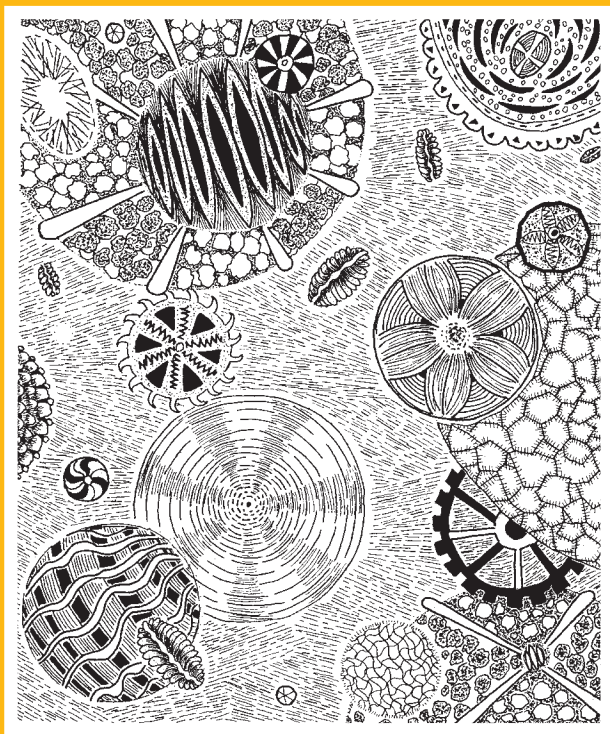


Antibiotic Guidelines 2015-2016



Treatment Recommendations For Adult Inpatients

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Introduction

Antibiotic resistance is now a major issue confronting healthcare providers and their patients. Changing antibiotic resistance patterns, rising antibiotic costs and the introduction of new antibiotics have made selecting optimal antibiotic regimens more difficult now than ever before. Furthermore, history has taught us that if we do not use antibiotics carefully, they will lose their efficacy. As a response to these challenges, the Johns Hopkins Antimicrobial Stewardship Program was created in July 2001. Headed by an Infectious Disease physician (Sara Cosgrove, M.D., M.S.) and an Infectious Disease pharmacist (Edina Avdic, Pharm.D., M.B.A), the mission of the program is to ensure that every patient at Hopkins on antibiotics gets optimal therapy. These guidelines are a step in that direction. The guidelines were initially developed by Arjun Srinivasan, M.D., and Alpa Patel, Pharm.D., in 2002 and have been revised and expanded annually.

These guidelines are based on current literature reviews, including national guidelines and consensus statements, current microbiologic data from the Hopkins lab, and Hopkins' faculty expert opinion. Faculty from various departments have reviewed and approved these guidelines. As you will see, in addition to antibiotic recommendations, the guidelines also contain information about diagnosis and other useful management tips.

As the name implies, these are only **guidelines**, and we anticipate that occasionally, departures from them will be necessary. When these cases arise, we will be interested in knowing why the departure is necessary. We want to learn about new approaches and new data as they become available so that we may update the guidelines as needed. You should also document the reasons for the departure in the patient's chart.

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How to use this guide

- Each section begins by giving recommendations for the choice and dose of antibiotics for the particular infection.
- **ALL DOSES IN THE TEXT ARE FOR ADULTS WITH NORMAL RENAL AND HEPATIC FUNCTION.**
 - If your patient does NOT have normal renal or hepatic function, please refer to the sections on antibiotic dosing to determine the correct dose.
- Following the antibiotic recommendations, we have tried to include some important treatment notes that explain a bit about WHY the particular antibiotics were chosen and that provide some important tips on diagnosis and management. PLEASE glance at these notes

when you are treating infections, as we think the information will prove helpful. All references are on file in the office of the Antimicrobial Stewardship Program (7-4570).

Contacting us

- Antibiotic approval: Use PING; search “antibiotic,” then select “Antibiotic Approval Pager”
 - Please do not send numeric pages
 - Please complete the form as accurately as possible.
 - ALL orders for restricted antibiotics MUST be approved unless they are part of an approved order.
 - Please see page 6 for more information about obtaining approval.
- Antimicrobial Stewardship Program: 7-4570
- Infectious Diseases Consults: 3-8026
- Critical Care and Surgery Pharmacy (Zayed 3121): 5-6505
- Adult Inpatient Pharmacy (Zayed 7000): 5-6150
- Weinberg pharmacy: 5-8998
- Bayview Inpatient Pharmacy: 0-0958
- Microbiology lab: 5-6510

A word from our lawyers

The recommendations given in this guide are meant to serve as treatment guidelines. They should NOT supplant clinical judgment or Infectious Diseases consultation when indicated. The recommendations were developed for use at The Johns Hopkins Hospital and thus may not be appropriate for other settings. We have attempted to verify that all information is correct but because of ongoing research, things may change. If there is any doubt, please verify the information in the guide by calling the antibiotics pager using PING (search “antibiotic”) or Infectious Diseases.

Also, please note that these guidelines contain cost information that is confidential. Copies of the book should not be distributed outside of the institution without permission.

Obtaining ID approval

The use of restricted and non-formulary antimicrobials requires pre-approval from Infectious Diseases. This approval can be obtained by any of the following methods.

Approval method	Notes
PING: "antibiotic"	The pager is answered between 8 a.m. and 10 p.m. PING the ID consult pager if you fail to get a response from the ID approval pager within 10 minutes.
Overnight Approval	Restricted antibiotics ordered between 10 p.m. and 8 a.m. must be approved by noon the following morning. <ul style="list-style-type: none"> • Please remember to sign out the need for approval if you go off shift before 8 a.m.
Ordersets (e.g. neutropenic fever, etc.)	These forms are P&T-approved for specific agents and specific indications.

Selected formulary antimicrobials and restriction status

The following list applies to ALL adult floors and includes the status of both oral and injectable dosage forms, unless otherwise noted.

Unrestricted	Restricted (requires ID approval)
Amoxicillin	Amikacin
Amoxicillin/clavulanate	Aztreonam
Ampicillin/sulbactam (Unasyn [®])	Cefepime
Ampicillin IV	Ceftaroline ¹
Azithromycin	Ceftazidime
Cefazolin	Ceftolozane/tazobactam ¹
Cefdinir	Ciprofloxacin
Cefotetan	Colistin IV
Cefpodoxime	Cytomegalovirus Immune Globulin (Cytogam [®]) ²
Ceftriaxone	Daptomycin ¹
Cefuroxime IV	Fosfomycin ³
Cephalexin	Linezolid
Clarithromycin	Meropenem
Clindamycin	Moxifloxacin
Dicloxacillin	Nitazoxanide ⁴
Doxycycline	Palivizumab (Synagis [®]) ⁵
Ertapenem	Piperacillin/tazobactam (Zosyn [®])
Erythromycin	Quinupristin/dalfopristin (Synercid [®])
Gentamicin	Ribavirin inhaled ⁵
Metronidazole	Telavancin ¹
Minocycline	Tigecycline
Nitrofurantoin	Vancomycin
Oxacillin	
Penicillin V/G	
Ribavirin oral	
Rifampin	
Streptomycin	
Tobramycin	
Trimethoprim/sulfamethoxazole	
Amphotericin B deoxycholate (Fungizone [®])	Liposomal amphotericin B (AmBisome [®])
Flucytosine	Micafungin
Itraconazole oral solution	Fluconazole ⁶
	Posaconazole
	Voriconazole

¹Approval must be obtained from Antimicrobial Stewardship Program 24h/7 days a week

²Approval required, except for solid organ transplant patients

³Approval must be obtained 24h/7 days a week

⁴Approval must be obtained from Polk Service or ID Consult

⁵Approval must be obtained from ID attending physician 24h/7 days a week

⁶Oral Fluconazole, when used as a single-dose treatment for vulvovaginal candidiasis or when used in compliance with the SICU/WICU protocol, does not require ID approval

Restricted antimicrobials that are ordered as part of a P&T-approved critical pathway or order set do NOT require ID approval.

REMINDER: the use of non-formulary antimicrobials is strongly discouraged. ID approval MUST be obtained for ALL non-formulary antimicrobials.

NOTE: Formulary antivirals (e.g. Acyclovir, Ganciclovir) do NOT require ID approval.

Antibiotics

Ceftaroline

Ceftaroline is a cephalosporin with *in vitro* activity against staphylococci (including MRSA), most streptococci, and many Gram-negative bacteria. It does NOT have activity against ***Pseudomonas*** spp. or ***Acinetobacter*** spp. or Gram negative anaerobes.

Acceptable uses (Cases must be discussed with Infectious Diseases and Antimicrobial Stewardship Program)

- Select cases of MRSA pneumonia or other severe infections when Gram negative coverage is also needed
- Bacteremia or endocarditis caused by MRSA in a patient failing Vancomycin therapy as defined by:
 - Clinical decompensation after 3–4 days
 - Failure to clear blood cultures after 7 days despite Vancomycin troughs of 15–20 mcg/mL
 - MIC of Vancomycin is 2 mcg/mL

Unacceptable uses

- Treatment of community-acquired bacterial pneumonia (CAP) or skin and soft tissue infections (SSTI) where other more established and less expensive options are available
- Initial therapy for Gram-positive or Gram-negative infections

Dose

- 600 mg IV Q12H has been studied for CAP and SSTI
- 600 mg IV Q8H for MRSA bacteremia salvage therapy or other serious infections
- Must adjust for worsening renal function and dialysis (see p. 155 for dose adjustment recommendation).

Laboratory interactions

- Ceftaroline may result in positive direct Coombs' test without hemolytic anemia. However, if drug-induced hemolytic anemia is suspected, discontinue Ceftaroline.

Ceftolozane/tazobactam

Ceftolozane/tazobactam is a novel cephalosporin and β -lactamase-inhibitor combination. It has activity against Gram-negative organisms and some strains of multi-resistant *Pseudomonas* spp. It does NOT have activity against carbapenemase-producing Enterobacteriaceae. It also has *in vitro* activity against some streptococci and some Gram-negative anaerobes, but it does not have reliable *Staphylococcus* spp. activity.

Acceptable uses (Cases must be discussed with Infectious Diseases and Antimicrobial Stewardship Program)

- Management of infections due to multi-drug resistant *Pseudomonas* spp. infections on a case by case basis

Unacceptable uses

- Empiric treatment of complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI) as current standard regimens are sufficient for coverage of the typical pathogens involved in these infections and less expensive options are available

Dose

- 1.5 g IV Q8H has been studied for cUTI and in combination with metronidazole for cIAI
- Serious infections including pneumonia: 3 g IV Q8H
- Must adjust dose for worsening renal function and dialysis (see p.155 for dose adjustment recommendation).

Colistin (Colistimethate)

Colistin is a polymixin antibiotic. It has *in vitro* activity against *Acinetobacter* spp. and *Pseudomonas* spp. but does NOT have activity against *Proteus*, *Serratia*, *Providentia*, *Burkholderia*, *Stenotrophomonas*, Gram-negative cocci, Gram-positive organisms, or anaerobes.

Acceptable uses

- Management of infections due to multi-drug resistant *Acinetobacter* and *Pseudomonas* on a case by case basis.

Unacceptable uses

- Monotherapy for empiric treatment of suspected Gram-negative infections

Dose

- Loading dose: 5 mg/kg once
- Maintenance dose: 2.5 mg/kg Q12H; must adjust for worsening renal function and dialysis (see p. 155 for dose adjustment recommendation).

Toxicity

- Renal impairment, neuromuscular blockade, neurotoxicity
- Monitoring: BUN, creatinine twice-weekly

Hidden Content - JHH Internal use only

Reference:

Loading dose of colistin: Clin Infect Dis 2012; 54:1720-6.

Daptomycin

Daptomycin is a lipopeptide antibiotic. It has activity against most strains of staphylococci and streptococci (including MRSA and VRE). It does NOT have activity against Gram-negative organisms.

Acceptable uses (Cases must be discussed with Infectious Diseases and Antimicrobial Stewardship Program)

- Bacteremia or endocarditis caused by MRSA or Methicillin-resistant coagulase-negative staphylococci in a patient with serious allergy to Vancomycin
- Bacteremia or endocarditis caused by MRSA in a patient failing Vancomycin therapy as defined by:
 - Clinical decompensation after 3–4 days
 - Failure to clear blood cultures after 7 days despite Vancomycin troughs of 15–20 mcg/mL (high risk of Daptomycin resistance; check Daptomycin MIC and obtain follow up blood cultures)
 - MIC of Vancomycin is 2 mcg/mL
- Therapy for VRE infections other than pneumonia, on a case by case basis

Unacceptable uses

- Daptomycin should NOT be used for treatment of pneumonia due to its inactivation by pulmonary surfactant.
- Initial therapy for Gram-positive infections
- VRE colonization of the urine, respiratory tract, wounds, or drains

Dose

- Bacteremia: 6–12 mg/kg IV Q 24H
- Endocarditis: 6–12 mg/kg IV Q 24H
- Dose adjustment is necessary for CrCl < 30 ml/min (see p. 155 for dose adjustment recommendation).

Toxicity

- Myopathy (defined as CK \geq 10 times the upper limit of normal without symptoms or \geq 5 times the upper limit of normal with symptoms).
- Eosinophilic pneumonia
- Monitoring: CK weekly, more frequently during initial therapy.

Reference:

Daptomycin in *S. aureus* bacteremia and infective endocarditis: N Engl J Med 2006; 355: 653–65.

Ertapenem

Ertapenem is a carbapenem antibiotic. It has *in vitro* activity against many Gram-negative organisms including those that produce extended spectrum beta-lactamases (ESBL), but it does not have activity against *Pseudomonas spp.* or *Acinetobacter spp.* Its anaerobic and Gram-positive activity is similar to that of other carbapenems, except it does not have activity against *Enterococcus spp.*

Acceptable uses

- Mild to moderate intra-abdominal infections (biliary tract infections, diverticulitis, secondary peritonitis/GI perforation)
- Moderate diabetic foot infections without osteomyelitis
- Moderate surgical-site infections following contaminated procedure
- Pelvic inflammatory disease
- Urinary tract infections caused by ESBL-producing organisms
- Pyelonephritis in a patient who is not severely ill

Unacceptable uses

- Severe infections in which *Pseudomonas spp.* are suspected.

Dose

- 1 g IV or IM Q24H, must adjust for worsening renal function and dialysis (see p. 155 for dose adjustment recommendation)

Toxicity

- Diarrhea, nausea, headache, phlebitis/thrombophlebitis

Fosfomycin

Fosfomycin is a synthetic, broad-spectrum, bactericidal antibiotic with *in vitro* activity against large number of Gram-negative and Gram-positive organisms including *E. coli*, *Klebsiella spp.*, *Proteus spp.*, *Pseudomonas spp.*, and VRE. It does not have activity against *Acinetobacter spp.* Fosfomycin is available in an oral formulation only in the U.S. and its pharmacokinetics allow for one-time dosing.

Acceptable uses

- Management of uncomplicated UTI in patients with multiple antibiotic allergies and/or when no other oral therapy options are available.

- Uncomplicated UTI due to VRE
- Salvage therapy for UTI due to multi-drug resistant Gram-negative organisms (e.g. *Pseudomonas spp.*) on case by case basis.

NOTE: Susceptibility to Fosfomycin should be confirmed prior to initiation of therapy.

Unacceptable uses

- Fosfomycin should NOT be used for management of any infections outside of the urinary tract because it does not achieve adequate concentrations at other sites.
- Treatment of asymptomatic bacteriuria (see p. 110)

Dose

- Uncomplicated UTI: 3 g (1 sachet) PO once.
- Complicated UTI: 3 g (1 sachet) PO every 1-3 days (up to 21 days of treatment)
- Frequency adjustment may be necessary in patients with CrCl < 50 mL/min. Contact the ID Pharmacist for dosing recommendations.
- Powder should be mixed with 90–120 mL of cool water, stirred to dissolve and administered immediately.

Toxicity

- Diarrhea, nausea, headache, dizziness, asthenia and dyspepsia

Linezolid

Acceptable uses

- Documented Vancomycin intermediate *Staphylococcus aureus* (VISA) or Vancomycin resistant *Staphylococcus aureus* (VRSA) infection
- Documented MRSA or Methicillin-resistant coagulase-negative staphylococcal infection in a patient with serious allergy to Vancomycin
- Documented MRSA or Methicillin-resistant coagulase-negative staphylococcal infection in a patient failing Vancomycin therapy (as defined below):
 - Bacteremia/endocarditis: failure to clear blood cultures after 7 days despite Vancomycin troughs of 15–20 mcg/mL. Should be used in combination with another agent
 - Pneumonia: worsening infiltrate or pulmonary status in a patient with documented MRSA pneumonia after 2 to 3 days or if the MIC of Vancomycin is 2 mcg/mL, or if achieving appropriate vancomycin trough is unlikely (e.g., obesity)
 - Cases should be discussed with Infectious Diseases or Antimicrobial stewardship
- High suspicion of CA-MRSA necrotizing pneumonia in a seriously ill patient

- Documented VRE infection
- Gram-positive cocci in chains in blood cultures in an ICU, or oncology transplant patient known to be colonized with VRE

Unacceptable uses

- Prophylaxis
- Initial therapy for staphylococcal infection
- VRE colonization of the stool, urine, respiratory tract, wounds, or drains

Dose

- 600 mg IV/PO Q12H
- Skin and skin-structure infections: 400 mg IV/PO Q12H

Toxicity

- Bone marrow suppression (usually occurs within first 2 weeks of therapy)
- Optic neuritis and irreversible sensory motor polyneuropathy (usually occurs with prolonged therapy > 28 days)
- Case reports of lactic acidosis
- Case reports of serotonin syndrome when co-administered with serotonergic agents (SSRIs, TCAs, MAOIs, etc.)
- Monitoring: CBC weekly

Tigecycline

Tigecycline is a tetracycline derivative called a glycylcycline. It has *in vitro* activity against most strains of staphylococci and streptococci (including MRSA and VRE), anaerobes, and many Gram-negative organisms with the exception of *Proteus spp.* and *Pseudomonas aeruginosa*. It is FDA approved for skin and skin-structure infections and intra-abdominal infections.

NOTE: Peak serum concentrations of Tigecycline do not exceed 1 mcg/mL which limits its use for treatment of bacteremia

Acceptable uses

- Management of intra-abdominal infections in patients with contraindications to both beta-lactams and fluoroquinolones
- Management of infections due to multi-drug resistant Gram-negative organisms including *Acinetobacter spp.* and *Stenotrophomonas maltophilia* on a case by case basis
- Salvage therapy for MRSA/VRE infections on a case by case basis

Dose

- 100 mg IV once, then 50 mg IV Q12H
- 100 mg IV once, then 25 mg IV Q12H if severe hepatic impairment (Child - Pugh 10–15)

Toxicity

- Nausea and vomiting

Trimethoprim/sulfamethoxazole (Bactrim[®], TMP/SMX)

Trimethoprim/sulfamethoxazole is a sulfonamide antibiotic. It has *in vitro* activity against *Enterobacteriaceae* spp., *B. cepacia*, *S. maltophilia*, *Acinetobacter* spp., *Achromobacter* spp., *Nocardia* spp., *Listeria*, *Pneumocystis jirovecii* (PCP), staphylococci (including *S. aureus* and Coagulase-negative staph), but does NOT cover *Pseudomonas* spp. It has variable activity against streptococci and no activity against anaerobes.

Acceptable uses

- Urinary tract infections (UTI)
- *S. aureus* skin and soft-tissue infections (SSTI)
- *Pneumocystis jirovecii* pneumonia (PCP) treatment and prophylaxis
- *S. maltophilia* infections
- *Nocardia* infections
- Gram-negative bacteremia when organism is susceptible
- Salvage therapy for MRSA bacteremia in combination with another agent
- Empiric coverage of *Listeria* meningitis in patients with penicillin allergies
- Suppressive therapy and in some cases treatment for bone and joint infections

Unacceptable uses

- Monotherapy for *S. aureus* bacteremia

Dose

- Trimethoprim/sulfamethoxazole dosing is based on trimethoprim component
- TMP/SMX has excellent bioavailability, thus conversion from IV to PO is 1:1 (80/400 mg IV = 1 SS tab; 160/800 mg IV = 1 DS tab)
- Use adjusted BW= $[(IBW + 0.4 (ABW - IBW))]$ in obese patients (>30% over IBW)

Treatment

- UTI: 1 DS tab Q12H
- SSTI: 1-2 DS tab Q12H
- PCP: 15-20 mg/kg/day (in divided doses, Q6-Q8H)
- MRSA bacteremia: 10-15 mg/kg/day (in divided doses, Q6-Q8H)
- *S. maltophilia* infections: 15 mg/kg/day (in divided doses, Q6-Q8H)

- Nocardia infections: 15 mg/kg/day (in divided doses, Q6-Q8H); lower doses (5-10 mg/kg/day) can be used after several weeks of therapy or cutaneous infections
- Meningitis: 20 mg/kg/day (in divided doses, Q6H)
- Other infections: 8-10 mg/kg/day (in divided doses, Q6-12H)
- Must adjust dose for worsening renal function and dialysis (see p.155 for dose adjustment recommendation).

Prophylaxis

- PCP: 1 SS daily or 1 DS 3 times/week
- Toxoplasmosis: 1 DS daily

Toxicity

- Common: hypersensitivity (1.6-8%), GI-upset, pseudo elevation in creatinine (18%)
- Common with higher doses: hyperkalemia, myelosuppression
- Occasional: nephrotoxicity, photosensitivity, methemoglobinemia (with severe G6PD deficiency)
- Rare: aseptic meningitis, hepatotoxicity, toxic epidermal necrolysis (TEN), SJS, Sweet's syndrome

Drug Interaction

- Warfarin, methotrexate, phenytoin, digoxin, sulfonylureas, procainamide, oral contraceptives

Antifungals

Liposomal Amphotericin B (AmBisome®)

NOTES:

- Dosing of AmBisome and Amphotericin B deoxycholate is **significantly different**. Do not use AmBisome doses when ordering Amphotericin B deoxycholate and vice versa.
- Amphotericin B deoxycholate is preferred in patients with end-stage renal disease on dialysis who are anuric.

AmBisome, like all Amphotericin B products, has broad spectrum antifungal activity with *in vitro* activity against *Candida*, *Aspergillus*, *Zygomycosis* and *Fusarium*.

Acceptable uses

- Candidal endophthalmitis, endocarditis, CNS infection—first line therapy
- Cryptococcus meningitis—first line therapy
- Zygomycoses (*Mucor*, *Rhizopus*, *Cunninghamella*)—first line therapy
- Neutropenic fever if receiving Voriconazole or Posaconazole prophylaxis
- Alternative treatment of invasive aspergillosis
- Alternative treatment of candidemia, candida peritonitis

Dose

- Candidemia, histoplasmosis, other non-invasive candida infections: 3 mg/kg/day
- Candidal endophthalmitis, endocarditis, CNS infection, *C. krusei* candidemia: 5 mg/kg/day
- Invasive filamentous fungi: 5 mg/kg/day
- Neutropenic fever, candidemia in neutropenic patient: 3–5 mg/kg/day
- Cryptococcal meningitis: 3–4 mg/kg/day

Toxicity

- Infusion-related reactions: fever, chills, rigors, hypotension
- Renal impairment (enhanced in patients with concomitant nephrotoxic drugs)
- Electrolyte imbalances
- Pulmonary toxicity (chest pain, hypoxia, dyspnea), anemia, elevation in hepatic enzymes—rare
- Monitoring: BUN/creatinine, K, Mg, Phos at baseline and daily in hospitalized patients; AST/ALT at baseline and every 1-2 weeks

Micafungin

NOTE: Micafungin does not have activity against *Cryptococcus*.

Aspergillosis

• Acceptable uses

- In combination with Voriconazole for confirmed invasive aspergillosis (see p. 133)
- Refractory disease- for use in combination with Voriconazole, Posaconazole or AmBisome® for confirmed invasive aspergillosis.

• Unacceptable uses

- Micafungin alone or in combination with other antifungal agents is not recommended for empiric therapy in patients with CT findings suggestive of aspergillosis (e.g., **possible** aspergillosis) without plans for diagnostic studies.
- Micafungin does not have good *in vitro* activity against zygomycoses (*Mucor*, *Rhizopus*, *Cunninghamella*, etc.).

Candidiasis

• Acceptable uses

- Treatment of invasive candidiasis due to *C. glabrata* or *C. krusei*.
- Treatment of invasive candidiasis in patients who are NOT clinically stable due to candidemia or have received prior long-term azole therapy.
- Alternative treatment of recurrent esophageal candidiasis.
- Alternative treatment of endocarditis.

• Unacceptable uses

- Micafungin has poor penetration into the CNS and urinary tract. It should be avoided for infections involving those sites.

Neutropenic fever

- Micafungin can be used for neutropenic fever in patients who are not suspected to have aspergillosis or zygomycosis.

Dose

- Candidemia, invasive candidiasis, neutropenic fever: 100 mg IV Q24H
- Candidal endocarditis: 150 mg IV Q24H
- Recurrent esophageal candidiasis: 150 mg IV Q24H
- Invasive aspergillosis: 100–150 mg IV Q24H
- Obese patients
 - 100–150 kg: 150 mg IV Q24
 - > 150 kg: Consult ID Pharmacist

Drug Interactions

- Close monitoring is recommended when Micafungin is used with the following agents concomitantly:

- Sirolimus – levels of Sirolimus may be increased, monitor for Sirolimus toxicity
- Nifedipine – levels of Nifedipine may be increased, monitor for Nifedipine toxicity
- Itraconazole – levels of Itraconazole may be increased, monitor for Itraconazole toxicity

Toxicity

- Infusion-related reactions (rash, pruritis), phlebitis, headache, nausea and vomiting, and elevations in hepatic enzymes.
- Monitoring: AST/ALT/bilirubin at baseline and every 1–2 weeks after.

Posaconazole

Posaconazole is a broad spectrum azole anti-fungal agent. It has *in vitro* activity against *Candida*, *Aspergillus*, *Zygomycosis* and *Fusarium spp.*

Acceptable uses

- Treatment of invasive zygomycosis in combination with Amphotericin B
- Monotherapy for zygomycosis after 7 days of combination therapy with Amphotericin B
- Prophylaxis in patients with hematologic malignancy
- Treatment of aspergillosis in patients with Voriconazole intolerance

Unacceptable uses

- Candidiasis/Neutropenic fever
- First-line treatment of aspergillosis

Dose

NOTES:

- Each dose of suspension should be given with a full meal or with liquid nutritional supplements if patients cannot tolerate full meals. Can also be given with an acidic beverage (e.g. ginger ale).
- Delayed release tablets and oral suspension cannot be used interchangeably due to differences in the dosing of each formulation.

Prophylaxis

- Oral Suspension: 200 mg PO Q8H
- Extended Release Tablet: 300 mg PO daily

Treatment

- Oral Suspension: 200 mg PO Q6H for 7 days, then 400 mg PO Q8-Q12H
- Extended Release Tablet: 300 mg PO Q12H for 1 day, then 300 mg PO daily

Therapeutic monitoring:

- Posaconazole trough levels should be considered in patients who are:
 - Not responding to therapy for at least 7 days
 - Being treated for uncommon or less susceptible organisms
 - Experiencing mucositis or malabsorption syndrome
 - Unable to consume high fat meals (if receiving the suspension)

Drug Interactions: See Table on p. 21

Toxicity

- GI upset (~40%), headaches, elevation in hepatic enzymes. Rare but serious effects include QTc prolongation.
- Monitoring: AST/ALT/bilirubin at baseline and every 1–2 weeks after

References:

Clinical efficacy of new antifungal agents: *Curr Opin Microbiol.* 2006;9:483-88.
 Posaconazole: a broad spectrum triazole antifungal: *Lancet Infect Dis.* 2005; 5:775-85.

Voriconazole

NOTE: Voriconazole does not cover zygomycoses (*Mucor*, *Rhizopus*, *Cunninghamella*, etc.).

Acceptable uses

- Aspergillosis
- *Scedosporium apiospermum*
- Prophylaxis in patients with hematologic malignancy

Unacceptable uses

- Candidiasis / Neutropenic fever
 Voriconazole should not be used as first-line therapy for the treatment of candidiasis or for empiric therapy in patients with neutropenic fever.

Dose

- Loading dose: 6 mg/kg IV/PO Q12H x 2 doses
- Maintenance dose: 4 mg/kg IV/PO Q12H
 - Dose adjustment is necessary for hepatic insufficiency:
 - Child - Pugh (A or B): ↓ maintenance dose by 50%
 - Child - Pugh (C): Use only if benefits outweigh risks. Consult ID pharmacist for dose adjustment recommendations.
- Dose escalation may be necessary for some patients due to subtherapeutic levels.
- Dose based on actual body weight unless patient >30% over IBW; then use adjusted body weight. (Adj. BW).

$$\text{Adj. BW} = \lceil \text{IBW} + 0.4 (\text{ABW} - \text{IBW}) \rceil$$

IBW - Ideal Body Weight

ABW - Actual Body Weight

Therapeutic monitoring

- Voriconazole trough levels should be considered in patients who are:
 - Not responding to therapy after at least 5 days of therapy using a mg/kg dosing strategy
 - Receiving concomitant drugs that may increase or decrease Voriconazole levels
 - Experiencing adverse events due to Voriconazole
 - Experiencing GI dysfunction
- Voriconazole trough levels should be obtained 5–7 days after start of therapy (performed M–F).
- Goal trough: 2–5.5 mcg/mL. Levels < 1 mcg/mL have been associated with clinical failures and levels >5.5 mcg/mL with toxicity.

Drug Interactions: See Table on p. 21

Toxicity

- Visual disturbances (~30%) usually self-limited, rash, fever, elevations in hepatic enzymes.
- Monitoring: AST/ALT/bilirubin at baseline and every 1–2 weeks after

References:

Voriconazole: Clin Infect Dis 2003; 36:630.

Voriconazole in neutropenic fever: N Engl J Med 2002;346(4):225.

Voriconazole TDM: Clin Infect Dis 2008; 46:201.

Azole drug interactions

The following list contains major drug interactions involving drug metabolism and absorption. This list is not comprehensive and is intended as a guide only. You must check for other drug interactions when initiating azole therapy or starting new medication in patients already receiving azole therapy.

Drug metabolism:

Cytochrome (CYP) P450 inhibitors: decrease the metabolism of certain drugs (CYP450 substrates) resulting in increased drug concentrations in the body (occurs immediately)

Cytochrome (CYP) P450 inducers: increase the metabolism of certain drugs (CYP450 substrates) resulting in decreased drug concentrations in the body (may take up to 2 weeks for upregulation of enzymes to occur)

Drug absorption/penetration:

P-glycoprotein (P-gp) inhibitor: decrease the function of the efflux pump, resulting in increased absorption/penetration of P-gp substrates

P-glycoprotein inducer: increase the function of the efflux pump, resulting in decreased absorption/penetration of P-gp substrates

Potency of Cytochrome P450 inhibition: Voriconazole > Itraconazole > Posaconazole > Fluconazole

POSACONAZOLE (substrate and inhibitor for P-gp efflux, inhibitor of CYP3A4)

	Drug	Recommendations
Contraindicated	Commonly prescribed: sirolimus Less commonly prescribed: cisapride, ergot alkaloids, pimozide, quinidine, triazolam	Do not use
Warning/precaution	Cyclosporine Metoclopramide, proton pump inhibitors Midazolam Tacrolimus Cimetidine, efavirenz, phenytoin, rifabutin, rifampin	↓ cyclosporine dose to 3/4 and monitor levels May ↓ posaconazole concentrations when using suspension Consider dose reducing ↓ tacrolimus dose to 1/2 and monitor levels Avoid concomitant use unless benefit outweighs risk If used together, monitor effects of drugs and consider decreasing dose when posaconazole is added
	Amiodarone, atazanavir, digoxin, erythromycin, all calcium channel blockers, ritonavir, statins (avoid lovastatin and simvastatin), vinca alkaloids	Monitor effect of drugs and consider decreasing dose when posaconazole is added

ITRACONAZOLE and major metabolite hydroxyitraconazole (substrate and inhibitor of CYP3A4 and P-gp efflux)

	Drug	Recommendations
Contraindicated	Commonly prescribed: statins (lovastatin, simvastatin) Less commonly prescribed: cisapride, dofetilide, ergot alkaloids, nisoldipine, oral midazolam, pimozide, quinidine, triazolam	Do not use
Warning/precaution	Commonly prescribed: atorvastatin, benzodiazepines, chemotherapy (busulfan, docetaxel, vinca alkaloids), cyclosporine, digoxin, efavirenz, eletriptan, fentanyl, oral hypoglycemics, indinavir, IV midazolam, nifedipine, ritonavir, saquinavir, sirolimus, tacrolimus, verapamil, steroids (budesonide, dexamethasone, fluticasone, methylprednisolone), warfarin Less commonly prescribed: alfentanil, buspirone, cimetidine, disopyramide, felodipine, trimetrexate Commonly prescribed: carbamazepine, efavirenz, isoniazid, nevirapine, phenobarbital, phenytoin, rifabutin, rifampin, antacids, H2 receptor antagonists, proton pump inhibitors Clarithromycin, erythromycin, fosamprenavir, indinavir, ritonavir, saquinavir	↑ plasma concentration of the interacting drug, monitor levels when possible, monitor for drug toxicity and consider dose reduction ↓ plasma concentration of itraconazole, if possible avoid concomitant use or monitor itraconazole levels ↑ plasma concentration of itraconazole, monitor itraconazole levels and monitor for toxicity

3.2 Agent-specific guidelines: Antifungals

VORICONAZOLE (substrate and inhibitor of CYP2C19, CYP2C9, and CYP3A4)

	Drug	Recommendations
Contraindicated	Commonly prescribed: carbamazepine, rifabutin, rifampin, ritonavir 400 mg Q12H Less commonly prescribed: long-acting barbiturates, disipride, ergot alkaloids, pmozide, quinidine, St. John's Wort	Do not use
Warning/precaution	Cyclosporine Efavirenz Tacrolimus Sirolimus Omeprazole Maraviroc Methadone Phenytoin Ritonavir low dose (100 mg Q12H) Warfarin	↓ cyclosporine dose to ½ and monitor levels ↑ voriconazole dose to 5 mg/kg IV/PO Q12H and ↓ efavirenz to 300 mg PO daily ↓ tacrolimus dose to ½ and monitor levels ↓ sirolimus dose by 75% and monitor levels ↓ omeprazole dose to ½ ↓ maraviroc dose to 150 mg twice daily Monitor effect of the interacting drug and consider decreasing dose ↑ voriconazole to 5 mg/kg IV/PO Q12H and monitor levels Avoid this combination unless benefits outweigh risks Monitor INR levels
	Commonly prescribed: all benzodiazepines (avoid midazolam and triazolam), all calcium channel blockers, fentanyl, oxycodone & other long acting opioids, NSAIDs, oral contraceptives, statins (avoid lovastatin and simvastatin), sulfonyleureas, vinca alkaloids, pomalidomide, simeprevir, boceprevir, telaprevir Less commonly prescribed: alfentanil	Monitor effect of drugs and consider decreasing dose when voriconazole is added

FLUCONAZOLE (substrate of CYP3A4 and inhibitor of CYP3A4, CYP2C9, and CYP2C19, interactions are often dose dependent)

	Drug	Recommendations
Contraindicated	Cisapride	Do not use
Warning/precaution	Commonly prescribed: cyclosporine, glipizide, glyburide, phenytoin, rifabutin, tacrolimus, warfarin Less commonly prescribed: oral midazolam, theophylline, tolbutamide Rifampin	↑ plasma concentration of the interacting drug, monitor levels when possible, monitor for drug toxicity and consider dose reduction ↓ plasma concentration of fluconazole, consider increasing fluconazole dose

Pneumococcal vaccination

There are two types of pneumococcal vaccines that are recommended by ACIP guidelines for adult patients: Pneumococcal polysaccharide (**Pneumovax 23[®]**, PPV23) and Pneumococcal conjugate vaccine (**Prenvar 13[®]**, PCV13). Most patients should receive both vaccines in sequential order, but NEVER together. See table below for indications for each vaccine.

Indications for pneumococcal vaccines for adults ≥ 19 years of age

Risk group	Prenvar 13 [®]	Pneumovax 23 [®]
All adults ≥ 65 years of age	Yes	Yes
CSF leak or cochlear implants	Yes	Yes
Functional or anatomic asplenia	Yes	Yes, revaccinate 5 years after first dose
Immunocompetent persons with certain chronic medical conditions (e.g. heart disease*, lung disease†, liver disease, DM), alcoholism, cigarette smoking	No	Yes
Immunocompromised host: congenital/acquired immunodeficiencies, HIV, chronic renal failure, nephrotic syndrome, hematologic malignancies, organ transplant, long-term immunosuppressive therapy (e.g. steroids, active chemotherapy, radiation)	Yes	Yes, revaccinate 5 years after first dose

*Including CHF, cardiomyopathies, excluding hypertension; †Including COPD, emphysema, asthma

Timing and sequential administration of pneumococcal vaccines

- No history or unknown history of pneumococcal vaccination and both vaccines are indicated, patient should receive Prenvar 13[®] first followed by Pneumovax 23[®] at a minimum of 8 weeks later (ideally 6-12 months)
- If patient has received Pneumovax 23[®] and both vaccines are indicated, the patient should receive Prenvar 13[®] (minimum 1 year separation)
- If patient has received Prenvar 13[®] ≥ 8 weeks ago, and both vaccines are indicated, the patient should receive Pneumovax 23[®] (minimum 8 weeks separation)
- If patient has received both vaccines ≥ 5 years ago and revaccination is needed with Pneumovax 23[®], a second dose should be administered (minimum 5 years apart)
- Patients who are severely immunocompromised (e.g. BMT, solid organ transplant) should follow institutional policy when available or consult ID for optimal timing of vaccine administration

Reference:

ACIP Recommendations: MMWR 2014;63(37);822-825 and MMWR 2012;61(40);816-819.

Organism-specific guidelines

Anaerobes

Although anaerobic bacteria dominate the human intestinal microbiome only a few species seem to play an important role in human infections. Infections caused by anaerobes are often polymicrobial.

- Gram-negative bacilli - *Bacteroides* spp., *Prevotella* spp., *Porphyromonas* spp., *Fusobacterium* spp.
- Gram-negative cocci - *Veillonella* spp.
- Gram-positive bacilli - *Propionibacterium* spp., *Lactobacillus* spp., *Actinomyces* spp., *Clostridium* spp.
- Gram-positive cocci - *Peptostreptococcus* spp. and related genera

Clinical diagnosis of anaerobic infections should be suspected in the presence of foul smelling discharge, infection in proximity to a mucosal surface, gas in tissues or negative aerobic cultures. Proper specimen collection is critical; refer to specimen collection guidelines at <http://www.hopkinsmedicine.org/microbiology/specimen/index.html>

Treatment Notes

Hidden Content
- JHH Internal use only

- Surgical debridement of anaerobic infections is important because anaerobic organisms can cause severe tissue damage.
- Ampicillin/sulbactam and Clindamycin are considered to be effective empiric therapy against Gram-positive anaerobes seen in infections

above the diaphragm. Metronidazole is not active against microaerophilic streptococci (e.g. *S. anginosus* group) and should not be used for these infections.

- Vancomycin is also active against many Gram-positive anaerobes (e.g. *Clostridium* spp., *Peptostreptococcus* spp., *P. acnes*).
- Empiric double coverage with Metronidazole AND carbapenems (Meropenem, Ertapenem) or beta-lactam/beta-lactamase inhibitors (Ampicillin/Sulbactam, Piperacillin/Tazobactam, Amoxicillin/Clavulanic acid) is NOT recommended given the excellent anaerobic activity of these agents.
- *B. fragilis* group resistance to Clindamycin, Cefotetan, Cefoxitin, and Moxifloxacin has increased and these agents should not be used empirically for treatment of severe infections where *B. fragilis* is suspected (e.g. intra-abdominal infections).
- Most resistance in the *B. fragilis* group is caused by beta-lactamase production, which is screened for by the JHH micro lab.
- *Bacteroides thetaiotaomicron* is less likely to be susceptible to Piperacillin/Tazobactam; therefore, when this organism is isolated or strongly suspected (e.g. Gram negative rods in anaerobic blood cultures in a patient on Piperacillin/tazobactam) alternative agents with anaerobic coverage should be used until susceptibilities are confirmed.
- Tigecycline is active against a wide spectrum of gram-positive and gram-negative anaerobic bacteria *in vitro* but clinical experience with this agent is limited.

Propionibacterium acnes

Indications for consideration of testing for *P. acnes*:

- CNS shunt infections
- Prosthetic shoulder joint infections
- Other implantable device infections

Diagnosis

- Cultures should be held for 10-14 days if high suspicion for *P. acnes* as growth is slow
- Collection of tissue and fluid specimens for culture is preferred. Do not send swabs for culture
- Multiple representative specimens (preferably 3) should be sent for shoulder joint infections to assist in distinguishing contaminants from pathogenic isolates — these could include synovial fluid, any inflammatory tissue, and synovium
- Tissue specimens should also be sent for histopathology

Treatment

- Penicillin G 2-3 million units IV Q4H (preferred)

OR

- PCN allergy : Vancomycin (see dosing section, p. 150)

NOTES

- **ID consult recommended for assistance with choice and duration of antibiotic therapy**
- *P. acnes* is usually a contaminant in blood culture specimens. Draw repeat cultures and consider clinical context before treatment
- Rare reports of spinal infections have been noted for *P. acnes*
- All *P. acnes* isolates at JHH are susceptible to Penicillin (see anaerobic antibiogram p. 24)
- Metronidazole does not have activity against *P. acnes*. Tetracyclines are not routinely tested and resistance rates are variable.
- Broader spectrum agents such as Meropenem and Piperacillin/tazobactam would be expected to be active for Penicillin susceptible isolates, but these are not first-line therapy
- Susceptibility data should be used to help guide therapeutic decisions
- Consider removal of associated hardware

Streptococci

Viridans group Streptococci (alpha-hemolytic streptococci)

Normal microbiota of the oral cavity and GI tract; single blood cultures growing these organisms often represent contamination or transient bacteremia

Five groups

- *S. anginosus* group (contains *S. intermedius*, *anginosus*, and *constellatus*): commonly cause abscesses; majority are Penicillin susceptible
- *S. bovis* group [contains *S. gallolyticus* subspecies *gallolyticus* (associated with colon cancer—colonoscopy mandatory, endocarditis also present in > 50% of cases) and subspecies *pasteurinus* (associated with hepatobiliary disease, endocarditis less common)]; majority are Penicillin susceptible
- *S. mitis* group (contains *S. mitis*, *oralis*, *gordonii*, and *sanguinous*): commonly cause bacteremia in neutropenic patients and endocarditis; many have Penicillin resistance
- *S. salivarius* group: less common cause of endocarditis; majority are Penicillin susceptible
- *S. mutans* group: common cause of dental caries; uncommon cause of endocarditis; majority are Penicillin susceptible

Beta-hemolytic Streptococci

All are susceptible to Penicillin

Variable rates of resistance to Clindamycin; ask the microbiology laboratory to perform susceptibility testing if you plan to use Clindamycin or macrolides for moderate to severe infections.

While anti-staphylococcal penicillins (Oxacillin and Nafcillin) are the agents of first choice for susceptible *S. aureus* infections, their activity against streptococci is sub-optimal

High rates of resistance to tetracyclines and TMP/SMX preclude their empiric use for infections suspected to be caused by beta-hemolytic streptococci

- *S. pyogenes* (group A strep): pharyngitis, skin and soft tissue infections including erysipelas, cellulitis, necrotizing fasciitis; Clindamycin resistance in 1.5-5.2%; macrolide resistance in 4-7%.
- *S. agalactiae* (group B strep): neonatal infections, infections of the female genital tract, skin and soft tissue infections, bacteremia; Clindamycin resistance in 16-26%; macrolide resistance in 7-32%.

- Group C and G streptococci: infections similar to *S. pyogenes* and *S. agalactiae*; associated with underlying diseases (e.g. diabetes, malignancy, cardiovascular disease); Clindamycin resistance in ~16% of group C and ~33% of group G isolates; macrolide resistance in ~25% of group C and ~28% of group G isolates.

Streptococcus pneumoniae

- Common cause of respiratory tract infections including otitis media, sinusitis, pneumonia via local spread from the nasopharynx; infections involving the CNS, bones/joints and endocarditis via hematogenous spread
- Genetically, *S. pneumoniae* is in the *S. mitis* group of viridans group streptococci; consequently, rapid molecular tests may not be able to distinguish *S. pneumoniae* and streptococci in the *S. mitis* group.
- Penicillin is the agent of first choice for serious *S. pneumoniae* infections when it is susceptible
- Penicillin and Ceftriaxone susceptibility breakpoints are different for CNS and non-CNS sites

MIC breakpoints for Penicillin and Ceftriaxone against *S. pneumoniae*

Antibiotic	Susceptible	Intermediate	Resistant
Penicillin (oral)	≤ 0.06	0.12-1	≥ 2
Penicillin (parenteral)			
Non-CNS	≤ 2	4	≥ 8
CNS	≤ 0.06		≥ 0.12
Ceftriaxone			
Non-CNS	≤ 1	2	≥ 4
CNS	≤ 0.5	1	≥ 2

- Addition of Vancomycin to Ceftriaxone is not indicated in the empiric treatment of non-CNS infections caused by *S. pneumoniae* due to low rates of resistance

Multi-drug resistant Gram-negative rods

Patients with infection or colonization with the resistant organisms listed below should be placed on CONTACT precautions (see isolation chart on p. 141)

Extended spectrum beta-lactamase (ESBL)-producing organisms

- ESBLs are enzymes that confer resistance to all penicillins, cephalosporins, and Aztreonam.
- They are most commonly seen in *K. pneumoniae* and *K. oxytoca*, *E. coli*, and *P. mirabilis*, and these organisms are automatically screened by the JHH microbiology lab for the presence of ESBLs.

- Risk factors for infection or colonization: recent hospitalization at an institution with a high rate of ESBLs, residence in a long-term care facility and prolonged use of broad spectrum antibiotics.

Treatment:

- Meropenem 1 g IV Q8H (2 g IV Q8H for CNS infections) should be used for ALL severe infections if the organism is susceptible.
- Ertapenem 1 g IV Q24H can be used for uncomplicated UTI or soft tissue infection with adequate source control if the organism is susceptible.
- Ciprofloxacin or TMP/SMX can be used as alternatives to Ertapenem for uncomplicated UTI or soft tissue infection with adequate source control if the organism is susceptible. Nitrofurantoin may also be used for uncomplicated UTI if the organism is susceptible.

Carbapenemase-producing Enterobacteriaceae (CRE)

- Carbapenemases are enzymes that confer resistance to all penicillins, cephalosporins, carbapenems and Aztreonam.
- JHH microbiology lab is no longer performing the modified Hodge test
- If carbapenem is resistant JHH microbiology lab will report organism as “carbapenem resistant”; however, the exact mechanism of resistance is not tested for at this time.

Treatment:

- Meropenem 2 g IV Q8H infused over 3 hours should be included in most regimens based on data from small, retrospective studies showing benefit even when the isolate is intermediate or resistant.
- At least one additional agent should be added based on susceptibilities (e.g. Amikacin, Tigecycline, Colistin) except for UTI.

Multi-drug resistant (MDR) gram-negative organisms: defined as organisms susceptible to NO MORE than ONE of the following antibiotic classes: carbapenems, aminoglycosides, fluoroquinolones, penicillins, or cephalosporins. **Note:** susceptibility to sulfonamides, tetracyclines, polymixins, and Sulbactam are NOT considered in this definition

Treatment

MDR <i>Pseudomonas aeruginosa</i>	MDR <i>Acinetobacter baumannii/calcoaceticus</i> complex
<ul style="list-style-type: none"> • Ceftolozane/tazobactam (if susceptible) OR • Anti-pseudomonal β-lactam <u>PLUS</u> aminoglycoside if synergy predicted or confirmed OR • Colistin (if susceptible) 	<ul style="list-style-type: none"> • β-lactam <u>PLUS</u> aminoglycoside if synergy expected OR • Colistin (if susceptible) OR • Ampicillin/sulbactam (if susceptible) <u>PLUS</u> aminoglycoside (Sulbactam component has <i>in vitro</i> activity against <i>Acinetobacter</i> spp.) OR • Tigecycline (if susceptible; for infections other than bacteremia)

*Combination therapy should be considered in severe infections.

Synergy:

- If the organism is intermediate to a beta-lactam and susceptible to aminoglycosides, synergy can be assumed.
- The microbiology lab does not perform synergy testing.

Antibiotic doses for MDR and carbapenemase-producing infections – normal renal and hepatic function

- Meropenem: 2 g IV Q8H, infuse over 3 hours
- Cefepime: 2 g IV Q8H, infuse over 3 hours
- Ceftazidime/Cefepime: 2 g IV bolus loading dose over 30 minutes, then 6 g IV as continuous infusion over 24 hours
- Piperacillin/tazobactam: 3.375 g IV bolus loading dose over 30 minutes, then continuous infusion 3.375 g IV Q4H infused over 4 hours **OR** 4.5 g IV Q6H, infuse over 4 hours
- Colistin: 5 mg/kg once, then 2.5 mg/kg IV Q12H (for additional information, see p. 9)
- Ampicillin/sulbactam: 3 g IV Q4H (for MDR *A. baumannii* only)
- Aminoglycosides (for dosing, see p. 146)
- Tigecycline: 100-150 mg IV Q12H
- Ceftolozane/tazobactam 1.5-3 g IV Q8H

References:

- ESBLs and clinical outcomes. Clin Infect Dis 2015; 60(9): 1319-25.
Current therapies for *P. aeruginosa*. Crit Care Clin 2008;24:261.
Combination therapy for CRE. Clin Microbiol Infec 2014;20: 862-72.

Interpreting the microbiology report

Interpretation of preliminary microbiology data

Gram-positive cocci	Gram-negative cocci
<p>Aerobic In clusters</p> <ul style="list-style-type: none"> • Coagulase (+): <i>S. aureus</i> • Coagulase (-): <i>S. epidermidis</i>, <i>S. lugdunensis</i> <p>In pairs/chains</p> <ul style="list-style-type: none"> • Diplococcus, Quellung positive: <i>S. pneumoniae</i> • Alpha-hemolytic: Viridans group <i>Streptococci</i>, <i>Enterococcus (faecalis and faecium)</i> • Beta-hemolytic: <ul style="list-style-type: none"> Group A strep (<i>S. pyogenes</i>), Group B strep (<i>S. agalactiae</i>), Group C, D, G strep <p>Anaerobic: <i>Peptostreptococcus spp.</i></p>	<p>Aerobic Diplococcus: <i>N. meningitidis</i>, <i>N. gonorrhoeae</i>, <i>Moraxella catarrhalis</i> Cocco-bacillus: <i>H. flu</i>, <i>Acinetobacter spp.</i>, HACEK organisms</p> <p>Anaerobic: <i>Veillonella spp.</i></p>
Gram-positive rods	Gram-negative rods
<p>Aerobic Large: <i>Bacillus spp.</i> Cocco-bacillus: <i>Listeria monocytogenes</i>, <i>Lactobacillus spp.</i> Small, pleomorphic: <i>Corynebacterium spp.</i> Branching filaments: <i>Nocardia spp.</i>, <i>Streptomyces spp.</i></p> <p>Anaerobic Large: <i>Clostridium spp.</i> Small, pleomorphic: <i>P. acnes</i>, <i>Actinomyces spp.</i></p>	<p>Aerobic Lactose fermenting: <i>Citrobacter spp.</i>, <i>Enterobacter spp.</i>, <i>E. coli</i>, <i>Klebsiella spp.</i>, <i>Serratia spp.*</i> Non-lactose fermenting</p> <ul style="list-style-type: none"> • Oxidase (-): <i>Acinetobacter spp.</i>, <i>Burkholderia spp.</i>, <i>E. coli</i> (rare), <i>Proteus spp.</i>, <i>Salmonella spp.</i>, <i>Shigella spp.</i>, <i>Serratia spp.*</i>, <i>Stenotrophomonas maltophilia</i> • Oxidase (+): <i>P. aeruginosa</i>, <i>Aeromonas spp.</i>, <i>Vibrio spp.</i>, <i>Campylobacter spp.</i> (curved) <p>Anaerobic: <i>Bacteroides spp.</i>, <i>Fusobacterium spp.</i>, <i>Prevotella spp.</i></p>

* *Serratia spp.* can appear initially as non-lactose fermenting due to slow fermentation.

The Johns Hopkins microbiology laboratory utilizes standard reference methods for determining susceptibility. The majority of isolates are tested by the automated system.

The minimum inhibitory concentration (MIC) value represents the concentration of the antimicrobial agent required at the site of infection for inhibition of the organism.

The MIC of each antibiotic tested against the organism is reported with one of three interpretations S (susceptible), I (intermediate), or R (resistant). The highest MIC which is still considered susceptible represents the breakpoint concentration. This is the highest MIC which is usually associated with clinical efficacy. MICs which are $\frac{1}{2}$ – $\frac{1}{8}$ the

breakpoint MIC are more frequently utilized to treat infections where antibiotic penetration is variable or poor (endocarditis, meningitis, osteomyelitis, pneumonia, etc.). Similarly, organisms yielding antibiotic MICs at the breakpoint frequently possess or have acquired a low-level resistance determinant with the potential for selection of high-level expression and resistance. This is most notable with cephalosporins and *Enterobacter spp.*, *Serratia spp.*, *Morganella spp.*, *Providencia spp.*, *Citrobacter spp.* and *Pseudomonas aeruginosa*. These organisms all possess a chromosomal beta-lactamase which frequently will be over-expressed during therapy despite initial *in vitro* susceptibility. The intermediate (I) category includes isolates with MICs that approach attainable blood and tissue levels, but response rates may be lower than fully susceptible isolates. Clinical efficacy can potentially be expected in body sites where the drug is concentrated (e.g., aminoglycosides and beta-lactams in urine) or when a higher dose of the drug can be used (e.g., beta-lactams). The resistant (R) category indicates the organism will not be inhibited by usually achievable systemic concentrations of the antibiotic of normal doses.

NOTE: MIC values vary from one drug to another and from one bacterium to another, and thus MIC values are NOT comparable between antibiotics or between organisms.

Spectrum of antibiotic activity

The spectrum of activity table is an approximate guide of the activity of commonly used antibiotics against frequently isolated bacteria. It takes into consideration JHH specific resistance rates, *in vitro* susceptibilities and expert opinion on clinically appropriate use of agents. For antibiotic recommendations for specific infections refer to relevant sections of the JHH Antibiotic Guidelines.

Gram Category	Species	Antibiotic Class																								
		Penicillin G	Ampicillin	Ampicillin/sulbactam	Oxacillin/Nafcillin	Piperacillin/tazobactam	Cefazolin	Cefotetan	Ceftriaxone	Cefepime	Aztreonam	Ertapenem	Meropenem	Moxifloxacin	Ciprofloxacin	Azithromycin	Gent/Tobra/Amikacin	Vancomycin	Linezolid	Daptomycin	TMP/SMX	Clindamycin	Doxycycline	Colistin	Metronidazole	
GRAM-NEGATIVE	Atypicals																									
	Abdominal anaerobes																									
	Oral anaerobes																									
	<i>Pseudomonas</i> spp.																									
	<i>Enterobacter</i> spp.																									
	<i>Serratia</i> spp.																									
	<i>Proteus</i> spp.																									
	<i>Kebsiella</i> spp.																									
	<i>E. coli</i>																									
	<i>H. influenzae</i>																									
GRAM-POSITIVE	Viridans strep.																									
	<i>S. pneumoniae</i>																									
	β -hemolytic strep.																									
	Coag. neg. staph																									
	MSSA																									
	MRSA																									
	<i>E. faecalis</i>																									
	VRE																									

Active

Less active or potential resistance

Not active

5.2 Spectrum of antibiotic activity

Interpretation of rapid diagnostic tests

The JHH microbiology lab performs rapid nucleic acid microarray testing on blood cultures growing Gram-positive organisms and peptide nucleic acid fluorescence in situ hybridization (PNA-FISH) testing on blood cultures growing yeast.

Nucleic acid microarray testing (Verigene®) for Gram-positive cocci in blood cultures

- Detects and identifies the nucleic acids of 12 Gram-positive bacterial genera/species and 3 resistance markers.
- Bacteria species: *S. aureus*, Coagulase-negative staphylococci, *S. lugdunensis*, *Staphylococcus* spp. *E. faecalis*, *E. faecium*, *S. pyogenes* (group A streptococci), *S. agalactiae* (group B streptococci), *S. pneumoniae*, *S. anginosus*, *Streptococcus* spp. (e.g., group C and G streptococci, viridans group streptococci, etc.), *Listeria* spp.
- Resistance markers: *mecA*, *vanA*, *vanB*
 - If *S. aureus* is *mecA* positive the organism is resistant to Methicillin and is reported as MRSA
 - If *S. aureus* is *mecA* negative the organism is susceptible to Methicillin and is reported as MSSA
 - If *E. faecalis/faecium* is *vanA/B* positive the organism is resistant to Vancomycin and is reported as VRE; note that all Vancomycin-resistant *E. faecalis* are susceptible to Ampicillin at JHH
- Results of the test are reported within 3-4 hours after the blood cultures turn positive
- Testing is performed only on the first positive blood culture
- Testing is NOT performed on blood cultures growing more than one Gram positive organism but is performed on blood cultures growing both Gram positive and negative organisms
- If the test is negative it will be reported as negative for the following organisms: *Staphylococcus* spp., *Streptococcus* spp., *E. faecalis*, *E. faecium*, *Listeria* spp.

Organism	Preferred empiric therapy (% susceptible in blood at JHH)	Alternative empiric therapy if PCN allergic
MSSA	Oxacillin (100%)	Non-severe PCN allergy: Cefazolin Severe PCN allergy: Vancomycin ¹
MRSA	Vancomycin (100%)	Daptomycin
Coagulase-negative staphylococci	Single positive cultures are often a contaminant; no treatment recommended. See p. 60 of the JHH Antibiotic Guidelines for information and indications for treatment. Call the microbiology lab for more information and further work up if infection suspected (5-6510).	
<i>S. lugdunensis</i>	Vancomycin (100%) ²	Oxacillin (96%) or Daptomycin
<i>E. faecalis</i>	Ampicillin (98%)	Vancomycin (95%) ¹
<i>E. faecium</i> (VRE)	Linezolid (87%) ³	Daptomycin (97%)
<i>E. faecium</i> (not VRE)	Vancomycin (100%) ³	Linezolid
<i>Streptococcus</i> spp.	Non-oncology patient: Ceftriaxone ⁴ Oncology patient: Vancomycin ⁴	Severe PCN allergy: Vancomycin ¹
<i>S. anginosus</i>	Penicillin G (100%)	Non-severe PCN allergy: Ceftriaxone Severe PCN allergy: Vancomycin ¹
<i>S. pyogenes</i> (group A strep)	Penicillin G (100%)	Non-severe PCN allergy: Cefazolin Severe PCN allergy: Vancomycin ¹
<i>S. agalactiae</i> (group B strep)	Penicillin G (100%)	Non-severe PCN allergy: Cefazolin Severe PCN allergy: Vancomycin ¹
<i>S. pneumoniae</i> (not meningitis)	Ceftriaxone (100%) ⁴	Severe PCN allergy: Vancomycin ¹
<i>S. pneumoniae</i> (meningitis)	Ceftriaxone + Vancomycin	Severe PCN allergy: Chloramphenicol + Vancomycin ¹
<i>Listeria</i> spp.	Ampicillin (100%)	Trimethoprim/sulfamethoxazole

¹Consult allergy for skin testing /desensitization

²Narrow to Oxacillin if found to be susceptible

³Narrow to Ampicillin if found to be susceptible

⁴Narrow to Penicillin G if found to be susceptible

PNA-FISH for yeast

- If PNA-FISH shows *C. albicans*, most non-oncology patients without prior azole exposure can be treated with fluconazole. For more information see p. 117 and 134.
- If PNA-FISH shows *C. glabrata*, treat with Micafungin until susceptibilities available. For more information see p. 117 and 134.
- If PNA-FISH negative for *C. albicans* or *C. glabrata*, most cases can be treated as unspciated candidemia, unless cryptococcus is suspected (send serum cryptococcal antigen). For more information see p. 117 and 134.

Biliary tract infections – cholecystitis and cholangitis

EMPIRIC TREATMENT

Community-acquired infections in patients without previous biliary procedures AND who are not severely ill

- Ceftriaxone 1 g IV Q24H
- OR
- Ertapenem 1 g IV Q24H
- OR
- Severe PCN allergy: Ciprofloxacin 400 mg IV Q12H

Hospital-acquired infections OR patients with multiple therapeutic biliary manipulations (e.g. stent placement/exchange, bilio-enteric anastomosis of any severity) OR patients who are severely ill

- Piperacillin/tazobactam 3.375 g IV Q6H
- OR
- Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H
- OR
- Severe PCN allergy: Aztreonam 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H ± Vancomycin (see dosing section, p. 150)

In severely ill patients with cholangitis and complicated cholecystitis, **adequate biliary drainage** is crucial as antibiotics will not enter bile in the presence of obstruction.

Duration

- Uncomplicated cholecystitis: treat only until obstruction is relieved. NO post-procedure antibiotics are necessary if the obstruction is successfully relieved.
- Complicated cholecystitis: 4 days, unless adequate source control is not achieved.
- Biliary sepsis: 4-7 days, unless adequate source control is not achieved.

TREATMENT NOTES

Microbiology

- Gram-negative rods – *E. coli*, *Klebsiella spp.*, *Proteus spp.*, *P. aeruginosa* (mainly in patients already on broad-spectrum antibiotics or those who have undergone prior procedures)
- Anaerobes – *Bacteroides spp.*, generally in more serious infections, or in patients with a history of biliary manipulations; rare in uncomplicated and community-acquired infections
- *Enterococcus spp.* – treatment not always indicated; use clinical judgment
- Yeast – rare

Management

- In cases of uncomplicated acute cholecystitis, antibiotics should be given until the biliary obstruction is relieved (either by surgery, ERCP, or percutaneous drain).
- Treatment of enterococci is usually not needed in mild/moderate disease.
- Yeast generally should be treated only if they are recovered from biliary cultures, not empirically.

References:

Biliary tract infections: Drugs 1999;57(1):81-91.

IDSA Guidelines for Intra-abdominal Infections: Clin Infect Dis 2010;50:133–164.

Short course therapy for IAI: N Engl J Med 2015;372:1996–2005.

Diverticulitis

EMPIRIC TREATMENT

NOTE: Patients with uncomplicated diverticulitis (defined as CT confirmed left-sided disease without abscess; free air or fistula ± fever and elevated inflammatory markers), can be treated conservatively without antibiotics based on a RCT.

Mild/moderate infections – can be oral if patient can take PO

- Amoxicillin/clavulanate 875 mg PO Q12H
OR
- Ceftriaxone 1 g IV Q24H PLUS Metronidazole 500 mg IV/PO Q8H
OR
- Ertapenem 1 g IV Q24H
OR
- Severe PCN allergy: [Ciprofloxacin 400 mg IV Q12H OR Ciprofloxacin 500 mg PO Q12H] PLUS Metronidazole 500 mg IV/PO Q8H

Severe infections

- Piperacillin/tazobactam 3.375 g IV Q6H
OR
- Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H
OR
- Severe PCN allergy: [Ciprofloxacin 400 mg IV Q12H OR Aztreonam 1 g IV Q8H] PLUS Metronidazole 500 mg IV Q8H

Duration

- 4 days, unless adequate source control is not achieved.

TREATMENT NOTES

Microbiology

- Almost all infections are polymicrobial
- Most commonly isolated aerobic organisms – *E. coli*, *K. pneumoniae*, *Enterobacter spp.*, *Proteus spp.*, *Enterococcus spp.*
- Most commonly isolated anaerobic organisms – *B. fragilis*, *Prevotella*, *Peptostreptococci*

Other considerations

- Antimicrobial treatment for acute uncomplicated diverticulitis may not accelerate recovery or prevent complications/recurrence.
- CT scan is important in assessing need for drainage in severe disease.

Reference:

IDSA Guidelines for Intra-abdominal Infections: Clin Infect Dis 2010;50:133–164.

Antibiotics in acute uncomplicated diverticulitis. Br J Surg 2012;99:532–539.

Short course therapy for IAI: N Engl J Med 2015;372:1996–2005.

Pancreatitis

TREATMENT

- Antibiotic prophylaxis is NOT indicated in patients with severe acute pancreatitis (SAP), including those with sterile pancreatic necrosis.
- Antimicrobial therapy has no effect on morbidity and mortality, and prophylactic antibiotics have been associated with a change in the spectrum of pancreatic isolates from enteric Gram-negatives to Gram-positive organisms and fungi.
- Infected pancreatic necrosis is defined by CT scan with gas in the pancreas and/or percutaneous or surgical specimen with organisms evident on gram stain or culture. Therapy should be directed based on culture results.
- In patients presenting with suspected abdominal sepsis, consider empiric therapy:
 - Piperacillin-tazobactam 4.5 g IV Q6H
 - OR**
 - Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H
 - OR**
 - Severe PCN allergy: Ciprofloxacin 400 mg IV Q12H PLUS Metronidazole 500 mg IV Q8H

Pancreatic penetration of selected antibiotics**Good (>40%; MIC exceeded for most relevant organisms):**

fluoroquinolones, carbapenems, Ceftazidime, Cefepime, Metronidazole, Piperacillin-tazobactam

Poor (<40%): aminoglycosides, first-generation cephalosporins, Ampicillin

Duration

For infected pancreatic necrosis, continue antibiotics for 14 days after source control is obtained. Continuation of antibiotics beyond this time places the patient at risk for colonization or infection with resistant organisms and drug toxicity.

TREATMENT NOTES

- Infection develops in 30–50% of patients with necrosis documented by CT scan or at the time of surgery.
- Peak incidence of infection occurs in the 3rd week of disease
- There is insufficient evidence to recommend selective gut decontamination in management of pancreatitis.

References:

Lack of utility of prophylactic antibiotics: *Ann Surg* 2007;245:674.
Guidelines for management of SAP: *Crit Care Med* 2004;32:2524.

Peritonitis**DEFINITIONS**

Primary peritonitis is spontaneous infection of the peritoneal cavity, usually associated with liver disease and ascites [spontaneous bacteria peritonitis (SBP)].

Secondary peritonitis is infection of the peritoneal cavity due to spillage of organisms into the peritoneum, usually associated with GI perforation.

Tertiary peritonitis is a recurrent infection of the peritoneal cavity following an episode of secondary peritonitis.

Primary peritonitis/Spontaneous bacterial peritonitis (SBP)**EMPIRIC TREATMENT**

- Ceftriaxone 1 g IV Q12H

OR

- Severe PCN allergy: Moxifloxacin 400 mg IV/PO Q24H (call ID or Antimicrobial Stewardship to discuss regimens for patients who have been taking fluoroquinolones for SBP prophylaxis).

- Patients with serum creatinine >1 mg/dL, BUN >30 mg/dL or total bilirubin >4 mg/dL should also receive Albumin (25%) 1.5 g/kg on day 1 and 1 g/kg on day 3 (round to the nearest 12.5 g).

Duration

- Treat for 5 days

PROPHYLAXIS

Cirrhotic patients with gastrointestinal hemorrhage

- Ciprofloxacin 500 mg PO BID for 7 days
- Ceftriaxone 1 g IV Q24H can be used only if patient is NPO, then switch to Ciprofloxacin 500 mg PO BID once bleeding is controlled

Non-bleeding cirrhotic patients with ascites

- TMP/SMX 1 DS PO once daily

OR

- If sulfa allergic, Ciprofloxacin 500 mg PO daily

TREATMENT NOTES

Microbiology

- Gram-negative rods (Enterobacteriaceae, esp. *E. coli* and *K. pneumoniae*), *S. pneumoniae*, enterococci, and other streptococci.
- Polymicrobial infection should prompt suspicion of GI perforation.

Diagnostic criteria

- 250 PMN per mm³ of ascitic fluid.
- Positive culture with < 250 PMN should prompt repeat tap. If PMN > 250 OR culture remains positive, patient should be treated.

Follow-up

- Consider repeat paracentesis after 48 hours of therapy.
- Consider changing antibiotics if ascites fluid PMN has not dropped by 25% after 48 hours and/or patient is not clinically responding.

Notes on prophylaxis against SBP

- All patients with cirrhosis and upper GI bleed should receive prophylaxis for 7 days (50% develop SBP after bleed).
- Patients who get SBP should get lifelong prophylaxis to prevent future episodes (40–70% risk of recurrence in 1 year).
- Prophylaxis should be considered for those with low protein concentrations in ascites (< 10 g/L) or immunosuppression while patient is in hospital.

References:

Diagnosis, treatment and prophylaxis of SBP: *J Hepatol* 2000;32:142.

Management of variceal hemorrhage in cirrhosis: *Hepatology* 2007;46:922–38.

Secondary peritonitis/GI perforation

EMPIRIC TREATMENT

Perforation of esophagus, stomach, small bowel, colon, or appendix

Patient mild to moderately ill

- Ertapenem 1 g IV Q24H

OR

- Severe PCN allergy: Ciprofloxacin 400 mg IV Q12H PLUS Metronidazole 500 mg IV Q8H

Patient severely ill or immunosuppressed

- Piperacillin/tazobactam 3.375 g IV Q6H

OR

- Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS [Aztreonam 1 g IV Q8H **OR** Ciprofloxacin 400 mg IV Q8H] PLUS Metronidazole 500 mg IV Q8H

Empiric antifungal therapy is generally not indicated for GI perforation unless patient has one of the following risk factors:

Esophageal perforation, immunosuppression, prolonged antacid or antibiotic therapy, prolonged hospitalization, persistent GI leak.

Recommendations for patients who are clinically stable and have not received prior long-term azole therapy:

- Fluconazole 400-800 mg IV/PO Q24H

Recommendations for patients who are NOT clinically stable or have received prior long-term azole therapy:

- Micafungin 100 mg IV Q24H

Duration of therapy for secondary peritonitis/GI perforation

	Stomach	Small Bowel	Colon	Appendix
Uncomplicated				
Definition	Operated on within 24 hours	Operated on within 12 hours	Operated on within 12 hours	Non-necrotic or gangrenous appendix
Duration	24-48 hours	24-48 hours	24-48 hours	24 hours
Complicated				
Definition	Late operation or no operation; or necrotic/gangrenous appendix			
Duration	4 days unless adequate source control is not achieved			

TREATMENT NOTES

- Causative agents for small bowel, colon, appendix: anaerobes (esp. *B. fragilis*), Enterobacteriaceae (esp. *E. coli*, *K. pneumoniae*, *Enterobacter spp.*, *Proteus spp.*); infections usually polymicrobial.
- Pathogens causing tertiary peritonitis are variable and are often resistant to or not covered by the initial antimicrobial regimen; thus, a change in antimicrobials is advised.
- A change in antimicrobials therapy should be considered in patients with hospital-acquired infections who are already on antimicrobials.
- Treatment of enterococci remains controversial but should be considered in critically ill or immunocompromised patients or when they are a dominant organism in the peritoneal culture.
- Treatment of *Candida spp.* is generally indicated only when they are recovered from blood or are a dominant organism in the peritoneal culture in critically ill or immunocompromised patients.
- Postoperative antibiotics for appendicitis are unnecessary unless there is clinical evidence of peritonitis, abscess, or gangrene.
- Antibiotics are adjunctive to source control, which is an absolute necessity.
- Lack of source control is defined as on-going contamination and/or an undrained collection of infection.

Reference:

IDSA Guidelines for Intra-abdominal Infections: Clin Infect Dis 2010;50:133–164.

Short course therapy for IAI: N Engl J Med 2015;372:1996–2005.

Peritonitis related to peritoneal dialysis

EMPIRIC TREATMENT

Mild to moderate illness: intraperitoneal therapy is preferred in most cases.

Anuric patient

- Cefazolin 15 mg/kg in one bag Q24H (1 g if patient < 65 kg) PLUS
- Gentamicin 2 mg/kg in one bag loading dose, then Gentamicin 0.6 mg/kg in one bag Q24H

Patient with urine output > 100 mL/day

- Ceftazidime 1 g in one bag Q24H

Severe illness: systemic therapy is preferred.

- FIRST DOSE: Vancomycin (see dosing section, p. 150) IV PLUS ONE of the following:
[Gentamicin 2 mg/kg IV OR Ceftazidime 1 g IV OR Ciprofloxacin 400 mg IV]

- MAINTENANCE DOSE: Dose per drug levels and/or renal function; consult pharmacy for recommendations for redosing and monitoring

Duration: 10–14 days

TREATMENT NOTES

Microbiology

- Most cases caused by contamination of the catheter
- Cultures may be negative in 5–20%
- Gram-positive cocci (*S. aureus*, coagulase-negative staphylococci, *Enterococcus spp.*), Gram-negative rods, yeast (much less common)

Diagnosis

- All patients with suspected PD-related peritonitis should have PD fluid sampled for cell count, differential, gram stain, culture AND amylase. WBC > 100/mm³ with > 50% PMN suggests infection.
- Elevated amylase suggests pancreatitis or bowel perforation.
- In symptomatic patients with cloudy fluid accompanied by abdominal pain and/or fever, empiric treatment should be started given the high likelihood of infection.
- In symptomatic patients with clear fluid, another PD fluid exchange, with a dwell time of at least 2 hours, should be sampled. The decision to start empiric therapy in these cases will depend on how sick the patient appears.
- In asymptomatic patients with cloudy fluid, it is reasonable to delay therapy pending the results of cell count, gram stain, and culture.

Reference:

ISPD Guidelines for Peritoneal Dialysis-related Infections: Perit Dial Int 2010;30: 393–423.

Clostridium difficile infection (CDI)

Diagnosis and testing

- Case definition of *C. difficile* diarrhea: passage of ≥ 3 unformed stools in ≤ 24 hours AND either a positive stool test for *C. difficile* or colonoscopic/histopathologic finding of pseudomembranous colitis.
- The microbiology lab uses a real-time PCR assay to detect the toxin B gene, the toxin responsible for CDI. Thus, patients who are colonized with toxigenic strains will test positive even if they do not have active infection and clinical correlation with positive test results is important. The sensitivity of real time PCR is $> 90\%$ compared to toxigenic culture.
- Do NOT send stool for *C. difficile* testing if patients do not have diarrhea or ileus. Hard stool, fluid obtained from colonoscopy and rectal swabs will be rejected by the microbiology lab.
- In patients receiving laxatives, it is recommended to discontinue laxatives for 24-48 hours prior to *C. difficile* stool test to see if diarrhea improves, unless the patient is clinically unstable.
- Because of enhanced sensitivity of PCR, duplicate testing is not necessary or recommended. Testing is restricted to one specimen within 7 days. Call the Laboratory Medicine resident or faculty member on call for those rare instances when a second specimen is required.
- Stool for *C. difficile* testing should be collected prior to starting treatment for *C. difficile*.
- Specimens should be hand carried to the lab as soon as possible after collection. If they cannot be transported promptly, the samples should be refrigerated.
- Do NOT send follow-up *C. difficile* PCR during treatment or to document resolution of disease, as utility of the results has not been demonstrated.

TREATMENT

- **STOP ALL ANTIMICROBIAL AGENTS WHENEVER POSSIBLE.**
- Oral therapy must be used whenever possible as the efficacy of IV Metronidazole is poorly established for CDI and there is no efficacy of IV Vancomycin for CDI.

Treatment depends on clinical severity

Infection severity	Clinical manifestations
Asymptomatic carriage*	<i>C. difficile</i> PCR positive without diarrhea, ileus, or colitis
Mild or moderate	<i>C. difficile</i> PCR positive with diarrhea but no manifestations of severe disease
Severe	<i>C. difficile</i> PCR positive with diarrhea and one or more of the following attributable to CDI : <ul style="list-style-type: none"> • WBC \geq 15,000 • Increase in serum creatinine > 50% from baseline
Severe Complicated	Criteria as above plus one or more of the following attributable to CDI : <ul style="list-style-type: none"> • Hypotension • Ileus • Toxic megacolon or pancolitis on CT • Perforation • Need for colectomy • ICU admission for severe disease

Infection severity	Treatment
Asymptomatic carriage	Do NOT treat; treatment can promote relapsing disease
Mild or moderate	<ul style="list-style-type: none"> • Metronidazole 500 mg PO/NGT Q8H Unable to tolerate oral therapy <ul style="list-style-type: none"> • Metronidazole 500 mg IV Q8H (suboptimal; see note at start of CDI section above)
Severe	<ul style="list-style-type: none"> • Vancomycin solution 125 mg PO/NGT Q6H
Severe Complicated	<ul style="list-style-type: none"> • Consult surgery for evaluation for colectomy and ID • Vancomycin solution 500 mg by NGT Q6H <u>PLUS</u> Metronidazole 500 mg IV Q8H[†] Unable to tolerate oral therapy or complete ileus <ul style="list-style-type: none"> • Vancomycin 500 mg in 500 ml NS Q6H as retention enema via Foley catheter in rectum + Metronidazole 500 mg IV Q8H

*15-25% of hospitalized patients are colonized with *C. difficile*.

[†] Vancomycin dose can be decreased to 125 mg PO Q6H and Metronidazole can be stopped once the patient has stabilized.

Other indications for oral Vancomycin use

- No response to oral Metronidazole after 5 days of therapy
- Second episode of recurrent disease
- Patients with significant side effects to Metronidazole
- Patients who are pregnant
- Consider in patients > 65 years given reports of increased morbidity from CDI.

Duration

- 10–14 days

Approach to patients who need to continue broad spectrum antibiotic therapy

- Determine the shortest possible course of antibiotic therapy.
- Replace the antibiotic that induced CDI, particularly cephalosporins, Clindamycin, and fluoroquinolones.
- If the inducing agent is replaced and the CDI resolves, complete a standard 10-14 day course of CDI therapy; there is no need to extend CDI therapy until the end of the course of antibiotic therapy.
- If the inducing agent cannot be stopped or replaced, consider continuing CDI therapy until the end of the course of antibiotic therapy (data are limited); CDI therapy should not be continued beyond the end of antibiotic therapy if the patient remains asymptomatic.

Recurrent disease

- Resistance to Metronidazole or Vancomycin has not been documented conclusively.
- Recurrent disease after a complete course of therapy occurs in ~ 25% of patients. Relapse is due to failure to eradicate spores (60%) or acquisition of a new strain (40%). Document recurrent disease with repeat stool testing.
- First recurrence should be treated the same as the initial episode; severe disease should be treated with Vancomycin.
- Second recurrence should be treated with Vancomycin taper followed by pulse dosing or fecal microbiota transplant (consult GI).
- If serious or multiple recurrences, consult ID.

Vancomycin taper regimen

125 mg 4 times daily × 10–14 days

125 mg BID × 7 days

125 mg daily × 7 days

125 mg every 2–3 days for 2–8 weeks (pulse dosing)

NOTES**Management**

- Surgical intervention for colectomy should be considered early if the patient is clinically unstable secondary to CDI.
- Treatment of CDI should be continued in patients who have a subtotal colectomy with preservation of the rectum.
- Most patients with severe CDI should undergo abdominal CT to rule out toxic megacolon or pancolitis.

- Do NOT send follow-up *C.difficile* PCR to document resolution of disease.
- Do not use antimotility agents.
- Stop proton pump inhibitors (PPIs) whenever possible as data suggest PPIs increase the risk of CDI.
- The offending antimicrobial agents should be discontinued. If antimicrobials are still required, it is best to avoid cephalosporins, Clindamycin, and fluoroquinolones.
- Prophylactic use of oral Metronidazole or Vancomycin in patients receiving antimicrobial therapy for treatment of underlying infection (other than CDI) is not recommended and may increase the patient's risk for CDI.

Infection control

- Patients with CDI should be placed in contact precautions and single rooms for the duration of hospitalization.
- Use soap and water rather than alcohol-based hand gel upon exiting the room of a patient with CDI.

References:

SHEA/IDSA Consensus Guidelines for CDI: Infect Control Hosp Epidemiol 2010; 31:431–454.

Lack of utility of treating CDI carriers: Ann Intern Med 1992; 117:297-302.

Colectomy in CDI: Ann Surg 2007; 245:267-72.

Infectious diarrhea

- **For treatment of *C. difficile* infection, see p. 47.**
- Carefully assess the patient before prescribing antimicrobials.
- Most infectious diarrhea is self-limited and only requires supportive management.
- Treatment with antibiotics is not recommended for most mild-moderate disease; see specific indications in table below.
- Viral pathogens, such as Norovirus and Rotavirus commonly cause diarrhea and do not require antibiotics.
- Antibiotic use may lead to adverse outcomes (e.g. hemolytic uremic syndrome with Shiga toxin-producing *E. coli*).
- Antimotility agents should not be used in patients with bloody diarrhea, fever, or elevated WBC.

Microbiology

- Common non-viral pathogens in acute community-acquired diarrhea: *Salmonella*, *Shigella*, Shiga toxin-producing *E. coli*, *Campylobacter*, *C. difficile* (usually with antibiotic exposure).
- Nosocomial diarrhea: *C. difficile*
- Persistent diarrhea if immunocompromised (most likely causes vary depending on type of immunocompromise): *Giardia*, *Cryptosporidium*, *Cyclospora*, *Isospora*, *Microsporidia*, Cytomegalovirus (CMV).

Diagnosis

- Not every diarrheal illness requires stool culture. Decision to test should be based on suspicion for specific pathogens and/or clinical judgment of illness severity.
- Patients with febrile diarrheal illnesses with clinical features of moderate to severe disease should receive empiric therapy only after a fecal specimen is obtained for appropriate testing.
- Fecal specimens from patients hospitalized for > 3 days should not be submitted for routine stool culture unless a high suspicion for specific pathogen exists and/or if the patient is immunocompromised.
- Multiple stool examinations for ova and parasites (O&P) are of low yield.
- Fecal leukocyte/lactoferrin assessments should not be used to determine the therapeutic approach.

Treatment of infectious diarrhea

Organism/Indications for treatment	Treatment
Bacteria	
<p><i>Campylobacter</i> spp.</p> <p>Treatment recommended for:</p> <ul style="list-style-type: none"> • Severe illness • Age < 6 months or > 50 years • Gross blood in stool • High fever • Worsening or relapsing symptoms • Pregnancy • Immunocompromised host 	<ul style="list-style-type: none"> • Azithromycin 500 mg PO daily for 1–3 days
<p><i>E. coli</i> (enterotoxigenic, enteropathogenic, enteroinvasive) or empiric therapy of traveler's diarrhea</p>	<ul style="list-style-type: none"> • Ciprofloxacin 500 mg PO BID <p>Duration: 1–3 days</p>
<p>Shiga toxin producing <i>E. coli</i> (including <i>E. coli</i> O157:H7)</p>	<p>Treatment not recommended. Antibiotic use associated with development of hemolytic uremic syndrome.</p>
<p>Non-typhoid <i>Salmonella</i> spp.</p> <p>Treatment recommended for:</p> <ul style="list-style-type: none"> • Severe illness requiring hospitalization • Age < 6 months or > 50 years • Bacteremia • Presence of prostheses • Valvular heart disease • Severe atherosclerosis • Malignancy or other immunocompromise 	<ul style="list-style-type: none"> • Ciprofloxacin 500 mg PO BID <p>OR</p> <ul style="list-style-type: none"> • TMP/SMX 160/800 mg PO BID (if susceptible) <p>OR</p> <ul style="list-style-type: none"> • Ceftriaxone 1 g IV Q24H <p>Duration: 5–7 days; 14 days for immunocompromised host</p>
<p><i>Shigella</i> spp.</p> <p>Treatment always recommended even if result returns when patient is asymptomatic.</p>	<ul style="list-style-type: none"> • TMP/SMX 160/800 mg PO BID (if susceptible) <p>OR</p> <ul style="list-style-type: none"> • Ciprofloxacin 500 mg PO BID <p>Duration: 3 days; 7 days for immunocompromised host</p>
<p><i>Vibrio parahaemolyticus</i></p> <p>Note: Associated with shellfish consumption</p> <p>Treatment recommended for severe illness</p>	<ul style="list-style-type: none"> • Ciprofloxacin 500 mg PO BID x 3 days
<p><i>Yersinia</i> spp.</p> <p>Treatment recommended for:</p> <ul style="list-style-type: none"> • Immunocompromised host • Bacteremia • Pseudoappendicitis syndrome 	<ul style="list-style-type: none"> • TMP/SMX 160/800 mg PO BID x 3–5 days (if susceptible) <p>OR</p> <ul style="list-style-type: none"> • Ciprofloxacin 500 mg PO BID x 3 days <p>OR</p> <ul style="list-style-type: none"> • Doxycycline 100 mg PO BID x 3 days (not for bacteremia)

Parasites	
<p><i>Entamoeba histolytica</i></p> <p>Treat all (even asymptomatic)</p> <p><i>E. dispar</i> & <i>E. moshkovskii</i> infections do not require treatment</p>	<ul style="list-style-type: none"> • Metronidazole 750 mg PO TID x 5–10 days OR • Tinidazole 1 g PO Q12H x 3 days • PLUS all patients should receive Paromomycin 500 mg PO TID x 7 days after the course of 1st agent complete Asymptomatic patients • Paromomycin 500 mg PO TID x 7 days
<p><i>Giardia spp.</i></p>	<ul style="list-style-type: none"> • Metronidazole 250-500 mg PO TID x 7–10 days OR • Tinidazole 2 g PO once

References:

IDSA Guidelines for Management of Infectious Diarrhea; Clin Infect Dis 2001;32:331–50.

Infectious diarrhea in developed and developing countries: J Clin Gastroenterol 2005;39:757–773.

***Helicobacter pylori* infection**

NOTE: CONSIDER WITHHOLDING THERAPY INITIATION UNTIL PATIENT DISCHARGED FROM HOSPITAL UNLESS ACUTE ULCER IS PRESENT

Established indications for testing for *H. pylori* and treating positive patients

- Active peptic ulcer disease (PUD) – gastric or duodenal
- Confirmed history of PUD (not previously treated for *H. pylori*)
- Gastric MALT lymphoma (low grade)
- Following resection of gastric cancer
- Family history of gastric cancer in a 1st degree relative
- Atrophic gastritis

Other indications where testing for *H. pylori* and treating positive patients can be considered: nonulcer dyspepsia, long term PPI use, persons using NSAID/ASA, unexplained iron deficiency anemia or vitamin B12 deficiency, family members of patients with *H. pylori* with mild dyspepsia.

First-line treatment

- Amoxicillin 1 g PO Q12H PLUS Clarithromycin 500 mg PO Q12H PLUS Pantoprazole 40 mg PO Q12H
- OR**
- PCN allergy
 - Clarithromycin 500 mg PO Q12H PLUS Metronidazole 500 mg PO Q12H PLUS Pantoprazole 40 mg PO Q12H
 - OR**
 - Tetracycline 500 mg PO Q6H PLUS Metronidazole 500 mg PO Q8H PLUS Bismuth subsalicylate 525 mg PO Q6H PLUS Pantoprazole 40 mg PO Q12H

- **Duration:** 10–14 days

Documented recurrence of *H. pylori* disease

- If possible, avoid antibiotics previously used to treat *H. pylori*
- Tetracycline 500 mg PO Q6H PLUS Metronidazole 500 mg PO Q8H PLUS Bismuth subsalicylate 525 mg PO Q6H PLUS Pantoprazole 40 mg PO Q12H
- **Duration:** 14 days

TREATMENT NOTES

Diagnosis

- PPIs, H₂RA, Bismuth, and antibiotics with activity against *H. pylori* should be withheld for at least 4 weeks prior to testing.

- *H. pylori* stool antigen is the only FDA approved test (>90% sensitivity and specificity).
- Urea breath test may be optimal but not commonly available.
- Endoscopy PLUS rapid urease test (80–95% sensitivity; 92–100% specificity).
- *H. pylori* serology does not document current infection and should not be used for clinical diagnosis.

Management

- First line treatment eradication rates estimated between 50–75%. Failure most often due to Clarithromycin resistance (10–15%) and/or non-adherence.
- H₂-receptor antagonists (e.g. Ranitidine) can be substituted for the PPI if patients are unable to tolerate PPIs or if drug interactions are a concern.
- Amoxicillin PLUS Tetracycline can NOT be used together in treatment due to low response rates.
- Do not substitute Doxycycline/Minocycline for Tetracycline or Azithromycin for Clarithromycin.
- In patients with positive test results endoscopy is mandatory for age > 45-50 years, presence of mass GI bleeding, anemia, weight loss, or family history of gastric cancer.
- Test of cure is recommended > 4–8 weeks post treatment.

References:

Maastricht III Consensus Report. *Gut* 2007;56:772-781.
ACG Guidelines. *Am J Gastroenterol* 2007;102:1808-1825.

Pelvic inflammatory disease

- Includes salpingitis, tubo-ovarian abscess and pelvic peritonitis.
- For treatment of post-operative peritonitis or wound infection, see p. 44 and p. 105.

TREATMENT

NOTE: Avoid use of fluoroquinolones for *N. gonorrhoeae* due to resistance (~10% in Baltimore City)

- Cefotetan 2 g IV Q12H PLUS Doxycycline* 100 mg PO BID for 14 days

OR

- Ertapenem 1 g IV Q24H PLUS Doxycycline* 100 mg PO BID for 14 days

OR

- PCN allergy: Clindamycin 600-900 mg IV Q8H PLUS Gentamicin (see dosing section, p. 146)

Step-down therapy once patient is afebrile

- Preferred: Doxycycline 100 mg PO BID ± [Clindamycin 450 mg PO QID **OR** Metronidazole 500 mg PO BID] to complete 14 days total

*Azithromycin 1 g PO once weekly for 2 weeks can be used in the case of Doxycycline contraindication or intolerance.

TREATMENT NOTES

Microbiology: *N. gonorrhoeae*, *C. trachomatis*, *Gardnerella* spp, *Ureaplasma urealyticum*, anaerobes (*Prevotella* spp., *B. fragilis*), Gram-negative rods, Streptococci

Treatment of partners

- All women diagnosed with acute PID should be offered HIV testing.
- Male partners of women who have PID often are asymptomatic.
- Sex partners (male or female) of patients who have PID should be examined and treated empirically for *C. trachomatis* and *N. gonorrhoeae* if they have had sexual contact with the patient during the 60 days preceding onset of symptoms in the patient, regardless of the pathogens isolated from the patient.

Endomyometritis

TREATMENT

- Same as for PID but no need for addition of Doxycycline/Azithromycin

Duration

- Treat until patient afebrile for 24–48 hours

Bacterial vaginosis

TREATMENT

- Metronidazole gel 0.75%, one full applicator (5 g) intravaginally, once daily for 5 days (**preferred**)

OR

- Metronidazole 500 mg PO BID for 7 days

OR

- Clindamycin 300 mg PO BID for 7 days

TREATMENT NOTES

Microbiology: anaerobic bacteria (*Prevotella* spp, *Mobiluncus* spp.), *G. vaginalis*, *Ureaplasma*, *Mycoplasma*.

- Treatment is recommended in all symptomatic women and high risk asymptomatic pregnant women.

Trichomoniasis (*T.vaginalis*)

NOTE: Treatment of partner recommended.

TREATMENT

- Metronidazole 2 g PO once

OR

- Metronidazole 500 mg PO BID for 7 days

Uncomplicated gonococcal urethritis, cervicitis, proctitis

TREATMENT (includes treatment for *C. trachomatis*):

- Ceftriaxone 250 mg IM once PLUS Azithromycin 1 g orally (**preferred**)

OR

- Ceftriaxone 250 mg IM once PLUS Doxycycline 100 mg PO BID for 7 days

OR

- Severe PCN allergy: Azithromycin 2 g PO once (premedicate with antiemetic or give snack before administration)

TREATMENT NOTES

- HIV testing recommended
- The use of Ceftriaxone is preferred over Cefixime and Cefpodoxime due to increasing MICs for oral cephalosporins.

- Dual therapy recommended for *N. gonorrhoeae* even if *C. trachomatis* is excluded.
- Send gonorrhea culture (not nucleic acid amplification test) if you suspect a treatment failure.

Syphilis

SCREENING

- Screening algorithm at JHH: a treponemal-specific antibody test (CIA) if positive, followed by RPR. A confirmatory FTA-ABS is provided if RPR is negative.
- A positive CIA, a negative RPR and a positive FTA may be due to: (1) old treated syphilis (2) old untreated syphilis (3) early syphilis.
- Get history and call Baltimore City Health Department 410-396-4448 for prior history of syphilis treatment in Maryland
- If penicillin allergic, ID consults is recommended to guide therapy

Algorithm for reverse sequence syphilis screening

CIA		
CIA positive		CIA negative
RPR positive	RPR negative	
<ul style="list-style-type: none"> • Consistent with syphilis infection (past or present) • Requires historical and clinical evaluation to determine prior treatment history 	Treponemal test that uses a different antigen (FTA-ABS or TPPA)	
	FTA-ABS positive <ul style="list-style-type: none"> • Possible syphilis infection • Requires historical and clinical evaluation 	FTA-ABS negative <ul style="list-style-type: none"> • Syphilis unlikely • If patient at high risk for syphilis, retest in one month
		<ul style="list-style-type: none"> • If incubating or primary syphilis is suspected, treat for early syphilis

Neurosyphilis diagnosis

- Requires both clinical (neurological symptoms) and laboratory criteria.
- Laboratory criteria (any combination of): serological evidence of syphilis, positive CSF VDRL (50% sensitivity; high specificity), CSF pleocytosis (>5 WBC/ml if HIV-; >10-20 WBC/ml if HIV+), CSF elevated protein concentration (>50 mg/dl)
- Lumbar puncture (LP) should be obtained in patients with positive serological tests for syphilis plus neurological symptoms, serological treatment failure (lack of four-fold decline in RPR titer), evidence of tertiary syphilis
- Consider LP in asymptomatic HIV+ patients with a CD4 count ≤ 350 cells/ml or RPR titer $\geq 1:32$

TREATMENT

Early syphilis (primary, secondary, and early latent syphilis within one year after infection)

- Penicillin G Benzathine (Bicillin® L-A) 2.4 million units IM once
- Severe PCN allergies: Doxycycline 100 mg PO BID for 2 weeks

Note: due to increased resistance (~45% of strains in Baltimore are resistant), Azithromycin is not recommended.

Late latent syphilis (asymptomatic infection with positive serology >1 year after infection or latent syphilis of unknown duration)

- Penicillin G Benzathine (Bicillin® L-A) 2.4 million units IM weekly for 3 weeks (total of 3 doses)

Neurosyphilis (can occur during any stage of syphilis)

- Penicillin G 3–4 million units IV Q4H for 10–14 days

Syphilis in pregnancy

- Penicillin is the only recommended therapy in pregnant patients with any kind of syphilis. Allergy consult for penicillin desensitization is recommended.

References:

Sexually transmitted diseases CDC treatment guidelines. MMWR 2010/59 (RR12); 1–110.

Azithromycin vs. Doxycycline for PID. *Obstet Gynecol* 2007; 110(1):53–60.

Discordant Results from Reverse Sequence Syphilis Screening. MMWR 2011/60 (05);133–137

Management of catheter-related bloodstream infections (CR-BSI)

Diagnosis

- If there is more than minimal erythema or ANY purulence at the exit site, the catheter is likely infected. It should be removed and replaced at a different site.
- When CR-BSI is suspected, 2–3 sets of blood cultures should be drawn with AT LEAST one (and preferably > 1) from peripheral sites. Blood cultures drawn through non-tunneled catheters are more likely to yield contaminants.
- The utility of cultures of the catheter tip itself is not well defined, and should ONLY be sent when there is a clinical suspicion of infection, NOT routinely when lines are removed. They MUST be accompanied by two sets of blood cultures obtained as detailed above.
 - Technique: The exit site should be cleaned with alcohol. The catheter should be grasped a few centimeters proximal to the exit site. A 5 cm segment of catheter including the tip should be cut off with sterile scissors and placed in a sterile container.
- In instances where the blood and catheter tip are cultured at the same time and the blood cultures are negative but the catheter tip culture is positive, antibiotics are generally not recommended, even for patients with valvular heart disease or immunosuppression.
 - The exception is patients whose catheter tips grow *S. aureus* and have negative blood cultures. These patients should receive 5–7 days of antibiotics.
 - All patients should be followed closely, and repeat cultures should be sent if clinically indicated.
- When a catheter-related BSI is associated with catheter dysfunction, consider the possibility of suppurative thrombophlebitis.

EMPIRIC TREATMENT

- Vancomycin (see dosing section, p. 150) ± Cefepime 1–2 g IV Q8H (use higher dose if pseudomonas suspected)

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) ± [Ciprofloxacin 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] ± Tobramycin (see dosing section, p. 146)

Empiric treatment – Gram-positive cocci in clusters in 2 or more sets of blood cultures

- Vancomycin (see dosing section, p. 150)

Coagulase-negative staphylococci (CoNS)

NOTE: Single positive cultures of CoNS should NOT be treated unless they are confirmed by follow-up cultures, the patient is immunosuppressed and/or critically ill, or the patient has implanted hardware. In these cases, treatment can be started but repeat cultures should be sent PRIOR to initiation of therapy to confirm the diagnosis.

- Vancomycin (see dosing section, p. 150)

Change to

- Oxacillin 2 g IV Q4H if susceptible (preferred to Vancomycin)

Duration:

- 3–7 days if catheter removed (preferred)
- 10–14 days if catheter salvage attempt

Methicillin-susceptible *Staphylococcus aureus*

- Oxacillin 2 g IV Q4H if susceptible

OR

- Non-anaphylactic PCN allergy: Cefazolin 2 g IV Q8H

OR

- Anaphylactic PCN allergy: Vancomycin (see dosing section, p. 150)

Methicillin-resistant *Staphylococcus aureus*

- Vancomycin (see dosing section, p. 150)
- Vancomycin allergy or intolerance (not red man syndrome)
 - Daptomycin 8-10 mg/kg IV Q 24H
- OR
- Ceftaroline 600 mg IV Q 8H
- Vancomycin failure: consult ID

TREATMENT NOTES

- Remove catheter. High relapse rates if catheter is not removed.
- Vancomycin is inferior to Oxacillin for treatment of MSSA.
- Patients with *S. aureus* bacteremia should have an echocardiogram to rule out endocarditis. Transthoracic echo is acceptable only if the study adequately views the left-sided valves; most experts recommend TEE.
- Linezolid should not be used routinely for treatment of *S. aureus* bacteremia
- Criteria for a 14 day course of therapy
 - Endocarditis excluded with TEE (preferred); high quality TTE may be adequate in select patients
 - No implanted prostheses
 - Follow-up blood cultures drawn 2-4 days after the initial cultures are negative for *S. aureus*

- The patient defervesces with 72 hours of initiation of effective antistaphylococcal therapy
- The patient has no localizing signs or symptoms of metastatic staphylococcal infection
- Source control has been obtained
- Absence of other conditions that may affect ability to clear infection based on clinical judgment (e.g. poorly controlled diabetes)
- All other patients should receive 4-6 weeks of therapy based on extent of infection

Enterococcus faecalis

NOTE: Can be contaminants. Draw repeat cultures to confirm before starting treatment. 100% of *E. faecalis* blood isolates at JHH are susceptible to Ampicillin, which should be used unless the patient has a PCN allergy.

- Ampicillin 2 g IV Q4H

OR

- PCN allergy: Vancomycin (see dosing section p. 150)

Duration: 7–14 days

Enterococcus faecium

NOTE: Can be contaminants. Draw repeat cultures to confirm before starting treatment. The majority (78%) of *E. faecium* blood isolates at JHH are resistant to Vancomycin. If the isolate is susceptible to Ampicillin or Vancomycin, these agents should be used preferentially at the doses listed above for *E. faecalis* bacteremia.

- Linezolid 600 mg IV/PO Q12H

OR

- Daptomycin 8–12 mg/kg IV Q24H

TREATMENT NOTES

- Consider echocardiogram if there is persistent bacteremia (> 3 days) on antibiotics.
- The addition of Gentamicin does not appear to change outcomes in CR-BSI caused by *Enterococcus* in the absence of endocarditis.

Gram-negative bacilli

Antibiotic selection based on organism and susceptibilities.

Duration: 7–10 days

TREATMENT NOTES

- Catheters are less commonly the source of the infection; however, most advocate catheter removal if the catheter is the source.

Candida spp.

- Refer to p. 117 for treatment of candidemia

CATHETER SALVAGE

- Catheter removal is **STRONGLY** recommended for infections with *S. aureus*, yeast and *Pseudomonas*, as the chance of catheter salvage is low and the risk of recurrent infection is high.
- Catheters associated with tunnel infections **CANNOT** be salvaged and should be removed.
- When catheter salvage is attempted, systemic antibiotics should be given through the infected line.
- Antibiotic used as lock therapy should preferentially match antibiotic used for systemic therapy.

Antibiotic Lock Therapy (ALT)

- Antibiotic lock therapy can be used for catheter salvage in addition to systemic antibiotics when feasible.
- Catheter removal should be performed if cultures remain positive after 72 hours of appropriate antibiotic lock therapy

Acceptable uses:

- Salvage of long-term catheters that cannot be removed (e.g. dialysis catheters, implantable permanent ports or central venous catheters for chemotherapy) when there are **NO** systemic complications (hemodynamic instability, tissue hypoperfusion, septic thrombosis, infectious endocarditis or distant septic metastases) or signs of local infection.

Unacceptable uses:

- Short-term venous catheters
- Complicated CRBSI (e.g. tunnel or port-pocket infection, severe sepsis, septic shock, endocarditis, osteomyelitis and hematogenous seeding at other sites)
- Catheter salvage with *S. aureus* infection.

Duration: 7–14 days

Standardized Concentrations of Antibiotics for ALT

Antibiotic	Heparin (optional)
Vancomycin 5 mg/mL in 0.9% NS	0 or 5000 units
Gentamicin 5 mg/mL in 0.9% NS	2500 units

- ALT should be instilled in the lumen of the catheter when not in use.
- Dwell times should be at minimum of 8–12 hours per day (up to 24–48 h)
- ALT volume needed will vary by type of catheter and available number of lumens. In general, 2–5 mL should be sufficient.

References:

Stability and compatibility of antimicrobial lock solutions. *Am J Health-Syst Pharm.* 2013;70:2185-2198.

IDSA Guidelines for the Diagnosis and Management of Intravascular Catheter-related Infections: *Clin Infect Dis* 2009;49:1-45.

Treatment of native valve endocarditis

NOTES:

- Beta-lactams are **highly preferable** to Vancomycin if the organism is susceptible and if the patient is not severely allergic. Strongly consider PCN desensitization for allergic patients.
- Infectious Diseases consultation is advised for cases of left-sided infective endocarditis and prosthetic valve endocarditis, particularly in those in which the preferred antibiotic cannot be used or in which the organism is resistant to usual therapy.
- Therapeutic monitoring:
 - Vancomycin
 - Goal trough level: 15–20 mcg/mL
 - Gentamicin for Gram-positive synergy
 - Daily dosing
 - Goal trough level: <1 mcg/mL
 - Traditional dosing (Q8H)
 - Goal peak level: 3–4 mcg/mL
 - Goal trough level: <1 mcg/mL
 - See p. 148 and p. 150 for details

Viridans streptococci or *S. bovis* with PCN MIC \leq 0.12 mcg/mL

- Penicillin G 3 million units IV Q4H for 4 weeks
OR
- Non-severe PCN allergy: Ceftriaxone 2 g IV/IM Q24H for 4 weeks
OR
- [Penicillin G 3 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H for 2 weeks] PLUS Gentamicin 3 mg/kg IV Q24H for 2 weeks
OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 4 weeks

Criteria for 2 week treatment:

- Patient does not have cardiac or extracardiac abscess
- CrCl >20 mL/min
- Patient does not have impaired 8th cranial nerve function
- Patient does not have *Abiotrophia*, *Granulicatella*, or *Gemella spp.*

Viridans streptococci or *S. bovis* with PCN MIC > 0.12 mcg/mL and \leq 0.5 mcg/mL

- [Penicillin G 4 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H for 4 weeks] PLUS Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 4 weeks

Viridans streptococci or *S. bovis* with PCN MIC > 0.5 mcg/mL and *Abiotrophia defectiva*, *Granulicatella* spp. and *Gemella* spp.

- Consult ID

TREATMENT NOTES

- All patients with *S. bovis* biotype I endocarditis should undergo GI work-up to rule out underlying cancer.

***Staphylococcus aureus* – Methicillin susceptible, native valve, right-sided involvement only**

- Oxacillin 2 g IV Q4H
 - Use Nafcillin for Oxacillin-induced hepatitis

Criteria for 2-week treatment:

- Patient is an injecting drug user with minimal other comorbidities
- Left-sided endocarditis is ruled out with TEE (preferred) or high quality TTE
- Treatment is with Oxacillin or Nafcillin
- Patient does not have AIDS (CD4 < 200)
- Patient does not have an implanted prosthesis (dialysis graft, etc)
- Blood cultures are negative within 4 days after starting therapy
- There is no evidence of embolic disease OTHER than septic pulmonary emboli
- Vegetations are all < 2 cm in size
- If patient does not meet criteria for 2-week treatment, treat for 4 weeks

***Staphylococcus aureus* – Methicillin susceptible, native valve, left-sided involvement**

- Oxacillin 2 g IV Q4H

OR

- Non-severe PCN allergy: Cefazolin 2 g IV Q8H

OR

- Severe PCN allergy: Strongly consider PCN desensitization or Vancomycin (see dosing section, p. 150)
- The addition of Gentamicin to a beta-lactam may help clear blood cultures faster but does not appear to affect mortality. It particularly should be avoided in the elderly and in those with baseline renal impairment.

***Staphylococcus aureus* – Methicillin resistant, native valve**

- Vancomycin (see dosing section, p. 150)

Duration

- Uncomplicated: 6 weeks
- Complicated (perivalvular abscess formation, metastatic complication, poor controlled diabetes mellitus): 6 or more weeks based on clinical picture and response to therapy
- ID and cardiac surgery consults recommended for complicated diseases

***S. pneumoniae*, and Group A streptococci**

- Penicillin G 3 million units IV Q4H for 4 weeks
OR
- Non-severe PCN allergy: Ceftriaxone 2 g IV Q24H for 4 weeks OR Cefazolin 2 g IV Q8H for 4 weeks
OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 4 weeks
- For *S. pneumoniae*, if PCN MIC ≥ 0.1 , consult ID

Groups B, C and G streptococci

- Penicillin G 3 million units IV Q4H for 4–6 weeks \pm Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy
OR
- Non-severe PCN allergy: Cefazolin 2 g IV Q8H for 4–6 weeks \pm Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy
OR
- Severe PCN allergy: Vancomycin (see dosing section, p. 146) for 4–6 weeks \pm Gentamicin 3 mg/kg IV Q24H for the first 2 weeks of therapy
- Consider an ID Consult

Enterococcus faecalis

- Ampicillin and Gentamicin susceptible: Ampicillin 2 g IV Q4H OR Penicillin G 4 million units IV Q4H PLUS Gentamicin 1 mg/kg IV Q8H BOTH for 4-6 weeks
- Ampicillin susceptible with contraindications for aminoglycosides or Gentamicin resistant: Ampicillin 2 g IV Q4H OR Penicillin G 4 million units IV Q4H PLUS Ceftriaxone 2 g IV Q12H BOTH for 4-6 weeks

OR

- Severe PCN allergy: Strongly consider PCN desensitization if PCN allergy is anaphylactic or Vancomycin (see dosing section, p. 146) PLUS Gentamicin 1 mg/kg IV Q8H BOTH for 4–6 weeks
- Treat for 4 weeks only when symptoms have been present for < 3 months AND there is a prompt response to therapy

Enterococcus faecium

- Consult ID

Reference:

Use of Ceftriaxone in enterococcal endocarditis: Clin Infect Dis 2013; 56:1261-8.

HACEK organisms (*Haemophilus parainfluenzae*, *H. aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominus*, *Eikenella corrodens*, *Kingella kingae*)

- Ceftriaxone 2 g IV/IM Q24H for 4 weeks

OR

- Severe PCN allergy: Consult ID

Gram-negative organisms, culture negative endocarditis, or fungal endocarditis

- Consult ID

Treatment of prosthetic valve endocarditis

- Generally caused by staphylococci in the first 1–2 years following valve replacement (both *S. aureus* and coagulase-negative staph). Etiologies are similar to native valve infections 2 or more years post-op.
- Medical treatment alone is often NOT effective.
- All patients should have a TEE.

EMPIRIC TREATMENT

- Vancomycin (see dosing section, p. 150) PLUS Gentamicin 1 mg/kg IV Q8H

Viridans streptococci or *S. bovis* with PCN MIC \leq 0.12 mcg/mL

- [Penicillin G 4 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H] for 6 weeks \pm Gentamicin 3 mg/kg IV Q24H for first 2 weeks of therapy

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 6 weeks

Viridans streptococci or *S. bovis* with PCN MIC > 0.12 mcg/mL

- [Penicillin G 4 million units IV Q4H OR Ceftriaxone 2 g IV/IM Q24H]
PLUS Gentamicin 3 mg/kg IV Q24H for 6 weeks

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) for 6 weeks

***Staphylococcus aureus*—Methicillin susceptible**

- Oxacillin 2 g IV Q4H for 6 weeks PLUS Gentamicin 1 mg/kg IV Q8H for first 2 weeks of therapy

AND

- Rifampin 300 mg PO Q8H for 6 weeks **after blood cultures have cleared**
- ID and cardiac surgery consults recommended

***Staphylococcus aureus*—Methicillin resistant or Coagulase-negative staphylococci**

- Vancomycin (see dosing section, p. 150) for 6 weeks PLUS Gentamicin 1 mg/kg IV Q8H for the first 2 weeks of therapy

AND

- Rifampin 300 mg PO Q8H for 6 weeks **after blood cultures have cleared**
- If coagulase-negative staphylococci is susceptible to Oxacillin then treat as *S. aureus* – Methicillin susceptible.
- ID and cardiac surgery consults recommended

Gram-negative organisms or culture negative endocarditis

- Consult ID

DUKE CRITERIA FOR INFECTIVE ENDOCARDITIS**Diagnostic criteria (Modified Duke criteria)**

Definite endocarditis

- Presence of 2 major criteria OR 1 major AND 3 minor OR 5 minor

Possible endocarditis

- Presence of 1 major AND 1 minor OR 3 minor criteria

Rejected endocarditis

- Firm alternate diagnosis that explains ALL manifestations of IE
(**NOTE:** simply having another infection does NOT exclude endocarditis)

Major criteria

Microbiologic

- Two separate blood cultures positive for a typical organism: viridans streptococci, *S. bovis*, HACEK, *S. aureus*, *Enterococcus* spp.
- Persistent bacteremia with any organism as evidenced by: 2 positive blood cultures drawn at least 12 hours apart OR 3/3 positive blood cultures with at least 1 hour between the first and last OR the majority of more than 4 cultures positive from any time period.
- Positive *Coxiella burnetti* (Q fever) culture or serology.

Echocardiographic (TEE strongly recommended for prosthetic valve)

- Vegetation (on valve or supporting structure OR in path of regurgitant jet)
- Abscess
- New dehiscence of prosthetic valve

Physical exam

- NEW regurgitant murmur (worsening of old murmur is NOT sufficient)

Minor criteria

- Predisposing condition: previous endocarditis, injection drug use, prosthetic valve, ventricular septal defect, coarctation of the aorta, calcified valve, patent ductus, mitral valve prolapse with regurgitation, IHSS or other valvular heart disease
- Fever $\geq 38.0^{\circ}\text{C}$ (100.4°F)
- Embolic events: arterial or pulmonary emboli, conjunctival hemorrhage, retinal hemorrhage, splinter hemorrhage, intracranial hemorrhage, mycotic aneurysm
- Immunologic phenomenon: Osler nodes, glomerulonephritis, positive rheumatoid factor
- Positive blood cultures that don't meet criteria above OR serologic evidence of active infection with an organism known to cause endocarditis BUT single positive cultures for coagulase-negative staphylococci are NOT considered even a minor criterion

References:

Oral therapy: Am J Med 1996; 101:68-76.

Short course therapy: Ann Intern Med 1994; 121:873-6.

Duke criteria: Clin Infect Dis 2000; 30:633-8.

AHA Scientific Statement on Infective Endocarditis: Circulation 2005; 111(23):e394-434.

TEE in *S. aureus* bacteremia: J Am Coll Cardiol 1997; 30: 1072-8.

MRSA bacteremia/endocarditis recommendations: Clin Infect Dis 2011; 52:e18-55

Permanent pacemaker (PPM) and implantable cardioverter-defibrillator (ICD) infections

NOTE: Obtain at least 2 sets of blood cultures before initiation of antibiotic therapy

EMPIRIC TREATMENT

- Vancomycin (see dosing section, p. 150). Narrow therapy based on culture results.

TREATMENT NOTES

Microbiology—staphylococci in 70-80% of cases (~50% coagulase-negative staphylococci and ~50% *S. aureus*)

Management

- If blood cultures are positive or endocarditis is suspected patients should undergo transesophageal echocardiography (TEE)
- Complete extraction recommended for patients with pocket infection and/or valvular or lead endocarditis
- At the time of extraction, tissue (rather than swabs) from the generator pocket should be sent for Gram-stain and culture and lead tips should be sent for culture.
- Note that because leads are extracted through an open generator pocket, they may become contaminated by the infected pocket; therefore, positive lead cultures are not always indicative of lead endocarditis in patient with negative blood cultures.
- Blood cultures should be obtained after device removal.
- Device reimplantation should be on the contra-lateral side whenever possible.
- Complete extraction is strongly recommended in all patients presenting with *S. aureus* bacteremia and no other source
- Complete extraction should be considered in patients with persistent positive blood cultures with other organisms (e.g. coagulase-negative staphylococci, enterococci, Gram-negative bacilli) on a case-by-case basis.
- Complete device and lead removal is recommended for patients with valvular endocarditis.
- Antimicrobial prophylaxis is NOT recommended for dental or other invasive procedures following placement

Reference:

AHA Scientific Statement on PPM and ICD infections: *Circulation* 2010; 121:458-477.

Reimplantation timing and duration of therapy

Diagnosis	Timing of reimplantation	Duration of therapy
Pocket site infection	Blood cultures negative for 72 hours and surgical site healing	7-10 days if device erosion without inflammation 10-14 days all others Oral therapy can be considered
Positive blood cultures with rapid clearance AND TEE with either no vegetation or uncomplicated lead vegetation	Post-explantation blood cultures negative for 72 hours	Non- <i>S. aureus</i> : 2 weeks IV therapy <i>S. aureus</i> : 4 weeks IV therapy
Sustained positive blood cultures AND TEE with no vegetation or uncomplicated lead vegetation	Post-explantation blood cultures negative for 72 hours	4 weeks IV therapy
Valve endocarditis	Blood cultures negative for 14 days	4-6 weeks IV therapy (see Endocarditis p. 65)

Reference:

AHA Scientific Statement on Cardiovascular Implantable Electronic Device Infections: Circulation 2010; 121:458-77.

Meningitis – Empiric treatment

TREATMENT

- **ANTIBIOTICS SHOULD BE STARTED AS SOON AS THE POSSIBILITY OF BACTERIAL MENINGITIS BECOMES EVIDENT, IDEALLY WITHIN 30 MINUTES.**
- **DO NOT WAIT FOR CT SCAN OR LP RESULTS. IF LP MUST BE DELAYED, GET BLOOD CULTURES AND START THERAPY.**
- Adjust therapy once pathogen and susceptibilities are known.
- Some advocate penicillin desensitization for pathogen-specific therapy in patients with severe allergies (p. 137).
- **Antibiotic doses are higher for CNS infections (p. 77).**
- Infectious Diseases consultation is advised for all CNS infections, particularly those in which the preferred antibiotic cannot be used or in which the organism is resistant to usual therapy.

Empiric therapy

Host	Pathogens	Preferred Abx	Alternative for serious PCN allergy (ID consult recommended)
Immunocompetent* age < 50	<i>S. pneumo</i> , <i>N. mening</i> , <i>H. influenzae</i>	Vancomycin <u>PLUS</u> Ceftriaxone	Moxifloxacin [†] <u>PLUS</u> Vancomycin
Immunocompetent* age > 50	<i>S. pneumo</i> , <i>Listeria</i> , <i>H. influenzae</i> , <i>N. mening</i> , Group B <i>streptococci</i>	Vancomycin <u>PLUS</u> Ceftriaxone <u>PLUS</u> Ampicillin	Moxifloxacin [†] <u>PLUS</u> Vancomycin <u>PLUS</u> TMP/SMX
Immuno- compromised [†]	<i>S. pneumo</i> , <i>N. mening</i> , <i>H. influenzae</i> , <i>Listeria</i> , (Gram-negatives)	Vancomycin <u>PLUS</u> Cefepime <u>PLUS</u> Ampicillin	Vancomycin <u>PLUS</u> TMP/SMX <u>PLUS</u> Ciprofloxacin
Post neurosurgery or penetrating head trauma	<i>S. pneumo</i> (if CSF leak), <i>H. influenzae</i> , <i>Staphylococci</i> , Gram-negatives	Vancomycin <u>PLUS</u> Cefepime	Vancomycin <u>PLUS</u> Ciprofloxacin
Infected shunt	<i>S. aureus</i> , coagulase- negative staphylococci, Gram-negatives (rare)	Vancomycin <u>PLUS</u> Cefepime	Vancomycin <u>PLUS</u> Ciprofloxacin

† Immunocompromised is defined as solid organ transplant, BMT in the past year, leukemia undergoing treatment, or neutropenia

‡ Allergy consult for beta-lactam desensitization

* Use of Dexamethasone

- Addition of dexamethasone is recommended in all adult patients with suspected pneumococcal meningitis (note that this will be most adult patients).
- Dose: 0.15 mg/kg IV Q6H for 2–4 days
- The first dose must be administered 10–20 minutes before or concomitant with the first dose of antibiotics.

- Administration of antibiotics should not be delayed to give dexamethasone.
- Dexamethasone should not be given to patients who have already started antibiotics.
- Continue dexamethasone only if the CSF Gram stain shows Gram-positive diplococci or if blood or CSF grows *S. pneumoniae*

Pathogen-specific therapy (ID consult recommended)

Pathogens	Preferred	Alternative for serious PCN allergy (Consult allergy for PCN skin testing ± desensitization)
<i>S. pneumo</i> PCN MIC ≤ 0.06 µg/ml AND/OR Ceftriaxone MIC < 0.5 µg/ml	Penicillin OR Ceftriaxone	Vancomycin OR Moxifloxacin OR Linezolid
<i>S. pneumo</i> PCN MIC > 0.1–1 µg/ml AND Ceftriaxone MIC < 1 µg/ml (ID consult recommended)	Ceftriaxone	Moxifloxacin OR Linezolid
<i>S. pneumo</i> PCN MIC > 1 µg/ml AND Ceftriaxone MIC ≥ 1 µg/ml (ID consult recommended)	Ceftriaxone <u>PLUS</u> Vancomycin <u>PLUS</u> Rifampin	Moxifloxacin OR Linezolid
<i>N. meningitidis</i> PCN susceptible (MIC < 0.1)	Penicillin OR Ceftriaxone ⁺	Consult ID
<i>H. flu</i> Non β-lactamase producer	Ampicillin OR Ceftriaxone	Ciprofloxacin*
<i>H. flu</i> β-lactamase producer	Ceftriaxone	Ciprofloxacin*
<i>Listeria</i>	Ampicillin ± Gentamicin [†]	TMP/SMX
<i>P. aeruginosa</i>	Cefepime OR Meropenem	Ciprofloxacin <u>PLUS</u> Aztreonam
<i>E. coli</i>	Ceftriaxone	Aztreonam OR Ciprofloxacin OR TMP/SMX
<i>K. pneumoniae</i>		
<i>Enterobacter</i> spp.	Meropenem	TMP/SMX or Ciprofloxacin
<i>S. aureus</i> –MSSA	Oxacillin	Vancomycin
<i>S. aureus</i> –MRSA	Vancomycin	
Coagulase-negative staphylococci if Oxacillin MIC ≤ 0.25	Oxacillin	Vancomycin
Coagulase-negative staphylococci Oxacillin MIC > 0.25	Vancomycin	
Enterococcus	Ampicillin <u>PLUS</u> Gentamicin [†]	Vancomycin <u>PLUS</u> Gentamicin [†]
Candida species	Amphotericin B	
Cryptococcus	Amphotericin B <u>PLUS</u> Flucytosine	

* Consider beta-lactam desensitization

+ Must give Ciprofloxacin 500 mg once to eradicate carrier state if PCN used as treatment

† Administer aminoglycosides systemically, not intrathecally

TREATMENT NOTES

Indications for head CT prior to LP

- History of CNS diseases (mass lesion, CVA)
- New-onset seizure (\leq 1 week)
- Papilledema
- Altered consciousness
- Focal neurologic deficit

Duration

- STOP treatment if LP culture obtained prior to antibiotic therapy is negative at 48 hours OR no PMNs on cell count
- *S. pneumoniae*: 10–14 days
- *N. meningitidis*: 7 days
- *Listeria*: 21 days
- *H. influenzae*: 7 days
- Gram-negative bacilli: 21 days

Adjunctive therapy

- Consider intracranial pressure monitoring in patients with impaired mental status.

Encephalitis

- Herpes viruses (HSV, VZV) remain the predominant causes of treatable encephalitis.
- CSF PCRs are rapid diagnostic tests and appear quite sensitive and specific.
- Have low threshold to treat if suspected as untreated mortality exceeds 70%.
- Treatment: Acyclovir 10 mg/kg IV Q8H for 14–21 days

Brain abscess

- Empiric treatment is guided by suspected source and underlying condition. While therapy should be adjusted based on culture results, anaerobic coverage should ALWAYS continue even if none are grown.

Source/ Condition	Pathogens	Preferred	Alternative for serious PCN allergy (ID consult recommended)
Unknown	<i>S. aureus</i> , Streptococci, Gram-negatives, Anaerobes	Vancomycin PLUS Ceftriaxone PLUS Metronidazole	Vancomycin PLUS Ciprofloxacin PLUS Metronidazole
Sinusitis	Streptococci (incl. <i>S. pneumoniae</i>), Anaerobes	[Penicillin OR Ceftriaxone] PLUS Metronidazole	Vancomycin PLUS Metronidazole
Chronic otitis	Gram-negatives, Streptococci Anaerobes	Cefepime PLUS Metronidazole	Aztreonam PLUS Metronidazole PLUS Vancomycin
Post neurosurgery	Staphylococci, Gram negatives	Vancomycin PLUS Cefepime	Vancomycin PLUS Ciprofloxacin
Cyanotic heart disease	Streptococci (esp. <i>S. viridans</i>)	Penicillin OR Ceftriaxone	Vancomycin

References:

IDSA Guidelines for Bacterial Meningitis: Clin Infect Dis 2004;39:1267.

Dexamethasone in adults with bacterial meningitis: N Eng J Med 2002;347:1549.

CNS shunt infection

Diagnosis

- Culture of cerebrospinal fluid remains the mainstay of diagnosis. Clinical symptoms may be mild and/or non-specific, and CSF chemistries and leukocyte counts may be normal.

Empiric Therapy

- Vancomycin (see dosing section, p. 150) PLUS Cefepime 2 g IV Q8H **OR**
- PCN Allergy: Vancomycin (see dosing section, p. 150) PLUS Ciprofloxacin 400 mg IV Q8H

TREATMENT NOTES

- **ID consult recommended for assistance with timing of shunt replacement and length of antibiotic therapy.**
- Removal of all components of the infected shunt with external ventricular drainage or intermittent ventricular taps in combination with the appropriate intravenous antibiotic therapy leads to the highest effective cure rates. Success rates are substantially lower when the infected shunt components are not removed.

- The role of intraventricular antibiotics is controversial, and generally limited to refractory cases or cases in which shunt removal is not possible. Intraventricular injection should be administered only by experienced physicians.

References:

IDSA Guidelines for the Management of Bacterial Meningitis: Clin Infect Dis 2004;39:1267.

Therapy in cerebrospinal fluid shunt infection. Neurosurgery 1980;7:459.

Antimicrobial doses for CNS infections – normal renal function

Antibiotics

- Aminoglycosides: see p. 145
- Ampicillin: 2 g IV Q4H
- Aztreonam: 2 g IV Q6H
- Ceftriaxone: 2 g IV Q12H
- Cefepime: 2 g IV Q8H
- Ciprofloxacin: 400 mg IV Q8H (based on limited data)
- Moxifloxacin: 400 mg IV Q24H
- Meropenem: 2 g IV Q8H
- Metronidazole: 500 mg IV Q6H
- Oxacillin: 2 g IV Q4H
- Penicillin: 4 million units IV Q4H (24 million units per day)
- Rifampin: 600 mg IV Q12–24H
- TMP/SMX: 5 mg/kg (TMP component) IV Q6H
- Vancomycin: load with 25–35 mg/kg, then 15–20 mg/kg Q8–12H (minimum 1 g Q12H)
 - Vancomycin should be administered to maintain serum trough concentrations close to 20 mcg/mL.

Antifungals

- Amphotericin: 0.7–1 mg/kg IV Q24H
- AmBisome®: 3–4 mg/kg IV Q24H for Cryptococcal meningitis
- AmBisome®: 5 mg/kg IV Q24H for Candida meningitis
- Fluconazole: 800–1200 mg IV/PO Q24H (can give in divided doses)
- Flucytosine: 25 mg/kg PO Q6H

Intraventricular antibiotics (ID consult recommended)

- Amikacin: 30 mg Q24H (contains preservative)
- Gentamicin: 5 mg Q24H
- Tobramycin: 5 mg Q24H
- Vancomycin: 20 mg Q24H

Acute bacterial rhinosinusitis (ABRS)

NOTE: Sinusitis in immunocompromised hosts can be caused by fungi and other less-common pathogens; consultation with ID and ENT is recommended to guide management and therapy.

Most rhinosinusitis does not require antibiotic treatment; treatment should be considered in the following scenarios:

- Persistent symptoms of acute rhinosinusitis ≥ 10 days without improvement
- Fever $\geq 39^\circ\text{C}$ and purulent nasal discharge or facial pain lasting >3 -4 days from the beginning of illness
- New onset of fever, headache or increase in nasal discharge following viral URI that lasted 5-6 days and was initially improving

EMPIRIC TREATMENT

Oral regimens

- Amoxicillin/clavulanate 875 mg PO Q12H
OR
- Amoxicillin/clavulanate XR 2 g PO Q12H for patients with severe infection (e.g. systemic toxicity with fever of 39°C), antibiotic use in previous 30 days, immunocompromised
OR
- Non-severe PCN allergy: Cefpodoxime 200 mg PO Q12H
OR
- Severe PCN allergy: Moxifloxacin 400 mg PO daily

Parenteral regimens

- Ampicillin/sulbactam 1.5 g IV Q6H
OR
- Non-severe PCN allergy: Ceftriaxone 1 g IV Q24H
OR
- Severe PCN allergy: Moxifloxacin 400 mg IV Q24H

Duration

- 5-7 days

TREATMENT NOTES

Microbiology

- Predominantly *S. pneumoniae*, *H. influenzae*, *M. catarrhalis*
- Gram-negative enteric bacilli are rare

Management

- ABRS is rarely present prior to 7–10 days of symptoms; typical inciting etiologies of acute sinusitis include allergies and viral URI

- Cultures by direct sinus aspiration or endoscopically guided culture of the middle meatus should only be obtained in patients who fail empiric antibiotic therapy. Nasopharyngeal swab is NOT recommended for obtaining culture data.
- Confirmation of diagnosis with imaging is not recommended for uncomplicated ABRS. Consider CT in those with severe disease with possible extension to the orbit or intracranial space.
- Intranasal saline irrigation (physiologic or hypertonic) and intranasal corticosteroids are recommended as adjuncts to antibiotic therapy and can also provide symptomatic relief in patients in whom antibiotic are not indicated
- Macrolides (Clarithromycin, Azithromycin) are not recommended for initial empiric therapy due to high rates of resistance of *S. pneumoniae* (55% at JHH)
- Despite IDSA guidelines supporting use of Doxycycline as an alternative agent for ABRS, Doxycycline is NOT recommended for initial empiric therapy at JHH due to high rates of resistance of *S. pneumoniae* (27%) and *H. influenzae* (35%)
- Routine coverage for MRSA in initial empiric therapy for ABRS is not recommended

Reference:

IDSA guidelines for ABRS. Clin Infect Dis 2012; 54(8):e72-e112.

Orbital cellulitis

Preseptal cellulitis (>90% of cases)

- Involves tissues anterior to the orbital septum
- Presents with fever, eyelid erythema and soft tissue swelling but no orbital congestion

Postseptal cellulitis

- Signs of periorbital cellulitis as well as limitation of ocular movements, pain with ocular movement, and/or proptosis
- Severe infection can also involve visual loss, subperiosteal abscess, globe displacement, abscess formation
- Often associated with sinusitis
- Can be associated with cavernous sinus thrombosis

EMPIRIC TREATMENT

- Ampicillin/sulbactam 3 g IV Q6H

OR

- Non-severe PCN allergy: Ceftriaxone 2 g IV daily

OR

- Severe PCN allergy: Moxifloxacin 400 mg IV daily

Add Vancomycin (see dosing section, p. 150) in patients with history of MRSA colonization or infection, evidence of abscess or bone involvement, orbital trauma, recent ophthalmic surgery or severe infection

Oral step down therapy (for patients without culture data to guide therapy and without evidence of bony involvement or cavernous sinus thrombosis)

- Amoxicillin/clavulanate 875 mg PO Q12H

OR

- Non-severe PCN allergy: Cefpodoxime 400 mg PO Q12H

OR

- Severe PCN allergy: Moxifloxacin 400 mg PO daily

Duration

- 7 days up to 6 weeks if evidence of bony involvement

TREATMENT NOTES

Microbiology

- *S. aureus*, beta-hemolytic streptococci, *S. pneumoniae*, *H. influenzae*, *M. catarrhalis* (cultures are infrequently positive)

Management

- Imaging is recommended in post-septal cellulitis (CT or MRI)
- Consultation with ID, ENT, and ophthalmology recommended

- Post-septal cellulitis in immunocompromised hosts can be caused by fungi and molds; empiric antifungal therapy is recommended in consultation with ID
- Post-septal cellulitis with abscess formation should prompt immediate surgical intervention
- Response to appropriate antibiotic therapy should occur in 24 – 48 hours
- Poor response to antibiotics, worsening visual acuity or pupillary changes and/or evidence of an abscess are indications for surgery

COPD exacerbations

EMPIRIC TREATMENT

- Doxycycline 100 mg PO BID for 5 days
OR
- Azithromycin 500 mg PO/IV Q24H for 3 days
OR
- Amoxicillin/clavulanate 875 mg PO BID for 5 days
OR
- Cefpodoxime 200 mg PO BID for 5 days
OR
- Cefdinir 300 mg PO BID for 5 days

TREATMENT NOTES

Microbiology

- Predominantly *H. influenzae*, *M. catarrhalis*, *S. pneumoniae*
- *Pseudomonas*, *Enterobacteriaceae* are less common and seen in patients with severe COPD and extensive antibiotic exposure.

Management

- Empiric use of fluoroquinolones is discouraged and should only be considered if past or present microbiologic evidence indicates infection with a pathogen(s) that is resistant to standard therapy (e.g. *Pseudomonas*, *Enterobacteriaceae*).
- IV antibiotics should only be used if the patient cannot tolerate PO antibiotics.
- Antibiotics are not indicated for asthma flares in the absence of pneumonia.

Prophylactic antibiotics for the prevention of COPD exacerbations

- Prophylactic antibiotics have been shown to reduce rates of exacerbations and improve reported quality of life but not to decrease all-cause or respiratory-associated mortality
- Prolonged Azithromycin use has been associated with hearing loss and QT prolongation; patients with baseline QT-prolongation were not included in clinical trials
- The decision to initiate prophylactic antibiotics should be made on a case-by-case basis and should take in to account patient preferences, financial constraints, risk factors for adverse events and input from the patient's pulmonologist
- Recommended regimen: Azithromycin 250 mg PO daily
- Baseline audiometry and EKG is recommended

References:

American College of Physicians Position Paper: *Ann Intern Med* 2001; 134:600.
 Duration of therapy: *Thorax* 2008; 63(5):415–22.
 Azithromycin for prevention: *N. Engl. J Med* 2011; 365: 689; *Cochrane Database Syst Rev* 2013 Nov 28.

Community-acquired pneumonia (CAP) in hospitalized patients

NOTE: If patient is coming from a nursing home or long-term care facility, see Healthcare-acquired pneumonia, p. 87.

EMPIRIC TREATMENT

Patient NOT in the ICU

- Ampicillin/sulbactam 1.5 g IV Q6H PLUS Azithromycin 500 mg IV/PO once daily
- OR**
- Ceftriaxone 1 g IV Q24H PLUS Azithromycin 500 mg IV/PO once daily
- OR**
- Moxifloxacin 400 mg IV/PO Q24H

In non-critically ill patients, consider switch to oral agents as soon as patient is clinically improving and eating (see next page for oral options and doses).

Patient in the ICU

Not at risk for infection with *Pseudomonas* (see risks below)

- Ceftriaxone 1 g IV Q24H PLUS Azithromycin 500 mg IV Q24H
- OR**
- PCN allergy: Moxifloxacin 400 mg IV Q24H

At risk for infection with *Pseudomonas* (see risks below)

- Cefepime 1-2 g IV Q8H PLUS Azithromycin 500 mg IV Q24H
- OR**
- Piperacillin/tazobactam 4.5 g IV Q6H PLUS Azithromycin 500 mg IV Q24H
- OR**
- Severe PCN allergy: Moxifloxacin 400 mg IV Q24H PLUS Aztreonam 2 g IV Q8H
- Sputum gram stain may help determine if *Pseudomonas* is present.
- **Narrow coverage** if *Pseudomonas* is NOT present on culture at 48 hours.

Risks for *Pseudomonas* and other resistant Gram-negative organisms: bronchiectasis; broad-spectrum antibiotics for > 7 days in the past month; prolonged hospitalization > 7 days; debilitated nursing home resident; recent mechanical ventilation > 48 H; immunocompromised due to solid organ transplant, hematologic malignancy, BMT, active chemotherapy, prednisone > 20 mg daily for > 3 weeks.

DIAGNOSIS

- Immunocompetent patients **MUST** have a chest X-ray infiltrate to meet diagnostic criteria for pneumonia.
- Sputum and blood cultures should be sent on all patients admitted to the hospital **BEFORE** antibiotics are given.
- *S. pneumoniae* urine antigen should be obtained in all patients with CAP. It has specificity of 96% and positive predictive value of 88.8-96.5%. It is particularly useful if antibiotics have already been started or cultures cannot be obtained.

- The legionella urine antigen is the test of choice for diagnosing legionella infection. This test detects only *L. pneumophila* serogroup 1, which is responsible for 70–80% of infections.

DURATION

- Therapy can be stopped after the patient is:
 - Afebrile for 48–72 hours

AND

 - Has no more than one of the following signs and symptoms: HR > 100 beats/min, RR > 24 breaths/min, BP < 90 mmHg, O₂ sat < 90%, altered mental status.
- Suggested duration of therapy based on patient specific factors:
 - **3–5 days:** Patient without immunocompromise or structural lung disease
 - **7 days:** Patients with moderate immunocompromise and/or structural lung disease
 - **10–14 days:** Patients with poor clinical response, who received initial inappropriate therapy, or who are significantly immunocompromised
- Uncomplicated bacteremic pneumococcal pneumonia— prolonged course of antibiotic therapy not necessary, treat as pneumonia
- Cough and chest X-ray abnormalities may take 4–6 weeks to improve. There is NO need to extend antibiotics if the patient is doing well otherwise (e.g. no fever).

Other causes of pneumonia

- Suspected aspiration: Additional empiric coverage for aspiration is justified only in classic aspiration syndromes suggested by loss of consciousness (overdose, seizure) **PLUS** gingival disease or esophageal motility disorder. Ceftriaxone, Cefepime, and Moxifloxacin have adequate activity against most oral anaerobes. For classic aspiration, Clindamycin 600 mg IV Q8H can be added to regimens not containing Piperacillin/tazobactam.
- Community-acquired MRSA: Necrotizing pneumonia with cavitation in absence of risk factors for aspiration listed above is concerning for CA-MRSA pneumonia, particularly if associated with a preceding or concomitant influenza-like illness. In these cases, Linezolid 600 mg IV/PO Q12H can be added while awaiting culture data. Infectious Diseases consult is strongly recommended. Use of Linezolid monotherapy for MRSA bacteremia, even if associated with a pulmonary source, is not recommended. In the absence of necrotizing pneumonia with cavitation, empiric coverage for CA-MRSA can be deferred until sputum and blood culture results return given their high diagnostic yield for CA-MRSA.
- Respiratory viruses: Respiratory viruses can cause primary viral pneumonia as well as lead to bacterial superinfection. Strongly consider testing all patients with CAP during respiratory virus season (see p. 93).

References:

- IDSA/ATS Consensus Guidelines for CAP: Clin Infect Dis 2007;44:S27.
S. pneumo antigen: Arch Intern Med 2011;171(2):166–72
 3 days of therapy for CAP: BMJ 2006;332:1355.

Pathogen-specific and step-down therapy

Organism	Preferred therapy	PCN allergy	Notes
<i>S. pneumoniae</i> PCN susceptible	Penicillin G 1 million units IV Q6H OR	Non-severe reaction: Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID	91% of <i>S. pneumoniae</i> isolates at JHH (excluding oncology) are susceptible and 9% are intermediate to PCN, 45% are susceptible to Erythromycin (Erythromycin susceptibilities predict Azithromycin susceptibilities for <i>S. pneumoniae</i>), and 100% are susceptible to Moxifloxacin
	Amoxicillin 500 mg PO TID	Severe reaction: Azithromycin* [500 mg PO daily X 3 days OR 500 mg once, then 250 mg PO daily X 4 days] OR Moxifloxacin 400 mg IV/PO daily (if Erythromycin resistant)	
<i>S. pneumoniae</i> PCN intermediate or urine antigen positive	Penicillin G 1 million units IV Q6H OR Amoxicillin 1 g PO TID	Same as above	
	<i>S. pneumoniae</i> PCN resistant, cephalosporin susceptible	Ceftriaxone 1 g IV Q24 OR Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID	None of the <i>S. pneumoniae</i> isolates at (excluding oncology) are resistant JHH to PCN
<i>H. influenzae</i> non-beta-lactamase producing (Ampicillin susceptible)	Ampicillin 1 g IV Q6H OR Amoxicillin 500 mg PO TID	Moxifloxacin 400 mg IV/PO Q24H	75% of <i>H. influenzae</i> isolates at JHH (excluding oncology) are susceptible to Ampicillin, 100% to Ceftriaxone, 65% to Tetracycline, and 100% to Moxifloxacin
		Azithromycin* [500 mg PO daily X 3 days OR 500 mg once, then 250 mg PO daily X 4 days] OR Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID OR Doxycycline† 100 mg PO BID OR Moxifloxacin 400 mg IV/PO daily (if resistant to other options)	

Pathogen-specific and step-down therapy

Organism	Preferred therapy	PCN allergy	Notes
<i>H. influenzae</i> beta-lactamase producing (Ampicillin resistant)	Ampicillin/subactam 1.5 g Q6H OR Amoxicillin/clavulanate 875 mg PO BID	Azithromycin* 500 mg PO daily X 3 days OR 500 mg once, then 250 mg PO daily X 4 days OR Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID OR Doxycycline† 100 mg PO BID OR Moxifloxacin 400 mg IV/PO Q24H (if resistant to other options)	
<i>L. pneumophila</i>	Azithromycin 500 mg IV/PO Q24H OR Moxifloxacin 400 mg IV/PO Q24H	Azithromycin 500 mg IV/PO Q24H x 7-10 days OR Moxifloxacin 400 mg IV/PO Q24H X 10-14 days	
Culture and urine antigen negative	Cefpodoxime 200 mg PO BID OR Cefdinir 300 mg PO BID OR Amoxicillin/clavulanate XR 2 g PO BID	Moxifloxacin 400 mg IV/PO Q24H	45% of <i>S. pneumoniae</i> isolates at JHH (excluding oncology) are susceptible to Erythromycin (Erythromycin susceptibilities predict Azithromycin susceptibilities for <i>S. pneumoniae</i>) and 73% are susceptible to Tetracycline; therefore, these agents are suboptimal for empiric step-down therapy

*If Erythromycin susceptible; † If Tetracycline susceptible

Healthcare-acquired pneumonia (NOT ventilator-associated)

NOTE: If the patient is on antibiotic therapy or has recently been on antibiotic therapy, choose an agent from a different class.

EMPIRIC TREATMENT

Patient with mild to moderate illness (e.g., not in or transferring to the ICU/intermediate care unit, no or minimal oxygen requirement, no hypotension)

- Ceftriaxone* 1 g IV Q24H

OR

- Severe PCN allergy: Moxifloxacin 400 mg IV/PO Q24H

Patient with severe illness (e.g., in or transferring to the ICU/intermediate care unit, concern for sepsis, significant oxygen requirement, multi-lobe consolidation)

- Cefepime* 2 g IV Q8H ± Vancomycin† (see dosing section, p. 150)

OR

- Piperacillin/tazobactam* 4.5 g IV Q6H ± Vancomycin† (see dosing section, p. 150)

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS Ciprofloxacin 400 mg IV Q8H ± Gentamicin (see dosing section, p. 146)

*Consider adding Azithromycin 500 mg IV/PO Q24H if the patient is immunosuppressed or coming from a nursing home or long term care facility to cover Legionella

†Add Vancomycin in patients with a history of MRSA colonization or infection, necrotizing pneumonia, pneumonia after a respiratory viral illness, ill patients coming from a nursing home or long term care facility, sepsis)

Patient with history of or risk factors for Pseudomonas and other resistant Gram-negative organisms (e.g., bronchiectasis; broad-spectrum antibiotics for > 7 days in the past month; prolonged hospitalization > 7 days; debilitated nursing home resident; recent mechanical ventilation > 48 hours; immunocompromised due to solid organ transplant, hematologic malignancy, BMT, active chemotherapy, prednisone > 20 mg daily for > 3 weeks): treat as severe illness with tailoring of antibiotic based on past culture data

NOTE: Always narrow therapy based on cultures results

Oral step down therapy (if no sputum culture data to guide therapy)

- Cefpodoxime 400 mg PO BID (if on Ceftriaxone) OR Moxifloxacin 400 mg PO daily

Duration: if pneumonia confirmed 5-7 days; if pneumonia diagnosis is questionable and patient improves, can considered stopping therapy after 3 days

TREATMENT NOTES

Microbiology

- Enterococci and candida species are often isolated from the sputum in hospitalized patients. In general, they should be considered to be colonizing organisms and should not be treated with antimicrobials.

Antimicrobial management of “aspiration events”

- Prophylactic antibiotics ARE NOT recommended for patients who are at increased risk for aspiration.
- Immediate treatment is indicated for patients who have small-bowel obstructions or are on acid suppression therapy given the increased risk of gastric colonization.
- Antibiotic treatment of patients who develop fever, leukocytosis and infiltrates in the first 48 hours after an aspiration is likely unnecessary since most aspiration pneumonias are chemical and antibiotic treatment may only select for more resistant organisms.
- Treatment IS recommended for patients who have symptoms for more than 48 hours or who are severely ill.

References:

Aspiration pneumonitis and aspiration pneumonia: N Engl J Med 2001;344(9):665.
ATS/IDSA Guidelines for HAP/VAP: AJRCCM 2005;171:388.

Ventilator-associated pneumonia (VAP)

- Sputum cultures should be obtained prior to starting antibiotics or if patient is failing therapy by endotracheal suction or invasive techniques. ET suction appears just as sensitive but less specific than invasive methods.
- **Empiric treatment MUST be narrowed as soon as sputum culture results are known.**
- If the patient is on antibiotic therapy or has recently been on antibiotic therapy, choose an agent from a different class.

Optimal treatment can likely be based on severity of illness as determined by the Clinical Pulmonary Infection Score (CPIS).

Calculating the Clinical Pulmonary Infection Score (CPIS)

	0 points	1 point	2 points
Temperature (°C)	36.5 to 38.4	38.5 to 38.9	≤ 36.4 or ≥ 39
Peripheral WBC	4,000 – 11,000	< 4,000 or > 11,000 > 50% bands: add 1 extra point	
Tracheal secretions	None	Non-purulent	Purulent
Chest X-ray	No infiltrate	Diffuse or patchy infiltrates	Localized infiltrate
Progression of infiltrate from prior radiographs	None		Progression (ARDS, CHF thought unlikely)
Culture of ET suction	No growth/light growth	Heavy growth Same bacteria on gram stain: add 1 extra point	
Oxygenation (PaO₂/FiO₂)	> 240 or ARDS		≤ 240 and no ARDS

EMPIRIC TREATMENT

If the CPIS is ≤ 6

- VAP is unlikely
- If VAP strongly suspected see treatment recommendations below
- If CPIS remains ≤ 6 after 3 days, antibiotics can be stopped in most cases

If the CPIS is > 6

Early-onset VAP (occurring within 72 hours of hospitalization and patient has not been hospitalized or resided in a nursing home, long-term care or rehabilitation facility in the past 3 months)

Etiology: *S. pneumoniae*, *H. influenzae*, *S. aureus*

- Ceftriaxone 1 g IV Q24H
- OR**
- Severe PCN allergy: Moxifloxacin 400 mg IV Q24H

Late-onset VAP (all VAP that is not early-onset)

Etiology: *S. aureus*, *P. aeruginosa*, other Gram-negative bacilli

- Vancomycin (see dosing section, p. 150) PLUS [Piperacillin/tazobactam 4.5 g IV Q6H OR Cefepime 2 g IV OR Q8H] \pm Gentamicin (see dosing section, p. 146)
- OR**
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS [Ciprofloxacin 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] PLUS Gentamicin (see dosing section, p. 146)

Enterococci and candida species are often isolated from sputum in hospitalized patients. In general, they should be considered to be colonizing organisms and should not be treated with antimicrobials.

If the patient is immunocompromised, consider adding Azithromycin 500 mg Q24H to Piperacillin/tazobactam, Cefepime or Aztreonam to cover *Legionella*

Duration

- **3 days** if CPIS remains ≤ 6 in patients with initial CPIS ≤ 6 ; VAP is unlikely
- **7 days** if the patient has clinical improvement
- If symptoms persist at 7 days consider alternative source and/or bronchoscopy with quantitative cultures
- VAP associated with *S. aureus* bacteremia should be treated for at least 14 days

TREATMENT NOTES

- Treatment MUST be narrowed based on culture results
- Tobramycin is recommended as a second agent to broaden empiric coverage rather than fluoroquinolones because of high rates of resistance to fluoroquinolones in the institution.
- Antimicrobial therapy should be tailored once susceptibilities are known. Vancomycin should be stopped if resistant Gram-positive organisms are not recovered. Gram-negative coverage can be reduced to a single susceptible agent in most cases. The benefits of combination therapy in the treatment of *Pseudomonas* are not well documented; if it is desired, then consider giving it for the first 72 hours of therapy only.

Diagnosis

- VAP is difficult to diagnose.
- Bacteria in endotracheal suction may represent tracheal colonization and NOT infection.
- Quantitative cultures of BAL fluid can help distinguish between colonization and infection; $\geq 10^4$ cfu/ml is considered significant growth.

Other considerations

- Tracheal colonization of Gram-negatives and *S. aureus* is not eradicated even though lower airways are sterilized. Thus, post-treatment cultures in the absence of clinical deterioration (fever, rising WBC, new infiltrates, worsening ventilatory status) are not recommended.
- Inadequate initial treatment of VAP is associated with higher mortality (even if treatment is changed once culture results are known).

References:

- ATS/IDSA Guidelines for HAP/HAV: AJRCCM 2005;171:388.
Clinical response to VAP: AJRCCM 2001;163:1371-1375.
VAP: Arch Intern Med 2000;160:1926-6.
Mini-BAL: Chest 1998;113:412-20.
CPIS score: Am Rev Respir Dis 1991;143:1121-1129.
Determining course of therapy using CPIS Score: Am J Respir Crit Care Med 2000; 162:505 and Intensive Care Med 2004; 30: 735-738.

Antibiotic selection and dosing for cystic fibrosis patients

- Therapy should be based on culture and susceptibility data when available; the agent with the narrowest spectrum of activity should be selected preferentially
- If possible, stop failing antibiotics when initiating new antibiotics
- High doses of antibiotics should be used to maximize lung penetration and reduce the risk of emergence of resistance (see below)

TREATMENT NOTES FOR SPECIFIC ORGANISMS

- ***Pseudomonas aeruginosa***
 - Piperacillin, Cefepime, and Ceftazidime should be used preferentially to Meropenem to minimize the induction of resistance to beta-lactams by Meropenem
 - These agents are generally combined with high-dose aminoglycosides based on *in vitro* evidence that there is synergy against *Pseudomonas*
 - For patients with penicillin allergy, Ciprofloxacin or Aztreonam can be combined with an aminoglycoside; desensitization to beta-lactams or carbapenems should be strongly considered
 - In patients intolerant or resistant to aminoglycosides, Colistin can be added
 - Continuous infusion of beta-lactams can be considered in some patients; see p. 28 for more information.
 - Inhaled Tobramycin and Colistin can be used as adjunctive therapy
- ***Stenotrophomonas maltophilia***
 - *S. maltophilia* isolated from sputum usually represents colonization.
 - If superinfection is suspected, TMP/SMX is the first line agent.
 - Ticarcillin/clavulanate OR Minocycline may be used if susceptible in patients who are allergic or intolerant or resistant to TMP/SMX.
- ***Staphylococcus aureus***
 - *S. aureus* isolated from sputum can indicate colonization or infection.
 - Whether treating colonization with *S. aureus* in CF patients improves outcomes is an area of active research, although historically such colonization has not been successfully eradicated with antimicrobial therapy. If this is attempted, possible agents include Dicloxacillin, Cefazolin or Cephalexin for MSSA and Clindamycin, TMP/SMX, Doxycycline, and Minocycline for MRSA.
 - Oxacillin is the drug of choice for MSSA pneumonia; Vancomycin or Linezolid can be used for MRSA pneumonia.

Antibiotic doses for cystic fibrosis infections – normal renal function

- Ceftazidime: 2 g IV Q8H
- Piperacillin/tazobactam: 3.375 g IV Q4H
- Cefepime: 2 g IV Q8H
- Meropenem: 2 g IV Q8H
- Ciprofloxacin: 750 mg PO Q12H OR 400 mg IV Q8H
- Aztreonam: 2 g IV Q8H
- Ticarcillin/clavulanate: 3.1 g IV Q4H
- TMP/SMX for *S. maltophilia*: 5 mg/kg IV/PO Q8H
- TMP/SMX for *S. aureus*: 2 DS tablets PO BID
- Colistin: 3-6 mg/kg/day IV divided in 3 doses
- Inhaled Tobramycin (TOBI®): 300 mg Q12H
- Inhaled Colistin: 75-150 mg Q12H depending on the delivery system

Intravenous Tobramycin dosing and monitoring:

- Loading dose: 10 mg/kg/day given over 1 hour.
- Peak is recommended after first dose, 1 hour after the end of infusion with goal of 20-30 and trough at 23 hours with goal < 1 mcg/mL.
- Doses can be increased up to 12 mg/kg/day if adequate peaks are not achieved. If trough is too low or too high, interval should be changed.

Respiratory virus diagnosis and management

Diagnosis

- Respiratory virus testing should be obtained year round on any patient for whom there is a clinical suspicion of respiratory virus infection. In addition, during influenza and RSV season testing should be obtained in patients with:
 - Fever and influenza-like symptoms (sore throat, myalgia, arthralgia, cough, runny nose and/or headache)
 - Suspected bronchiolitis or pneumonia
 - COPD/asthma exacerbation or respiratory failure
 - Unexplained CHF exacerbation
 - Elderly patients with unexplained new onset malaise
 - Pregnant patients with unexplained respiratory symptoms
 - Nonspecific symptoms and a documented exposure to someone with a respiratory illness
- Respiratory virus testing at JHH (one NP flocked swab should be submitted for either panel)
 - Testing for immunocompetent hosts: rapid nucleic acid test for RSV and influenza A/B
 - Testing for immunocompromised hosts, patients being admitted to the ICU, and patients with structural lung disease: extended panel for RSV, influenza A/B, adenovirus, human metapneumovirus, parainfluenza 1-3, and rhinovirus

Treatment of influenza in inpatients

- Empiric treatment of adult inpatients should be considered in the following situations during influenza season:
 - Patients with fever and influenza-like symptoms, unexplained interstitial pneumonia or new respiratory failure without an obvious non-influenza cause
- Treatment should be initiated in all patients who are admitted to the hospital and have influenza with symptom onset in the past 48-72 hours
- The utility of treatment of patients who present late in the course of disease is uncertain and the decision to treat these patients can be made on a case-by-case basis
- Antiviral choice is dependent on the susceptibility of circulating strains which may vary from season to season (see www.hopkinsmedicine.org/amp for current recommendations)
- Duration: 5 days except for patients with solid organ transplant, hematologic malignancy, or BMT in whom 10 days can be given because of prolonged viral shedding

Infection control

- All individuals with suspected respiratory virus infection should be placed on droplet precautions. A private room is required, unless patients are cohorted. When outside of their room (i.e. during transport) patients should wear a mask.
- All health care workers must receive the influenza vaccine yearly.
- Personnel with direct patient care or working in clinical areas who have not received the influenza vaccine are required to wear a mask when within 6 feet of a patient. The dates of the mask requirement are determined by HEIC and based on influenza activity in the local community.
- No one with fever may work until at least 24 hours after fever has resolved (without antipyretics). All personnel with respiratory symptoms and fever must call or report to their supervisor and must call Occupational Health Services (OHS).
- Afebrile employees who have respiratory systems must wear a surgical mask during patient contact (≤ 6 ft).
- If an unvaccinated HCW is exposed to a patient with documented influenza who was not on Droplet Precautions, notify HEIC and call Occupational Health Services (OHS) immediately. OHS will decide whether to recommend post-exposure prophylaxis.

Anti-influenza agents

Medication	Adult dosing	Side effects	Notes
Oseltamivir	Treatment: 75 mg PO twice a day for 5 days Prophylaxis: 75 mg PO once a day	Common: nausea, vomiting Severe: hypersensitivity, neuropsychiatric	Dose adjustment needed for GFR <60 mL/min
Zanamivir	Treatment: 10 mg (2 oral inhalations) twice daily for 5 days Prophylaxis: 10 mg (2 oral inhalations) once a day	Common: diarrhea, nausea, cough, headache, and dizziness Severe: bronchospasm, hypersensitivity, laryngeal edema, facial swelling	Should NOT be used in patients with chronic underlying airway diseases

Tuberculosis (TB) infection

Latent TB infection (LTBI)

- Previous infection with *M. tuberculosis* (MTB) that has been contained by the host immune response
- Patient may have a positive test (see below) or suggestive radiographic findings such as calcified granulomata or minimal apical scarring, but do not have symptoms of active TB disease
- Not infectious and does not require isolation

Tests to diagnose latent LTBI

- Both Tuberculin skin test (TST) and Interferon gamma release assay (IGRA) are imperfect, and may offer discordant results (~20%). Sensitivity of TST and IGRA are similar.
- Both tests should be interpreted in the context of epidemiologic risk of TB exposure
- LTBI therapy should not be initiated until active TB is excluded (by symptoms and radiography). Individuals with signs or symptoms of active TB require further diagnostic workup before LTBI therapy.
- LTBI therapy should not be started in the hospital without a clear follow-up plan

Tuberculin skin test (TST)

- Intradermal injection of purified protein derivative (PPD) and measurement of induration diameter in 48-72
- Criteria for a positive test are
 - ≥ 5 mm – high risk of developing active TB (e.g., HIV infection, close contact of TB case, immunocompromised)
 - ≥ 10 mm – other risk factors for TB infection (HCW, IDU, DM)
 - ≥ 15 mm – no risk factors for TB

Interferon gamma release assay (IGRA)

- IGRAs measure lymphocyte release of interferon gamma in response to stimulation by MTB antigens.
- IGRAs are less affected by BCG vaccination status or infection with most atypical mycobacteria (except *M. marinum* and *M. kansasii*) than TST
- Quantiferon-Gold-In-Tube (QGIT) is used at JHH. Results are reported as positive, negative, or indeterminate. An indeterminate result means that the test result is not valid, which can be due to errors in specimen collection (most common-insufficient/incorrect shaking of tubes after blood draw or processing delays), or associated with certain conditions such as HIV with a low CD4 count, steroid use or other immunosuppression, and malnutrition [albumin <3.5]. Indeterminate results often require a repeat test (ensure proper specimen collection).
- When pre-test probability or prevalence of LTBI is $<5\%$ (e.g., US-born without foreign travel), PPV of IGRA is reduced (70-90%, i.e., false-positives) while NPV is high (99%).
- When pre-test probability for infection is high (e.g., foreign-born, ~30% LTBI prevalence), PPV of IGRA increases to ~95-99%, but NPV decreases (80-90%, i.e., false-negatives).

- Quantitative results may be helpful to guide interpretation. Consider ID consultation for results near the threshold for QGIT positive: antigen > 0.35. Serial testing is not advised without ID consultation.
- IGRAs do not have good sensitivity or specificity for diagnosis of active TB

Active TB infection

- Active replication of MTB causing pulmonary or extrapulmonary signs or symptoms
- Confirmed by positive AFB smear, MTB direct test or culture
- Requires airborne isolation

When to suspect active TB disease

High-risk individuals

- Recent exposure to a person with known TB; history of a positive TST; HIV infection; injection or non-injection drug use; foreign birth or residence in a region in which TB incidence is high; residents and employees of high-risk congregate settings (e.g. prisons); membership in a medically underserved, low-income population; anti-TNF alpha therapy

Clinical syndromes

- Cough of ≥ 2 wk duration, with at least one additional symptom, including fever, night sweats, weight loss, or hemoptysis
- Any unexplained respiratory illness of ≥ 2 wk duration in a patient at high risk for TB
- Any patient with HIV infection and unexplained cough and fever
- Any patient on anti-TNF alpha therapy with unexplained fever
- Community-acquired pneumonia which has not improved after 7 days of appropriate treatment
- Incidental findings on chest radiograph suggestive of TB (even if symptoms are minimal or absent) in a patient at high risk for TB

Radiographic findings

- Primary TB (often unrecognized): Can resemble CAP and involve any lobes; hilar adenopathy, pleural effusions are common; cavitation is uncommon. Findings often resolve after 1–2 months. These are common findings in patients with advanced HIV infection and TB.
- Reactivation TB: Infiltrates with or without cavitation in the upper lobes or the superior segments of the lower lobes; hilar adenopathy is variable; CT scan may have “tree-in-bud” appearance.

Diagnosis

- Patients with characteristic syndromes and radiographic findings should have expectorated sputum obtained for AFB smear and culture.
- Sensitivity of AFB smear on expectorated sputum is 50–70%; it is lower in HIV+ patients. Morning expectorated sputum, induced sputum, bronchoscopy have higher sensitivity. AFB culture of lower respiratory tract specimens is considered the gold standard.
- AFB smear and culture should be obtained regardless of CXR findings in patients with high clinical suspicion, HIV infection or other immunocompromised states. CXR is normal in approximately 10% of HIV-infected patients with pulmonary TB.

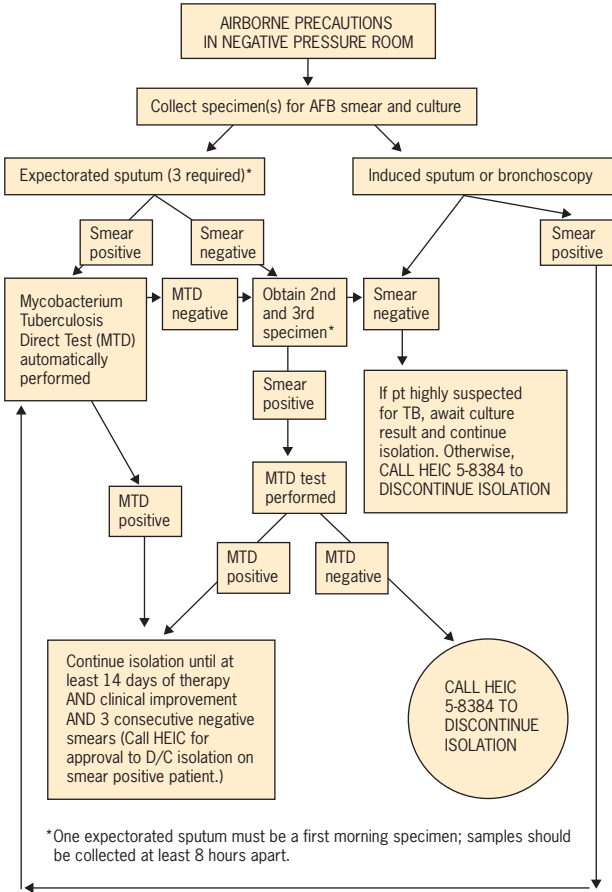
- Obtain at least 3 sputum specimens (induced or expectorated) when trying to diagnose TB in patients who are smear negative so as to increase the chance of isolating the organism for diagnosis and susceptibility testing.

Infection control

Airborne precautions are required in the following cases:

- Suspicion of disease sufficiently high to warrant obtaining sputum AFB smear/culture as described above
- Positive AFB smear or culture until diagnosis of TB vs. NTM is confirmed

Algorithm for isolation when active TB is suspected



- Known active pulmonary or laryngeal TB (if patient is currently on TB treatment, consult with HEIC and patient's local health department to obtain treatment history in order to determine if infectious at the time of current hospitalization; in meantime airborne precautions are required)

TREATMENT

Active TB

- ID consult is strongly recommended
- Therapy should be initiated for patients with positive AFB smear and clinical findings consistent with active TB.
- Therapy should be considered for patients with negative AFB smears when suspicion of TB is high and no alternate diagnosis exists. Multiple specimens should be obtained for culture prior to treatment.
- Four drugs are necessary for initial phase (2 months).
 - Isoniazid (INH) 300* mg (5 mg/kg) PO daily
 - Rifampin (RIF) 600* mg (10 mg/kg) PO daily
 - Pyrazinamide (PZA) 1000 mg PO daily (40–55 kg) OR 1500 mg PO daily (56–75 kg) OR 2000* mg PO daily (76–90 kg)
 - Ethambutol (EMB) 800 mg PO daily (40–55 kg) OR 1200 mg PO daily (56–75 kg) OR 1600* mg PO daily (76–90 kg)
- *Max dose regardless of weight.
- Pyridoxine 25 mg PO daily is recommended to prevent INH associated peripheral neuropathy in patients with HIV, malnutrition, alcohol abuse, diabetes mellitus, renal failure or in pregnant or breastfeeding women.

Drug toxicity and monitoring

- Isoniazid: asymptomatic elevation in hepatic enzymes, serious and fatal hepatitis, peripheral neurotoxicity
- Rifampin: orange discoloration of body fluids, hepatotoxicity, pruritis with or without rash
- Pyrazinamide: hepatotoxicity, nongouty polyarthralgia, asymptomatic hyperuricemia, acute gouty arthritis
- Ethambutol: retrobulbar and peripheral neuritis
- Monitoring: baseline hepatic transaminases, bilirubin, alkaline phosphatase, creatinine and CBC are recommended for all adults initiating TB treatment. Monthly hepatic panel is recommended for patients with baseline abnormalities, history of liver disease or viral hepatitis, chronic alcohol consumption, HIV, IVU, pregnancy or immediate post-partum state or those taking other potentially hepatotoxic medications. Therapy should be discontinued immediately if AST and ALT are >3 times the upper limit of normal (ULN) in the presence of jaundice or hepatitis symptoms or >5 times the ULN in the absence of symptoms.

References:

ATS/IDSA/CDC Guidelines for diagnosis of TB: Am J Respir Care Med 2000;161:1376.
 ATS/IDSA/CDC Guidelines for treatment of TB: MMWR;52:RR-11.

Sepsis with no clear source

NOTE: Refer to specific sections of these guidelines for empiric treatment recommendations for specific sources of infection

EMPIRIC TREATMENT

Cultures MUST be sent to help guide therapy.

- [Piperacillin/tazobactam* 4.5 g IV Q6H OR Cefepime* 2 g IV Q8H] ± Vancomycin (see dosing section, p. 150) (if at risk for MRSA) ± Gentamicin (see dosing section, p. 146)

OR

- Severe PCN allergy: [Aztreonam 2 g IV Q8H OR Ciprofloxacin 400 mg IV Q8H] PLUS Gentamicin (see dosing section, p. 146) PLUS Vancomycin (see dosing section, p. 150)

***NOTE:** If patient has history of ESBL-producing organism or has suspected intra abdominal sepsis and recent prolonged exposure (≥ 7 days) to Piperacillin/tazobactam or Cefepime, substitute with Meropenem 1 g IV Q8H.

Risk factors for MRSA

- Central venous catheter in place
- Other indwelling hardware
- Known colonization with MRSA
- Recent (within 3 months) or current prolonged hospitalization > 2 weeks
- Transfer from a nursing home or subacute facility
- Injection drug use

TREATMENT NOTES

- For patients with renal insufficiency or aminoglycoside intolerance, a beta-lactam may be combined with a fluoroquinolone **IF** 2 agents are needed.
- Potential sources (e.g., pneumonia, peritonitis, etc.) should be considered when selecting therapy.
- Empiric therapy is **ONLY** appropriate while cultures are pending (72 hours max).
- Vancomycin should almost always be stopped if no resistant Gram-positive organisms are recovered in cultures.

Skin, soft-tissue, and bone infections

Cellulitis

- Always elevate affected extremity. Treatment failure is more commonly due to failure to elevate than failure of antibiotics.
- Improvement of erythema can take days, especially in patients with lymphedema, because dead bacteria in the skin continue to induce inflammation.

Non-suppurative cellulitis

Defined as cellulitis with intact skin and no evidence of purulent drainage. Usually caused by beta-hemolytic streptococci (e.g. group A, B, C, G streptococci) and MSSA.

TREATMENT

Oral (mild disease)

- Amoxicillin/clavulanate 875 PO Q12H

OR

- Cephalexin 500 mg PO Q6H

OR

- PCN allergy: Clindamycin 300 mg PO Q8H

Parenteral (moderate to severe disease)

- Ampicillin/sulbactam 1.5 g IV Q6H

OR

- Cefazolin 1 g IV Q8H

OR

- PCN allergy: Clindamycin 600 mg IV Q8H

Duration: 5-7 days

TREATMENT NOTES

- All beta-hemolytic streptococci are susceptible to penicillin
- Clindamycin resistance is seen in 16-33% of group B, C, and G strep but remains low in group A strep (4-7%)
- Duration: 5-7 days

Suppurative cellulitis

Defined as cellulitis with purulent drainage or exudates in the absence of a drainable abscess. Usually caused by *S. aureus* (MSSA and MRSA).

TREATMENT

Oral (mild disease)

- TMP/SMX 1-2 DS tab PO BID

OR

- Doxycycline 100 mg PO BID OR Minocycline 100 mg PO BID

OR

- Clindamycin 300 mg PO Q8H

OR

- Clindamycin 600 mg IV Q8H (if parenteral therapy is needed)

Parenteral (moderate to severe disease)

- Vancomycin (see dosing section, p. 150)

Duration: 5-7 days

TREATMENT NOTES

- Resistance to fluoroquinolones in *S. aureus* is common and develops quickly; > 95% of MRSA isolates are resistant to fluoroquinolones. Monotherapy with fluoroquinolones for *S. aureus* infections is not recommended.
- Rifampin should NEVER be used as monotherapy because resistance develops rapidly.
- There is no evidence that Linezolid is superior to TMP/SMX, Doxycycline, or Clindamycin in the management of skin infection or osteomyelitis. Linezolid should only be considered when the *S. aureus* isolate is resistant to or the patient is intolerant to these agents.

Less common causes of cellulitis

- With bullae, vesicles, and ulcers after exposure to seawater or raw oysters, consider *Vibrio vulnificus*, especially in patients with liver disease. Rare, but rapidly fatal if untreated. Treat with Ceftriaxone 1 g IV Q24H PLUS Doxycycline 100 mg PO BID.
- Neutropenic, solid organ transplant, and cirrhotic patients may have cellulitis due to Gram-negative organisms. Consider expanding coverage in these cases.
- If eschar, consider angioinvasive organisms (GNR, aspergillosis, mold). ID consult is recommended.
- Animal and human bites: *Pasteurella multocida* should be covered in cat and dog bites. Treat with Amoxicillin/clavulanate 875 mg PO BID OR Ampicillin/sulbactam 1.5–3 g IV Q6H. If PCN allergy: Moxifloxacin 400 mg PO/IV Q24H.

Cutaneous abscess

- Incision and drainage (I&D) is the primary treatment for a cutaneous abscess.
- Lesions that appear superficial can often have associated abscess formation that is not clearly appreciated without debridement of the wound or, on occasion, additional imaging.
- At the time of I&D, a sample should be obtained for culture and sensitivity testing.
- Most studies that have been published to date suggest that antibiotics are adjunct to I&D in the management of uncomplicated skin abscesses caused by CA-MRSA.

- Indications for antimicrobial therapy in patients with cutaneous abscesses:
 - Severe or rapidly progressive infections
 - The presence of extensive associated cellulitis
 - Signs and symptoms of systemic illness
 - Associated septic phlebitis
 - Diabetes or other immune suppression
 - Advanced age
 - Location of the abscess in an area where complete drainage is difficult (e.g. face, genitalia)
 - Lack of response to incision and drainage alone
- Therapy should be given **before** incision and drainage in patients with prosthetic heart valves or other conditions placing them at high risk for endocarditis.

EMPIRIC TREATMENT

If antibiotic treatment is thought to be necessary, regimens are the same as for suppurative cellulitis above.

Management of recurrent MRSA skin infections

1. Education regarding approaches to personal and hand hygiene

- Practice frequent hand hygiene with soap and water and/or alcohol based hand gels, especially after touching infected skin or wound bandages.
- Cover draining wounds with clean, dry bandages
- Do not share personal items (e.g. razors; used towels and clothing before washing)
- Regular bathing
- Avoid all shaving
- Launder clothing, sheets, towels in hottest suitable temperature
- Clean all personal sporting clothing/equipment

2. Decontamination of the environment

- Clean high touch areas in the bathroom with a disinfectant active against *S. aureus* daily (e.g., 10% dilute bleach).

3. Topical decolonization (consider if a patient has ≥ 2 episodes in 1 year or other household members develop infection)

- Mupirocin twice daily for 5 days may be considered in patients with documented evidence of MRSA nasal colonization; Mupirocin therapy should be initiated after resolution of acute infection. Mupirocin should not be used in patients or patients' family members who are not documented to have MRSA nasal colonization.

- Bathing or showering with chlorhexidine or hexachlorophine (or dilute bleach baths) every other day for 1 week then twice weekly; do not get these substances into ears or eyes
- Systemic antibiotics are NOT recommended solely for decolonization

4. Evaluation of other family members

- Intra-family transmission should be assessed and if present, all members should participate in hygiene and decolonization strategies above, starting at that same time and after the acute infection is controlled.

NOTE: Data on efficacy and durability of the decontamination and decolonization strategies described above are limited.

References:

TMP/SMX for MRSA: Ann Intern Med 1992;117:390-8.

IDSA Guidelines for treatment of MRSA infections: Clin Infect Dis 2011;52:1-38.

Etiology of suppurative cellulitis: Medicine 2010;89:217-226.

Diabetic foot infections

EMPIRIC TREATMENT

Treatment depends on clinical severity

Infection Severity	Clinical Manifestations
Uninfected	No purulence or inflammation*
Mild	Presence of purulence and ≥ 1 sign of inflammation* and cellulitis (if present) ≤ 2 cm around ulcer limited to skin or superficial subcutaneous tissue
Moderate	Same as mild PLUS at least one of the following: > 2 cm of cellulitis, lymphangitic streaking, spread beneath the superficial fascia, deep tissue abscess, gangrene, involvement of muscle, tendon, joint, or bone
Severe	Any of above PLUS systemic toxicity or metabolic instability
*erythema, pain, tenderness, warmth, induration	

MILD INFECTIONS

Oral regimens

- Amoxicillin/clavulanate 875 mg PO BID
- OR**
- Cephalexin 500 mg PO QID
- OR**
- Clindamycin 300 mg PO TID (covers MRSA)

Parenteral regimens

- Clindamycin 600 mg IV Q8H (covers MRSA)
- OR**

- Oxacillin 1-2 g IV Q4H
OR
- Cefazolin 1 g IV Q8H

MODERATE INFECTIONS

- Ertapenem 1 g Q24H
OR
- [Ciprofloxacin* 500 mg PO BID OR Ciprofloxacin* 400 mg IV Q12H] PLUS ONE of the following [Clindamycin 600 mg IV Q8H/300 mg PO TID OR Metronidazole 500 mg IV/PO TID]
- * BUT avoid fluoroquinolones in patients who were on them as outpatients

If patient at risk for MRSA, add Vancomycin to regimens that do not include Clindamycin.

Risk factors for MRSA

- History of colonization or infection with MRSA
- Recent (within 3 months) or current prolonged hospitalization > 2 weeks
- Transfer from a nursing home or subacute facility
- Injection drug use

SEVERE INFECTIONS

- Piperacillin/tazobactam 4.5 g IV Q6H
OR
- [Ciprofloxacin* 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] PLUS Clindamycin 600 mg IV Q8H
- * Avoid fluoroquinolones in patients who were on them as outpatients.

If patient at risk for MRSA (see above)

- Piperacillin/tazobactam 4.5 g IV Q6H PLUS Vancomycin (see dosing section, p. 150)

OR

- [Ciprofloxacin* 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] PLUS Metronidazole 500 mg IV Q8H PLUS Vancomycin (see dosing section, p. 150)
- * Avoid fluoroquinolones in patients who were on them as outpatients

TREATMENT NOTES

Management

- A multidisciplinary approach to management should include wound care consultation, assessment of vascular supply, vascular and/or general surgery consultation and infectious diseases consultation.
- Consider necrotizing fasciitis in patients who are severely ill.
- Antibiotic therapy should be narrowed based on culture results.

Microbiology

- Cellulitis without open wound or infected ulcer, antibiotic naïve: beta-hemolytic streptococci, *S. aureus*
- Infected ulcer, chronic or previously treated with antibiotics: *S. aureus*, beta-hemolytic streptococci, Enterobacteriaceae
- Exposure to soaking, whirlpool, hot tub: usually polymicrobial, may involve *Pseudomonas*
- Chronic wounds with prolonged exposure to antibiotics: aerobic Gram-positive cocci (GPC), Diphtheroids, Enterobacteriaceae, other Gram-negative rods (GNR) including *Pseudomonas*
- Necrosis or gangrene: mixed aerobic GPC and GNR, anaerobes

Diagnosis

- Cultures of the ulcer base after debridement can help guide therapy. Biopsy of unexposed bone is NOT recommended. Avoid swabbing non-debrided ulcers or wound drainage.
- Ulcer floor should be probed carefully. If bone can be touched with a metal probe then the patient should be treated for osteomyelitis with antibiotics in addition to surgical debridement.
- Plantar fasciitis and a deep foot-space infection can be present. Consider imaging to look for deep infections.
- Putrid discharge is diagnostic of the presence of anaerobes.
- MRI is more sensitive and specific than other modalities for detection of soft-tissue lesions and osteomyelitis.

Duration

- Duration of treatment will depend on rapidity of response and presence of adequate blood supply.
- Likely need shorter treatment with adequate surgical intervention (7–10 days post-op) and longer for osteomyelitis.
- Change to oral regimen when patient is stable.

Reference:

IDSA Guidelines for diabetic foot infection. Clin Infect Dis 2012;54:132-173.

Surgical-site infections (SSI)

EMPIRIC TREATMENT

Infections following clean procedures (e.g. orthopedic joint replacements, open reduction of closed fractures, vascular procedures, median sternotomy, craniotomy, breast and hernia procedures)

- Oxacillin 1–2 g IV Q4H
OR
- Cefazolin 1 g IV Q8H
OR

- PCN allergy: Clindamycin 600 mg IV Q8H

OR

- Involvement of hardware or MRSA suspected: Vancomycin (see dosing section, p. 150)

Exception: Saphenous vein graft harvest site infections should be treated with Ertapenem 1 g IV Q24H

Infections following contaminated procedures (GI/GU procedures, oropharyngeal procedures, obstetrical and gynecology procedures)

Patients not on broad-spectrum antibiotics at time of surgery and not severely ill

- Ertapenem 1 g IV Q24H

OR

- PCN allergy: [Ciprofloxacin 500 mg PO BID OR Ciprofloxacin 400 mg IV Q12H] PLUS Clindamycin 600 mg IV Q8H

Patients on broad-spectrum antibiotics at time of surgery or severely ill

- Piperacillin/tazobactam 3.375 g IV Q6H ± Vancomycin (see dosing section, p. 150) (if hardware present or MRSA suspected)

OR

- Non-severe PCN allergy: Cefepime 1 g IV Q8H PLUS Metronidazole 500 mg IV Q8H ± Vancomycin (see dosing, p. 150) (if hardware present or MRSA suspected)

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS [Ciprofloxacin 400 mg IV Q8H OR Aztreonam 2 g IV Q8H] PLUS Metronidazole 500 mg IV/PO Q8H

Deep fascia involvement

- Treat as necrotizing fasciitis (see subsequent section)

TREATMENT NOTES

Microbiology

- Following clean procedures (no entry of GI/GU tracts)
 - *Staphylococcus aureus*
 - Streptococci, group A (especially with early onset, < 72 hours)
 - Coagulase-negative staphylococci
- Following clean-contaminated and contaminated procedures (entry of GI/GU tracts with or without gross contamination)
 - Organisms above
 - Gram-negative rods
 - Anaerobes (consider *Clostridia* spp. in early-onset infection, 1–2 days)

- Generally, empiric use of Vancomycin is not indicated because the percentage of SSIs caused by MRSA is low at Johns Hopkins Hospital (10–20%)

Risk factors for MRSA

- History of colonization or infection with MRSA
- Recent (within 3 months) or current prolonged hospitalization >2 weeks
- Transfer from a nursing home or subacute facility
- Injection drug use

Other management issues

- Many advocate that ALL infected wounds be explored both to debride and to assess depth of involvement.
- Superficial infections may be adequately treated with debridement alone.
- Deeper infections (cellulitis, panniculitis) need adjunctive antibiotics.
- Infections that extend to the fascia should be managed as necrotizing fasciitis.
- Patients with hypotension should have their wounds explored even if they are unremarkable on physical exam.

Serious, deep-tissue infections (necrotizing fasciitis)

THESE ARE SURGICAL EMERGENCIES! ANTIBIOTICS ARE ONLY AN ADJUNCT TO PROMPT DEBRIDEMENT!

ID should also be consulted

EMPIRIC TREATMENT (adjunct to surgery)

- Vancomycin (see dosing section, p. 150) PLUS [Piperacillin/tazobactam 3.375 g IV Q6H OR Cefepime 1 g IV Q8H] PLUS Clindamycin 600-900 mg IV Q8H

OR

- Severe PCN allergy: Vancomycin (see dosing section, p. 150) PLUS [Ciprofloxacin 400 mg IV Q8H ± Gentamicin (see dosing section, p. 146)] PLUS Clindamycin 600-900 mg IV Q8H

TREATMENT NOTES

Conventional nomenclature and microbiology

Pyomyositis

- *S. aureus* most commonly
- Clostridial myonecrosis – *Clostridia* spp. (esp. *C. perfringens*)
- Group A streptococcal myonecrosis

Fasciitis

- Type 1 – Polymicrobial infections with anaerobes, streptococci and Gram-negative rods (Fournier’s gangrene is a type 1 necrotizing fasciitis of the perineum)
- Type 2 – Group A streptococci predominate
- Cases of fasciitis caused by community-associated MRSA strains have been reported

Diagnosis

- Can be difficult – gas production is not universal and is generally absent in streptococcal diseases.
- Maintain high index of suspicion when:
 - Patients are very ill from cellulitis (hypotension, toxic appearance)
 - Pain out of proportion to physical findings
 - Anesthesia over affected area
 - Risk factors such as diabetes, recent surgery or obesity
 - Findings such as skin necrosis or bullae
 - Putrid discharge with thin, “dishwater” pus
- CT scan can help with diagnosis but if suspicion is moderate to high, surgical exploration is the preferred diagnostic test. DO NOT delay surgical intervention to obtain CT.

Reference:

IDSA guidelines for SSTI: Clin Infect Dis 2005; 41:1373–406.

Vertebral osteomyelitis, diskitis, epidural abscess

NOTE: In absence of bacteremia, clinical instability, or signs and symptoms of spinal cord compromise strong consideration should be given to withholding antibiotics until samples of abscess or bone can be obtained for Gram-stain and culture.

EMPIRIC TREATMENT

- Vancomycin (see dosing section, p. 150) ± [Ceftriaxone 2 g Q12H **OR** Cefepime 2 g IV Q8H]
- OR**
- Severe PCN allergy: Vancomycin (see dosing section, p. 150) ± Ciprofloxacin 400 mg IV Q8H
- Narrow therapy based on culture results.

TREATMENT NOTES**Microbiology**

- Gram-positive cocci in 75% of cases with majority *S. aureus*
- Gram-negative rods in ~10%

Management

- Obtain two sets of blood cultures, ESR, and CRP prior to starting antibiotic therapy.
- Most intravenous drug users and patients without significant co-morbidities do not require empiric coverage for Gram-negative rods.
- Empiric Gram-negative coverage should be used in patients with diabetes, hardware in place or recent surgery, and recurrent urinary tract infections.
- MRI with contrast is the imaging method of choice.
- If blood cultures are negative CT guided needle biopsy/aspiration should be obtained for Gram stain and cultures.
- Emergent surgical consultation is recommended for patients with signs and symptoms of spinal cord compromise.
- Surgical therapy is preferred in many cases of epidural abscess/osteomyelitis (e.g. extensive infection, pre-vertebral abscess, spine instability, hardware involvement). CT-guided aspiration and/or antibiotic therapy alone may be considered in some circumstances. Discussion with infectious diseases and surgery is recommended to optimize management.
- Patients should have frequent assessment of neurologic function, particularly at the time of initial presentation.
- All patients require monitoring for adequate response throughout the treatment course; ID follow up highly recommended.

Duration

- Epidural abscess without osteomyelitis: 4–6 weeks
- Vertebral osteomyelitis ± epidural abscess: 6–12 weeks
- In patients with hardware present prolonged oral suppressive therapy is generally required after completion of IV antibiotics; these decisions should be made in consultation with infectious diseases.

References:

Spinal epidural abscess: N Engl J Med 2006;355:2012–20.

Spinal epidural abscess: Q J Med 2008;101:1–12.

Bacterial urinary tract infections (UTI)

Management of patients WITHOUT a urinary catheter

NOTE: Ciprofloxacin is not recommended for empiric treatment for in-patients with non-catheter associated UTI at JHH due to the low rate of *E. coli* susceptibility (71%).

Category	Definition	Empiric treatment	Notes
Asymptomatic bacteriuria	Positive urine culture \geq 100,000 CFU/mL with no signs or symptoms	No treatment unless the patient is: <ul style="list-style-type: none"> • Pregnant • About to undergo a urologic procedure • Post renal transplant • Neutropenic 	<ul style="list-style-type: none"> • Obtaining routine cultures in asymptomatic patients is not recommended • Antibiotics do not decrease asymptomatic bacteriuria or prevent subsequent development of UTIs • The prevalence of asymptomatic bacteriuria is high: 1%-5% in premenopausal women, 3%-9% in postmenopausal women, 40%-50% in long-term care residents and 9%-27% in women with diabetes.
Acute cystitis	Signs and symptoms (e.g. dysuria, urgency frequency, suprapubic pain) AND pyuria ($>$ 10 WBC/hpf) AND positive urine culture \geq 100,000 CFU/mL <ul style="list-style-type: none"> • Uncomplicated: female, no urologic abnormalities, no stones, no catheter • Complicated: male gender, possible stones, urologic abnormalities, pregnancy 	<p><u>Uncomplicated:</u></p> <ul style="list-style-type: none"> • Nitrofurantoin (Macrobid®) 100 mg PO Q12H for 5 days (NOT in patients with CrCl $<$ 50 ml/min) <p>OR</p> <ul style="list-style-type: none"> • Cephalexin 500 mg PO Q6H for 5 days <p>OR</p> <ul style="list-style-type: none"> • Cefpodoxime 100 mg PO Q12H for 5 days <p>OR</p> <ul style="list-style-type: none"> • Cefdinir 300 mg PO Q12H for 5 days <p>OR</p> <ul style="list-style-type: none"> • TMP/SMX 1 DS tab PO Q12H for 3 days <p>OR</p> <ul style="list-style-type: none"> • IV option: Cefazolin 1 g IV Q8H for 3 days <p><u>Complicated:</u></p> <ul style="list-style-type: none"> • Same regimens as above except duration is 7-14 days 	<ul style="list-style-type: none"> • UTIs in men are traditionally considered complicated. UTIs in men in the absence of obstructive pathology (e.g. BPH, stones, strictures) are uncommon. Please critically evaluate your diagnosis of UTI in male patients. • Oral therapy is preferred and should be given unless patient is unable to tolerate oral therapy • If IV beta-lactams are used empirically for 3 days, no additional therapy is needed for uncomplicated cystitis • If IV beta-lactams are used empirically for $<$3 days or treating complicated cystitis, the patient can be switched to an appropriate oral beta-lactam and duration of IV therapy should be counted towards total duration of therapy • Oral Fosfomycin can be used if susceptible for Gram-negative MDR organisms (susceptibilities must be requested)

Category	Definition	Empiric treatment	Notes
Acute pyelonephritis	Signs and symptoms (e.g. fever, flank pain) AND pyuria AND positive urine culture $\geq 100,000$ CFU/mL Many patients will have other evidence of upper tract disease (i.e. leukocytosis, WBC casts, or abnormalities upon imaging)	<ul style="list-style-type: none"> Ceftriaxone 1 g IV Q24H OR Ertapenem 1 g IV Q24H (if history of ESBL) OR PCN allergy: Aztreonam 1 g IV Q8H OR Gentamicin (see dosing section, p. 147) Duration: 7–14 days <p>Hospitalized > 48H</p> <ul style="list-style-type: none"> Cefepime 1 g IV Q8H OR PCN allergy: Aztreonam 1 g IV Q8H OR Gentamicin (see dosing section, p. 147) Duration: 7–14 days 	<ul style="list-style-type: none"> Oral step-down therapy should be used if organism is susceptible Duration of empiric IV therapy should be counted towards total duration of therapy <u>Oral step-down therapy, if organism is susceptible:</u> <ul style="list-style-type: none"> Ciprofloxacin 500 mg PO Q12H for 7 days TMP/SMX 1 DS PO Q12H for 7–10 days Cefpodoxime 400 mg PO Q12H for 14 days Oral Fosfomycin can be considered if susceptible for Gram-negative MDR organisms (susceptibilities must be requested). Consult ID Pharmacist for dosing.
Urosepsis	SIRS with urinary source of infection	<ul style="list-style-type: none"> Cefepime 1 g IV Q8H OR PCN allergy: Aztreonam 1 g IV Q8H \pm Gentamicin (see dosing section, p. 147) Duration: 7–10 days 	<ul style="list-style-type: none"> Oral Ciprofloxacin or TMP/SMX have excellent bioavailability and should be used as step-down therapy if organism is susceptible Oral beta-lactams should not be used for bacteremia due to inadequate blood concentrations Duration of empiric IV therapy should be counted towards total duration of therapy

DIAGNOSIS

Specimen collection: The urethral area should be cleaned with an antiseptic cloth and the urine sample should be collected midstream or obtained by fresh catheterization. Specimens collected using a drainage bag or taken from a collection hat are not reliable and should not be sent.

Interpretation of the urinalysis (U/A) and urine culture

- Urinalysis and urine cultures must be interpreted together in context of symptoms
- **Urinalysis/microscopy:**
 - Dipstick
 - Nitrites indicate bacteria in the urine
 - Leukocyte esterase indicates white blood cells in the urine
 - Bacteria: presence of bacteria on urinalysis should be interpreted with caution and is not generally useful
 - Pyuria (more sensitive than leukocyte esterase): >10 WBC/hpf or >27 WBC/microliter
- **Urine cultures:**
 - If U/A is negative for pyuria, positive cultures are likely contamination
 - Most patients with UTI will have $\geq 100,000$ colonies of a uropathogen. Situations in which lower colony counts may be significant include: patients who are already on antibiotics at the time of culture, symptomatic young women, suprapubic aspiration, and men with pyuria.

TREATMENT NOTES

- Pyuria either in the setting of negative urine cultures or in patients with asymptomatic bacteriuria usually requires no treatment. If pyuria persists consider other causes (e.g. interstitial nephritis or cystitis, fastidious organisms).
- Follow-up urine cultures or U/A are only warranted for ongoing symptoms. They should NOT be acquired routinely to monitor response to therapy.
- See p. 114 for discussion of treatment options for VRE and renal concentrations of antibiotics.

Management of patients WITH a urinary catheter

Category	Definition	Empiric treatment
Asymptomatic bacteriuria	Positive urine culture $\geq 100,000$ CFU/mL with no signs or symptoms of infection NOTE: obtaining routine cultures in asymptomatic patients is not recommended	Remove the catheter No treatment unless the patient is: <ul style="list-style-type: none"> • Pregnant • About to undergo a urologic procedure • Post renal transplant • Neutropenic Antibiotics do not decrease asymptomatic bacteriuria or prevent subsequent development of UTI
Catheter-associated UTI (CA-UTI)	Signs and symptoms (fever with no other source is the most common; patients may also have suprapubic or flank pain) AND pyuria (>10 WBC/hpf) AND positive urine culture $\geq 1,000$ CFU/mL (see information below regarding significant colony counts)	<ul style="list-style-type: none"> • Remove catheter when possible Patient stable with no evidence of upper tract disease: <ul style="list-style-type: none"> • If catheter removed, consider observation alone OR • Ertapenem 1 g IV Q24H OR • Ceftriaxone 1 g IV Q24H OR • Ciprofloxacin 500 mg PO BID or 400 mg IV Q12H (avoid in pregnancy and in patients with prior exposure to quinolones) • Duration: see below Patient severely ill, with evidence of upper tract disease, or hospitalized >48 H: <ul style="list-style-type: none"> • Cefepime 1 g IV Q8H OR • PCN allergy: Aztreonam 1 g IV Q8H • Duration: see below
Urosepsis in a patient with nephrostomy tubes	SIRS with urinary source and nephrostomy tubes	<ul style="list-style-type: none"> • Piperacillin/tazobactam 3.375 mg IV Q6H If prior urine culture data are available, tailor therapy based on those results

DIAGNOSIS

Specimen collection: The urine sample should be drawn from the catheter port using aseptic technique, **NOT** from the urine collection bag. In patients with long term catheters (≥ 2 weeks), replace the catheter before collecting a specimen. Urine should be collected before antibiotics are started.

Symptoms: Catheterized patients usually lack typical UTI symptoms. Symptoms compatible with CA-UTI include:

- New fever or rigors with no other source
- New onset delirium, malaise, lethargy with no other source
- CVA tenderness, flank pain, pelvic discomfort
- Acute hematuria

Interpretation of the urinalysis (U/A) and urine culture

- Pyuria: In the presence of a catheter, pyuria does not correlate with the presence of symptomatic CA-UTI and must be interpreted based on the clinical scenario. The absence of pyuria suggests an alternative diagnosis.
- Positive urine culture: $\geq 1,000$ colonies

DURATION

The duration of treatment has not been well studied for CA-UTI and optimal duration is not known.

- 7 days if prompt resolution of symptoms
- 10–14 days if delayed response
- 3 days if catheter removed in female patient \leq 65 years with lower tract infection.

TREATMENT NOTES

- Remove the catheter whenever possible
- Replace catheters that have been in \geq 2 weeks if still indicated
- Prophylactic antibiotics at the time of catheter removal or replacement are NOT recommended due to low incidence of complications and concern for development of resistance.
- Catheter irrigation should not be used routinely

Treatment of Enterococci

- Almost all *E. faecalis* isolates are susceptible to Amoxicillin 500 mg PO TID OR Ampicillin 1 g IV Q6H and should be treated with these agents. For patients with PCN allergy: Nitrofurantoin (Macrobid®) 100 mg PO Q12H (do NOT use in patients with CrCl < 50 mL/min).
- *E. faecium* (often Vancomycin resistant)
 - Nitrofurantoin (Macrobid®) 100 mg PO Q12H if susceptible (do NOT use in patients with CrCl < 50 mL/min).
 - Tetracycline 500 mg PO Q6H if susceptible
 - Fosfomycin 3 g PO once (if female without catheter or catheter is removed; ask the micro lab for susceptibility)
 - Linezolid 600 mg PO BID OR Fosfomycin 3 g PO every 2–3 days (max 21 days) if complicated UTI or catheter can not be removed

Renal excretion/concentration of selected antibiotics

Good (\geq 60%): aminoglycosides, Amoxicillin, Amoxicillin/clavulanate, Fosfomycin, Cefazolin, Cefepime, Cephalexin, Ciprofloxacin, Colistin, Ertapenem, Trimethoprim/sulfamethoxazole, Vancomycin, Amphotericin B, Fluconazole, Flucytosine

Variable (30-60%): Cefpodoxime, Linezolid (30%), Doxycycline (29–55%), Ceftriaxone, Tetracycline (~60%)

Poor (<30%): Azithromycin, Clindamycin, Moxifloxacin, Oxacillin, Tigecycline, Micafungin, Posaconazole, Voriconazole

References:

- Pyuria and urinary catheters: Arch Int Med 2000;160(5):673-77.
 IDSA Guidelines for treatment of uncomplicated acute bacterial cystitis and pyelonephritis in women: Clin Infect Dis 1999;29:745.
 IDSA Guidelines for treatment of CA-UTI: Clin Infect Dis 2010;50:625–63.

Candidiasis in the non-neutropenic patient

Oropharyngeal disease (thrush)

Initial treatment

- Clotrimazole 10 mg troche 5 times a day
- OR**
- Nystatin suspension 500,000 units/5mL 4 times a day

Recurrent or intractable disease

- Fluconazole 100–200 mg PO once daily

Duration: 5–10 days

NOTE: If refractory to Fluconazole consider fungal culture and susceptibilities

Esophageal candidiasis

Initial treatment

- Fluconazole 200–400 mg IV/PO once daily

Duration: 14–21 days

Relapse

- Fluconazole 400–800 mg IV/PO once daily

Refractory to Fluconazole 800 mg daily (fungal culture and susceptibilities are recommended)

- Micafungin 150 mg IV once daily
- OR**
- Amphotericin B 0.3–0.7 mg/kg IV once daily
- OR**
- Oral therapy: Itraconazole oral solution 200 mg daily

Duration: 14–21 days

Candiduria

- Urinary catheter removal will resolve the candiduria in 40% of cases.

TREATMENT

Asymptomatic cystitis

- Therapy not usually indicated
- Consider in the following conditions (see regimens under “symptomatic cystitis”):
 - Neutropenic patients
 - Renal transplant
 - Urinary obstruction or abnormal GU tract
 - When recovered in urine prior to urologic procedures

Symptomatic cystitisPreferred therapy

- Fluconazole 200 mg IV/PO once daily

Duration: 7–14 days

Fluconazole-resistant organism suspected or confirmed

- Amphotericin B 0.3-0.6 mg/kg IV once daily

Duration: 1–7 days

Pyelonephritis

NOTE: Candida pyelonephritis is usually secondary to hematogenous spread except for patients with renal transplant or abnormalities of the urogenital tract.

Preferred therapy

- Fluconazole 200–400 mg IV/PO once daily

Duration: 14 days

Fluconazole-resistant organism suspected or confirmed

- Amphotericin B 0.5–0.7 mg/kg IV once daily

OR

- Micafungin 100 mg IV once daily

Duration: 14 days

TREATMENT NOTES

- Remove urinary catheter if possible.
- Therapy of candiduria in the non-neutropenic, non-ICU catheterized patient has not been shown to be beneficial and promotes resistance.
- AmBisome®, Voriconazole, Itraconazole, and Posaconazole are not recommended due to poor penetration into the urinary tract.
- Micafungin penetrates poorly in the urine, but does penetrate into renal tissue.
- Amphotericin B bladder washes are not recommended.

Candida vaginitisInitial Therapy

- Fluconazole 150 mg PO X 1 dose

OR

- Miconazole 2% cream 5 g intravaginally once daily X 7 days

Recurrent (> 4 episodes/year of symptomatic infection)

- Fluconazole 150 mg PO Q72H X 3 doses, then 150 mg a week X 6 months

Candidemia

- YEAST IN A BLOOD CULTURE SHOULD NOT BE CONSIDERED A CONTAMINANT.

NOTE: Micafungin does not have activity against *Cryptococcus*

TREATMENT**Unspciated candidemia**

Patients who are clinically stable and have not received prior long-term azole therapy

- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily

Patients who are NOT clinically stable due to Candidemia or have received prior long-term azole therapy

- Micafungin 100 mg IV once daily

If the yeast is *C. albicans* or *C. glabrata* based on PNA FISH results, follow the recommendations for *C. albicans* or *C. glabrata* noted below. Otherwise, await speciation before modifying therapy as recommended below, unless the patient becomes clinically unstable on Fluconazole.

Candida albicans

- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily

Patients who are NOT clinically stable due to Candidemia or have received prior long-term azole therapy

- Micafungin 100 mg IV once daily

Patients should be transitioned to Fluconazole once stable.

Candida glabrata

- Micafungin 100 mg IV once daily

OR

- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily IF the isolate is susceptible with MIC \leq 8 mcg/mL and the patient is stable.

If isolate is intermediate to Fluconazole and oral therapy is desired, consult ID. Other azoles such as Voriconazole should not be used in Fluconazole-resistant strains due to the same mechanism of resistance.

Candida krusei

- Micafungin 100 mg IV once daily

Fluconazole should NEVER be used to treat infections due to *C. krusei* because the organism has intrinsic resistance to Fluconazole. This mechanism of resistance is not shared with Voriconazole; therefore, oral Voriconazole can be used if isolate is susceptible (for dosing see Voriconazole specific guidelines, p. 19).

Candida lusitanae

- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily
- C. lusitanae* is resistant to Amphotericin B in approximately 20% of cases.

Candida parapsilosis

- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily

Fluconazole-intermediate isolate

- Fluconazole 800 mg IV/PO once daily

Fluconazole-resistant isolate

- Micafungin 100 mg IV once daily

If the patient is not responding to Micafungin then consider changing to Amphotericin B. The minimum inhibitory concentrations (MICs) of echinocandins are higher for *C. parapsilosis* than any other *Candida* spp.; this has led to concern that some infections with *C. parapsilosis* may not respond well to echinocandins.

Candida tropicalis

- Fluconazole 800 mg IV/PO X 1 dose, then 400 mg IV/PO once daily

Fluconazole-intermediate isolate

- Fluconazole 800 mg IV/PO once daily

Fluconazole-resistant isolate

- Micafungin 100 mg IV once daily

TREATMENT NOTES**Amphotericin B use in Candidemia**

- Amphotericin B is highly effective against all *Candida* spp. except for *C. lusitanae*; however, azoles and echinocandins are favored in susceptible strains over Amphotericin B products due to toxicity.

Doses for Candidemia

- Amphotericin B 0.7 mg/kg IV once daily

OR

- AmBisome® 3 mg/kg IV once daily (if patient cannot tolerate conventional Amphotericin B)

Duration

- 14 days following documented clearance of blood cultures and clinical symptoms
- Patients with persistent candidemia and/or metastatic complications (e.g. endophthalmitis, endocarditis) need a longer duration of therapy and evaluation by Ophthalmology and ID.

Hidden Content - JHH Internal use only

Non-pharmacologic management

- Removal of all existing central venous catheters is highly recommended.
- Patients should have blood cultures daily or every other day until candidemia is cleared.
- Patients should have an ophthalmologic examination to exclude candidal endophthalmitis prior to discharge, preferably once the candidemia is controlled.
- Echocardiography can be considered if the patient has persistent candidemia on appropriate therapy.

Endophthalmitis

- Management in conjunction with Ophthalmology
- Due to poor CNS and vitreal penetration, treatment with echinocandins is NOT recommended.

Preferred therapy

- Amphotericin B 1 mg/kg IV once daily ± Flucytosine 25 mg/kg PO Q6H
OR
- AmBisome® 5 mg/kg IV once daily ± Flucytosine 25 mg/kg PO Q6H

Alternate therapy

- Fluconazole 400-800 mg IV/PO once daily ± Flucytosine 25 mg/kg PO Q6H

Duration: 4–6 weeks

Endocarditis

Consultation with ID and Cardiac Surgery is recommended. Surgical valve replacement is considered a critical component for cure. If the patient is not a candidate for surgery then life-long Fluconazole suppression is likely required.

Preferred therapy

- AmBisome® 5 mg/kg IV once daily

Alternative therapy

- Micafungin 150 mg IV once daily ± Fluconazole 400–800 mg IV/PO once daily

Duration: 6 weeks or longer

Notes on antifungal susceptibility testing

- Susceptibility testing for Fluconazole, Itraconazole, Voriconazole, Flucytosine, and Micafungin is performed routinely on the first yeast isolate recovered from blood.
- Fluconazole and Micafungin susceptibility are reported on all isolates.
- Organisms that have Micafungin MICs in the range of 1–2 mcg/mL (reported as susceptible) may not respond to treatment. ID consult is recommended in these cases.
- Susceptibility testing for conventional Amphotericin B is done routinely for *C. lusitaniae* and *C. guilliermondii*, and for other organisms by request.
- If the organism is intermediate (I) to Fluconazole, then 800 mg IV/PO once daily can be used. This choice is NOT recommended in an immunocompromised patient, in a patient who is clinically unstable due to candidemia, or in patients with endocarditis, meningitis or endophthalmitis.
- Susceptibility testing should be considered when:
 - Mucocutaneous candidiasis is refractory to Fluconazole
 - Treating osteomyelitis, meningitis, or endophthalmitis with Fluconazole
 - Blood cultures are persistently positive on Fluconazole
- Non-routine susceptibility testing can be arranged by calling the mycology lab at 5-6148

Notes on Fluconazole prophylaxis

- Fluconazole prophylaxis should be limited to the following settings
 - Patients expected to remain in the **SICU or WICU** for ≥ 72 hours (Criteria from Hopkins SICU prophylaxis study; prophylaxis in other ICUs has NOT been studied and is NOT recommended).
 - Neutropenic patients undergoing bone marrow transplantation or treatment for leukemia/lymphoma
 - Patients who are post-op from liver or pancreas transplants.
- Fluconazole prophylaxis should be stopped when SICU or WICU patients are transferred to the floor

References:

IDSA Guidelines for Treatment of Candidiasis: Clin Infect Dis 2009;48:503-535.
Fluconazole prophylaxis in surgical patients: Ann Surg 2001;233:542–8.

Pre-operative and pre-procedure antibiotic prophylaxis

For specific procedures and agents see “Peri-operative antibiotic prophylaxis document” at www.insidehopkinsmedicine.org/amp

Drug	Usual dose	Redosing during procedure
Cefazolin	< 120 kg: 2 g ≥ 120 kg: 3 g	Q4H (Q2H for cardiac surgery) Q4H (Q2H for cardiac surgery)
Cefotetan	< 120 kg: 2 g ≥ 120 kg: 3 g	Q6H
Clindamycin	600 mg	Q6H
Ciprofloxacin	400 mg	None
Gentamicin	5 mg/kg	None
Metronidazole	500 mg	None
Vancomycin	< 70 kg: 1 g 71-99 kg: 1.25 g > 100 kg: 1.5 g	Q12H

Important notes

- **Timing is crucial. Antibiotics must be in the skin when the incision is made to be effective.**
- Cephalosporins can be administered over 3–5 min IV push just before the procedure and will achieve appropriate skin levels in minutes. Vancomycin and Ciprofloxacin must be given over 60 min. Clindamycin should be infused over 10–20 min.
- For antibiotics with longer infusion times (e.g. Vancomycin, Ciprofloxacin) the infusion should start 30 minutes prior to incision
- **Post-procedure doses are NOT needed (exceptions are noted in table). Single doses pre-procedure have been as effective as post-procedure doses in all studies.**
- Patients receiving pre-operative antibiotics generally do NOT need additional antibiotics for endocarditis prophylaxis.
- Prophylaxis for patients already on antibiotics:
 - For antibiotics other than Vancomycin: Hold standing dose until 1 hour before incision
 - For Vancomycin: Redose a full dose if 8 hours have passed since the last dose or a half dose if fewer than 8 hours have passed in patient with normal renal function
- Gentamicin should be given as a single dose of 5 mg/kg to maximize tissue penetration and minimize toxicity.
 - If on dialysis or CrCl < 20 mL/min, use 2 mg/kg
 - Do not redose
 - Use actual body weight unless patient is ≥ 20% over ideal body weight (see p. 145)

Procedure	Prophylaxis recommendations	PCN allergy alternate prophylaxis
Urologic surgery/procedures		
Transrectal prostate biopsy ¹	Cefazolin	Ciprofloxacin OR Gentamicin ²
Transurethral surgery (e.g. TURP, TURBT, ureteroscopy, cystourethroscopy)	Cefazolin	Gentamicin ²
Lithotripsy	Cefazolin	Gentamicin ²
Nephrectomy or radical prostatectomy	Cefazolin	Clindamycin
Radical cystectomy, ileal conduit, cystoprostatectomy or anterior exenteration	Cefotetan	Clindamycin PLUS Gentamicin ²
Penile or other prostheses	[Cefazolin OR Vancomycin] PLUS Gentamicin ²	[Clindamycin OR Vancomycin] PLUS Gentamicin ²
Cardiac surgery		
Median sternotomy, heart transplant ³	Cefazolin	Vancomycin
Median sternotomy, heart transplant with previous VAD or MRSA colonization/infection ³	Cefazolin PLUS Vancomycin	Vancomycin
Pacemaker or ICD insertion	Cefazolin	Clindamycin OR Vancomycin
Pacemaker or ICD insertion with MRSA colonization/infection or generator exchange	Cefazolin PLUS Vancomycin	Vancomycin
VAD insertion	Cefazolin	Vancomycin
VAD insertion with MRSA colonization/infection	Cefazolin PLUS Vancomycin	Vancomycin
VAD insertion with open chest ³	Cefazolin PLUS Vancomycin	Vancomycin PLUS Ciprofloxacin
Lung transplant ⁴	Cefepime	Consult transplant ID
Vascular surgery		
Carotid and brachiocephalic procedures without prosthetic grafts	Prophylaxis not recommended	Prophylaxis not recommended
Upper extremity procedures with prosthetic grafts and lower extremity procedures	Cefazolin	Clindamycin OR Vancomycin
Abdominal aorta procedure or groin incision	Cefotetan	Vancomycin + Gentamicin ²
Thoracic surgery		
Lobectomy, pneumonectomy, lung resection, thoracotomy, VATS	Cefazolin	Clindamycin
Esophageal cases	Cefotetan	Clindamycin
Neurosurgery		
Craniotomy, cerebrospinal fluid-shunting procedures, implantation of intrathecal pumps	Cefazolin	Clindamycin
Laminectomy	Cefazolin	Clindamycin
Spinal fusion	Cefazolin	Clindamycin OR Vancomycin
Spinal fusion with MRSA colonization/infection	Cefazolin PLUS Vancomycin	Vancomycin
Transsphenoidal procedures	Ceftriaxone	Moxifloxacin 400 mg
Orthopedic surgery		
Clean operations involving hand, knee, or foot, arthroscopy	Prophylaxis not recommended	Prophylaxis not recommended
Total joint replacement	Cefazolin	Vancomycin
Total joint replacement with MRSA colonization/infection	Cefazolin PLUS Vancomycin	Vancomycin
Open reduction of fracture/internal fixation	Cefazolin	Clindamycin OR Vancomycin
Lower limb amputation	Cefotetan	Clindamycin PLUS Gentamicin ²
Spinal fusion	Cefazolin	Clindamycin OR Vancomycin
Spinal fusion with MRSA colonization/infection	Cefazolin PLUS Vancomycin	Vancomycin
Laminectomy	Cefazolin	Clindamycin

Procedure	Prophylaxis recommendations	PCN allergy alternate prophylaxis
General surgery		
Procedures involving entry into lumen of upper GI tract, gastric bypass procedures, pancreaticoduodenectomy, highly selective vagotomy, Nissen fundoplication	Cefotetan	Clindamycin ± Gentamicin ²
Biliary tract procedures (e.g. cholecystectomy, choledochenterostomy)	Cefotetan	Clindamycin ± Gentamicin ²
Hepatectomy	Cefotetan	Clindamycin ± Gentamicin ²
Whipple procedure or pancreatectomy	Cefotetan	Clindamycin <u>PLUS</u> Ciprofloxacin
Small bowel procedures	Cefotetan	Clindamycin <u>PLUS</u> Gentamicin ²
PEG	Cefazolin OR Cefotetan	Clindamycin ± Gentamicin ²
Appendectomy (if complicated or perforated, treat as secondary peritonitis)	Cefotetan	Clindamycin <u>PLUS</u> Gentamicin ²
Colorectal procedures, penetrating abdominal trauma	Cefotetan	Clindamycin <u>PLUS</u> Gentamicin ²
Inguinal hernia repair	Cefazolin	Clindamycin
Complicated, emergent or repeat inguinal hernia repair	Cefotetan	Clindamycin ± Gentamicin ²
Mastectomy	Prophylaxis not recommended	Prophylaxis not recommended
Mastectomy with lymph node dissection	Cefazolin	Clindamycin <u>PLUS</u> Gentamicin ²
Gynecologic surgery		
Cesarean delivery procedures	Cefazolin	Clindamycin <u>PLUS</u> Gentamicin ²
Hysterectomy (vaginal or abdominal)	Cefazolin OR Cefotetan	Clindamycin <u>PLUS</u> Gentamicin ²
Oncology procedures	Cefotetan	Clindamycin <u>PLUS</u> Gentamicin ²
Repair of cystocele or rectocele	Cefazolin	Clindamycin
Head and neck surgery		
Parotidectomy, thyroidectomy, tonsillectomy	Prophylaxis not recommended	Prophylaxis not recommended
Reconstructive procedure w/prosthesis placement	Cefazolin	Clindamycin
Adenoidectomy, rhinoplasty, tumor-debulking, or mandibular fracture repair	Cefotetan OR Clindamycin	Clindamycin
Major neck dissection	Cefazolin	Clindamycin
Plastic surgery		
Clean with risk factors or clean-contaminated	Cefazolin	Clindamycin
Tissue expander insertion/implants/all flaps	Cefazolin	Clindamycin
Rhinoplasty	No prophylaxis OR Cefazolin	No prophylaxis OR Clindamycin
Abdominal transplant surgery		
Pancreas or pancreas/kidney transplant	Cefotetan	Clindamycin <u>PLUS</u> Ciprofloxacin
Renal transplant/adult live donor	Cefazolin	Clindamycin
Liver transplant ⁴	Cefotetan	Clindamycin <u>PLUS</u> Ciprofloxacin

¹If pre-op rectal screen performed: see p. 124

²Do not give additional doses of Gentamicin post-op for prophylaxis

³For open chest, continue antibiotic prophylaxis until closure

⁴Listed recommendations are for patients with no relevant microbiology data that would suggest resistant organisms; prophylactic regimen should be tailored based on known microbiology data with assistance of transplant ID (page in PING)

Procedure	Prophylaxis recommendations	PCN allergy alternate prophylaxis
Interventional radiology procedures		
Biliary/GI; chemo embolization/percutaneous liver ablation (hx. of biliary surgery/instrumentation); cecostomy	Cefotetan	Clindamycin <u>PLUS</u> Gentamicin
Chemo embolization; fibroid/urine artery embolization; percutaneous liver/renal/lung* ablation; vascular malformation embolization†	Prophylaxis not recommended	
Urologic procedure (not ablation)	Cefazolin	Gentamicin
Lymphangiogram/embolization	Cefazolin	Clindamycin
Placement of tunneled catheters (e.g. central line); venous/arterial procedures.	Prophylaxis not recommended	
Placement of implantable access port (e.g. Mediport®)	Cefazolin	Clindamycin

*Pre-treatment w/ antibiotics can be considered for patients w/ COPD or h/o recurrent post-obstructive pneumonia

† Lymphatic or patients w/ necrotic skin undergoing vascular graft should receive prophylaxis w/Cefazolin

Prophylaxis for Prostate Biopsy Based on Rectal Screen Results		
	Pre-op prophylaxis regimen¹	Post-op oral options²
Ciprofloxacin susceptible	Ciprofloxacin 750 mg PO 2 hours before procedure for any renal function	Ciprofloxacin 500 mg PO once 12 hours after the procedure. If GFR <30 ml/min no need for post-op dose.
Ciprofloxacin resistant, TMP/SMX susceptible	TMP/SMX 1 DS 1 hour before procedure, and 1 DS 3 hours before	TMP/SMX 1 DS PO once 12 hours after the procedure. If GFR <30 ml/min no need for post-op dose.
Ciprofloxacin and TMP/SMX resistant, Cefazolin susceptible	Cefazolin 2 g IV push (3-5 min) within an 1 hour of procedure	Cefpodoxime 100 mg PO once OR Cefdinir 300 mg PO once
Ciprofloxacin, TMP/SMX, Cefazolin resistant	Gentamicin 5 mg/kg IV once over 30-60 min OR Ceftriaxone 1 g IV over 30 min if susceptible	No need for additional doses as Gentamicin and Ceftriaxone retain therapeutic levels for 24 hours
Other resistance patterns	Call ID Pharmacist	

¹ All doses are for any renal function ² Post-op antibiotics are not required by SCIP

Prophylaxis against bacterial endocarditis

NOTES:

- Patients who have received antibiotics for surgical prophylaxis do not need additional prophylaxis for endocarditis.

Antibiotic prophylaxis solely to prevent endocarditis is not recommended for GU or GI tract procedures.

Cardiac conditions associated with a high risk of endocarditis for which prophylaxis is recommended prior to some dental and respiratory tract procedures and procedures involving infected skin or musculoskeletal tissue

- Prosthetic cardiac valve
- Previous episode of infective endocarditis
- Congenital heart disease (CHD)
 - Unrepaired cyanotic CHD, including palliative shunts and conduits
 - Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure
 - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device
- Cardiac transplantation recipients who develop cardiac valvulopathy

Antibiotic prophylaxis is recommended for the following dental procedures ONLY:

- Manipulation of gingival tissues or periapical region of teeth
- Perforation of oral mucosa

Antibiotic prophylaxis is recommended for the following respiratory tract procedures ONLY:

- Incision or biopsy of the respiratory mucosa

Antibiotic regimens

- Amoxicillin 2 g PO 1 hour before procedure
OR
- PCN allergy: Clindamycin 600 mg PO 1 hour before procedure
OR
- PCN allergy: Azithromycin 500 mg PO 1 hour before procedure
OR
- Patient unable to take oral medication: Ampicillin 2 g IM/IV 1 hour before procedure OR Cefazolin 1 g IM/IV 5 minute push prior to procedure

Reference:

AHA Guidelines for Prevention of Infective Endocarditis: Circulation 2007; 116:1736–54.

Prophylactic antimicrobials for patients with solid organ transplants

NOTE: All doses assume normal renal function; dose modifications may be indicated for reduced CrCl.

Kidney, kidney-pancreas, pancreas transplants

Indication	Agent and dose	Duration
Anti-viral prophylaxis (CMV, HSV, VZV)		
CMV D-/R-	Acyclovir 400 mg PO BID OR Valacyclovir 500 mg PO BID	3 months
CMV D+ or D-/R+	Valganciclovir [†] 450 mg PO daily	3 months
CMV D+/R-	Valganciclovir [†] 900 mg PO daily	6 months
Anti-fungal prophylaxis		
Kidney	Clotrimazole troches 10 mg PO QID OR Nystatin suspension 500,000 units QID	1 month [‡]
Pancreas and kidney	Fluconazole 400 mg PO daily	1 month
PCP prophylaxis	First line: TMP/SMX one SS tablet PO daily Second line: Atovaquone 1500 mg PO daily Third line: Dapsone* 100 mg PO daily OR aerosolized Pentamidine	6 months

Acute rejection treated with Thymoglobulin or Muromonab (OKT3)

Anti-viral prophylaxis (CMV, HSV, VZV)

CMV D-/R-	Acyclovir 400 mg PO BID OR Valacyclovir 500 mg PO BID	3 months
CMV D+ or D-/R+	Valganciclovir [†] 450 mg PO daily	3 months
CMV D+/R-	Valganciclovir [†] 900 mg PO daily	3 months

Anti-fungal prophylaxis	Clotrimazole troches 10 mg PO QID	1 month
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PCP prophylaxis	First line: TMP/SMX one SS tablet PO daily Second line: Atovaquone 1500 mg PO daily Third line: Dapsone* 100 mg PO daily OR aerosolized Pentamidine	6 months
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Liver transplants

Indication	Agent and dose	Duration
Anti-viral prophylaxis (CMV, HSV, VZV)		
CMV D-/R-	Acyclovir 400 mg PO BID OR Valacyclovir 500 mg PO BID	3 months
CMV D+ or D-/R+	Valganciclovir [†] 450 mg PO daily	3 months
CMV D+/R-	Valganciclovir [†] 900 mg PO daily, followed by PCR monitoring	6 months
Anti-fungal prophylaxis	Fluconazole 400 mg PO daily	6 weeks
PCP prophylaxis	First line: TMP/SMX one SS tablet PO daily Alternatives: Atovaquone 1500 mg PO daily or Dapsone 100 mg PO daily	12 months

Heart transplants		
Indication	Agent and dose	Duration
Anti-viral prophylaxis (CMV, HSV, VZV)		
CMV D-/R-	No prophylaxis unless HSV IgG or VZV IgG positive. If positive serology, Valacyclovir 500 mg PO BID	3 months
CMV D+ or D-/R+	Valganciclovir† 900 mg PO daily	3 months
CMV D+/R-	Valganciclovir† 900 mg PO daily	6 months
Anti-fungal prophylaxis	Nystatin suspension 500,000 units QID	Until prednisone dose \leq 10 mg/d x 3 months
PCP prophylaxis	First line: TMP/SMX SS one tablet PO daily OR TMP/SMX one DS tablet PO three times/week Second line: Dapsone* 100 mg PO daily Third line: Atovaquone 1500 mg PO daily	12 months
Toxoplasmosis prophylaxis		
Toxo R+	First line: TMP/SMX one SS tablet PO daily Second line: Dapsone* 100 mg PO daily <u>PLUS</u> Pyrimethamine and Leucovorin	12 months
Toxo D+ or unknown-donor status	First line: TMP/SMX one SS tablet PO daily Second line: Dapsone* 100 mg PO daily <u>PLUS</u> Pyrimethamine and Leucovorin	12 months- Lifelong
Lung transplants		
Indication	Agent and dose	Duration
Anti-viral prophylaxis		
CMV D-/R- Received non-leukoreduced or CMV unscreened PRBCs	Ganciclovir 5 mg/kg IV Q12H x 14 days, then Ganciclovir 5 mg/kg IV Q24H x 16 days, then Valacyclovir 500 mg PO BID or Acyclovir 800 mg PO TID x 1 year followed by Acyclovir 200 mg PO TID	Lifelong
CMV D-/R- Received leukoreduced or CMV(-) PRBCs	Valacyclovir 500 mg PO BID or Acyclovir 800 mg PO TID x 1 year followed by Acyclovir 200 mg PO TID	Lifelong
CMV D+ or D-/R+	Ganciclovir 5 mg/kg IV Q12H x 14 days, then Valganciclovir 900 mg PO daily x 3 months (until CMV shell vial negative from 3 month surveillance bronchoscopy), then Valacyclovir 500 mg po BID or Acyclovir 800 mg PO TID x 1 year, then Acyclovir 200 mg PO TID lifelong.	Lifelong
CMV D+/R-	Ganciclovir 5 mg/kg IV Q12h x 14 days, then Ganciclovir 5 mg/kg IV daily x 3 months, then Valganciclovir 900 mg PO daily (until CMV shell	Lifelong

vial negative from 6 month surveillance BAL), then Valacyclovir 500 mg PO BID or Acyclovir 800 mg PO TID x 1 year, then Acyclovir 200 mg PO TID lifelong.

Anti-fungal prophylaxis		
No <i>Aspergillus</i> colonization	Inhaled Amphotericin B per protocol	During initial hospitalization stay
	Nystatin 500,000 units NG Q6H until extubated, then Clotrimazole troches 10 mg PO Q6H until prednisone dose < 10 mg daily	3–6 months
<i>Aspergillus</i> colonization	Voriconazole (dosed by weight) < 69 kg: Voriconazole 200 mg PO BID ≤ 69 kg to < 94 kg: Voriconazole 300 mg PO BID ≥ 94 kg: Voriconazole 400 mg PO BID	3–6 months
PCP prophylaxis		
	First line: TMP/SMX one DS tablet PO three times/week OR TMP/SMX one SS tablet PO daily Second line: Dapsone* 100 mg PO daily Third line: Atovaquone 1500 mg PO daily	Lifelong

D = donor, R = recipient, (-) = seronegative, (+) = seropositive

NOTES:

TMP/SMX therapy reduces risk of infection with *Listeria* spp., *Nocardia* spp., and Toxoplasmosis, but does not eliminate risk.

For splenectomized patients, antibacterial prophylaxis with Amoxicillin 500 mg PO BID (or Doxycycline if PCN allergy) is recommended for 1 year.

*Recommended screening for G6PD deficiency prior to initiation of Dapsone.

†If Valgancyclovir is stopped prior to recommended duration of therapy due to intolerance, recommend initiation of Acyclovir or Valacyclovir for antiviral prophylaxis.

‡INKTP–3 months

Neutropenic fever

NOTE: These guidelines were developed for use in BMT and leukemia patients and may not be fully applicable in other instances.

Definitions

- Neutropenia: ANC < 500/mm³
- Fever: Temp > 38.0° C times two at least 2 hours apart OR
Temp > 38.3° C times one

TREATMENT

Always tailor antibiotics based on susceptibility profiles

If the patient is hypotensive or otherwise unstable, see “Treatment of clinically unstable patients” (opposite).

Initial fever

- Cefepime 2 g IV Q8H ± Vancomycin* (see dosing section p. 150)
OR
- Piperacillin/tazobactam 3.375 g IV Q4H ± Vancomycin* (see dosing section p. 150)

*Indications for Vancomycin: suspected CR-BSI, skin and soft-tissue infections, pneumonia, severe oral or pharyngeal mucositis, history of MRSA infection or colonization.

OR

- Severe PCN allergy (anaphylaxis or Stevens-Johnson Syndrome):
Strongly consider allergy consult to verify allergy in patients with unclear histories (see section on Penicillin allergy, p. 137)
- Aztreonam 2 g IV Q8H PLUS Gentamicin[†] (see dosing section, p. 146)
PLUS Vancomycin (see dosing section, p. 150)

[†]If strong concern for nephrotoxicity and no prior fluoroquinolone use, can substitute Ciprofloxacin 400 mg IV Q8H for Gentamicin.

Step-down therapy for discharge

- Ciprofloxacin 750 mg PO BID PLUS Amoxicillin/clavulanate 875 mg PO BID
OR
- Moxifloxacin 400 mg PO daily

Persistent fever or new fever after 4-7 days in clinically stable patients without established bacterial infection

- Continue antibiotics above and ADD antifungal coverage

If receiving Fluconazole prophylaxis or no fungal prophylaxis:

- Micafungin 100 mg IV Q24H if sinus and/or chest CT not suggestive of fungal infection

OR

- Voriconazole 6 mg/kg IV/PO Q12H times two doses then 4 mg/kg IV/PO Q12H if chest CT suggestive of fungal infection

If receiving Voriconazole or Posaconazole prophylaxis or sinus CT suggestive of fungal infection:

- AmBisome® 5 mg/kg IV Q24H

Clinically unstable patient and/or persistent fever despite appropriate antibacterial and antifungal coverage

- Consult Oncology/Transplant ID
- Vancomycin (see dosing section, p. 150) PLUS Meropenem 1 g IV Q8H ± Amikacin if patient unstable (see dosing section p. 146)

OR

- Severe PCN allergy: Consult Oncology/Transplant ID

Prophylactic antimicrobials for patients with expected prolonged neutropenia

NOTE: All doses assume normal renal function; dose modifications may be indicated for reduced CrCl.

1. Leukemia patients

Indication	Agent and dose	Duration
Antibacterial prophylaxis	Moxifloxacin 400 mg PO daily PLUS Amoxicillin 500 mg PO TID (start on day 5)	Day 1 until ANC > 100/mm ³ OR initiation of "First Fever" antibiotics
Antifungal prophylaxis	First line: Voriconazole (see dosing in BMT section) Second line: Posaconazole suspension 200 mg PO TID OR 300 mg tablet daily Alternatives: Micafungin 100 mg IV Q24H OR Fluconazole 400 mg PO daily	Day 1 until ANC > 100/mm ³
Antiviral prophylaxis	Valacyclovir 500 mg PO BID OR Acyclovir 800 mg PO BID If vomiting or diarrhea: Acyclovir 250 mg/m ² IV Q12H†	Day 1 until ANC > 100/mm ³
PCP prophylaxis in high risk patients‡	First line: TMP/SMX one SS tab PO daily Second line: Dapsone 100 mg PO daily Third line: Atovaquone 750 mg PO BID	Day 1 until immunosuppression resolves

2. Lymphoma, myeloma patients

Indication	Agent and dose	Duration
Antibacterial prophylaxis (lymphoma only)	Moxifloxacin 400 mg PO daily	Day 7 of chemo until ANC > 500/mm ³
Antifungal prophylaxis	Fluconazole 200 mg PO daily	Day 1 through all cycles of chemotherapy in high risk patients.
Antiviral prophylaxis	Valacyclovir 500 mg PO BID OR Acyclovir 800 mg PO BID If vomiting or diarrhea: Acyclovir 250 mg/m ² IV Q12H†	Day 7 through all cycles of chemotherapy
PCP prophylaxis in high risk patients‡	First line: TMP/SMX one SS tab PO daily Second line: Dapsone 100 mg PO daily Third line: Atovaquone 750 mg PO BID	Day 7 through all cycles of chemotherapy

3. Bone marrow transplant patients/peripheral blood stem cell transplant patients		
Indication	Agent and dose	Duration
Antibacterial prophylaxis*	Moxifloxacin 400 mg PO daily	Day zero until engraftment
Antifungal prophylaxis	Fluconazole 400 mg PO daily	Day zero until ANC > 500/mm ³
Antifungal prophylaxis in patients with GVHD [†]	First line: Posaconazole suspension 200 mg PO TID OR 300 mg tablets daily Second line: Voriconazole (dosed by weight) <69 kg Voriconazole 200 mg PO BID ≤69 kg to <94 kg Voriconazole 300 mg PO BID ≥94 kg Voriconazole 400 mg PO BID	
Antiviral prophylaxis	Valacyclovir 500 mg PO BID OR Acyclovir 800 mg PO BID If vomiting or diarrhea: Acyclovir 250 mg/m ² IV Q12H [†]	Day zero until 1 yr (allogeneic transplants) or 6 months (autologous transplants)
PCP prophylaxis [‡]	First line: TMP/SMX one SS tab PO daily Second line: TMP/SMX DS tab 2 times weekly OR Dapsone 100 mg PO daily Third line: Atovaquone 750 mg PO BID Fourth line: Pentamidine 300 mg INH Q28 days	Allogeneic transplant: Day 21 or engraftment (whichever is later) until at least 1 year (longer if steroids or ongoing risk) Autologous transplant: Engraftment until 6 months

NOTES:

TMP/SMX therapy reduces risk of infection with encapsulated bacteria, *Listeria* spp., *Nocardia* spp., and Toxoplasmosis, but does not eliminate risk. It is the preferred antibiotic regimen for PCP prophylaxis.

*In patients with fluoroquinolone allergy or who cannot tolerate a fluoroquinolone due to QTc prolongation, consider Cefpodoxime 400 mg PO BID.

[†]Acyclovir should be dosed by ideal body weight

[‡]Myeloma patients if on steroids; Lymphoma patients if HIV+, on chronic steroids, fludarabine. Leukemia patients: ALL, chronic steroids, s/p BMT until 1 year after transplant, or patient who received cladribine, fludarabine, or alemtuzumab.

¶Other prophylaxis in acute GVHD: Moxifloxacin, TMP/SMX.

Guidelines for the use of antifungal agents in hematologic malignancy patients

Filamentous fungi

ID consult recommended for assistance with antifungal selection

TREATMENT

Aspergillus spp.

Initial therapy

- Voriconazole 6 mg/kg IV/PO Q12H times two doses then 4 mg/kg IV/PO Q12H (see Voriconazole guidelines, p. 19, for more information).

OR

- AmBisome® 5 mg/kg IV Q24H

NOTES:

- Voriconazole is considered by many to be the first-line treatment of suspected filamentous fungal infections in the immunocompromised host as most of these infections are caused by *Aspergillus* species. Although the data are limited, Voriconazole appears more effective than Amphotericin for this very serious infection.
- Combination antifungal therapy consisting of Voriconazole PLUS Micafungin should be considered for the treatment of confirmed invasive aspergillosis that is documented by culture, positive galactomannan assay, or histopathology for the first two weeks of therapy. Longer duration of combination therapy has not been evaluated.

Fusarium spp.

- ID consult should be involved in these cases.
- Voriconazole 6 mg/kg IV/PO Q12H times two doses then 4 mg/kg IV/PO Q12H PLUS Ambisome 5 mg/kg IV Q24H (see Voriconazole guidelines, p. 19, for more information). Dose escalation may be necessary for some patients.

Scedosporium apiospermum

- Voriconazole 6 mg/kg IV/PO Q12H times two doses then 4 mg/kg IV/PO Q12H PLUS Micafungin 100 mg IV Q24H (see Voriconazole guidelines, p. 19, for more information).

NOTE:

- Treatment with other agents has yielded disappointing results. Voriconazole appears to be the best option but the data are limited.

Zygomycoses (*Mucor*, *Rhizopus*, *Cunninghamella*, etc.).

- AmBisome® 5 mg/kg IV once daily PLUS a second antifungal agent
- ID consult required.
- Surgical debridement and correction of underlying risk factors (e.g. acidosis, hyperglycemia) are critical.

Candida**TREATMENT**

- YEAST IN A BLOOD CULTURE SHOULD NEVER BE CONSIDERED A CONTAMINANT.
 - See sections below on empiric therapy and on pathogen-specific therapy.

Unspciated candidemia

- Micafungin 100 mg IV Q24H
- OR**
- AmBisome® 5 mg/kg IV Q24H

If the yeast is *C. albicans* or *C. glabrata*, the recommendations for *C. albicans* noted below can be followed. If the yeast is not *C. albicans*, await speciation before modifying therapy as recommended below.

NOTE: Micafungin does not cover *Cryptococcus*

Candida albicans

- Micafungin 100 mg IV Q24H
- OR**
- AmBisome® 3–5 mg/kg IV Q24H

NOTE: Patients who are clinically stable and no longer neutropenic can be switched to Fluconazole if the organism is susceptible.

Candida glabrata

- Micafungin 100 mg IV Q24H
- OR**
- AmBisome® 5 mg/kg IV Q24H

Candida krusei

- Micafungin 100 mg IV Q24H
- OR**
- AmBisome® 5 mg/kg IV Q24H

NOTE: *C. krusei* is intrinsically resistant to Fluconazole and these infections can be difficult to treat. In stable patients, Voriconazole can be used if susceptible and oral therapy is desired. (See p. 19 for dosing).

Candida parapsilosis

- AmBisome® 3–5 mg/kg IV Q24H

NOTES:

- Most *C. parapsilosis* isolates remain susceptible to Fluconazole, which can be used in stable and non-neutropenic patients.
- There are limited data that suggest that Micafungin may be inferior to Amphotericin B in these infections.

Candida tropicalis

- Micafungin 100 mg IV Q24H
OR
- AmBisome® 3–5 mg/kg IV Q24H

TREATMENT NOTES

Hidden Content
- JHH Internal use only

Notes on antifungal susceptibility testing

- Susceptibility testing for Fluconazole, Itraconazole, Voriconazole, Flucytosine (5-FC), and Micafungin is performed routinely on the first yeast isolate recovered from blood.

- Fluconazole and Micafungin susceptibilities are reported on all blood isolates.
- Organisms that have Micafungin MICs in the range of 1–2 mcg/mL (reported as susceptible) may not respond to treatment. ID consult is recommended in these cases.
- Susceptibility testing for conventional Amphotericin B is done routinely for *C. lusitaniae* and *C. guillemondii* and for other organisms by request.
- Susceptibility testing should be considered when:
 - Mucocutaneous candidiasis is refractory to Fluconazole
 - Treating osteomyelitis, meningitis, or endophthalmitis with Fluconazole
 - Blood cultures are persistently positive on Fluconazole
- Non-routine susceptibility testing can be arranged by calling the mycology lab at 5-6148

Reference:

IDSA Guidelines for Treatment of Candidiasis: Clin Infect Dis 2009;48:503.

Approach to the patient with a history of penicillin allergy

Penicillin reactions – Incidence

- 80-90% of patients who report they are “allergic” to PCN actually have negative skin tests and are not at increased risk of an allergic reaction.
- Penicillin reactions of some type occur in 0.7 to 10% of all patients who get the drug.
 - BUT: The incidence of anaphylactic reactions is 0.004% to 0.015%.
- Rates of cross-reaction allergies to cephalosporins are unknown but thought to be low.
- Rates of PCN and carbapenem skin test cross reactivity are 47%, although clinical rates of hypersensitivity reactions in patients with reported PCN allergy who receive carbapenems are 9–11%.
- Cross reactions to monobactams (Aztreonam) do NOT appear to occur.

Penicillin skin testing

- When done correctly, is highly predictive of serious, anaphylactic reactions.
- Patients with a negative skin test are NOT at risk for anaphylactic reactions.
- Rarely, skin test negative patients may get mild hives and itching following penicillin administration but these RESOLVE with continued treatment.
- Skin tests cannot predict dermatologic or GI reactions or drug fevers.
- Skin testing is now available at JHH. Please consult Allergy and Immunology.

Penicillin reactions—Types

- **Immediate** (type 1) – Anaphylaxis, hypotension, laryngeal edema, wheezing, angioedema, urticaria
 - Almost always occur **within 1 hour** of administration. Hypotension **always** occurs soon after administration
 - Can be predicted by skin tests
- **Accelerated** – Laryngeal edema, wheezing, angioedema, urticaria (NOT hypotension)
 - Occur within 1-72 hours of administration
 - Can be predicted by skin tests
- **Late** – Rash (maculopapular or morbilliform or contact dermatitis), destruction of RBC, WBC, platelets, serum sickness
 - Almost always occur after 72 hours of administration
 - Rashes sometimes go away despite continued treatment
 - Maculopapular and morbilliform rashes DO NOT progress to Stevens-Johnson syndrome
 - Late reactions are NOT predicted by skin tests
- **Stevens-Johnson Syndrome** – exfoliative dermatitis with mucous membrane involvement

- Almost always occur after 72 hours of administration
- NOT predicted by a history of rash OR by skin tests

Approach to the patient with reported penicillin allergy

- Brief, focused history can be VERY helpful.
- Questions to ask:
 1. How long after beginning penicillin did the reaction occur?
 2. Was there any wheezing, throat or mouth swelling, urticaria?
 3. If a rash occurred, what was the nature of the rash? Where was it and what did it look like?
 4. Was the patient on other medications at the time of the reaction?
 5. Since then, has the patient ever received another penicillin or cephalosporin (ask about trade names like: Augmentin, Keflex, Trimox, Ceftin, Vantin)?
 6. If the patient received a beta-lactam, what happened?

Interpreting the history of the patient reporting penicillin allergy

- **ANY patient who has a history consistent with an immediate reaction (laryngeal edema, wheezing, angioedema, urticaria) SHOULD NOT receive beta-lactams without undergoing skin testing first EVEN IF they have received beta-lactams with no problems after the serious reaction.**
 - Patients who report non-anaphylactic reactions and have received other penicillins without problems DO NOT have penicillin allergy and are not at increased risk for an allergic reaction compared to the general population.
 - Patients who report non-anaphylactic reactions and have received cephalosporins can get cephalosporins but not necessarily PCNs.
 - Patients who report a history of a non-urticarial rash that is NOT consistent with Stevens-Johnson syndrome (target lesions with mucous membrane inflammation) and developed after ≥ 72 hours of penicillin are not at increased risk for an adverse reaction. They should, however, be watched closely for development of rashes.
 - Patients who report reactions consistent with serum sickness (rare) can receive either penicillins or cephalosporins with careful monitoring for recurrence.
 - Patients who report GI symptoms (diarrhea, nausea) probably do not have penicillin allergy and do not appear to be at increased risk for an adverse reaction. They should be closely observed for recurrent symptoms and be given supportive therapy if they occur.

References:

JAMA 2001;285:2498.

Use of carbapenems in patients with PCN allergy: J Antimicrob. Chemother 2004;54:1155-7.

Ann Intern Med 2007;146:266-9.

Hospital Epidemiology and Infection Control (HEIC)

- Consult the HEIC website or JHH policies online (HPO) (www.hopkinsmedicine.org/heic) for detailed isolation charts, HEIC policies, and surveillance information

Hand hygiene

- If hands are not visibly soiled, then alcohol-based hand sanitizers are recommended for cleaning. If hands are visibly soiled, wash hands with soap and water for at least 15 seconds.
- Hand hygiene is required upon entering a patient room, upon exiting, between patients in a semi-private room, and other times per hospital policy.
- Use soap and water upon **exiting** the room of a patient with *C. difficile* infection.
- No artificial fingernails are permitted for any staff member who has patient contact or handles sterile supplies.

Bloodborne pathogen exposures (needlestick or other exposure)

The prompt treatment of injuries and exposures is vital to prevent the transmission of disease. Whatever the exposure, IMMEDIATE cleaning of the exposure site is the first priority.

- Skin wounds should be cleaned with soap and water
- Mucous membranes should be flushed thoroughly with water
- Eyes should be irrigated with a liter of normal saline

After cleaning the exposure site, call 5-STIX (5-7849) and follow instructions to contact the ID physician. Workplace injuries should be reported immediately on the “Employee Report of Incident Form” and to the **Occupational Injury Clinic** (Blalock 139, Monday–Friday, 7:30 a.m. to 4 p.m., 5-6433), and to your supervisor.

Standard Precautions

• Routine hand hygiene	• Bag contaminated linen at point of use
• Consistent and correct glove use	• Regular cleaning of environmental surfaces
• Appropriate use of gowns to prevent contamination of uniform/clothing	• Routine cleaning or disposal of patient-care equipment
• Appropriate use of masks, eye protection and face shields (i.e., when suctioning, or when splash likely)	• Strict adherence to occupational safety requirements

Communicable diseases—exposures and reporting

HEIC should be notified:

- If patients or HCWs are exposed to a communicable disease (i.e. meningococcal disease, varicella, TB etc.)
- About HCWs with acute hepatitis A, B or C, Salmonella, Shigella, Campylobacter, or pneumonia requiring hospital admission
- About any unusual occurrence of disease or cluster, particularly diseases that have the potential to expose many susceptible individuals
- Suspicion or diagnoses of the following diseases (diseases with ☎ require immediate notification by phone or pager). If disease is in a HCW, notify HEIC and Occupational Health (98 N. Broadway, Suite 421, Monday–Friday, 7:30 a.m. to 4:00 p.m., 5-6211) immediately

Anthrax ☎	Rabies ☎
Avian Influenza ☎	Ricin toxin ☎
Botulism ☎	Rubella (German measles)
Brucellosis	Salmonellosis
Creutzfeldt-Jakob disease (CJD) ☎	SARS ☎
Diphtheria ☎	Scabies
Glanders ☎	Shigellosis
Highly resistant organisms (i.e. VISA, VRSA) ☎	Smallpox (orthopox viruses) ☎
Legionellosis	Streptococcal Group A or B invasive disease ☎
Measles (rubeola) ☎	Tuberculosis ☎
Meningococcal disease ☎	Tularemia ☎
Monkeypox ☎	Varicella (chickenpox or disseminated zoster) ☎
Mumps	Viral hemorrhagic fever ☎
Pertussis ☎	Yellow Fever ☎
Plague ☎	
Poliomyelitis	
Q Fever	

Physicians are required to report communicable disease to the Baltimore City Health Department (410-396-4436, fax: 410-625-0688). For a complete list of communicable diseases, see the HEIC Web site, the DHMH Web site, <http://ideha.dhmh.maryland.gov/SitePages/what-to-report.aspx> or the BCHD Web site, www.baltimorehealth.org/acd.html.

JHH Precautions Categories

These precaution categories must be used in addition to Standard Precautions. The following table includes general requirements for precaution categories. The complete table and the type of isolation required for each organism can be found on the HEIC website. If recommendations on this table cannot be followed, please contact HEIC.

(sign color)	Contact Precautions (pink)	Droplet Precautions (orange)	Airborne Precautions (blue) ¶
Private room	Required unless cohorted	Required unless cohorted*	Required
Door closed	No	No	Yes
Mask/Eye Protection	No	If within 6 feet of patient	PAPR or N95† to enter room‡
Gown and Gloves	To enter room	To enter room	No
Examples	MRSA, <i>C. diff.</i> , zoster§	Influenza, bacterial meningitis	TB, disseminated zoster§

* Required for pertussis and diphtheria

† Fit-testing is required to use an N95 mask for airborne precautions

‡ HCWs who are Varicella-immune do not have to wear a PAPR or N95 if patient is in isolation for zoster or chickenpox

§ Disseminated zoster, zoster in an immunocompromised host, and chickenpox require both Contact and Airborne Precautions

Disease-specific infection control recommendations

Carbapenem-resistant Enterobacteriaceae (CRE)

Routine active surveillance cultures for CRE are performed in patients who have been hospitalized in a country other than the U.S. **in the past 6 months.** Patients are placed on Contact Precautions pending culture results. The results are to be used for isolation purposes, not to guide therapy or clinical care. **The overwhelming majority of positive surveillance cultures represents colonization, not infection, and should not prompt any antimicrobial therapy.**

Creutzfeldt-Jakob disease (CJD)

CJD, variant CJD and other diseases caused by prions are resistant to a number of standard sterilization and disinfection procedures. Iatrogenic transmission of CJD has been associated with percutaneous exposure to medical instruments contaminated with prion/central nervous system (CNS) tissue residues, transplantation of CNS and corneal tissues and recipients of human growth hormone and gonadotropin. Transmission of CJD has not been associated with environmental contamination or from person-to-person via skin contact. The following additional precautions must be made when processing equipment that could be contaminated with prion related material:

- Notify HEIC and the unit manager/charge nurse immediately of any suspected or confirmed CJD case and refer to the CJD policy on the HEIC Web site.
- Use disposable equipment whenever possible. If non-disposable equipment is used, Central Sterile Department shall be notified prior to the start of the procedure.
- Label all laboratory and pathology requisitions as suspected CJD and notify the lab before sending specimens.
- The following are considered highly infective and should be handled with extreme caution: brain, spinal cord, optic tissues and pituitary gland
- The following are considered to be of lower infectivity: CSF, kidney, liver, lung, lymph nodes, spleen, placenta, tonsillar tissue and olfactory tissue.

Methicillin-resistant *Staphylococcus aureus* (MRSA)

Routine active surveillance cultures for MRSA are performed on select units to identify patients with MRSA. When a culture is positive for MRSA the patient is placed on **Contact Precautions.** The results are to be used for isolation purposes, not to guide therapy or clinical care. **The overwhelming majority of positive surveillance cultures**

represents colonization, not infection, and should not prompt any antimicrobial therapy.

Surveillance cultures should be obtained upon admission and weekly in the following units: MICU, WICU, CVSICU, SICU, CTU (9W), NCCU, CCU/PCCU, PICU, NICU, oncology units, Nelson 4.

To remove a patient from MRSA precautions, cultures from the original site of infection and 2 nares cultures taken ≥ 72 hours apart must be negative. Nares cultures should not be sent if the patient has received antibiotics active against MRSA in the previous 48 hours. Once this is accomplished, call HEIC to review culture data and initiate deflagging.

Pertussis

All patients with pertussis should be placed on **Droplet Precautions** for five days from the start of therapy. If the patient is not on therapy, Droplet Precautions should be continued for three weeks from the onset of cough. Private room is required.

Treatment:

- Azithromycin 500 mg PO once on day 1, then 250 mg PO daily on days 2–5

OR

- Macrolide allergy: TMP/SMX 1 DS tablet PO BID for 14 days

Prophylaxis with the above regimens is required for all household contacts within three weeks of exposure. Use the same antibiotic as for treatment. All household contacts and HCWs with exposure to the patient should also have up-to-date immunizations for *Bordetella pertussis*.

Scabies

All patients with conventional or Norwegian scabies should be placed on **Contact Precautions**. Norwegian scabies is a severe form of heavy mite infestation.

- Private room required.
- Patients with conventional scabies must be treated with a scabicide once, and the precautions may be discontinued 24 hours after the treatment is completed.
- Patients with Norwegian scabies require 2 treatments with a scabicide 1 week apart. Contact precautions may be discontinued 24 hours after the second treatment is completed.
- Infested clothing and linen should be sealed in a plastic bag for 48 hours. The mite will not survive off a human host for more than 48 hours. Clothing/patient belongings should be sent home with the patient's family/caretaker. Linens and clothing should be washed in the washing machine on the hot cycle.

- If prolonged skin-to-skin contact occurs with a scabies patient, prophylactic treatment is required. Healthcare workers should contact HEIC if an exposure is suspected.

Vancomycin-resistant enterocci (VRE)

Routine active surveillance cultures for VRE are performed on select units to identify patients with VRE. Surveillance culture results are found in the electronic patient record with the test name “Bacteriology-Stool-VRE Stool Surv. Cult.” When a culture grows VRE, the patient is flagged for **Contact Precautions**. The results are to be used for isolation purposes, not to guide therapy or clinical care. **The overwhelming majority of positive surveillance cultures represents colonization, not infection, and should not prompt any antimicrobial therapy.**

Surveillance cultures should be obtained upon admission and weekly in the following units: MICU, WICU, CVSICU, SICU, CTU (9W), BMT and Leukemia units, NCCU, PICU.

The patient must be off antibiotics for ≥ 48 hours and cultures from original site of infection AND 3 stool or perirectal cultures taken ≥ 1 week apart must be negative. Once this is accomplished, call HEIC to review culture data and initiate deflagging.

Varicella-Zoster

Immunocompetent patients with disseminated zoster and all immunosuppressed patients with zoster need **Contact AND Airborne Precautions**. The following definitions apply to patients with zoster:

- **Immunosuppressed:** bone marrow transplant within the past year; acute leukemia; solid organ transplant recipients; patients receiving cytotoxic or immunosuppressive treatments, including steroid treatment for ≥ 30 days with the following doses: dexamethasone 3 mg daily, cortisone 100 mg daily, hydrocortisone 80 mg daily, prednisone 20 mg daily, methylprednisone 16 mg daily; HIV+ patients with $CD4 < 200$
- **Disseminated:** lesions outside of 2 contiguous dermatomes

Aminoglycoside dosing and monitoring

Aminoglycosides enhance the efficacy of some antibiotics. Except for urinary tract infections, aminoglycosides should seldom be used alone to treat infections.

Aminoglycoside dosing weight:

Calculate Ideal Body Weight (IBW)

$$IBW \text{ female (kg)} = (2.3 \times \text{inches over } 5') + 45.5$$

$$IBW \text{ male (kg)} = (2.3 \times \text{inches over } 5') + 50$$

For patients < 20% over IBW, use Actual Body Weight (ABW)

For patients ≥ 20% over IBW, use Dosing Body Weight (DBW)

$$(DBW) = [IBW + 0.4 (ABW - IBW)]$$

Estimation of creatinine clearance (CrCl) by Cockcroft-Gault equation:

(If a patient's renal function is declining, this equation may overestimate CrCl)

$$CrCl = \frac{(140 - \text{age}) (\text{weight in kg}^*)}{72 (\text{serum creatinine})} \times 0.85 \text{ (if female)}$$

* Use Actual Body Weight (ABW) unless patient ≥ 20% over IBW, use DBW as described above

Extended-interval dosing, also sometimes referred to as “once-daily” administration, utilizes higher dose and less frequent aminoglycoside administration, whereas patient-specific dosing, previous referred to as “traditional dosing”, typically utilizes smaller doses with more frequent administration. See table below for dosing recommendation based on indication and patient's renal function. For mycobacterial infections, urinary tract infections, SICU/WICU protocol and gram-positive synergy (e.g. endocarditis), please see separate sections below. For cystic fibrosis patients, see the Cystic Fibrosis section (p.92)

Aminoglycoside dosing for Gram-negative infections

	Patient-specific dosing	Extended-interval dosing																								
Indications	Renal failure, on HD/CVVHD, endocarditis, Gram-negative infections (in combination with beta-lactams), CNS infections, septic shock, burn patients, patients with altered volume status (e.g. ascites, anasarca, trauma)	<ul style="list-style-type: none"> Normal renal function (CrCl >60 mL/min) and all other indications not listed under patient specific dosing 																								
Dosing	<p>Dose (mg) = desired peak x [Weight (kg) x Vd (L/kg)]</p> <ul style="list-style-type: none"> Desired peak: choose from below Weight: ABW or DBW Volume of distribution (Vd) typically ranges between 0.25 – 0.5 L/kg in most patients. Higher Vd should be used in critically ill and volume overloaded patients. <p>Dosing interval based on CrCl: CrCl >60: Q8H* CrCl 30-60: Q12 CrCl <30/CVHD/HD: dose by level</p> <p>*If targeting high peaks, use maintenance dose frequency of Q12-24H.</p>	<p>Gentamicin/Tobramycin: 5-7 mg/kg IV Q24H</p> <p>Amikacin: 15-20 mg/kg IV Q24H</p>																								
Desired Peaks and Troughs	<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr style="background-color: #FFD700;"> <th style="width: 15%;">Peak</th> <th style="width: 20%;">Gentamicin/ Tobramycin</th> <th style="width: 20%;">Amikacin</th> </tr> </thead> <tbody> <tr> <td>Pneumonia</td> <td>10 mcg/mL</td> <td>25-35 mcg/mL</td> </tr> <tr> <td>Septic shock</td> <td></td> <td></td> </tr> <tr> <td>Endocarditis</td> <td>8-10 mcg/mL</td> <td>20-30 mcg/mL</td> </tr> <tr> <td>Osteomyelitis</td> <td></td> <td></td> </tr> <tr> <td>MDR organisms</td> <td>10-20 mcg/mL based on MIC</td> <td>45-50 mcg/mL based on MIC</td> </tr> <tr> <td>Trough</td> <td>Gentamicin/ Tobramycin</td> <td>Amikacin</td> </tr> <tr> <td>All Indications</td> <td><1-2 mcg/mL</td> <td><10 mcg/mL</td> </tr> </tbody> </table>	Peak	Gentamicin/ Tobramycin	Amikacin	Pneumonia	10 mcg/mL	25-35 mcg/mL	Septic shock			Endocarditis	8-10 mcg/mL	20-30 mcg/mL	Osteomyelitis			MDR organisms	10-20 mcg/mL based on MIC	45-50 mcg/mL based on MIC	Trough	Gentamicin/ Tobramycin	Amikacin	All Indications	<1-2 mcg/mL	<10 mcg/mL	<p>This dosing strategy is designed to target the following:</p> <p>Peak Gentamicin/Tobramycin: 16-20 mcg/mL Amikacin: 40-60 mcg/mL</p> <p>Trough Gentamicin/Tobramycin: <1 mcg/mL Amikacin: <4 mcg/mL</p>
Peak	Gentamicin/ Tobramycin	Amikacin																								
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All Indications	<1-2 mcg/mL	<10 mcg/mL																								
Therapeutic Drug Monitoring	<p>Trough: draw 30 minutes prior to the 3rd dose</p> <p>Peak: obtain 1 hour after end of infusion, after the 3rd dose.</p> <p>Frequency of monitoring</p> <ul style="list-style-type: none"> Once a week after desired peak/trough is established in patients with normal renal function More than once weekly: <ul style="list-style-type: none"> After changes in dosing regimen Patient is on dialysis Patient in acute renal failure, SCr increased by 0.5 mg/dL or 30% from baseline Major changes in the patient's volume status 	<p>If the patient meets ANY of the criteria below, a trough level is recommended prior to the 2nd dose:</p> <ul style="list-style-type: none"> Concomitant nephrotoxic medications Contrast exposure Age ≥ 60 years Patient is in the ICU Other risks for nephrotoxicity (e.g. diabetes, kidney TX) <p>If trough higher than desired troughs, use patient specific dosing to adjust dose.</p>																								

Aminoglycoside dosing in mycobacterial infections

Amikacin is the preferred agent to treat all mycobacterial infections, except *Mycobacterium chelonae*. For *M. chelonae* infections, Tobramycin is the recommended aminoglycoside. Streptomycin is another aminoglycoside sometimes used to treat mycobacterial infections such as *M. tuberculosis*. Please contact the Antimicrobial Stewardship Program pharmacist for Tobramycin/Streptomycin dosing recommendation for this indication.

Amikacin:

Normal renal function:

Once daily: 15 mg/kg IV Q24H (or 10 mg/kg IV Q24H if >50 years of age)

Thrice weekly: 25 mg/kg IV three times a week (may be more difficult to tolerate)

Abnormal renal function: Discuss with pharmacy clinical specialist

Therapeutic drug monitoring: Peak and trough not generally necessary, except in those with renal insufficiency (GFR <60 mL/min) and if SCr increases by 0.5 mg/dL or >30% from baseline while patient on aminoglycoside therapy. Check a trough concentration to monitor for toxicity. Peaks in the low 20 mcg/mL range are acceptable, and trough concentrations are preferably <4 mc/mL or undetectable.

Aminoglycoside dosing in urinary tract infections

CrCl (mL/min)	Gentamicin/Tobramycin	Amikacin
≥60	3 mg/kg IV Q24H or 1 mg/kg IV Q8H	10 mg/kg IV Q24H or 3 mg/kg IV Q8H
40-59	1 mg/kg Q12H	3 mg/kg IV Q12H
20-39	1 mg/kg Q24H	3 mg/kg IV Q24H
<20	1 mg/kg ONCE*	3 mg/kg IV ONCE*

*Give one dose, check level in 24 hours, redose when Gentamicin/Tobramycin level <1 mcg/mL or Amikacin <4 mcg/mL

Aminoglycosides are highly concentrated in urine; therefore, therapeutic drug monitoring is not necessary in patients with normal renal function. Suggested doses in the above table will likely provide adequate urine concentrations for highly susceptible organisms. Trough should be checked to monitor for toxicity in patients with renal insufficiency (GFR <60 mL/min) and if SCr increases by 0.5 mg/dL or >30% from baseline while patient on aminoglycoside therapy.

- **Gentamicin/Tobramycin:** desired trough <1 mcg/mL or undetectable.
- **Amikacin:** desired trough <4 mcg/mL or undetectable.

Aminoglycoside dosing in the SICU/WICU

Gentamicin/Tobramycin

Loading dose **4 mg/kg** using **actual body weight**, followed by a patient-specific maintenance dose.

Amikacin

Loading dose **16 mg/kg** using **actual body weight**, followed by a patient-specific maintenance dose.

Therapeutic Drug Monitoring

After loading dose: 1 hour peak and 8 hour level after the end of the infusion to facilitate calculating patient specific kinetic parameters.

Aminoglycoside dosing for Gram-positive synergy

Dosing for patients with normal renal function:

- **Gentamicin:** 3 mg/kg IV once daily is recommended for treatment of endocarditis with Viridans streptococci or *S. bovis* in patients with normal renal function ($\text{CrCl} \geq 60$ ml/min).
- **Gentamicin:** 1 mg/kg IV Q8H is recommended for treatment Enterococcal and other Gram-positive endocarditis infections in patients with normal renal function ($\text{CrCl} \geq 60$ ml/min). Patients >65 years old should be started on Q12H if normal renal function.

Dosing adjustment for renal insufficiency

CrCl (mL/min)	Dosing
40–59	1 mg/kg Q12H
20–39	1 mg/kg Q24H
<20	1 mg/kg ONCE*

* Give one dose, check level in 24 hours, redose when level <1 mg/L

NOTE: See infective endocarditis guidelines (p. 65) for duration.

THERAPEUTIC DRUG MONITORING

- Peak and trough are recommended around the third dose to assure appropriate dosing.
- Desired serum concentrations of **Gentamicin**
 - **Peak levels:** 3–5 mcg/mL
 - **Trough levels:** < 1 mcg/mL

Monitoring for toxicity for inpatients

NEPHROTOXICITY

- Serum creatinine should be measured at least every other day. If creatinine increases by 0.5 mg/dL or >30% from baseline, use patient specific dosing.
- Measure serum aminoglycoside levels as needed. See each dosing section above for frequency.
- Some data suggest that lowest level of nephrotoxicity occurs when aminoglycosides are administered during the activity period (e.g. 13:30), therefore afternoon administration is preferred.

OTOTOXICITY

- Consider biweekly clinical screening for ototoxicity
 - Check baseline visual acuity using a Snellen pocket card
 - To screen for ototoxicity, have patient shake head and then re-read card.
 - Concern should be raised if patient loses 2 lines of visual acuity. Consider formal audiology testing.
 - Contact Audiology (5-6153) for help with testing for ototoxicity

References:

PK/PD parameter: *J Infect Dis* 1987; 155:93–99

Once daily nomograms review: *Pharmacotherapy* 2002; 22(9):1077–1083.

Patient-specific dosing: *Crit Care Med* 1991; 19:1480–1485.

SICU/WICU dosing: *Surgery* 1998; 124:73-8.

Nephrotoxicity: *Antimicrob Agents and Chemother* 2003; 47:1010.

ATS/IDSA Mycobacterium Guidelines: *Am J Respir Crit Care Med* 2007; 175:367–416.

Gram-positive Synergy: *Circulation* 2005; 111(23): e394–434.

Vancomycin dosing and monitoring

DOSING

1. Estimate creatinine clearance (CrCl) using Cockcroft-Gault equation:

$$\text{CrCl} = \frac{(140 - \text{age}) (\text{weight in kg})}{72 (\text{serum creatinine}^*)} \times 0.85 (\text{if female})$$

* For patients with low muscle mass (i.e. many patients > 65 yrs), some advocate using a minimum value of 1 to avoid overestimation of CrCl

2. Patients who are seriously ill with complicated infections such as **meningitis, pneumonia, osteomyelitis, endocarditis, and bacteremia** and normal renal function should receive initial loading dose of 20-25 mg/kg, followed by **15-20 mg/kg Q8-12H** using **Actual Body Weight (ABW)**. For other indications see nomogram dosing below.
3. Calculate maintenance dose (using ABW) based on estimated or actual CrCl. See suggested nomogram dosing below.

Note: Younger patients with normal renal function may need higher or more frequent dosing than suggested below.

Weight (kg)	CrCl (mL/min)			
	>60	30-59	15-29	<15
<40	Consult Pharmacy			
40-60	750 mg Q12H	750 mg Q24H	750 mg Q48H	1000 mg, then redose by level [†]
60-75	1000 mg Q12H	1000 mg Q24H	1000 mg Q48H	1000 mg, then redose by level [†]
75-90	1250 mg Q12H	1250 mg Q24H	1250 mg Q48H	1250 mg, then redose by level [†]
90-110	1500 mg Q12H	1500 mg Q24H	1500 mg Q48H	1500 mg, then redose by level [†]
110-125	1750 mg Q12H	1750 mg Q24H	1750 mg Q48H	1750 mg, then redose by level [†]
125-140	2000 mg Q12H	2000 mg Q24H	2000 mg Q48H	2000 mg, then redose by level [†]
>140	Consult Pharmacy			

[†]For patients with CrCl <15 mL/min and not receiving hemodialysis redose when random level <15-20 mcg/mL.

DOSING IN RENAL REPLACEMENT THERAPY

Dosing is dependent on type of renal replacement therapy.

Intermittent Hemodialysis (iHD)

- **Initial dose:** 15-20 mg/kg once
- Patients should be re-dosed based on serum levels drawn around the dialysis session. Consider redosing at 5-10 mg/kg.

- Pre-dialysis level (**preferred**): <25 mcg/mL (for meningitis consider re-dosing if <30 mcg/mL)
- Post-dialysis level: <20 mcg/mL)

Note: must wait 3–6 hours after the end of the dialysis to account for redistribution of tissue and plasma levels

- For patients with ESRD on a stable HD schedule, a regimen should be established that coincides with HD (e.g. 500 mg qHD). Once weekly serum levels can be drawn to monitor for accumulation.

Continuous Renal Replacement Therapy (e.g. CVVHD)

- **Loading dose:** 25-30 mg/kg once
- **Maintenance:** 15-20 mg/kg q24h (assuming no interruption in CRRT, e.g. line clotting)
 - Note: Dialysis flow rates >2.5 L/h - consult pharmacy
- **Monitoring:**
 - Patients with changing dialysis flow rates or dialysis held for >4 hours may need more frequent monitoring (consult pharmacy)
 - Patients on stable dialysis flow rates should have trough level checked prior to 4th dose

Peritoneal Dialysis (PD)

- **Initial dose:** 15-20 mg/kg once
- Consult pharmacy for recommendations for re-dosing and monitoring serum levels.

THERAPEUTIC DRUG MONITORING (LEVELS)

- **Trough levels** are the most accurate and practical method for monitoring Vancomycin effectiveness and toxicity.
- **Peak levels** should NOT be obtained.

Measuring serum Vancomycin levels

- Trough levels should be obtained within 30 minutes of the next dose at steady-state conditions (approximately before the 4th dose).
- In patients with ESRD on hemodialysis, it is preferable to obtain a pre-hemodialysis level with the routine laboratory venipuncture on the morning of hemodialysis. In the event a pre-hemodialysis level is not obtained, a post-hemodialysis level may be drawn at least six hours after the dialysis session.
- Trough levels should be considered in patients with any the following circumstances:
 - Receiving aggressive dosing (>1500 mg Q12H) or Q8H interval
 - Serious infections such as meningitis, endocarditis, osteomyelitis, and MRSA pneumonia.
 - Unstable renal function (change in SCr of 0.5 mg/dL or 50% from baseline) or dialysis

- Concurrent therapy with nephrotoxic agents (e.g. aminoglycosides, Colistin, Amphotericin B)
- Prolonged courses (≥ 5 days) of therapy.
- Frequency of monitoring Vancomycin trough levels:
 - Once-weekly monitoring is recommended for patients with stable renal function who have achieved desired trough levels.
 - More frequent monitoring is recommended for patients who are hemodynamically unstable and/or with changing renal function.

Desired Vancomycin trough levels

- Pneumonia, osteomyelitis, endocarditis, bacteremia: 15-20 mcg/mL
- CNS infections: 20 mcg/mL
- Neutropenic fever, skin and skin-structure infections: 10-15 mcg/mL
- Minimum serum trough concentrations >10 mcg/mL should always be maintained to avoid development of resistance.

Monitoring for Toxicity

- Serum creatinine should be measured at least every other day initially, then weekly if patient's renal function remains stable.
- Limited data suggest a direct causal relationship between nephrotoxicity and higher serum trough concentrations (>15 -20 mcg/mL). Monitor Vancomycin trough levels (see above for frequency and indications).
- Formal audiology testing is not recommended for patients receiving Vancomycin, unless signs and symptoms of ototoxicity became apparent.

References:

IDSA/ASHP/SIDP Guidelines therapeutic monitoring of Vancomycin: Am J Health-Syst Pharm. 2009; 66; 82.

Morse et al. Antimicrobial Agents Chemother 1987; 31:173-7.

Vandecasteele et al. Clin Infect Dis 2011; 53:124-9.

Barth et al. Kidney Int 1996; 50:929-36.

Recommendations for monitoring patients receiving long-term antimicrobial therapy

- Long term defined as ≥ 1 week, except for aminoglycosides and Amphotericin B (see below)
- For use once initial dosing and serum levels have been established
- These monitoring recommendations and monitoring for agents not listed should be individualized, based on each patient's clinical features, including general health status, age, underlying conditions and organ dysfunction, concomitant medications, drug treatment history, type of infection, and type and dose of antibiotic

Antimicrobial agent(s)	Test	Frequency	Other
Aminoglycosides (Amikacin, Gentamicin, Tobramycin, Streptomycin)	CBC BUN, Creatinine Aminoglycoside level – trough (see dosing section p. 145)	Weekly Twice weekly Weekly (twice weekly, if increased risk)	Clinical monitoring and patient education for hearing/vestibular dysfunction at each visit (see p. 149 for vestibular screening method)
Amphotericin B, Ambisome®	BUN, Creatinine, K, Mg, Phos CBC, AST, ALT CBC, BUN, Creatinine	Twice weekly 1–2 weeks Weekly	
β -lactams (Aztreonam, carbapenems, cephalosporins, penicillins) Oxacillin, Nafcillin, carbapenems Penicillin G potassium	add AST/ALT/bilirubin add K	Weekly Weekly	
Micafungin	AST/ALT/bilirubin	Weekly	Clinical monitoring for neurotoxicity (dizziness, paresthesia, vertigo, confusion, visual disturbances, ataxia)
Colistin	BUN, Creatinine	Weekly (twice weekly, if increased risk)	Clinical monitoring for myopathy
Daptomycin	CBC, BUN, Creatinine, CPK	Weekly	Clinical monitoring for peripheral neuropathy and optic neuritis
Linezolid	CBC	Weekly	Drug interactions (monitor start of any new medications)
Rifampin	CBC, AST/ALT/bilirubin	Weekly	Drug interactions (monitor start of any new medication), visual changes
Voriconazole /Posaconazole	CBC, AST/ALT/bilirubin	1 – 2 weeks	
Vancocycin	<u>Normal renal function:</u> CBC, BUN, Creatinine Vancocycin level – trough (see dosing section p. 150) <u>Dialysis:</u> Vancocycin level (see dosing section p. 150)	Weekly Weekly, unless change in creatinine (\uparrow 50% from baseline), then twice weekly At each dialysis session	

Reference: Practice Guidelines for Outpatient Parenteral Antimicrobial Therapy: Clin Infect Dis 2004; 38:1651.

Oral antimicrobial use in hospitalized patients

When using an agent that is considered to be bioequivalent (no significant difference in rate and extent of absorption of the therapeutic ingredient) via the parenteral and oral route, the oral formulation is preferred if the patient does not have the contraindications listed below.

Contraindications to oral therapy

- NPO (including medications)
- Inability to take other oral medications OR not tolerating a liquid diet/tube feeds
- Hemodynamic instability
- Receiving continuous NG suctioning
- Severe nausea, vomiting, diarrhea, GI obstruction, dysmotility, mucositis
- A malabsorption syndrome
- A concomitant disease state that contraindicates the use of oral medications

NOTE: There are only a limited number of agents that can be used orally for bacteremia or fungemia; these are noted in the table below.

Bioavailability of oral antimicrobials

Antimicrobial	% Oral absorption
Should NOT be used orally for bacteremia	
Amoxicillin	74 – 90%
Amoxicillin/Clavulanate (Augmentin®)	74 – 90%
Azithromycin*	38 – 83%
Cephalexin	90%
Cefpodoxime*	41 – 50%
Clindamycin	90%
Doxycycline	90 – 100%
Tetracycline	75 – 80%
Can be used orally for bacteremia or fungemia	
Ciprofloxacin [‡]	65 – 85%
Fluconazole	>90%
Linezolid [†]	100%
Metronidazole	100%
Moxifloxacin [‡]	90%
Trimethoprim/sulfamethoxazole [†]	100%
Voriconazole [‡]	60 – 96%

* Oral absorption is enhanced in presence of food

† Should not be used for *S. aureus* bacteremia

‡ Oral absorption is decreased in presence of food

¶ Inter-patient variability

∇ Do not use with continuous tube feeds (IV preferred). Patients with cyclic tube feeds: separate oral fluoroquinolone by 2 hours before and 6 hours after tube feeds.

Antimicrobial dosing in renal insufficiency

Dosing recommendations can vary according to indication and patient-specific parameters. All dosage adjustments are based on creatinine clearance calculated by Cockcroft-Gault equation.

$$\text{CrCl} = \frac{(140 - \text{age}) (\text{weight in kg})}{72 (\text{serum creatinine}^*)} \times 0.85 (\text{if female})$$

*For patients with low muscle, some advocate using a minimum of 1 to avoid overestimation of CrCl.

If patient is on hemodialysis (HD) schedule administration so that patient receives daily dose immediately AFTER dialysis. For assistance with dosage adjustments for patients receiving CVVHD or CVVHDF, please call pharmacy.

Drug	Typical dose (may vary)	CrCl (mL/min)	Dose adjustment for renal insufficiency
Acyclovir IV	5–10 mg/kg Q8H	>50 25–50 10–24 <10 or HD [†]	5–10 mg/kg Q8H 5–10 mg/kg Q12H 5–10 mg/kg Q24H 2.5–5 mg/kg Q24H
Acyclovir PO (Genital herpes)	200 mg 5x daily	>10 <10	200 mg 5x daily 200 mg Q12H
Acyclovir PO (Herpes Zoster)	800 mg 5x daily	>25 10–25 <10 or HD [†]	800 mg 5x daily 800 mg Q8H 800 mg Q12H
Amikacin			See section on aminoglycoside dosing
Amoxicillin	500–1000 mg Q12H	>30 10–30 <10 or HD [†]	500–1000 mg Q12H 250–875 mg Q12H 250–875 mg Q24H
Amoxicillin (pneumonia)	1 g Q8H	>30 10–30 <10 or HD [†]	1g Q8H 1g Q12H 1g Q24H
Amoxicillin/clavulanate	500–1000 mg Q12H	>30 10–30 <10 or HD [†]	500–1000 mg Q12H 250–500 mg Q12H 250–500 mg Q24H
Amphotericin B	0.7–1 mg/kg Q24H	–	No dosage adjustment
AmBisome [®]	3–5 mg/kg Q24H	–	No dosage adjustment
Ampicillin	1–2 g Q4–6H	>50 10–50 <10 or HD [†]	1–2 g Q4–6H 1–2 g Q6–8H 1–2 g Q8H
Ampicillin/sulbactam	1.5–3 g Q6H	≥30 15–29 ≤14 or HD [†]	1.5–3 g Q6H 1.5–3 g Q12H 1.5–3 g Q24H
Ampicillin/sulbactam (for Acinetobacter, E. faecalis)	3 g Q4H	≥50 10–50 HD [†]	3 g Q4H 3 g Q6H 3 g Q8H
Azithromycin	250–500 mg Q24H	–	No dosage adjustment
Aztreonam	1–2 g Q8H	≥30 10–29 <10 or HD [†]	1–2 g Q8H 1–2 g Q12H 1–2 g Q24H
Cefazolin	1–2 g Q8H	≥35 11–34 <10 or intermittent HD [†] HD [†]	1–2 g Q8H 1 g Q12H 1 g Q24H 2 g Q HD, if HD in 2 days OR 3g Q HD, if HD in 3 days

Drug	Typical dose (may vary)	CrCl (mL/min)	Dose adjustment for renal insufficiency
Cefdinir	300 mg Q12H	≥30 <30 HD†	300 mg Q12H 300 mg Q24H 300 mg QHD
Cefepime	1 g Q8H	>60 30–60 <29 or HD†	1 g Q8H 1 g Q12H 1 g Q24H
Cefepime (Central nervous system infections or <i>Pseudomonas</i>)	2 g Q8H	>60 30–60 11–29 <11 or HD†	2 g Q8H 1 g Q8H 1 g Q12H 1 g Q24H
Cefotetan	1–2 g Q12H	≥30 10–29 <10 or HD†	1–2 g Q12H 1–2 g Q24H 500 mg Q24H
Cefpodoxime	100–400 mg Q12H	≥30 <30 HD†	100–400 mg Q12H 100–400 mg Q24H 100–400 mg three times/week
Ceftaroline	600 mg Q12H	>50 30–50 15–29 <15 or HD†	600 mg Q12H 400 mg Q12H 300 mg Q12H 200 mg Q12H
Ceftaroline for MRSA	600 mg Q8H	>50 30–50 15–29 <15 or HD†	600 mg Q8H 400 mg Q8H 300 mg Q8H 400 mg Q12H
Ceftazidime	1–2 g Q8H For <i>Pseudomonas</i> 2 g Q8H	>50 30–50 15–29 <15 or HD†	1–2 g Q8H 1–2 g Q12H 1–2 g Q24H 1 g Q24H
Ceftolozane/tazobactam	1.5 g Q8H	>50 30–50 15–29 <29 or HD†	1.5 g Q8H 750 mg Q8H 375 mg Q8H Load with 750 mg, then 150 mg Q8H
Ceftolozane/tazobactam (Serious Infections)	3 g Q8H	>50 30–50 15–29 </29 or HD†	3 g Q8H 1.5 g Q8H 750 mg Q8H Load with 1.5 g, then 375 mg Q8H
Ceftriaxone	1–2 g Q24H	–	No dosage adjustment
Ceftriaxone (Central nervous system infections)	2 g Q12H	–	No dosage adjustment
Cephalexin	500 mg PO Q6H	>50 10–50 <10 or HD†	500 mg Q6H 500 mg Q8H 500 mg Q12H
Cidofovir	5 mg/kg Q week for 2 weeks, then every other week	≤55 or Cr>1.5	Not recommended
Ciprofloxacin IV	400 mg Q8–12H	≥30 <30 or HD†	400 mg Q8–12H 400 mg Q24H
Ciprofloxacin PO	250–750 mg Q12H	≥30 <30 or HD†	250–750 mg Q12H 250–500 mg Q24H
Clarithromycin	250–500 mg Q12H	≥30 <30	250–500 mg Q12H 250–500 mg Q24H
Clindamycin	PO: 300 mg Q8H IV: 600 mg Q8H	–	No dosage adjustment
Colistin (Colistimethate)	2.5 mg/kg Q12H	≥50 20–50 ≤20 or HD†	2.5 mg/kg Q12H 2.5 mg/kg Q24H 1.25 mg/kg Q24H

Drug	Typical dose (may vary)	CrCl (mL/min)	Dose adjustment for renal insufficiency
Daptomycin for endocarditis/bacteremia	6–10 mg/kg Q24H	≥30 <30 HD†	6–10 mg/kg Q24H 6–10 mg/kg Q48H 6–10 mg/kg Q48H
Dicloxacillin	250–500 mg Q6H	–	No dosage adjustment
Doxycycline	100 mg Q12H	–	No dosage adjustment
Ertapenem	1 g Q24H	≥30 <30 or HD†	1 g Q24H 500 mg Q24H
Ethambutol	15–25 mg/kg Q24H	≥10 <10 HD†	Normal dose Q24H Normal dose Q48H Normal dose QHD session
Fluconazole	200–800 mg Q24H	≥50 <50 or HD†	Normal dose (e.g. 100, 400, 800 mg) Q24H Load w/normal dose, then 50% of normal dose Q24H
Flucytosine (5-FC)	12.5–25 mg/kg Q6H	>40 20–40 10–19 <10 or HD†	12.5–25 mg/kg Q6H 12.5–25 mg/kg Q12H 12.5–25 mg/kg Q24H 12.5–25 mg/kg Q24–48H
Ganciclovir (Induction dose)	5 mg/kg Q12H	≥70 50–69 25–49 10–24 <10 or HD†	5 mg/kg Q12H 2.5 mg/kg Q12H 2.5 mg/kg Q24H 1.25 mg/kg Q24H 1.25 mg/kg three times/week, administer after HD
Ganciclovir (Maintenance dose)	5 mg/kg Q24H	≥70 50–69 25–49 10–24 <10 or HD†	5 mg/kg Q24H 2.5 mg/kg Q24H 1.25 mg/kg Q24H 0.625 mg/kg Q24H 0.625 mg/kg three times/week, administer after HD
Gentamicin	–	–	See section on aminoglycoside dosing
Isoniazid	300 mg Q24H	–	No dosage adjustment
Linezolid	600 mg Q12H	–	No dosage adjustment
Meropenem	1 g Q8H	>51 26–50 10–25 <10 or HD†	1 g Q8H 1 g Q12H 500 mg Q12H 500 mg Q24H
Meropenem (Meningitis, CRE infections)	2 g Q8H	>51 26–50 10–25 <10 or HD†	2 g Q8H 1 g Q8H 1 g Q12H 1 g Q24H
Metronidazole	500 mg Q8H	–	No dosage adjustment
Micafungin	100–150 mg Q24H	–	No dosage adjustment
Moxifloxacin	400 mg Q24H	–	No dosage adjustment
Nitrofurantoin (Macrobid®)	100 mg Q12H	≥50 <50	100 mg Q12H Not recommended
Osetamivir (Treatment)	75 mg Q12H	>60 30–60 10–29 <10 or HD†	75 mg Q12H 75 mg Q24H 30 mg Q24H 30 mg QHD session
Osetamivir (Prophylaxis)	75 mg Q24H	>60 30–60 10–29 <10 or HD†	75 mg Q24H 30 mg Q24H 30 mg Q48H 30 mg every other HD session
Oxacillin	1–2 g Q4–6H	–	No dosage adjustment
Penicillin G	3–4 million units Q4H	≥50 10–49 <10 or HD†	3–4 million units Q4H 1.5 million units Q4H 1.5 million units Q6H

Drug	Typical dose (may vary)	CrCl (mL/min)	Dose adjustment for renal insufficiency
Piperacillin/tazobactam	3.375–4.5 g Q6H	>40 20–40 <20 HD†	3.375 g Q6H (4.5 g Q6H for <i>Pseudomonas</i>) 2.25 g Q6H (3.375 g Q6H for <i>Pseudomonas</i>) 2.25 g Q8H (2.25 g Q6H for <i>Pseudomonas</i>) 2.25 g Q12H (2.25 g Q8H for <i>Pseudomonas</i>)
Posaconazole	See Posaconazole guidelines p. 18	–	No dosage adjustment
Pyrazinamide	15–30 mg/kg Q24H	≥10 <10 HD†	15–30 mg/kg Q24H 12–20 mg/kg Q24H 25–30 mg/kg QHD session
Quinupristin/dalfopristin	7.5 mg/kg Q8H	–	No dosage adjustment
Rifampin (TB)	600 mg Q24H	–	No dosage adjustment
Rifampin	300 mg Q8–12H	–	No dosage adjustment
Tigecycline	100 mg once, then 50 mg Q12H	–	No dosage adjustment
TMP/SMX (UTIs or cellulitis)	PO: 1–2 DS tab Q12H IV: 160–320 mg Q12H (Dosing is based on TMP component)	≥30 <30 or HD†	1–2 DS tab Q12 or 160–320 mg IV Q12H 1–2 DS tab Q24H or 160–320 mg IV Q24H
TMP/SMX (PCP or serious systemic infections)	5 mg/kg Q6–8H	≥30 <30 HD†	5 mg/kg Q6–8H 2.5 mg/kg Q6–8H 2.5 mg/kg Q8H
Valacyclovir (Genital herpes)	500–1000 mg Q12H	≥30 10–29 <10 or HD†	500–1000 mg Q12H 500–1000 mg Q24H 500 mg Q24H
Valacyclovir (Herpes Zoster)	1 g Q8H	≥50 30–49 10–29 <10 or HD†	1 g Q8H 1 g Q12H 1 g Q24H 500 mg Q24H
Valganciclovir (Induction dose)	900 mg Q12H	≥60 40–59 25–39 10–24 <10 or HD†	900 mg Q12H 450 mg Q12H 450 mg Q24H 450 mg Q48H Not recommended
Valganciclovir (Maintenance dose)	900 mg Q24H	≥60 40–59 25–39 10–24 <10 or HD†	900 mg Q24H 450 mg Q24H 450 mg Q48H 450 mg twice weekly Not recommended
Vancomycin	–	–	See section on vancomycin dosing
Voriconazole	See Voriconazole guidelines p. 19	–	No dosage adjustment is necessary for PO. IV should not be administered to patients with CrCl ≤50 mL/min due to accumulation of the vehicle.

†If patient is on hemodialysis (HD) schedule administration so that patient receives daily dose immediately AFTER dialysis. For assistance with dosage adjustments for patients receiving CVVHD or CVVHDF, please call pharmacy.

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Vancomycin

Important Phone Numbers

THE JOHNS HOPKINS HOSPITAL

Antibiotic Approval:	PING “JHH Antibiotic Approval Pager”
Antimicrobial Stewardship Program:	7-4570
Infectious Diseases Consults:	PING “JHH Infectious Diseases”
Oncology/Transplant Service (Transplant ID)	PING “Transplant/ Oncology Infectious Diseases”
Adult Inpatient Pharmacy (Zayed 7000):	5-6150
Critical Care and Surgery Pharmacy (Zayed 3121):	5-6505
Weinberg Pharmacy:	5-8998
Microbiology Lab:	5-6510
Hospital Epidemiology & Infection Control:	5-8384
HEIC Emergency Beeper:	3-3855

JOHNS HOPKINS BAYVIEW MEDICAL CENTER

Antibiotic Approval:	PING “Bayview Antibiotic Approval”
Infectious Disease Consults: . .	PING “Bayview Infectious Diseases”
Bayview Inpatient Pharmacy:	0-0958
Microbiology Lab:	5-6510
Hospital Epidemiology & Infection Control:	0-0515



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