I. **Purpose**

The goal of the Stanford Antimicrobial Safety and Sustainability Program (SASS) at Stanford Healthcare is to optimize the utilization of antimicrobial agents and patient outcome while minimizing unintended consequences of antimicrobial usage, including toxicity, the selection of pathogenic organism, and the emergence of resistance. The SASS, Antimicrobial Subcommittee, and Pharmacy & Therapeutics committee approves and maintains the list of restricted antimicrobials. This document details the criteria by which restricted antimicrobials should be used at SHC and the process by which these restrictions are enforced.

II. **Procedures**

A. **Prescribing Guidelines**

1. Restricted antimicrobials are classified into 3 categories:
   i. ID consult with approval required
   ii. Clinical criteria for use
      a. Empiric antimicrobial therapy of restricted agents are limited to ≤ 72 hours of therapy
   iii. Protected antimicrobials

**ID Consult Required**

The use of restricted antimicrobials requires pre-authorization from Infectious Disease by obtaining a consult. If the patient is clinically unstable or first doses are urgent, an automatic stop order for a 24-hour supply (or until the end of following weekday, excluding holidays) may be released by the pharmacist pending agreement by the primary team to consult ID within 24 hours (except for one-time doses, e.g. bezlotoxumab, dalbavancin). **It is the primary team physicians’ responsibility to follow-up with a maintenance order after ID approval. Verbal ID approval does not constitute as a consult.**

1. Artesunate
2. Baloxavir marboxil
3. Bezlotoxumab
4. Cefiderocol
5. Ceftaroline
6. Ceftazidime/avibactam
7. Ceftolozane/tazobactam (exception: selective CF team use)
8. Colistin (exception: selective CF team use)
9. Dalbavancin (exception: selective ED use)
10. Imipenem-cilastatin (exception: selective Pulmonary service use)
11. Letermovir (exception: selective BMT team use)
12. Maribavir
13. Plazomicin
14. Polymyxin B (exception: selective CF team use)

**Clinical Criteria**

Restricted antimicrobials that meet the P&T approved appropriate clinical criteria for use do not require Infectious Disease consult approval.

1. Daptomycin
2. Fidaxomicin
3. Fosfomycin
4. Linezolid
5. Peramivir
6. Tedizolid
B. Procedure

Chart Review:
- Validate order questions
- Indication
- Micro results
- ID consult note
- Progress note
- Outpatient note
Clarify with provider as needed

Protected Antimicrobials:
- Meropenem
- Ertapenem
- Vancomycin
- Caspofungin
no iVent required

Encourage review at 48-72 hours for appropriateness, de-escalation if possible: see Clinical Use Advisory/Guidelines on page 8

C. Clinical Documentation

The clinical pharmacist enters an I-Vent for all restricted antimicrobial orders.

I-Vent Documentation
- **Type:** Formulary Restriction
- **Sub-Type:** Meets criteria / Does not meet/exception
- **Documentation:** Relevant information regarding use

D. ASP pharmacist
1. Perform routine audits of use
2. Mediate (and escalate when necessary) cases where primary team disputes discontinuation of restricted ABX
3. The case will be escalated to the Antimicrobial Safety & Sustainability Program Directors, or if necessary, the Chief Medical Officer, for review if ID consult is not obtained.
4. Perform MUEs and report back utilization to Antimicrobial Subcommittee
Contact

A. Email
   1. ABX@stanfordhealthcare.org

B. Phone
   1. SASS medical director: 650-498-3787, 650-725-8304
   2. SASS pharmacist: 650-721-1908

III. Document Information

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D. Revisions
   Lina Meng, PharmD, BCPS, BCCCP; 03/2016, 3/2018, 04/2018, 09/2018; 01/2020; 09/2022
   Stan Deresinski, MD; 03/2016, 3/2018, 04/2018, 09/2018, 12/2018; 09/2022
   Marisa Holubar, MD; 03/2016, 3/2018, 04/2018, 09/2018; 09/2022
   Dora Ho MD, PhD; 03/2016, 3/2018, 04/2018, 09/2018, 12/2018; 09/2022
   William Alegria, PharmD; 01/2020; 09/2022
   David Ha, PharmD; 01/2020; 09/2022
   Thomas Leung, PharmD; 04/2022

E. Gatekeeper
   Pharmacy

F. Distribution
   This policy is kept in the Pharmacy Policies and Procedures Manual

G. Reviews/Revisions
   1. Approved by Antimicrobial Subcommittee: 10/15/2015; 08/17/2017; 11/17/17; 08/26/2021; 04/11/2022; 09/2022
   2. Approved by P&T Committee: 3/18/2016; 09/2017; 10/2022
<table>
<thead>
<tr>
<th>Anti-infective</th>
<th>Restriction Criteria/Acceptable Use</th>
<th>Unacceptable Uses</th>
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</table>
| Artesunate            | Infectious Diseases consultation required AND one of the following: 1) Confirmed diagnosis of severe malaria based on at least one of the following criteria  
|                       | a. High parasite density (≥ 5%)  
|                       | b. Impaired consciousness  
|                       | c. Seizures  
|                       | d. Circulatory collapse/shock  
|                       | e. Pulmonary edema or acute respiratory distress syndrome (ARDS)  
|                       | f. Acidosis  
|                       | g. Acute kidney injury  
|                       | h. Abnormal bleeding or disseminated intravascular coagulation (DIC)  
|                       | i. Severe anemia (Hgb < 7 g/dL) 2) Inability to take oral medications despite attempt after oral antiemetic |                                                        |
| Baloxavir marboxil    | Infectious Diseases consultation required AND The following criteria must be met (in addition to obtaining ID consultation):  
|                       | • Received oral oseltamivir for at least 48 hours AND increase in O2 requirement by at least 2L NC from baseline  
|                       | • Known oseltamivir-resistant influenza  
|                       | • Severe presentation requiring intubation or admission to the ICU  
|                       | **Baloxavir is limited to a 1-day course**                                                         |                                                        |
| Bezlotoxumab          | The following criteria must be met:  
|                       | 1) Recurrent disease within the last six months and unable to receive outpatient bezlotoxumab within 10 days of starting *C. difficile* treatment  
|                       | OR  
|                       | 2) ID consult required unless in patients with an initial CDI episode being treated with oral vancomycin and ≥ 2 of the following risk factors for recurrence and unable to receive outpatient bezlotoxumab within 10 days of starting *C. difficile* treatment  
|                       | a. Age ≥ 65  
|                       | b. Meets criteria for severe CDI  
|                       | c. Immunocompromised host (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications) | 1. Prophylaxis for *C. difficile* PCR+/Toxin-          |
| Cefiderocol           | Infectious Diseases consultation required                                                              |                                                        |
| Cefaroline            | Infectious Diseases consultation unless it is a continuation of therapy from outside hospital or outpatient use, which will require ASP review within 72 hours. Examples of use by ID:  
|                       | • Salvage for sustained MRSA bacteremia/endocarditis  
|                       | • Salvage for mixed infection that includes MRSA with susceptible gram negatives | 1. Selected over vancomycin in patients with renal failure solely as a reason to avoid vancomycin  
|                       | 2. Selected solely for convenience                                                                      |
| Ceftazidime/avibactam | Infectious Diseases consultation required for initiation unless use is continuation of ongoing therapy: in these cases, ASP will review case within 72h and determine if an ID consult is required. Example of use by ID:  
<p>|                       | • For patients with empiric or proven carbapenem resistant enterobacteriaciae (e.g. KPC)                 |                                                        |</p>
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<tr>
<td>Ceftolozane/tazobactam</td>
<td><strong>Infectious Diseases consultation required unless</strong>&lt;br&gt;1. Use by cystic fibrosis service for CF exacerbations in patients colonized/infected with MDR Pseudomonas aeruginosa susceptible to ceftolozane/tazobactam and unable to use other beta-lactams or fluoroquinolones&lt;br&gt;2. Use is continuation of ongoing therapy: in these cases, ASP will review case within 72h and determine if an ID consult is required</td>
<td>Prophylaxis</td>
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<tr>
<td>Colistin IV</td>
<td>Must meet one of the following requirements:&lt;br&gt;1. Infectious Diseases consultation required (note: polymyxin B preferred unless treatment of urinary tract infections) OR&lt;br&gt;2. Inhalation route&lt;br&gt;3. CF patient intolerant to Polymyxin B despite prolonging infusion</td>
<td>1. Inpatient use when alternatives are available&lt;br&gt;2. Continuation of therapy from outside hospital or outpatient use, ID Clinic- use requires re-evaluation upon admission</td>
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<tr>
<td>Dalbavancin</td>
<td>Must meet one of the following requirements:&lt;br&gt;1. Infectious Diseases consultation with approval required (inpatient use)&lt;br&gt;2. Emergency department use if ALL clinical criteria met:&lt;br&gt;   a. Requires anti-MRSA activity&lt;br&gt;   b. Not being admitted (inpatient or CDU)&lt;br&gt;   c. Unable to take oral medication OR no oral antibiotic options*&lt;br&gt;   * Based on susceptibility data, or has contraindications with oral antibiotics such as linezolid, TMP-SMX, etc.</td>
<td>1. Pneumonia due to inactivation by pulmonary surfactant&lt;br&gt;2. VRE/enterococcus colonization of urine, respiratory tract, wounds (or drains)&lt;br&gt;3. Surgical prophylaxis&lt;br&gt;4. An alternative for Vancomycin induced Red Man’s syndrome&lt;br&gt;5. Use in place of vancomycin for patients with elevated Scr (unless vancomycin induced nephrotoxicity†)&lt;br&gt;6. Meningitis due to poor CNS penetration/inadequate drug levels</td>
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<tr>
<td>Daptomycin</td>
<td>Infectious Diseases consultation required except for approved indications:&lt;br&gt;1. Serious infections due to vancomycin resistant gram-positive organisms or serious allergy/intolerance of vancomycin or linezolid&lt;br&gt;2. Probable (conditional 72-hour empiric use allowed) or proven vancomycin-resistant organisms (VRE), MRSA/CoNS endocarditis or bacteremia with suspected endocarditis; treatment of persistent MRSA bacteremia&lt;br&gt;3. Continuation of therapy from outside hospital or outpatient use</td>
<td>1.</td>
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<tr>
<td>Fidaxomicin</td>
<td>Infectious Diseases consultation required EXCEPT in the following:&lt;br&gt;1. Laboratory confirmed <em>Clostridioides difficile</em> infection (CDI) with toxin PCR+/EIA+&lt;br&gt;   a. Treatment usually not indicated for PCR+/EIA- results. ID consult required to continue therapy&lt;br&gt;2. Continuation of therapy that was started prior to admission&lt;br&gt;3. Probable CDI with toxin PCR testing ordered and results are pending (condition 24-hour empiric use allowed)&lt;br&gt;4. Discontinue fidaxomicin if CDI testing returns negative (EIA negative) or if testing rejected</td>
<td>1.</td>
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<td>Fosfomycin</td>
<td>Infectious Diseases consultation required except for:&lt;br&gt;1. Management of uncomplicated UTI with:&lt;br&gt;   a. No other oral options are available <strong>AND</strong>&lt;br&gt;   b. Susceptibility confirmed or requested (call lab to add on)</td>
<td>1. Pyelonephritis&lt;br&gt;2. Infections outside the urinary tract</td>
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<tr>
<td>Imipenem-Cilastatin</td>
<td>Infectious Diseases consultation required except for:&lt;br&gt;1. Pulmonology service when indicated for non-tuberculous mycobacterial infections</td>
<td>1.</td>
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<td>Letermovir</td>
<td>Infectious Diseases consultation required except for:&lt;br&gt;1. CMV prophylaxis in adult CMV-seropositive recipients of allogeneic HSCTs</td>
<td>1.</td>
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<td>Linezolid</td>
<td>Infectious Diseases consultation is required except for:&lt;br&gt;1. Treatment of proven VRE/VISA/VRSA infection&lt;br&gt;2. Treatment of proven MRSA pneumonia (including CF patients colonized with MRSA)&lt;br&gt;3. MRSA infections with no other acceptable treatment options</td>
<td>1. Use in place of vancomycin for patients with elevated Scr (unless vancomycin induced nephrotoxicity†)&lt;br&gt;2. Enterococcus faecalis that is susceptible to ampicillin (piperacillin) or vancomycin</td>
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<tr>
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<td>4. Linezolid may be considered for use in patients severely allergic to (not including Red Man’s Syndrome) or failing vancomycin</td>
<td>a. Allergy consult may be recommended to assess vancomycin allergy/intolerance</td>
<td>3. VRE/enterococcus colonization of urine/foley, respiratory tract, wounds, or drains</td>
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<td>5. Continuation of therapy from outside hospital or outpatient use</td>
<td>4. Prophylaxis</td>
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<td>6. Treatment of atypical mycobacterial or nocardial infections (not 1st line therapy)</td>
<td>5. An alternative for Vancomycin induced Red Man’s syndrome</td>
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<td><strong>7. Conditional 72-hour empiric use for:</strong></td>
<td>For isolates with a vancomycin MIC ≤ 2 mcg/mL (e.g., susceptible according to CLSI breakpoints), the patient’s clinical response should determine the continued use of vancomycin, independent of the MIC. (IDSA MRSA Guidelines 2011)</td>
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<td>a. Necrotizing fasciitis for MRSA and other gram positive bacteria, when anti-toxin properties are needed (in lieu of clindamycin)</td>
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<td>b. GPCs in blood or enterococcus in cultures while pending speciation/susceptibilities</td>
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<td>c. Suspected VRE infection</td>
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<td>*If no microbiological target is identified by 48-72h, ID consultation is required to continue linezolid.</td>
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<td><strong>Maribavir</strong></td>
<td>Must meet the following requirements:</td>
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<td>1. Infectious Diseases consultation required <strong>AND</strong> must meet the following criteria:</td>
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<td>a. Post-transplant CMV infection with two documented CMV viral loads in whole blood or plasma above the screening value</td>
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<td><strong>AND one of the following:</strong></td>
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<td>b. Refractory CMV infection, defined as documented failure to achieve &gt;1 log10 decrease in CMV DNA after 14-days or longer of treatment with ganciclovir, valganciclovir, foscarin, or cidofovir</td>
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<td>c. Genotypically proven resistance to treatment with ganciclovir, valganciclovir, foscarin, or cidofovir</td>
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<td>d. Intolerance to other CMV antivirals</td>
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<td>2. Continuation of therapy</td>
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<td><strong>Peramivir</strong></td>
<td>For treatment of influenza virus. Must meet both criteria:</td>
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<td>1. Patients who cannot tolerate oral medications</td>
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<td>2. Patient is located in the ICU or has an ID consult</td>
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<tr>
<td><strong>Plazomicin</strong></td>
<td>Infectious Diseases consultation required</td>
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<tr>
<td><strong>Polymyxin B</strong></td>
<td>Infectious Diseases consultation required unless use by Cystic fibrosis service /Lung Transplant service</td>
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<td>• <strong>Note:</strong> Colistin is preferred over Polymyxin B for urinary tract infections</td>
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<tr>
<td><strong>Remdesivir</strong></td>
<td>Infectious Diseases consultation is required except:</td>
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<td>1. Hospitalized patients with acute COVID-19 on supplemental oxygenation, but not on mechanical ventilation (total duration of therapy limited to 5-days)</td>
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<td><strong>Tedizolid IV/PO</strong></td>
<td>Infectious Diseases consultation is required except:</td>
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<tr>
<td>1. Alternative to linezolid in patients with significant drug interactions or toxicities (particularly with anticipated use &gt; 14 days)</td>
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<td>2. Caution with UTIs: less than 3% excreted as parent drug</td>
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<td><strong>Vancomycin induced nephrotoxicity:</strong> minimum of two or three consecutive documented increases in serum creatinine concentrations (defined as an increase of 0.5 mg/dl or a ≥50% increase from baseline, whichever is greater) after several days of vancomycin therapy (Rybak M et al, AJHP 2009. <a href="http://dx.doi.org/10.2146/ajhp080434">http://dx.doi.org/10.2146/ajhp080434</a>).**</td>
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<td><strong>Red-man’s Syndrome:</strong> Red man syndrome may occur if the infusion is too rapid. It is not an allergic reaction, but may be characterized by hypotension and/or a maculopapular rash appearing on the face, neck, trunk, and/or upper extremities. If this should occur, slow the infusion rate to over 1.5 to 2 hours per gram and increase the dilution volume. Reactions are often treated with antihistamines and steroids</td>
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</table>
Advisory on the Use of Protected Antibiotics

- Appropriate use of these antibiotics should be reviewed in 48 to 72 hours
- Random audits of use will be performed by SASS-ASP pharmacists
- Clinical Pharmacists should routinely refer to these guidelines (I-vents not needed for these agents)
- Clinical Pharmacists should remind teams to order appropriate cultures (blood, sputum if considering pneumonia, urine if considering UTI) prior to starting antibiotics

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>Empiric Criteria</th>
<th>Definitive Criteria</th>
</tr>
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</table>
| Meropenem     | • Nosocomial and sepsis coverage in patients with risk factors for MDRs including ESBL producing organisms  
  a. History of ESBL producing organism  
  b. Recent prolonged exposure (>5 days) to Zosyn®, cefepime, or other broad-spectrum antibiotic  
  c. Recent hospitalization at an institution with a high rate of ESBLs  
  d. Recent travel to areas with high rates of ESBLs (e.g. some countries in Asia)  
  • Clinically unstable (new or persistent fever, WBC increase, hemodynamic instability, etc) and already on broad-spectrum gram-negative agents (piperacillin/tazobactam, cefepime)  
  • Meningitis when listeria plus nosocomial gram-negative coverage is needed  
  • Infected pancreatic necrosis | Treatment of culture positive ESBL or de-repressed AmpC β lactamase infections  
  • ESBLs:  
    1. Zosyn®, Augmentin® potentially ineffective even if susceptible in in-vitro testing  
    2. Consider fluoroquinolones or ertapenem if susceptible  
  • De-repressed AmpC β lactamase  
    1. Consider Zosyn®, cefepime, fluoroquinolones or ertapenem if susceptible  
    2. Caution with 3rd generation cephalosporins (e.g. ceftriaxone), aztreonam |
| Ertapenem     | • Nosocomial coverage in patients with risk factors for ESBL producing gram-negative bacteria  
  o History of ESBL producing organism  
  o Recent prolonged exposure (>5 days) to piperacillin/tazobactam, cefepime, or other broad spectrum antibiotic  
  o Recent hospitalization at an institution with a high rate of ESBLs  
  o Recent travel to areas with high rates of ESBLs (e.g. some countries in Asia)  
  • Intra-abdominal infections but in many cases other options are preferred  
  Avoid if pseudomonas is a suspected or proven pathogen | Treatment of culture positive ESBL or de-repressed AmpC β lactamase infections if susceptible  
  • May be an option for once-daily IV therapy for transitioning to outpatient IV therapy if no PO options available  
  • Can be used for uncomplicated UTI due to ESBL or MDR bug in which it is the only reasonable option.  
    1. Fluoroquinolone, TMP/SMX, or nitrofurantoin may be considered as alternatives for uncomplicated UTI if the organism is susceptible. |
| Vancomycin    | Empiric use for suspected MRSA or ampicillin-resistant enterococcal infections.  
Empiric vancomycin should typically be stopped if no resistant GP organisms are recovered in cultures in 48 - 72 hours. | Proven infection with β-lactam resistant vancomycin-resistant Gram-positive organisms  
  • Purulent skin and soft tissue infection with suspected MRSA when parenteral therapy is indicated  
  • Treatment of infections caused by Gram-positive organisms in patients who have severe allergic reactions to beta-lactam antibiotics |
| Caspofungin   | 1. Empiric treatment of invasive candidiasis in high risk* patients  
  o *High risk: the presence of >2 of the following may be an indication for initiation of empiric anti-Candida therapy in persistently febrile patients despite receipt of broad spectrum antibacterials: prolonged central venous catheterization, recent major abdominal surgery, necrotizing pancreatitis, Candida colonization at more than one site, high dose (>20 mg prednisone equivalent per day) corticosteroid therapy, severe neutropenia.  
  o Note: Based on the 2016 Stanford antibiogram, fluconazole’s activity is similar to caspofungin’s against C. glabrata. 96% of C. glabrata isolates are susceptible/ susceptible-dose dependent to fluconazole (use fluconazole 800mg | Proven infection due to candida species that is either resistant to azoles or when patients are intolerant to azoles or amphotericin  
  • Salvage therapy for aspergillosis  
  *Of note, echinocandins do not achieve therapeutic concentration in urine, eyes, and CNS |
empirically pending MIC result), compared to 100% of isolates susceptible to caspofungin.

2. Empiric treatment of invasive candidiasis in patients with recent azole exposure or history of fluconazole-resistant *Candida* (e.g. *C. krusei*)

3. Proven or suspected invasive fungal infection in the immunocompromised host
   - Note that fluconazole should be used in susceptible *Candida* infections. *Candida* isolates that are fluconazole “susceptible, dose-dependent” may be treated with fluconazole dosed at ≥400mg daily. If you have questions, please discuss with SASS-ASP or ID team.

| Posaconazole IV/PO | 1. Suspected or proven invasive fungal infection due to susceptible organism  
|                    | 2. Prophylaxis of fungal infections in select immunocompromised patients at significant risk |
| Isavuconazole      | 1. Suspected or proven invasive fungal infection due to susceptible organism  
|                    | 2. Prophylaxis of fungal infections in select immunocompromised patients at significant risk |
| Vancomycin PO      | 1. Suspected fulminant *Clostridioides difficile* infection  
|                    |   - With CDI test ordered and PCR results pending  
|                    |   - Discontinue vancomycin if CDI testing returns negative or testing rejected  
|                    | 2. *Clostridioides difficile* prophylaxis  
| | 1. Treatment of proven *Clostridioides difficile* infection (PCR+/EIA+) if resources for fidaxomycin are unavailable  
| | 2. Proven fulminant *Clostridioides difficile* infection  
| | 3. Taper dose for the treatment of recurrent *Clostridioides difficile* infection  
| | 4. Administration with rifaximin for the treatment of recurrent *Clostridioides difficile* infection |