MANDATORY ID CONSULT

Antimicrobial Work Flow

1. If a restricted antimicrobial is ordered, the prescriber will be alerted that an ID Consult is required with use of the medication. Within the alert, the prescriber will be instructed to page the ID Fellow on call to initiate the consult.

2. The ID fellow will discuss the case with the prescriber, speak to the attending as needed (not required) and approve or deny the request. The ID Fellow will notify pharmacy as soon as possible by calling 5-7395 as to whether approval has been made or not. Drugs should be approved or denied within 30 minutes of the request.

3. Pharmacy will not verify order nor dispense restricted antimicrobial until notified by the ID Fellow to do so. If the pharmacist does not hear from the ID fellow within 30 minutes, they will page the ordering provider. If the pharmacy does not hear from the ID fellow within 60 minutes of the order, the pharmacist will page the ID fellow directly for approval.

4. For all drugs that are approved, an ID Consult will be performed by the appropriate ID Consulting Service based on patient’s current immunologic status. The consult may be a one-time consult or, if both teams determine future ID input to be necessary, the ID Service will remain involved in patient’s care. For denied requests, a consult is not required but is strongly suggested for complex patients, for those in which an alternative agent was suggested, and for those in which the primary team was not in full agreement with the decision.

5. Notes can be done with the Antimicrobial Approval template or New Consult templates available on Chasing Microbes. The Antimicrobial Approval template is set up to capture at least Level 3 charges. If the consult is more complex (i.e.CF patient), the billing level should be adjusted appropriately.

6. If a requested drug is denied and no consult note is written, the ID fellow should submit a BRIEF communications note in Powerchart and send this note to Kelly Flett. This note should include: drug requested, reason for request, brief rationale for denial, and alternative drug recommended.
# Antibacterials

<table>
<thead>
<tr>
<th><strong>Ceftaroline</strong></th>
<th>Pre-approved indication: CF with vancomycin allergy</th>
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| **Reason(s) for Restriction** | 1. Pediatric approved but we dose at higher than current package labeling ... see reference section  
2. Limited clinical data for MRSA outside of ABSSI  
3. Multiple MRSA agents available for most inpatients  
4. Repeat exposure to ceftaroline can lead to resistance (Evolution of Ceftaroline-Resistant MRSA in a Child with Cystic Fibrosis Following Repeated Antibiotic Exposure. PIDJ, 2016 Volume 35, Number 7, 813-15) |
| **Mechanism** | Cephalosporin that binds to PBP2a and causes a structural change that then allows it to bind to site of enzyme activity. |
| **Spectrum of Activity** | Active: MRSA, gram positive cocci and gram negative enteric (similar to ceftriaxone plus MRSA activity)  
NOT active: Pseudomonas, ESBL or ampC producing organisms, Enterococcus |
| **Infection Site Restrictions** | CNS – unknown distribution – USE vancomycin or linezolid for MRSA/Staph meningitis |
| **FDA Approved Indications** | Skin/soft tissue infection - MSSA and MRSA; CABP – MSSA only |
| **Dose** | Adults: Severe infections: 600 mg IV q8h infused over 2 hours  
SSTI and CABP (package labeling): 600 mg IV q12h infused over 1 hour  
Pediatrics: For CABP and SSTI (package labeling but use for these common conditions not recommended)  
>=2 months and <2 yr: 8 mg/kg/dose IV Q8hr  
>=2 yr to <33 kg: 12mg/kg/dose IV Q8hr  
>=33 kg: 400 mg IV Q8hr or 600 mg IV Q12 hr  
For serious MRSA infections:  
2 months to <=6 months: 10 mg/kg/dose IV Q8hr infused over 2 hours  
>6 months and < 40 kg: 15 mg/kg/dose IV Q8hr to be infused over 2 hours  
>40 kg: 600 mg IV Q8hr infused over 2 hours  
Renal Dose Adjustment: CrCl <50 mL/min/1.73m²  
Hepatic Dose Adjustment – None |
| **ADRs and Monitoring** | ADR: >10%: Hematologic: Positive Coombs’ test without hemolysis (~11%)  
Endocrine & metabolic: Hypokalemia (2%)  
Gastrointestinal: Diarrhea (5%), nausea (4%), constipation (2%), vomiting (2%)  
Hepatic: Transaminases increased (2%)  
Monitoring: LFTs, CHEM 7, and CBC weekly |
| **Susceptibility testing** | Need to request sensitivity testing by microbiology |
| **Other Concerns/Warnings** | Use with caution in patients with a history of penicillin, cephalosporin, or carbapenem allergy |
| **When to Use?** | Consider as additional agent for salvage therapy in MRSA bacteremia/endocarditis, pneumonia or other severe infections;  
**Unacceptable Uses:** CAP, Skin/Soft tissue infection or INITIAL therapy for gram positive/gram negative infection |
| **References** | • A Randomized, Prospective Study of Pediatric Patients With CAP Treated With Ceftaroline Versus Ceftriaxone. PIDJ, 2016 Volume 35, Number 7, 752-59.  
• A Multicenter, Randomized, Observer-blinded, Active-controlled Study Evaluating the Safety and Effectiveness of Ceftaroline Compared With Ceftriaxone Plus Vancomycin in Pediatric Patients With Complicated Community-acquired Bacterial Pneumonia. PIDJ, 2016 Volume 35, Number 7, 760-66.  
• A Multicenter, Randomized, Observer-Blinded, Active-Controlled Study to Evaluate the Safety and Efficacy of Ceftaroline versus Comparator in Pediatric Patients with Acute Bacterial Skin and Skin Structure Infection. Ahead of print PIDJ May 9, 2016. |
<table>
<thead>
<tr>
<th><strong>Ceftazidime/Avibactam (Avycaz™)</strong></th>
<th>No pre-approved indication</th>
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| **Reason(s) for Restriction**     | 1. No pediatric labeling so dose unknown (currently under investigation)  
|                                   | 2. Resistance testing should be performed prior to use in CF patients |
| **Mechanism**                     | Avibactam is a unique beta-lactamase active against ESBL-, KPC-, AmpC, and certain oxacillinases (confer resistance to penicillins, cephalosporins, and carbapenems). |
| **Spectrum of Activity**          | Active: Enterobacteriaceae including those producing the enzymes stated above; P. aeruginosa, except for multi-drug resistant strains that have lower susceptibility to Avycaz.  
|                                   | **NOT** active: Similar limited activity as ceftazidime for gram-positives and anaerobes (may have some anaerobic activity but IAI studies used combination of Avibactam with metronidazole); no activity for metallo-beta lactamase producers; poor activity against Acinetobacter |
| **Infection Site Restrictions**   | CNS - penetration of avibactam component unknown (ceftazidime does penetrate CNS) |
| **FDA Approved Indications**      | Complicated Intra-abdominal infection (in combination with metronidazole); Complicated UTI |
| **Dose**                          | Ordering at BCH is in terms of ceftazidime component  
|                                   | >/=40kg: 2g ceftazidime (2.5 g Avycaz) IV Q8hr infused over 2 hours  
|                                   | <40 kg: 50 mg/kg/dose ceftazidime IV Q8hr infused over 2 hours  
|                                   | **Renal Dose Adjustment** – CrCl <50 mL/min/1.73m²  
|                                   | CrCl 31 to 50 mL/minute: 1 gram ceftazidime (1.25 g Avycaz) Q 8 hours  
|                                   | CrCl 16 to 30 mL/minute: 750 mg ceftazidime (0.94 g Avycaz) Q 12 hours  
|                                   | CrCl 6 to 15 mL/minute: 750 mg ceftazidime (0.94 g Avycaz) Q 24 hours  
|                                   | CrCl ≤5 mL/minute: 750 mg ceftazidime (0.94 g Avycaz) Q 48 hours  
|                                   | ESRD on intermittent hemodialysis: Administer after hemodialysis on dialysis days; dose based upon patient’s estimated renal function (eg, CrCl 6 to 15 mL/minute or CrCl ≤5 mL/minute ).  
| **Hepatic Dose Adjustment**       | None |
| **ADRs and Monitoring**           | GI – nausea (10%), constipation (10%), vomiting (14%), abdominal pain (8%)  
|                                   | Hepatic – Alk Phos increased (9%), ALT increased (8%),  
|                                   | Neurologic – dizziness (6%)  
|                                   | Psychiatric - Anxiety (10%)  
|                                   | <5% incidence: rash, hypokalemia, eosinophilia, thrombocytopenia, acute renal failure |
| **Susceptibility testing**        | Send out requests can be done for any specimen type for the following list of organisms: E. coli, Enterobacter cloacae, Enterobacter aerogenes, K. pneumoniae, K. oxytoca, Proteus mirabilis, Providencia stuartii, Pseudomonas aeruginosa, Citrobacter freundii, Citrobacter koseri  
|                                   | Our micro laboratory anticipates adding testing for Pseudomonas sensitivity by end of 2016 |
| **Other Concerns/Warnings**       | Use with caution in patients with a history of penicillin, cephalosporin, or carbapenem allergy |
| **When to Use?**                  | Multi-drug resistant Enterobacteriaceae and Pseudomonas with confirmed sensitivity.  
<p>|                                   | <strong>Unacceptable Uses</strong>: CF patients without sensitivity testing indicating sensitive organism – at resistance testing for the first 3 CF patients colonized with pan-resistant Pseudomonas aeruginosa were RESISTANT to Zerbaxa |</p>
<table>
<thead>
<tr>
<th><strong>Ceftolozane / Tazobactam (Zerbaxa™)</strong></th>
<th>No pre-approved indication</th>
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| **Reason(s) for Restriction** | 1. No pediatric labeling so dose unknown  
2. Resistance testing should be performed prior to use in CF |
| **Mechanism** | New cephalosporin with heavier side chain more stable against AmpC beta-lactamases and more potent activity against Pseudomonas compared to ceftazidime |
| **Spectrum of Activity** | Active: Resistant gram negative bacteria including Pseudomonas and ESBL organisms  
NOT active: Similar limited activity as ceftazidime for gram-positives and anaerobes (may have some anaerobic activity but IAI studies used combination of Avibactam with metronidazole); no activity for metallo-beta lactamase producers; poor activity against Acinetobacter and Stenotrophomonas |
| **Infection Site Restrictions** | None |
| **FDA Approved Indications** | Complicated intra-abdominal infection; Complicated UTI (no pulmonary indication) |
| **Dose** | Ordering at BCH is in terms of ceftolozane component  
Adults with ciAI and cUTI (package-labeling): 1g ceftolozane + 500 mg tazobactam (1.5g Zerbaxa) IV Q8h  
**Pulmonary infections may need higher doses 2 g ceftolozane + 1 g tazobactam IV Q8hr (3g Zerbaxa) – currently being studies for VAP by manufacturer; see references** |
| **Renal Dose Adjustment** | CrCl < 50 mL/min/1.73m²: unknown  
CrCl 30-50 mL/min: 750mg Zerbaxa (500 mg ceftolozane + 250 mg tazobactam) IV Q8h  
CrCl 15-29 mL/min: 375 mg Zerbaxa (250 mg ceftolozane + 125 mg tazobactam) IV Q8h  
CrCl < 15 mL/min: unknown |
| **Hepatic Dose Adjustment** | None |
| **ADRs and Monitoring** | GI – nausea (3-8%) and diarrhea (2-6%),  
Headache (3-6%)  
Monitoring: LFTs, CHEM 7, and CBC weekly |
| **Susceptibility Testing** | Request sensitivity testing be sent to the company by microbiology. Sensitivity testing performed on isolates from urinary or intraabdominal sources |
| **Other Concerns/Warnings** | Use with caution in patients with a history of penicillin, cephalosporin, or carbapenem allergy |
| **When to Use?** | Multi-drug resistant Pseudomonas and Enterobacteriaceae; At BCH, isolates from CF patients have been resistant to Zerbaxa when tested.  
**Unacceptable Uses:** CF patients without sensitivity testing indicating sensitive organism; patients <18 years of age |
| **References** | A Prospective, Randomized, Double-Blind, Multicenter, Phase 3 Study to Assess the Safety and Efficacy of Intravenous Ceftolozane/Tazobactam Compared With Meropenem in Adult Patients With Ventilated Nosocomial Pneumonia  
A Phase 1, Non-comparative, Open-label Study to Characterize the Pharmacokinetics of a Single Intravenous Dose of Ceftolozane/Tazobactam in Pediatric Patients Receiving Standard of Care Antibiotic Therapy for Proven or Suspected Gram-negative Infection or for Peri-operative Prophylaxis  
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<tr>
<th><strong>Chloramphenicol</strong></th>
<th><strong>Pre-approved indication:</strong> Cystic Fibrosis</th>
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| **Reason for restriction** | 1. Not available in the United States  
2. Blood dyscrasias (e.g., aplastic anemia) with short and long term therapy – can be irreversible  
3. Gray baby syndrome in neonates  
4. Therapeutic Drug Monitoring |
| **Mechanism** | Protein synthesis inhibitor with broad bacteriostatic activity |
| **Spectrum of Activity** | Active: Many gram positive and gram negative organisms and most anaerobic bacteria; Notable coverage includes H. influenza, S. pneumonia, N. meningitides, Burkholderia cepacia, Brucella species, Rickettsia, Lymphogranulomapsittacosis, Bacteroides, and spirochetes. Many MRSA and VRE are sensitive.  
**NOT** active: Enterobacter, Acinetobacter, Serratia, Pseudomonas |
| **Infection Site Restrictions** | None: Distributes well into both inflamed and non-inflamed meninges |
| **FDA Approved Indications** | Treatment of serious infections due to organisms resistant to other less toxic antibiotics or when its penetrability into the site of infection is clinically superior to other antibiotics to which the organism is sensitive; Historically used for meningitis, enteric fever, and respiratory infections but more effective and safe antibiotics now available for these indications. |
| **Dose** | **Meningitis** - IV: Infants >30 days, Children and Adults: 25 mg/kg/dose every 6 hours  
Other infections - IV: Infants >30 days, Children and Adults: 12.5-25 mg/kg/dose every 6 hours; Maximum daily dose: 4 g/day  
**Renal Dose Adjustment** – Dose adjustment should be based on chloramphenicol concentrations  
**Hepatic Dose Adjustment** - Dose adjustment should be based on chloramphenicol concentrations |
| **ADRs - Monitoring** | Blood dyscrasias: Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) have occurred after both short-term and prolonged therapy  
Lab Monitor – baseline and Q2 days while on therapy, LFTs and BUN/Cr at baseline |
| **Therapeutic Drug Monitoring** | **Timing:** Peak concentration 0.5 - 1.5 hours after completion of IV dose  
**Goal Therapeutic levels:**  
- Meningitis and CF:  
  Peak (toxicity): 15-25 mcg/mL; toxic concentration: >40 mcg/mL  
  Trough (efficacy): 5-15 mcg/mL  
- Other infections:  
  Peak: 10-20 mcg/mL  
  Trough: 5-10 mcg/mL |
| **Other Concerns/Warnings** | 1. U.S. Boxed Warning: Blood dyscrasias: Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) occurred after both short-term and prolonged therapy. Can be irreversible.  
2. Use with caution in patients with G6PD deficiency  
3. Avoid use in neonates/premature infants – due to immature metabolic system and “grey baby” syndrome |
| **When to Use?** | Used rarely. Case reports of rare cases of meningitis (i.e. tularemia). Could be required for MDR organisms if no alternatives available.  
**Unacceptable Use:** Use in treating organisms that are sensitive to less toxic medications |

Updated 7/1/16
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<tr>
<th><strong>Colistin</strong></th>
<th><strong>Pre-approved indication:</strong> Cystic Fibrosis</th>
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| **Reason for restriction** | 1. Nephrotoxicity  
2. Neurotoxicity |
| **Mechanism** | Polymyxin antibiotic that electrostatically disrupts the outer membrane of gram negative bacteria |
| **Spectrum of Activity** | Active: common GNR, including Acinetobacter spp, Pseudomonas spp, Klebsiella, Enterobacter, E. coli, Salmonella, Shigella, Citrobacter, Yersinia pseudotuberculosis, H. influenza  
**NOT** active against gram positive bacteria, gram negative cocci, or anaerobes. No activity for Pseudomonas mallei, Burkholderia cepacia, Proteus species, Providencia species, Morganella morganii, Serratia species, Edwardsiella species, and Brucella species |
| **Infection Site Restrictions** | CNS – Poor penetration |
| **FDA Approved Indications** | Disease due to Gram-negative bacteria, Pseudomonas aeruginosa, Enterobacter aerogenes, Escherichia coli, and Klebsiella pneumonia |
| **Dose** | Non-CF patients: 2.5 mg/kg/dose colistin base IV Q12hr may be preferred to more frequent dosing intervals (colistin is a concentration dependent killer)  
CF patients, non-adult program: 1.7 mg/kg/dose colistin base IV Q8hr (same total daily dose of 5 mg/kg/day divided Q8hr due to CF literature pointing to less toxicities with this regimen)  
CF patients, adult program: 2.5 mg/kg/dose IV Q12hr (this CF team prefers Q12hr, as is the practice for the adult CF program at Brigham and Women’s)  
Obesity – Use Ideal Body Weight  
Renal Dose Adjustment: Required if CrCl <80 mL/min/1.73m²  
Hepatic Dose Adjustment – No hepatic elimination so no adjustment needed |
| **ADRs – Monitoring** | ADRs  
Nephrotoxicity: acute renal failure 33% - 60%  
CNS: Dizziness, headache, slurred speech, vertigo  
Fever  
Monitor: Renal function tests (urine output, BUN, serum creatinine, and creatinine clearance) at baseline and at least twice weekly during therapy |
| **Susceptibility Testing** | Need to request sensitivity testing by microbiology |
| **Other Concerns/Warnings** | CNS toxicity: Transient, reversible neurological disturbances (eg, dizziness, numbness, paresthesia, generalized pruritus, slurred speech, tingling, vertigo) may occur. Dose reduction may reduce neurologic symptoms; monitor closely.  
Safety: Potential for dosing errors due to lack of standardization in literature when referring to product and dose; colistimethate (inactive prodrug) and colistin base strengths are not interchangeable; verify prescribed dose is expressed in terms of colistin base activity prior to dispensing |
| **When to Use?** | Acceptable: Management of serious infections due to sensitive strains of certain gram-negative bacilli that are resistant to all currently available beta-lactams, aminoglycosides, and fluoroquinolones  
**Unacceptable use:** Patients with renal impairment or treatment of organisms that are sensitive to less toxic medications |
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<tr>
<th><strong>Daptomycin</strong></th>
<th>No pre-approved indication</th>
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| **Reason for restriction** | 1. No FDA pediatric approval  
2. Manufacturer now recommends avoiding use in patients <12 months due to musculoskeletal, neuromuscular and nervous system adverse effects observed in neonatal canine models  
3. Infection site restrictions  
4. High Cost |
| **Mechanism** | Lipopeptide antibiotic that depolarizes and disrupts the cell membrane of gram positive bacteria |
| **Spectrum of Activity** | Active: MSSA, MRSA, streptococci, enterococci – including VRE. Gram positive resistance is rare but has been reported  
**NOT** active: Gram negative and anaerobes |
| **Infection Site Restrictions** | Pneumonia - Do NOT use if lung coverage is desired as surfactant inactivates daptomycin  
CNS – Do NOT use – poor penetration and no clinical data for this setting to date |
| **FDA Approved Indications** | Adults: Endocarditis; Staphylococcus aureus bacteremia; Skin and soft tissue |
| **Dose** | CONCENTRATION dependent killer so dose matters  
< 2 years old – minimal PK data – 10-12 mg/kg/dose IV q24h  
2-5 years old – 8-10 mg/kg/dose IV q24h  
>= 6 years old – >=8 mg/kg/dose IV q24h  
Adults – Endocarditis – Staphylococcus: >= 8mg/kg/dose IV q24h  
Enterococcus: 10-12 mg/kg/dose IV q24h (please see endocarditis guideline for consideration of combination therapy of daptomycin with ampicillin or ceftaroline)  
Skin and soft tissue - 4 mg/kg/dose IV q24h |
| Obesity Adjustment: Use Actual Body Weight |
| Renal Dose Adjustment: CrCl < 30 mL/min/1.73m² |
| Hepatic Dose Adjustment – None |
| ADRs | • Effects on skeletal muscle that can manifest as myalgia or arthralgia or possibly rhabdomyolysis  
• Hypo/hyperkalemia  
• Eosinophilic pneumonia – reported in post-marketing surveillance; typical onset at 2-4 weeks |
| Labs Concerns/Warnings | • CK and CHEM7 baseline and weekly  
• For children < 2 years, consider sending daptomycin peak concentration – ask Sarah for form; send to Center for Anti-infective Research and Development (Hartford,CT) - contact Christina at (860) 545-3615. They do these in a batch format so results are often NOT “real time”. |
| Susceptibility Testing | Need to request sensitivity testing for MRSA by microbiology (VRE clinical isolates will automatically be tested) |
| **When to Use?** | Bacteremia or endocarditis caused by MRSA or Methicillin-resistant coagulase-negative staphylococci in patients with serious allergy to vancomycin OR failing vancomycin therapy OR vancomycin MIC >2 mcg/mL; VRE infection (NOT pneumonia) on a case by case basis, particularly if contra-indication to alternative therapies (i.e. linezolid) |
| **Unacceptable Use:** | 1. Treatment of gram-positive pneumonia or CNS infection  
2. Empiric coverage for VRE colonization of the urine, respiratory tract, wounds, or drains |
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<tr>
<th><strong>Ertapenem</strong></th>
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| **Reason for restriction** | 1. Carbapenem that does not cover Pseudomonas or Enterococci  
2. Use is restricted to x1 discharge dose for conversion to OPAT  
3. Brand name product and meropenem is cheaper alternative |
| **Mechanism** | Inhibition of cell wall synthesis by binding to penicillin-binding protein |
| **Spectrum of Activity** | Active: Broad gram-positive and gram-negative coverage, including anaerobes and most ESBL-producing bacteria  
BCH Formulary carbapenem is meropenem.  
**NOT** active: Pseudomonas aeruginosa, Acinetobacter, Enterococci and MRSA |
| **Infection Site Restrictions** | None – well distributed |
| **FDA Approved Indications** | Adult and Pediatric:  
2. Prophylaxis of surgical site infection following elective colorectal surgery. |
| **Dose** | <12 yrs and <\=33 kg: 15 mg/kg/dose IV q12h (max 500 mg IV q12hr)  
<12 yrs and >33 kg: 500 mg IV Q12hr  
\=/12 yrs AND >33 kg: 1000mg IV q24h  
Renal Dose Adjustment: If estimated CrCl <30 mL/min/1.73m² – reduce dose by 50%  
Hepatic Dose Adjustment: none |
| **ADRs - Monitoring** | ADRs:  
GI – Diarrhea, vomiting, nausea, abdominal pain  
Hematologic – Thrombocytosis, decreased hemoglobin/hematocrit  
CNS – Headache, fever, insomnia, dizziness  
Hepatic – LFT increased, alkaline phosphatase increased, total bilirubin increased  
Monitor: Weekly BMP, LFTs, and CBC for prolonged therapy |
| **Other Concerns/Warnings** | Cross-sensitivity in patients with penicillin allergy – up to 10%  
Carbapenems, including ertapenem, may decrease the serum concentration of divalproex sodium/valproic acid increasing the risk of breakthrough seizures. Concurrent use of carbapenem antibiotics with divalproex sodium/valproic acid is **NOT** recommended |
| **When to Use?** | Acceptable Use: One-time does to assess tolerance prior to discharge home for OPAT therapy (ertapenem is more convenient than meropenem for outpatient care)  
**Unacceptable Use**: All carbapenem inpatient therapy when meropenem can be used |
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<tr>
<th><strong>Fidaxomicin</strong></th>
<th><strong>No pre-approved indications</strong></th>
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| **Reasons for restriction** | 1. Pediatric Dose Unknown  
2. No recommendation in IDSA guidelines for C. difficile  
3. High Cost ($140/tablet) |
| **Mechanism** | Macrocyclic antibiotic that inhibits RNA polymerase |
| **Spectrum of Activity** | Active: Clostridia species, including Clostridium difficile  
**NOT** active: Gram-negative aerobes or anaerobes (eg, Bacteroides spp) |
| **Infection Site Restrictions** | MINIMAL systemic absorption – Use restricted to C. difficile infection only |
| **FDA Approved Indications** | C. difficile infection ONLY |
| **Dose** | Adults: 200 mg tablet PO BID with or without food  
Pediatric: Dosage unknown; Tablet can be split  
Renal Dose Adjustment: No dose adjustment needed  
Hepatic Dose Adjustment: No dose adjustment needed |
| **ADRs - Monitoring** | ADRs: All ADRs reported incidence ≤2% unless otherwise specified  
GI – Nausea (11%), vomiting (7%), abdominal pain (6%), GI hemorrhage (4%)  
Hematologic – anemia (2%), neutropenia (2%)  
Monitor: None recommended by manufacturer |
<p>| <strong>Other Concerns/Warnings</strong> | Use with caution in patients with macrolide allergy; may be at increased risk for hypersensitivity |
| <strong>When to Use?</strong> | Recurrent C. difficile - Some data have shown decrease in rate of reinfection when compared with vancomycin but studies excluded patients with history of &gt;1 recurrent CDAD episode within 3 months. For recurrent infections, consider rifaximin and/or Fecal Microbiota Transplant (call GI). |</p>
<table>
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<tr>
<th><strong>Moxifloxacin</strong></th>
<th><strong>Pre-approved indication – Patients &gt; 12 yrs of age</strong></th>
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| **Reasons for restriction** | 1. Pediatric dose unknown  
2. Toxicity Risk - QT prolongation |
| **Mechanism** | 4th generation quinolone that inhibits DNA gyrase |
| **Spectrum of Activity** | Active: similar to levofloxacin with additional anaerobic spectrum; Specifically active against S. pneumoniae, enteric gram-negatives, atypicals, *H.influenzae*, and anaerobes.  
NOT active: Pseudomonas; resistance to *Bacteroides* variable |
| **Infection Site Restrictions** | UTI – should NOT be used due to low urinary concentrations |
| **FDA Approved Indications** | Adults - Sinusitis, bronchitis, CAP, Skin/Skin Structure Infection, Intra-abdominal infection |
| **Dose** | Adults: if >/= 12 yrs and >40kg then 400 mg IV/PO q24h  
Pediatrics: 10 mg/kg/dose IV/PO q24h (Dose not well studied and requires compounding)  
Renal Dose Adjustment: No dosage adjustment needed  
Hepatic Dose Adjustment: No dosage adjustment is required but > 50% metabolized by liver consider closer monitoring of QT prolongation in this population |
| **ADRs - Monitoring** | ADRs  
- QTc prolongation and risk of Torsades  
- Hypo/hyperglycemia especially in diabetic patients  
- Seizures – lowers seizure threshold  
- Arthralgias and Achilles tendon rupture (black box warning) rarely occur  
Other adverse effects include GI side effects, headache, photosensitivity.  
Monitor: Baseline EKG and Glucose (consider twice weekly for inpatients) |
<p>| <strong>Other Concerns/Warnings</strong> | Achilles tendon rupture (black box warning similar to other fluoroquinolones) has been reported rarely in all age categories |
| <strong>When to Use?</strong> | Penicillin-allergic patients without other alternatives (clindamycin for gram positive, aztreonam for gram negative). Wide range of indications, including meningitis (CSF/Blood &gt; 50%). Outpatient therapy can be considered but suspension requires compounding. |</p>
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<tr>
<th><strong>Streptomycin</strong></th>
<th><strong>No pre-approved indications</strong></th>
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<tbody>
<tr>
<td><strong>Reason for Restriction</strong></td>
<td>Aminoglycoside with highest nephrotoxicity and requires IM dosing</td>
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<tr>
<td><strong>Mechanism</strong></td>
<td>Protein synthesis inhibitor and activity against outer membrane (likely accounts for bactericidal activity)</td>
</tr>
</tbody>
</table>
| **Spectrum of Activity** | Active: Gram-negative aerobic bacilli and mycobacteria, often in combination  
**NOT** active: Anaerobes; as single agent for streptococci or enterococci |
| **Infection Site Restrictions** | CNS - CSF/Blood 0-30% |
| **FDA Approved Indications** | Brucellosis, Gram negative septicemia, H. influenza infections, M. tuberculosis, Endocarditis, Plague, Pneumonia, Tularemia, UTI |
| **Dose** | Tuberculosis: 15-40 mg/kg/dose Qday (maximum 1 gram per dose)  
Obesity Dose Adjustment – use adjusted weight calculation  
Renal Dose Adjustment - adjustments required with CrCl <50 mL/min/1.73m²  
Hepatic Dose Adjustment – No adjustment necessary |
| **ADRs - Monitoring** | ADRs  
• Nephrotoxicity  
• Ototoxicity  
Monitor: Renal function and Hearing test |
| **Other Concerns/Warnings** | **Therapeutic drug monitoring required**  
Goal therapeutic concentrations: Peak: 20-30 mcg/mL; Trough: <5 mcg/mL  
Toxic concentrations: Peak: >50 mcg/mL; Trough: >10 mcg/mL |
| **When to Use?** | Multi Drug resistant TB with known sensitivity to Streptomycin (Amikacin is more commonly used)  
Can be considered for synergy for Enterococcus with high-level gentamicin resistance |
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<thead>
<tr>
<th><strong>Synercid (Quinupristin and Dalfopristin)</strong></th>
<th><strong>No pre-approved indications</strong></th>
</tr>
</thead>
</table>
| **Reason for restriction**                  | 1. Multiple toxicities – thrombophlebitis and myalgias  
2. Only covers E.faecium, **NOT** E. faecalis  
3. Limited dosing data in pediatrics |
| **Mechanism of Action**                     | Synergistic combination of two streptogramins that inhibit protein synthesis |
| **Spectrum of Activity**                    | Active: MSSA, MRSA, E. faecium  
**NOT** active: E. faecalis, Pseudomonas, aerobic gram negative enterics |
| **Infection Site Restrictions**             | None |
| **FDA Approved Indications**                | Approved for skin and skin structure infection. Limited pediatric experience and dosing recommendations for <12 years of age; VRE indication was removed by FDA |
| **Dose**                                    | Pediatrics and Adults for mild/moderate infection - 7.5 mg/kg/dose IV q12h  
For severe infection use 7.5 mg/kg/dose IV q8h (no max dose)  
Renal dose adjustment – No adjustment necessary  
Hepatic dose adjustment – Dose adjustment may be necessary but no recommendations available |
| **ADRs - Monitoring**                       | ADRs  
• Infusion site reactions are common  
• Hyperglycemia  
• Anemia  
• Increased LFTs, hyperbilirubinemia  
• Arthralgias, myalgias, increase in CPK  
• Diarrhea, nausea and vomiting  
Monitor: Infusion site for thrombophlebitis; Check LFTs, CBC, CPK |
| **Susceptibility Testing**                  | Enterococcus sensitivity testing can be performed upon request |
| **Other Concerns/Warnings**                 | Quinupristin/dalfopristin is a major inhibitor of cytochrome P450 3A4 (CYP3A4) isoenzymes, monitor medications such as tacrolimus and cyclosporine closely for increased levels, as well as other agents dependent on this pathway for metabolism |
| **When to Use?**                            | **VRE** (E. faecium) with resistance to other alternatives (i.e. daptomycin, tigecycline) and confirmed sensitivity  
**Unacceptable Use:** E. faecalis (use sensitivity data); MRSA with vancomycin failure (consider alternatives such as ceftaroline, daptomycin, linezolid) |

Updated 7/1/16
<table>
<thead>
<tr>
<th><strong>Tigecycline</strong></th>
<th>No pre-approved indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Reasons for restriction</strong></td>
<td>1. Infection Site Restriction – cannot be used for bacteremia</td>
</tr>
<tr>
<td><strong>Mechanism</strong></td>
<td>Tetracycline derivative - protein synthesis inhibitor with broader spectrum of activity than other tetracyclines.</td>
</tr>
<tr>
<td><strong>Spectrum of Activity</strong></td>
<td>Active: many GNR, Enterococci including VRE, S. aureus including MRSA, S. pneumoniae, and anaerobes</td>
</tr>
<tr>
<td></td>
<td><strong>NOT</strong> active: Pseudomonas, Proteus, Providencia</td>
</tr>
<tr>
<td><strong>Infection Site Restrictions</strong></td>
<td>BLOOD - Very large volume of distribution and distributes highly to tissue. Do NOT use for treatment of bacteremia (since it does not stay in blood!) due to increased mortality</td>
</tr>
<tr>
<td></td>
<td>UTI - Eliminated hepatically therefore low urinary concentrations and should not be used for UTI</td>
</tr>
<tr>
<td><strong>FDA Approved Indications</strong></td>
<td>Adults – Complicated skin and skin structure infection, intra-abdominal infection and CAP</td>
</tr>
<tr>
<td><strong>Dose</strong></td>
<td>Pediatric (age &gt;8) dosing based on new PK data (Purdy 2012)</td>
</tr>
<tr>
<td></td>
<td>&lt; 40 kg: 1.2 mg/kg/dose IV Q12 (max 50)</td>
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<tr>
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<td>40-80 kg: 1.2 mg/kg loading dose x 1 then 50mg IV Q12</td>
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<tr>
<td></td>
<td>&gt;80 kg: 100 mg loading dose x 1 then 50mg IV Q12</td>
</tr>
<tr>
<td></td>
<td>Renal Dose Adjustment: No dosage adjustment</td>
</tr>
<tr>
<td></td>
<td>Hepatic Dose Adjustment: For Child-Pugh class C reduce maintenance dose by 50%</td>
</tr>
<tr>
<td><strong>ADRs and Monitoring</strong></td>
<td>ADRs</td>
</tr>
<tr>
<td></td>
<td>• Severe nausea, vomiting and diarrhea. Consider pre-treatment with ondansetron.</td>
</tr>
<tr>
<td></td>
<td>• Discoloration of developing teeth</td>
</tr>
<tr>
<td></td>
<td>Monitor – Weekly LFTs</td>
</tr>
<tr>
<td><strong>Other Concerns/Warnings</strong></td>
<td>CONTRAINDIATED in Pregnant women and children &lt;8 yr of age.</td>
</tr>
<tr>
<td><strong>When to Use?</strong></td>
<td>• Mycobacterial infections (especially in CF)</td>
</tr>
<tr>
<td></td>
<td>• Intra-abdominal and pulmonary infections with contraindications to alternative agents</td>
</tr>
<tr>
<td></td>
<td>• Multi-drug resistant gram-negative organisms including Acinetobacter spp and Stenotrophomonas on a case by case basis;</td>
</tr>
<tr>
<td></td>
<td><strong>Unacceptable Use</strong>: Patients &lt; 8 years (can be considered in younger patients who have lost primary teeth)</td>
</tr>
</tbody>
</table>
## Antivirals

<table>
<thead>
<tr>
<th><strong>Cidofovir</strong></th>
<th><strong>No pre-approved indications</strong></th>
</tr>
</thead>
</table>
| **Reason for restriction** | 1. Nephrotoxicity  
2. Need for additional hydration and Probenecid |
| **Mechanism** | Monophosphate nucleotide analogue that undergoes cellular phosphorylation to a diphosphate form that competitively inhibits viral DNA polymerase; Does not require initial phosphorylation by viral kinases that lead to resistance associated with acyclovir and ganciclovir |
| **Spectrum of Activity** | Activity against herpesviruses (CMV, HSV, EBV, VZV, HHV), including TK-negative HSV and UL97 phosphotransferase-negative CMV and other DNA viruses (Adenovirus,BK)  
**NOT** active: RSV and other respiratory RNA viruses |
| **Infection Site Restrictions** | CNS – CSF/Blood 0% |
| **FDA Approved Indications** | CMV retinitis in HIV patients |
| **Dose** | 5 mg/kg/dose IV once per week  
**Obesity Dose Adjustment**: Use ideal body weight |
| **Renal Dose Adjustment** | • Use contraindicated with serum creatinine >1.5 mg/dL, Clcr <55 mL/minute, or urine protein ≥100 mg/dL (≥2+ proteinuria)  
• If the Scr >1.5 mg/dL, CICr <90 mL/minute/1.73 m2, >2+ proteinuria, the following dosing has been used for treatment of adenovirus post-transplant:  
  **Induction**: 1 mg/kg/dose 3 times/week on alternate days for 2 consecutive weeks  
  **Maintenance**: 1 mg/kg/dose every other week |
| **Hepatic Dose Adjustment** | No dosage adjustment recommended |
| **ADRs - Monitoring** | ADRs  
• Nephrotoxicity  
• Other ADRs > 10%:  
  Central nervous system: Chills, fever, headache, pain  
  Dermatologic: Alopecia, rash  
  Gastrointestinal: Nausea, vomiting, diarrhea, anorexia  
  Hematologic: Anemia, neutropenia (up to 24%)  
  Neuromuscular & skeletal: Weakness |
| **Other Concerns/Warnings** | Requires hydration and **probenecid** pre and post treatment with all doses of cidofovir. See online Formulary for dosing details |
| **When to Use?** | Adenovirus and BK virus in immunocompromised host  
Acyclovir-resistant HSV (foscarnet usually first line), CMV (ganciclovir is first line) |

Updated 7/1/16
<table>
<thead>
<tr>
<th><strong>Foscarnet</strong></th>
<th>No pre-approved indications</th>
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</table>
| **Reason for restriction** | 1. Nephrotoxicity  
2. Electrolyte imbalance  
3. Need for additional hydration |
| **Mechanism** | Pyrophosphate analog that binds to viral DNA polymerase without requiring further modification |
| **Spectrum of Activity** | Activity against herpes viruses: CMV (second line to ganciclovir), HSV-1, HSV-2, (second line to acyclovir,) VZV  
NOT active: EBV, Adenovirus, Respiratory viruses |
| **Infection Site Restrictions** | No evidence for CNS distribution |
| **FDA Approved Indications** | Acyclovir resistant HSV infection  
Treatment of CMV retinitis in HIV patients |
| **Dose** | CMV Induction: 60 mg/kg/dose IV every 8 hrs  
CMV Maintenance: 90-120 mg/kg/dose IV q24 hrs  
Acyclovir-resistant HSV: 40 mg/kg/dose IV q8-12 hrs  
Obesity: Dose Adjustment - Consider using ideal or adjusted body weight for dose calculation  
Renal Dose Adjustment: Adjust dose in patients with CrCl <90 mL/min/1.73m²  
Hepatic Dose Adjustment: No dose adjustment required |
| **ADRs – Monitoring** | ADRs  
• Nephrotoxicity – (12-33%): Black box warning  
• CNS – Fever 65% and Headache 26%, Seizures, Anxiety, confusion, depression, dizziness  
• Electrolytes disturbance: Hypokalemia 16-48%; Hypocalcemia 15-30%; Hypomagnesemia 15-30 %; Hypophosphatemia 8-26%  
Monitor: Electrolytes and renal function daily |
| **Other Concerns/Warnings** | Black box warnings –  
1. Nephrotoxicity occurs to some degree in the majority of patients treated with foscarnet  
2. Seizures related to plasma electrolyte/mineral imbalance may occur |
| **When to Use?** | Alternative to ganciclovir for CMV infection in non-engrafted SCT patients  
Ganciclovir-resistant CMV and acyclovir-resistant HSV |
<table>
<thead>
<tr>
<th><strong>Palivizumab</strong></th>
<th>Pre-approved indications: Prophylaxis per hospital guidelines</th>
</tr>
</thead>
</table>
| **Reason for restriction** | 1. High cost ($2400/100 mg vial)  
2. Little evidence for use in TREATMENT |
| **Mechanism** | Humanized monoclonal RSV antibody |
| **Spectrum of Activity** | Active: Respiratory syncytial virus (RSV) |
| **Infection Site Restrictions** | Only used in RSV pulmonary infections – prophylaxis or treatment |
| **FDA Approved Indications** | Prophylaxis only; Use in treatment is NOT approved by FDA, NOT recommended by AAP guidelines, and there is little literature to support its efficacy |
| **Dose** | Prophylaxis - 15 mg/kg/dose IM q-month during RSV season if patient meets criteria  
Treatment - 15 mg/kg/dose IV q14 days x2 doses has been reported |
| **Monitoring – ADRs** | ADR: Well tolerated  
Monitoring: None |
<p>| <strong>Other Concerns/Warnings</strong> | No concerns |
| <strong>When to Use?</strong> | Treatment of RSV infection with palivizumab remains controversial and has been done at BCH for treatment of established RSV infection in some of our immunocompromised hosts. Ribavirin is no longer on Hospital Formulary for treatment of established RSV infection. |</p>
<table>
<thead>
<tr>
<th><strong>Peramivir</strong></th>
<th><strong>No pre-approved indications</strong></th>
</tr>
</thead>
</table>
| **Reason for restriction** | 1. High cost ($950 for 600mg dose)  
2. Alternatives available (oseltamivir)  
3. No pediatric labeling so dose unknown |
| **Mechanism** | Neuraminidase inhibitor |
| **Spectrum of Activity** | Active: Influenza A and B |
| **Infection Site Restrictions** | Used only for influenza virus |
| **FDA Approved Indications** | Approved for uncomplicated influenza in adult patients. |
| **Dose** | Adult: 600mg IV Q24hr x 5 days  
Pediatrics: 10 mg/kg/dose IV Q24hr x 5 days (max 600mg IV Q24hr)  
<3 months: Unknown |
| **Renal Dose Adjustment** | Adjust for CrCl < 50 mL/min – please see Formulary for recommendations |
| **Hepatic Dose Adjustment** | |
| **Monitoring – ADRs** | ADR: Neutropenia (8%), Neuropsychiatric events (rare), Hypersensitivity reactions (occurs with other NA inhibitors)  
Monitoring: CBC with differential and CHEM 7 |
<p>| <strong>Other Concerns/Warnings</strong> | No concerns |
| <strong>When to Use?</strong> | ICU patients with influenza virus who cannot tolerate oral antivirals. Of note, efficacy data with one dose demonstrated 12-21 hour faster time to symptom recovery in acute uncomplicated cases. For ICU patients, the CDC recommends these a full 5 day treatment course. |</p>
<table>
<thead>
<tr>
<th><strong>Antifungals</strong></th>
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</thead>
<tbody>
<tr>
<td><strong>Flucytosine</strong></td>
</tr>
</tbody>
</table>
| **Reason for restriction** | 1. Serious Infection – Fungal Meningitis  
2. Therapeutic Drug Monitoring  
3. Hematologic toxicities  
4. Very high cost |
| **Mechanism** | Converted to 5-FU in fungal cells which is further converted to metabolites that inhibit fungal DNA and RNA synthesis |
| **Spectrum of Activity** | Active: Cryptococcus and Candida species; often active against Aspergillus  
NOT active: other fungi |
| **Infection Site Restrictions** | None  
CSF/Blood 60-100% |
| **FDA Approved Indications** | Candidiasis, Cryptococcal meningitis (HIV infection), Cryptococcosis |
| **Dose** | Neonates: See Neofax for dosage recommendations  
Body weight >2 kg: 50-150 mg/kg/day divided every 6 hours  
Note: Monitoring of serum concentrations recommended |
| **Obesity Dose Adjustment** | Use Ideal Body Weight |
| **Renal Dose Adjustment** | Dosage adjustments required if CrCl <50 mL/min/1.73m² |
| **Hepatic Dose Adjustment** | No adjustment needed |
| **ADRs - Monitoring** | ADRs  
• Agranulocytosis, anemia, aplastic anemia, eosinophilia, leukopenia, pancytopenia, thrombocytopenia,  
• Renal and Hepatic Dysfunction  
• Hypokalemia, hypoglycemia  
• GI: Abdominal pain, diarrhea, nausea, vomiting, xerostomia, anorexia  
• CNS: ataxia, confusion, fatigue, hallucinations, headache, psychosis, seizure, vertigo, pyrexia |
| **Other Concerns/Warnings** | Oral capsule formulation only (extemporaneous recipes available if liquid formulation needed)  
**Therapeutic Drug Monitoring**: Check before and after 4th dose  
– Trough: 25-50 mcg/mL (draw time just prior to dose administration)  
– Peak: 50-100 mcg/mL (draw time 2 hours after oral dose administration)  
Warning: peak levels should not exceed 100 mcg/mL to avoid toxic bone marrow and hepatic effects |
| **When to Use?** | Combination therapy for Cryptococcal or Candida Meningitis |

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<table>
<thead>
<tr>
<th><strong>Micafungin</strong></th>
<th>Preapproved indication: Neutropenic Fever (prophylaxis and empiric therapy)</th>
</tr>
</thead>
</table>
| **Reason for restriction** | 1. High Cost with alternatives often available  
2. Historically had limited pediatric dosing data |
| **Mechanism** | Noncompetitive inhibitor of 1,3-B-D-glucan synthase and thereby interferes with fungal cell wall synthesis |
| **Spectrum of Activity** | Active: Candida species (fungicidal), Aspergillus (fungiSTATIC)  
*Candida parapsilosis may become resistant with repeated exposure; C.guilliermondii can have higher MICs  
NOT active: Cryptococcus |
| **Infection Site Restrictions** | CNS – inadequate distribution (Ambisome better for CNS candida fungal infection) |
| **FDA Approved Indications** | Adults – Disseminated candidiasis, Aspergillosis, Esophageal candidiasis, Prophylaxis of Candida infection |
| **Dose** | **Infants <4 months:** Dosing unknown; Ambisome is drug of choice in this age group  
**Infants ≥4 months, Children, and Adolescents:**  
Aspergillosis (off package label use), esophageal candidiasis:  
<50 kg: 3 mg/kg IV Q24hr; >/=50 kg: 150 mg IV Daily  
(for Aspergillus higher dose range has been reported : 4 to 8.6 mg/kg/day)  
Candidemia, Disseminated Candidiasis, Candida Peritonitis and Abscesses:  
<50 kg: 2 mg/kg IV Q24 hr; >/=50 kg: 100 mg IV Q24 hr  
Prophylaxis in SCT: 1 to 1.5 mg/kg daily; maximum dose: 50 mg IV Q24 hr  
**Obesity Dose Adjustment:** No adjustment recommended  
**Renal Dose Adjustment:** No adjustment needed  
**Hepatic Dose Adjustment:** No adjustment needed |
| **ADRs - Monitoring** | ADRs  
- Hepatotoxicity  
- Hyperbilirubinemia  
- Neutropenia (5%)  
- Hyperkalemia (5%), hypernatremia (5%) and hypoglycemia (7%)  
Monitor - LFTs and Bilirubin at baseline and weekly, CBC with differential weekly |
| **Other Concerns/Warnings** | Hepatically eliminated by non-cytochrome p450 metabolism, limited drug interactions reported:  
1. Sirolimus – levels of sirolimus may be increased – monitor concentrations  
2. Nifedipine – levels of nifedipine may be increased, monitor for nifedipine toxicity  
3. Itraconazole – levels of itraconazole may be increased, monitor for intraconazole toxicity |
| **When to Use?** | • Invasive candidiasis in patients who are clinically unstable.  
• Esophageal candidiasis  
• Empiric therapy in fever and neutropenia per CPG |
<p>| <strong>Unacceptable Use:</strong> | Neonates; Fluconazole sensitive strain of candida in immunocompetent patient; Treatment of zygomycoses (Mucor, Rhizopus, etc); Empiric therapy for suspected aspergillus – Use voriconazole or Ambisome instead |</p>
<table>
<thead>
<tr>
<th><strong>Posaconazole</strong></th>
<th><strong>Pre-approved indications: Prophylaxis</strong></th>
</tr>
</thead>
</table>
| **Reason for restriction** | 1. Pediatric Dosing Unknown  
2. Complicated PO regimens  
3. Drug-Drug Interactions  
4. Therapeutic Drug Monitoring required  
5. High Cost (tab > suspension) |
| **Mechanism** | Inhibits 14-alpha-demethylase which inhibits ergosterol production |
| **Spectrum of Activity** | Active: Broad-spectrum azole antifungal that has activity against *Candida*, *Aspergillus* and *Zygomycosis* (no other azole covers zygomycetes) and *Fusarium*.  
**NOT** active: other fungi not listed above |
| **Infection Site Restrictions** | None |
| **FDA Approved Indications** | Does not have FDA pediatric dosing for <13 years of age |
| **Dose** | **Adults and age > 13y: Prophylaxis**  
DR tab: 300mg PO BID x 1day then 300 mg PO Daily  
Suspension – 200mg PO TID with HIGH FAT meal  
IV: 300 mg IV Q12 hr x 2 doses then 300 mg IV Q24 hr  
**Adults and age > 13y: Treatment:**  
DR tab: 300mg PO BID x 1 day then 300mg PO Daily (off label use)  
Suspension - 200 mg PO QID with HIGH FAT meals  
IV: 300 mg IV Q12 x 2 doses then 300 mg IV Q24  
**Pediatrics <13 y:** Unknown and a wide range of dosing have been used  
**Renal Dose Adjustment:** < 50 mL/minute/1.73 m2: Avoid intravenous formulation unless risk/benefit has been assessed; the intravenous vehicle (cyclodextrin) may accumulate.  
**Hepatic Dose Adjustment** – No adjustment necessary |
| **ADRs - Monitoring** | ADRs  
- Hepatotoxicity  
- Nausea  
- Rash  
- Thrombophlebitis – must use central IV for administration  
Monitor: LFTs and bilirubin at baseline then weekly |
| **Other Concerns/Warnings** | **Therapeutic Drug Monitoring** - Due to saturable absorption and need for high fat meals - Therapeutic Drug Monitoring is required to ensure adequate dose and absorption.  
- Check after 5-7 days of therapy  
  - Goal trough is >1 for treatment; goal > 0.5-0.7 for prophylaxis  
  - No data on upper level for toxicity but could consider dose reduction for levels > 4  
- Drug drug interaction – check with Micromedex, Lexicomp or pharmacy |
| **When to Use?** | Treatment of invasive zygomycosis in combination with Ambisome.  
Oropharyngeal candidiasis and fungal infections refractory to other agents.  
HIGH cost and challenging to achieve therapeutic levels with oral suspension |
<table>
<thead>
<tr>
<th>Unacceptable Use:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Candidiasis or Neutropenic Fever – Use micafungin</td>
</tr>
<tr>
<td>2. Primary treatment of aspergillosis – Formulary preference voriconazole or Ambisome due to better dosing data</td>
</tr>
</tbody>
</table>
Voriconazole

**Pre-approved indications:** Prophylaxis or continuation of home therapy

**Reason for restriction**
1. No FDA pediatric approval – Pediatric Dose Unknown
2. Drug – Drug Interactions
3. QT Prolongation
4. Therapeutic Drug Monitoring required
5. High Cost

Inhibition of 14-alpha-demethylase which inhibits ergosterol production and had broader spectrum than fluconazole

**Spectrum of Activity**
Active: Azole antifungal that covers Candida species (C. glabrata can be resistant) – fungiSTATIC (Enchinocandins or fluconazole preferred)
Aspergillus species - fungiCIDAL
N OT active: Zygomycetes

**Infection Site Restrictions**
Urinary Tract Infection - Voriconazole is eliminated hepatically and is unlikely to be useful in the treatment of candiduria – fluconazole is preferred in this setting.
CSF/Blood 22-100%

**FDA Approved Indications**
Adults and >/=12 yrs of age: Aspergillus, Invasive candidiasis, Disseminated candidiasis; scedosporium and fusarrium
Does not have FDA pediatric dosage recommendation for <12 years of age

**Dose**
Adults – Loading dose of 6 mg/kg/dose PO/IV q12h x2 doses then 4 mg/kg/dose PO/IV q12h
Pediatrics – 7-9 mg/kg/dose PO/IV q12h (max 350 mg/dose) – no loading dose
Historically, BCH has used 7 mg/kg/dose but European package labeling recommends 9mg/kg/dose and clinical studies are currently using this dose.

**Obesity Dose Adjustment:** Use actual body weight up to Adult maximums
Renal Dose Adjustment IV product not recommended if CrCl <50 mL/min/1.73m² due to the IV form containing a cyclodextrin vehicle that accumulates in renal dysfunction and may be nephrotoxic.
Hepatic Dose Adjustment – Adjustments required – 50% at child pugh class A and B. Contra-indicated in class C

**ADRs – Monitoring**
**ADRs**
- QT prolongation
- Electrolyte abnormalities
- Hepatotoxicity – LFTs at baseline and weekly
- Visual effects (see wavy lines or flashing) very common and visual hallucinations – if therapy continues >/=28days, then test visual acuity, visual field and color perception.
- Peripheral neuropathy with courses > 1 month
- Skin hypersensitivity

Monitor: CHEM10, LFTs baseline and weekly,
- Baseline EKG if risk factors such as other QT prolonging medications or electrolyte abnormalities
- Visual effects – if therapy continues >/=28days, test visual acuity, visual field and color perception.

**Other Concerns/Warnings**
- Therapeutic Drug Monitoring is required. Voriconazole has highly variable interpatient pharmacokinetics and nonlinear elimination making it a challenge to dose correctly.
  - Goal trough is 1-5.5 mcg/mL. Levels < 1 mcg/mL have been associated with clinical failures.
- Many drug-drug interactions - Voriconazole is a potent inhibitor and a substrate of the cytochrome p450 system so other potential drug-drug interactions must be reviewed. Check with Micromedex, Lexicomp or pharmacy

**When to Use?**
Use for invasive Aspergillus infection or pseudallescheria boydii (Scedosporium spp), Fusarium and other invasive molds

**Unacceptable Use:** Candidiasis/Neutropenic fever – Use fluconazole or micafungin

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<table>
<thead>
<tr>
<th><strong>Quinidine Gluconate</strong></th>
<th><strong>No pre-approved indications for non-cardiac use</strong></th>
</tr>
</thead>
</table>
| **Reason for Restriction** | 1. Cardiac Effects and need for monitoring  
2. Restriction to ICU |
| **Spectrum of Activity** | Active: *P. falciparum*, *P. vivax*, *P. malariae*; Likely active against *P. ovale*  
**NOT** active: not used outside of malariae |
| **Infection Site Restrictions** | None |
| **FDA Approved Indications** | Treatment of life-threatening *Plasmodium falciparum* malaria |
| **Dose** | 10 mg/kg (dosed by salt component) infused over 120 minutes, followed by 0.02 mg/kg/minute continuous infusion for ≥24 hours  
Renal Dose Adjustment - Dose adjustment if CrCl <10 mL/min/1.73m²  
Hepatic Dose Adjustment – No adjustment needed |
| **ADRs - Monitoring** | ADRs - QT prolongation  
Monitor - Patient must be on continuous EKG monitor during infusion of quinidine gluconate |
| **Other Concerns/Warnings** | Restricted use to ED and ICU: Cardiac monitor required during I.V. administration  
Contraindications:  
1) Patients who have a history of thrombocytic purpura during prior therapy with quinidine or quinine  
2) Patients with complete A-V block with an A-V junctional or idioventricular pacemaker  
3) Patients with intraventricular conduction defects (marked widening of QRS complex)  
4) Patients who might be adversely affected by anticholinergic agents (eg, myasthenia gravis)  
5) Concurrent use of cisapride, fosamprenavir, ritonavir, or quinolone antibiotics which prolong QT interval |
<p>| <strong>When to Use?</strong> | Severe malaria while awaiting IV artemunate – Artesunate is more effective in the treatment of severe malaria but must be obtained through the CDC. Consider giving initial dose of Coartem. Definition of severe malaria can be found at <a href="http://www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf">www.cdc.gov/malaria/resources/pdf/treatmenttable.pdf</a>. |</p>
<table>
<thead>
<tr>
<th><strong>Coartem</strong></th>
<th><strong>No pre-approved indications</strong></th>
</tr>
</thead>
</table>
| **Reason for restriction** | 1. Malaria  
2. High cost |
| **Spectrum of Activity** | Active: *P. falciparum* with chloroquine-resistance or unknown resistance  
**NOT** active: |
| **Infection Site Restrictions** | None |
| **FDA Approved Indications** | For malaria in all patients ≥5 kg |
| **Dose** | 5 kg to <15 kg: 1 tablet at hour 0 and at hour 8 on the first day and then 1 tablet BID on days 2 and 3 (total of 6 tablets per treatment course)  
15 kg to <25 kg: 2 tablets at hour 0 and at hour 8 on the first day and then 2 tablets BID on days 2 and 3 (total of 12 tablets per treatment course)  
25 kg to <35 kg: 3 tablets at hour 0 and at hour 8 on the first day and then 3 tablets BID on day 2 and 3 (total of 18 tablets per treatment course)  
≥35 kg: 4 tablets at hour 0 and at hour 8 on the first day and then four tablets BID on days 2 and 3 (total of 24 tablets per treatment course) |
| **Renal Dose Adjustment** | No adjustment necessary |
| **Hepatic Dose Adjustment** | No adjustment necessary |
| **ADRs - Monitoring** | ADRs  
- Cardiovascular: Palpitation, QT prolongation  
- Central nervous system: Headache, dizziness, fever, chills, sleep disturbances, fatigue  
- Gastrointestinal: Anorexia, nausea, vomiting, abdominal pain  
- Neuromuscular & skeletal: Weakness, arthralgia, myalgia  
- Respiratory: Cough  
Monitor ECG monitoring for evidence of QT interval prolongation, particularly in patients with risk factors for QT prolongation (eg, long QT syndrome, cardiac arrhythmias, electrolyte abnormalities, concomitant administration of other medications that prolong the QT interval) |
| **Other Concerns/Warnings** | Contraindications: Concurrent use with strong CYP3A4 inducers (e.g., rifampin, carbamazepine, phenytoin, St John’s wort) |
| **When to Use?** | The fixed-dose combination of Coartem is indicated for the treatment of **acute, uncomplicated malaria** infections due to *Plasmodium falciparum* in patients weighing greater than 5 kg.  
**Unacceptable Use** - Patients with severe or complicated *Plasmodium falciparum* malaria or for the prevention of malaria (alternatives are quinidine and Artesunate IV. Artesunate IV is only available through the CDC; dose of Coartem may be given with quinidine while awaiting IV Artesunate) |
## Comparison Table for Avycaz and Zerbaxa

<table>
<thead>
<tr>
<th></th>
<th>Ceftazidime-avibactam (Avycaz)</th>
<th>Ceftolozane-tazobactam (Zerbaxa)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gram positive spectrum</strong></td>
<td>Some streptococcal (no viridans Streptococcus), very limited staphylococcal, no enterococcal activity</td>
<td>Some streptococcal (questionable for S. pneumoniae), very limited staphylococcal or enterococcal activity</td>
</tr>
<tr>
<td><strong>Gram negative spectrum</strong></td>
<td><strong>Excellent activity for ESBL, KPC</strong>&lt;br&gt;Good activity for Pseudomonas (resistance reported)&lt;br&gt;Limited activity for Acinetobacter and Stenotrophomonas&lt;br&gt;No activity against metallo-B-lactamases</td>
<td><strong>Moderate activity for ESBL (58-78% ESBL K. pneumonia sensitive) and no KPC activity</strong>&lt;br&gt;<strong>Good activity for Pseudomonas (resistance reported)</strong>&lt;br&gt;Limited activity for Acinetobacter and Stenotrophomonas&lt;br&gt;No activity against metallo-B-lactamases</td>
</tr>
<tr>
<td><strong>Primary anticipated use</strong></td>
<td>Treatment of carbapenem resistant Enterobacteriaceae</td>
<td>Treatment of MDR Pseudomonas</td>
</tr>
<tr>
<td><strong>Pediatric Approval</strong></td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td><strong>Dosing interval with normal renal function</strong></td>
<td>Q8h</td>
<td>Q8h</td>
</tr>
<tr>
<td><strong>Susceptibility testing</strong></td>
<td>Send out. All specimen types accepted.</td>
<td>Send out. Limited specimen types accepted.</td>
</tr>
<tr>
<td><strong>Clinical Trials</strong></td>
<td>cUTI – comparable response rates to imipenem (phase II)&lt;br&gt;cIAI – comparable response rates (with metronidazole) to meropenem (phase II)&lt;br&gt;Monitor renal function closely (numerically lower cure rates in renal impairment)</td>
<td>cUTI - superior to levofloxacin for cUTI (phase III)&lt;br&gt;cIAI - Non-inferior to meropenem (phase III)&lt;br&gt;Monitor renal function closely (numerically lower cure rates in renal impairment)</td>
</tr>
</tbody>
</table>

**Document History:**

- Created 9/13/13
- Revised 7/1/15 (updated with most recent dosing and indications)
- Revised 11/16/15 (addition of peramivir and ceftolozane / tazobactam)
- Revised 7/1/15 (addition of ceftazidime/avibactam, updated all dosing)