 • Note: daptomycin, ceftaroline, or linezolid may be considered
 • Table 5 (PIDS/IDSA AHP guidelines) provide dosing recommendations

Woods CR et al. J Pediatric Infect Dis. 2021 Sep 23;10(8):801-844

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IV to PO?

- Oral preferred versus parenteral therapy when possible (*strong/low*)
- No longer bacteremic
- Tolerating a normal diet or other oral medications
- Clinical improvement (afebrile ≥ 48 hours, pain resolving)
- CRP trend
- Preferred PO options: cephalexin, dicloxacillin, clindamycin
 - Alternatives: linezolid, TMP/SMX, doxycycline (age > 8 years)

Woods CR et al. *J Pediatric Infect Dis.* 2021 Sep 23;10(8):801-844

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Length of Therapy

- Septic arthritis
 - 2-3 weeks: IV 2-4 days then PO switch
- Acute Osteomyelitis
 - 3-4 weeks: uncomplicated, IV then PO switch (*conditional/low*)
 - Longer durations for may be needed for complicated or non-*S. aureus* pathogens
 - ≥ 2 bones involved, slow or lack of response, need for multiple surgeries, prolonged bacteremia, endocarditis or other endovascular infection, initial concern for physeal injury or pathologic fracture

Woods CR et al. *J Pediatric Infect Dis.* 2021 Sep 23;10(8):801-844
Saavedra-Lozano J et al. *Pediatr Infect Dis J.* 2017; 36:788-99.

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Pediatric Conclusions

- Bacterial etiology of pediatric musculoskeletal infections varies depending on age of patient and geographic distribution
- Early diagnosis and surgical intervention are necessary
- Laboratory evaluation places a strong emphasis on pathogen identification to direct antimicrobial selection
- Empiric antibiotic therapy should provide coverage against *S. aureus*, and definitive therapy should provide the narrowest spectrum
- Switching to a PO antibiotic is recommended when feasible

Woods CR et al. *J Pediatric Infect Dis.* 2021 Sep 23;10(8):801-844

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Skin and Soft Tissue Infections and Bone and Joint Infections

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