

Stanford Antimicrobial Safety and Sustainability Program Antimicrobial Restriction Policy

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.**

ID team contact:

General ID:	24308
ICU-ID:	27190
ICHS:	17000
ITA/lung transplant:	17008

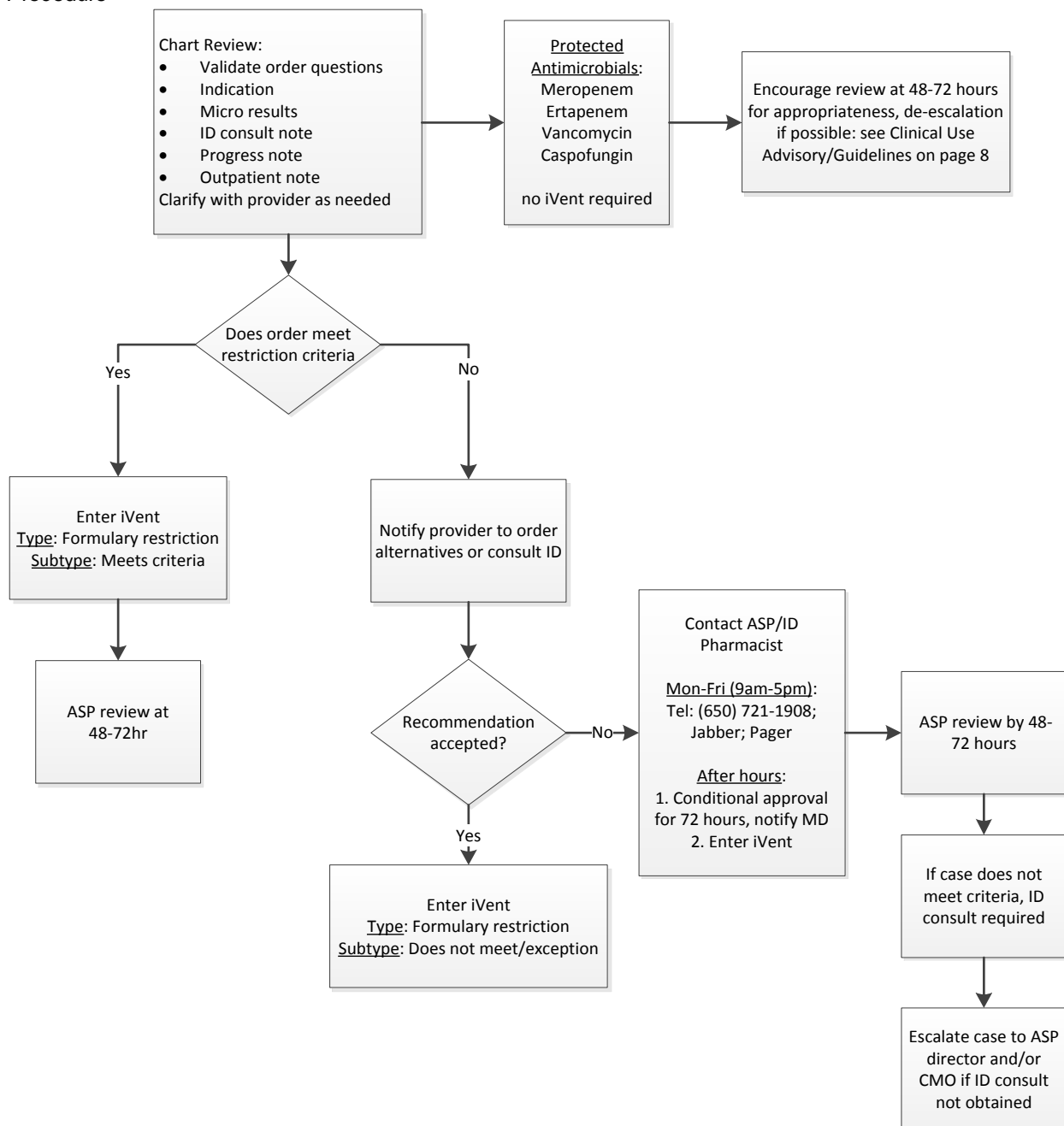
1. Baloxavir marboxil
2. Bezlotoxumab
3. Ceftaroline
4. Ceftazidime/avibactam
5. Ceftolozane/tazobactam (exception: selective CF team use)
6. Colistin (exception: selective CF team use)
7. Dalbavancin (exception: selective ED use)
8. Letermovir (exception: selective BMT team use)
9. Plazomicin
10. Polymyxin 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. Fosfomicin
4. Linezolid
5. Peramivir
6. Tedizolid

B. Procedure



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

- C. Original Authors
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- D. Revisions
 - Emily Mui, PharmD, BCIDP; 03/2016, 3/2018, 04/2018, 09/2018, 12/2018, 02/2019, 07/2019
 - Lina Meng, PharmD, BCPS, BCCCP; 03/2016, 3/2018, 04/2018, 09/2018
 - Stan Deresinski, MD; 03/2016, 3/2018, 04/2018, 09/2018, 12/2018
 - Marisa Holubar, MD; 03/2016, 3/2018, 04/2018, 09/2018
 - Dora Ho MD, PhD; 03/2016, 3/2018, 04/2018, 09/2018, 12/2018
- 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;
 - 2. Approved by P&T Committee: 3/18/2016; 09/2017

SHC Formulary Restricted Antimicrobials

Anti-infective	Restriction Criteria/Acceptable Use	Unacceptable Uses
Baloxavir marboxil	<p>Infectious Disease consult required AND The following criteria must be met (in addition to obtaining ID consultation):</p> <ul style="list-style-type: none"> • 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 <p>Baloxavir is limited to a 1-day course</p>	
Bezlotoxumab	<p>Infectious Disease consult required</p> <p>The following criteria must be met (in addition to obtaining ID consultation):</p> <ol style="list-style-type: none"> 1) Recurrent <i>C.difficile</i> infection disease 2) OR ≥2 of the following are present <ol style="list-style-type: none"> a. Age ≥65 years b. Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications) c. Severe CDI d. Continued broad spectrum antibiotic use 	<ol style="list-style-type: none"> 1. In conjunction with fidaxomicin 2. Prophylaxis for <i>C. difficile</i> PCR+/Toxin-
Ceftaroline	<p>Infectious Disease consult required unless it is a continuation of therapy from outside hospital or outpatient use, which will require ASP review within 72 hours.</p> <p>Examples of use by ID:</p> <ul style="list-style-type: none"> • Salvage for sustained MRSA bacteremia/endocarditis • Salvage for mixed infection that includes MRSA with susceptible gram negatives 	<ol style="list-style-type: none"> 1. Selected over vancomycin in patients with renal failure solely as a reason to avoid vancomycin 2. Selected solely for convenience
Ceftazidime/avibactam	<p>ID consult 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.</p> <p>Example of use by ID:</p> <ul style="list-style-type: none"> • For patients with empiric or proven carbapenem resistant enterobacteriaceae (e.g. KPC) 	
Ceftolozane/tazobactam	<p>ID consult required unless</p> <ol style="list-style-type: none"> 1. Use by cystic fibrosis service for CF exacerbations in patients colonized/infected with MDR <i>Pseudomonas aeruginosa</i> susceptible to ceftolozane/tazobactam and unable to use other beta-lactams or fluoroquinolones 2. Use is continuation of ongoing therapy: in these cases, ASP will review case within 72h and determine if an ID consult is required 	
Colistin IV	<p>Must meet one of the following requirements:</p> <ol style="list-style-type: none"> 1. ID consult required (note: polymyxin B preferred unless treatment of urinary tract infections) OR 2. Inhalation route 3. CF patient intolerant to Polymyxin B despite prolonging infusion 	Prophylaxis
Dalbavancin	<p>Must meet one of the following requirements:</p> <ol style="list-style-type: none"> 1. Infectious Disease consult with approval required (inpatient use) 2. Emergency department use if ALL clinical criteria met: <ol style="list-style-type: none"> a. Requires anti-MRSA activity b. Not being admitted (inpatient or CDU) c. Unable to take oral medication OR no oral antibiotic options* <p>* Based on susceptibility data, or has contraindications with oral antibiotics such as linezolid, TMP-SMX, etc.</p> 	<ol style="list-style-type: none"> 1. Inpatient use when alternatives are available 2. Continuation of therapy from outside hospital or outpatient use, ID Clinic- use requires re-evaluation upon admission

Anti-infective	Restriction Criteria/Acceptable Use	Unacceptable Uses
Daptomycin	ID consult required except for approved indications: <ol style="list-style-type: none"> Serious infections due to vancomycin resistant gram-positive organisms or serious allergy/intolerance of vancomycin or linezolid 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 Continuation of therapy from outside hospital or outpatient use 	<ol style="list-style-type: none"> Pneumonia due to inactivation by pulmonary surfactant VRE/enterococcus colonization of urine, respiratory tract, wounds (or drains) Surgical prophylaxis An alternative for Vancomycin induced Red Man's syndrome Use in place of vancomycin for patients with elevated SCr (unless vancomycin induced nephrotoxicity†) Meningitis due to poor CNS penetration/inadequate drug levels
Fidaxomicin	<ol style="list-style-type: none"> Recurrent <i>Clostridium difficile</i> infection ≥2 of the following risk factors for recurrence are present: <ol style="list-style-type: none"> Age ≥65 years Meets criteria for severe CDI (WBC>15k, SCr>1.5x baseline) Concomitant broad-spectrum antibiotic use for another diagnosed or suspected infection Significant immunocompromise (hematopoietic stem cell transplant, solid organ transplant, active malignancy, use of immunosuppressive medications) <p>Fidaxomicin is limited to a standard 10-day course. Fidaxomicin often requires prior authorization for outpatient use. Obtain confirmation of patient's outpatient prescription insurance coverage if applicable.</p>	<ol style="list-style-type: none"> <i>Clostridium difficile</i> infection prophylaxis Empiric for <i>Clostridium difficile</i> infection (must have proven <i>Clostridium difficile</i> infection by laboratory confirmation)
Fosfomycin	ID consult required except for: <ol style="list-style-type: none"> Management of uncomplicated UTI with: <ol style="list-style-type: none"> No other oral options are available AND Susceptibility confirmed or requested (call lab to add on) 	<ol style="list-style-type: none"> Pyelonephritis Infections outside the urinary tract
Letermovir	ID consult required except for: <ol style="list-style-type: none"> CMV prophylaxis in adult CMV-seropositive recipients of allogeneic HSCTs 	
Linezolid	ID consultation is required except for: <ol style="list-style-type: none"> Treatment of <u>proven</u> VRE/VISA/VRSA infection Treatment of <u>proven</u> MRSA pneumonia (including CF patients colonized with MRSA) MRSA infections with no other acceptable treatment options Linezolid may be considered for use in patients severely allergic to (not including Red Man's Syndrome) or failing vancomycin <ol style="list-style-type: none"> Allergy consult may be recommended to assess vancomycin allergy/intolerance Continuation of therapy from outside hospital or outpatient use Treatment of atypical mycobacterial or nocardial infections (not 1st line therapy) Conditional 72-hour empiric use for: <ol style="list-style-type: none"> Necrotizing fasciitis for MRSA and other gram positive bacteria, when anti-toxin properties are needed (in lieu of clindamycin) GPCs in blood or enterococcus in cultures while pending speciation/susceptibilities Suspected VRE infection <p>*If no microbiological target is identified by 48-72h, ID consultation is required to continue linezolid.</p> 	<ol style="list-style-type: none"> Use in place of vancomycin for patients with elevated SCr (unless vancomycin induced nephrotoxicity†) Enterococcus faecalis that is susceptible to ampicillin (piperacillin) or vancomycin VRE/enterococcus colonization of urine/foley, respiratory tract, wounds, or drains Prophylaxis An alternative for Vancomycin induced Red Man's syndrome <p>For isolates with a vancomycin MIC ≤ 2 mcg/mL (e.g., susceptible according to CLSI breakpoints), the patient's <u>clinical response should determine the continued use of vancomycin</u>, independent of the MIC. (IDSA MRSA Guidelines 2011)</p>
Peramivir	For treatment of influenza virus. Must meet both criteria: <ol style="list-style-type: none"> Patients who cannot tolerate oral medications Patient is located in the ICU or has an ID consult 2nd dose requires ID consultation 	
Plazomicin	ID consult required	
Polymyxin B	ID consult required unless use by Cystic fibrosis service /Lung Transplant service	

Anti-infective	Restriction Criteria/Acceptable Use	Unacceptable Uses
	<ul style="list-style-type: none"> Note: Colistin is preferred over Polymyxin B for urinary tract infections 	
Tedizolid IV/PO	ID consultation is required except: <ol style="list-style-type: none"> Alternative to linezolid in patients with significant drug interactions or toxicities (particularly with anticipated use > 14 days) 	<ol style="list-style-type: none"> See linezolid Caution with UTIs: less than 3% excreted as parent drug

†**Vancomycin induced nephrotoxicity:** 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. <http://dx.doi.org/10.2146/ajhp080434>.)

Red-man's Syndrome: 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

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

Antimicrobial	Empiric Criteria	Definitive Criteria
Meropenem	<ul style="list-style-type: none"> • Nosocomial and sepsis coverage in patients with risk factors for MDRs including ESBL producing organisms <ol style="list-style-type: none"> 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 (Zosyn®, cefepime) • Meningitis when listeria plus nosocomial gram negative coverage is needed • Infected pancreatic necrosis 	<p>Treatment of culture positive ESBL or de-repressed AmpC β lactamase infections</p> <ul style="list-style-type: none"> • ESBLs: <ol style="list-style-type: none"> 1. Zosyn®, Augmentin® potentially ineffective even if susceptible in in-vitro testing 2. Consider fluoroquinolones or ertapenem if susceptible • De-repressed AmpC β lactamase <ol style="list-style-type: none"> 1. Consider Zosyn®, cefepime, fluoroquinolones or ertapenem if susceptible • Caution with 3rd generation cephalosporins (e.g. ceftriaxone), aztreonam
Ertapenem	<ul style="list-style-type: none"> • Nosocomial coverage in patients with risk factors for ESBL producing gram-negative bacteria <ul style="list-style-type: none"> ○ History of ESBL producing organism ○ Recent prolonged exposure (>5 days) to Zosyn®, cefepime, or other broad spectrum antibiotic ○ Recent hospitalization at an institution with a high rate of ESBLs ○ 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 <p>Avoid if pseudomonas is a suspected or proven pathogen</p>	<ul style="list-style-type: none"> • 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. <ol style="list-style-type: none"> 1. Fluoroquinolone, TMP/SMX, or nitrofurantoin may be considered as alternatives for uncomplicated UTI if the organism is susceptible.
Vancomycin	<p>Empiric use for suspected MRSA or a mpidillin-resistant enterococcus infections.</p> <p>Empiric vancomycin should typically be stopped if no resistant GP organisms are recovered in cultures in 48 - 72 hours.</p>	<ul style="list-style-type: none"> • Proven infection with β-lactam resistant vancomycin-susceptible Gram positive organisms • <u>Purulent</u> 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	<ol style="list-style-type: none"> 1. Empiric treatment of invasive candidiasis in high risk* patients <ul style="list-style-type: none"> ○ *High risk: the presence of >2 of the following may be an indication for initiation of empiric anti-<i>Candida</i> therapy in persistently febrile patients despite receipt of broad spectrum antibacterials: prolonged central venous catheterization, recent major abdominal surgery, necrotizing pancreatitis, <i>Candida</i> colonization at more than one site, high dose (>20 mg prednisone equivalent per day) corticosteroid therapy, severe neutropenia. ○ Note: Based on the 2016 Stanford antibiogram, fluconazole's activity is similar to caspofungin's against <i>C. glabrata</i>. 96% of <i>C. glabrata</i> isolates are susceptible/susceptible-dose dependent to fluconazole (use fluconazole 800mg 	<ul style="list-style-type: none"> • 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 <p>*Of note, echinocandins do not achieve therapeutic concentration in urine, eyes, and CNS</p>

	<p>empirically pending MIC result), compared to 100% of isolates susceptible to caspofungin.</p> <ol style="list-style-type: none"> 2. Empiric treatment of invasive candidiasis in patients with recent azole exposure or history of fluconazole-resistant <i>Candida</i> (e.g. <i>C. krusei</i>) 3. Proven or suspected invasive fungal infection in the immunocompromised host <ul style="list-style-type: none"> o Note that fluconazole should be used in susceptible <i>Candida</i> infections. <i>Candida</i> 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	<ol style="list-style-type: none"> 1. Suspected or proven invasive fungal infection due to susceptible organism 2. Prophylaxis of fungal infections in select immunocompromised patients at significant risk 	
Isavuconazole	<ol style="list-style-type: none"> 3. Suspected or proven invasive fungal infection due to susceptible organism 4. Prophylaxis of fungal infections in select immunocompromised patients at significant risk 	