MICHIGAN MEDICINE
UNIVERSITY OF MICHIGAN

RESTRICTED ANTIMICROBIALS REQUIRING AST APPROVAL IN PATIENTS ON ADULT SERVICES

Use of certain antimicrobial agents is restricted at Michigan Medicine. Agents are classified as Tier I or Tier II agents depending on whether Antimicrobial Stewardship Team (AST) approval is required prior to dispensing.

TIER I RESTRICTED ANTIMICROBIALS

The use of the following agents (i.e., Tier I agents) requires AST (pager #30780) or ID approval prior to dispensing between the hours of 0700 and 2300. Please consult appropriate treatment guidelines.

Note: The below indications generally refer to appropriate EMPIRIC use. When cultures are available, antibiotic therapy should be escalated/de-escalated as appropriate based on organism and susceptibility. Restricted agents should only be utilized if narrower-spectrum agents are resistant or otherwise inappropriate. When cultures are not available, please refer to individual treatment guidelines for appropriate definitive therapy strategies.

UMHHC Policy 07-01-015 ("Use of Infectious Diseases Restricted Antimicrobials")
All treatment guidelines are available on the Antimicrobial Stewardship page

Restricted Antimicrobial			
Baloxavir	Eravacycline	Liposomal Amphotericin B	Posaconazole IV
Baricitinib (COVID)	Ertapenem	Meropenem	Rezafungin IV
Cefiderocol	Ethanol Lock Therapy	Meropenem-vaborbactam	Inhaled Ribavirin
Ceftazidime-avibactam	Fidaxomicin	Micafungin	Sulbactam-durlobactam
Ceftaroline	Imipenem	Minocycline IV	Tigecycline
Ceftolozane-tazobactam	Imipenem-relebactam	Omadacycline	Tocilizumab (COVID)
CMV-IGIV	Isavuconazole	Peramivir	Voriconazole
Dalbavancin	Letermovir	Polymyxins (Colistin & Polymyxin B)	
Daptomycin	Linezolid	Posaconazole delayed-release tablets & PO suspension	

Restricted Medication	Approved Reasons for Use
Baloxavir	• Influenza A or B infection with neuraminidase inhibitor-resistant strains
Baricitinib	• Treatment of laboratory confirmed COVID-19 in patients on dexamethasone and newly on mechanical ventilation (< 48 hours) or on HFNC/NIV

Cefiderocol	• Generally, for MDR/XDR *Pseudomonas aeruginosa*, use of cefiderocol should be considered when other novel agents are resistant (ceftolozane-tazobactam, imipenem-relebactam, meropenem-vaborbactam, ceftazidime-avibactam).
	  ○ If all are susceptible, ceftolozane-tazobactam remains our preferred agent for treatment of MDR/XDR *Pseudomonas aeruginosa*.
	  ○ If only resistance to only ceftolozane-tazobactam is seen, consultation with an infectious diseases pharmacist should occur for selection of the best agent for treatment.
	• For MDR *Acinetobacter baumannii*, combination therapy with cefiderocol should be considered, if susceptible (e.g., minocycline and cefiderocol may be appropriate for severe infections).
	• For *Stenotrophomonas maltophilia* that is resistant to levofloxacin, sulfamethoxazole-trimethoprim, minocycline, and ceftazidime, use of cefiderocol should be considered.
	• For CRE, meropenem-vaborbactam remains our preferred treatment for KPC-producing bacteria. Use of cefiderocol should be considered for MBL-producers and OXA-producers.

Ceftazidime-avibactam	• Treatment of documented carbapenamase-producing Enterobacteriaceae infection requiring intravenous therapy AND resistance or intolerance to all other beta-lactams, fluoroquinolones, and aztreonam.
Ceftaroline	• Treatment of Staphylococcus aureus bacteremia ○ Alternative therapy to vancomycin and daptomycin, depending on specific scenario (see complete recommendations)
Ceftolozane-tazobactam	• Treatment of documented ceftolozane-tazobactam-susceptible Pseudomonas infection requiring intravenous therapy AND resistance or intolerance to all other beta-lactams, fluoroquinolones, and aztreonam.
CMV-IGIV	• Documented CMV pneumonitis in combination with antiviral agent against CMV • Severe life-threatening or progressive end-organ disease in combination with antiviral agent against CMV • Consider in BMT patients if persistent or increasing CMV viremia after 21 days of ganciclovir or foscarnet in patients without end-organ disease • Prophylaxis in recipient -/donor + lung transplant patients per UMHS guidelines
Dalbavancin	• Patients who cannot be discharged with PICC vancomycin or daptomycin due to IV drug abuse, lack of access, psychological or social issues • Oral Linezolid is not option due to resistance, intolerance, or required duration therapy is > 2 weeks • Patients with psychological or social issues limiting the ability to administer IV antibiotics • Patients that require discharge to SAR or nursing home for the sole purpose of administering IV antibiotics • Patients with a history of frequent discharges against medical advice

Restricted Medication	Approved Reasons for Use

Daptomycin	• Surgical prophylaxis as per "Surgical Antimicrobial Prophylaxis Guidelines"
	• Empiric therapy for suspected VRE infections in patients receiving vancomycin with cultures demonstrating gram-positive cocci
	• Empiric therapy for ICU, transplant, and/or heme/onc patients with gram + cocci in pairs/chains from blood or other sterile sites
	• Empiric therapy for patients with E. faecium from blood pending susceptibilities
	• Documented MRSA or MRSE infection with documented allergy or intolerance to vancomycin
	• Documented infection due to vancomycin intermediate or resistant *Staph aureus* (MIC ≥ 4 mg/L)
	• Documented VRE infections; exception – urinary tract infections that are susceptible to alternative agents such as, ampicillin, doxycycline, or nitrofurantoin, etc.
	• Treatment of Bone and Joint Infections
	  ○ Alternative to vancomycin in patients with vancomycin allergy
	• Treatment of Infective Endocarditis
	  ○ Enterococci strains resistant to vancomycin, aminoglycosides, and penicillin
	  ○ Alternative for vancomycin allergy or failure in endocarditis due to methicillin-resistant staphylococci
	• Treatment of Staphylococcus aureus bacteremia
	  ○ Alternative therapy to vancomycin, depending on specific scenario (see complete recommendations)

Eravacycline	• Community-acquired, mild-moderate intra-abdominal infections who cannot tolerate formulary alternatives such as cefuroxime + metronidazole, ciprofloxacin + metronidazole, or vancomycin + aztreonam + metronidazole. Eravacycline, like tigecycline, may have a role in mixed intra-abdominal infections with VRE. Due to cost, eravacycline should be preferred to tigecycline for these indications. • Eravacycline should not be used for urinary tract infections. There is insufficient data supporting the efficacy of eravacycline for other infections, including more complicated intra-abdominal infections or infections due to multi-drug resistant Acinetobacter. Use tigecycline preferentially until such data supporting eravacycline emerge.
Ertapenem	• As a one-time dose prior to discharge for patients with ESBL and/or AmpC-producing organisms or infections where other once-daily antibiotic options are not possible • Treatment for refractory hidradenitis suppurativa in consultation with dermatology and infectious diseases when alternative therapies are not possible • Combination therapy with cefazolin for refractory methicillin-susceptible *Staphylococcus aureus* infections where meropenem is not an option • Surgical prophylaxis for patients colonized or infected with ESBL and/or AmpC-producing organisms
Ethanol Lock Therapy	• Eligible patients are those with either a history of recurrent CVAD related bloodstream infections or are at risk of limited venous access (venous access in patients who require anticipated long-term (i.e., > 6 months), have poor vascular access, or are at risk of losing venous access during periods of treatment). • There are extensive exclusion criteria. See complete guideline on Antimicrobial Stewardship website for full criteria for use.
Fidaxomicin	• Reserved for consideration of treatment of *C. difficile* infection in patients with documented recurrent disease who failed a recent oral vancomycin taper.
Imipenem	• Patients with a documented infection due to a gram-negative organism resistant to all other β-lactam antibiotics AND meropenem but susceptible to imipenem • Patients with infections due to *Nocardia spp*.

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Imipenem-Relebactam	• Infections due to MDR Pseudomonas, Ceftolozane-tazobactam will remain our drug of choice for MDR pseudomonas, if susceptible. Taking into consideration susceptibilities of other novel agents and co-infections, imipenem-cilastatin-relebactam may be considered for use when resistance to ceftolozane-tazobactam has been confirmed. Consultation with an ID pharmacist is recommended. • Infections due to CRE, meropenem-vaborbactam will remain the drug of choice for KPC-producing CRE. For OXA-producing CRE, ceftazidime-avibactam or cefiderocol will generally be used. However, in rare instances when resistance to meropenem-vaborbactam or ceftazidime-avibactam is confirmed, Imipenem-cilastatin-relebactam may be used if susceptible in consultation with ID pharmacists.

Isavuconazole	• Treatment of aspergillosis
	• Treatment of mucormycosis:
	  ○ Step-down therapy: After clinical improvement with Liposomal Amphotericin B
	  ○ Salvage therapy: In patients unable to tolerate Liposomal Amphotericin B due to severe adverse effects.

Letermovir	• Prophylaxis in CMV-seropositive allogeneic HSCT recipients with at least one of the following risk factors:
	  ○ Cord blood transplant recipient
	  ○ Receipt of a T-cell depleting agent: alemtuzumab, thymoglobulin, ATG
	  ○ Acute GVHD requiring ≥ 1 mg/kg/day of steroids within the first 100 days following transplant unless valganciclovir is deemed appropriate
	• Letermovir should be initiated no earlier than Day +10 following transplant and should be continued for 3 months following initiation.
	• Outpatient insurance coverage for letermovir should be verified.

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Linezolid	• Treatment of Bone and Joint Infections
	  ○ Alternative for vancomycin in patients with vancomycin allergy
	• Treatment of Vertebral Osteomyelitis, Discitis, and Spinal Epidural Abscess
	  ○ Vancomycin allergy or intolerance
	• Treatment of Infective Endocarditis
	  ○ Enterococci strains resistant to vancomycin, aminoglycosides, and penicillin
	• Treatment of Intra-Abdominal Infections
	  ○ Critically ill liver transplant recipients, patients with a previous history of VRE intra-abdominal infection, or patients with septic shock who are colonized with VRE
	• Treatment of Staphylococcus aureus bacteremia
	  ○ Alternative therapy to vancomycin and daptomycin, depending on specific scenario (see complete recommendations)
	• Treatment of Skin and Soft Tissue Infections in adult patients
	  ○ Purulent cellulitis
	  ▪ Alternative in patients intolerant to vancomycin
	  ○ Superficial Surgical Site Infections
	  ▪ Alternative for patients with high risk of MRSA or PCN/cephalosporin allergy and vancomycin allergy
	  ○ Deep Tissue Surgical Site Infections or any SSI complicated by sepsis/septic shock
	  ▪ Alternative for patients with vancomycin allergy
	  ○ Traumatic Wound Infections of Extremity
	  ▪ Patients at high risk of MRSA with vancomycin allergy
	  ▪ Patients with sepsis and traumatic wound infection or development of infection >5 days after injury or significant water exposure with vancomycin allergy
	  ○ Complicated SSTI without osteomyelitis
	  ▪ Alternative for vancomycin resistance, intolerance, or allergy
	• Treatment of Pneumonia
	  ○ Non-ICU patients:
	  ▪ No improvement or worsening pulmonary status with documented MRSA pneumonia after 3 days of vancomycin therapy
	  ▪ MRSA pneumonia with vancomycin MIC ≥ 2 mg/L
	  ▪ MRSA pneumonia with co-existent acute renal failure
	  ▪ MRSA pneumonia with respiratory failure
	  ○ ICU patients:
	  ▪ Gram-positive cocci in clusters on sputum or BAL culture, pending identification and susceptibility results
	  ▪ Documented MRSA pneumonia
	• Suspected VRE infections: cultures with gram-positive cocci in chains pending identification/susceptibilities in patients at high risk for VRE infection (BMT, Heme-onc, liver transplant, on vancomycin at time of culture, VRE colonized)
	• Infection at any non-urinary site with VRE
	• Infection at any site with vancomycin intermediate or resistant *Staph aureus* (MIC ≥ 4 mg/L)
	• Infection at any site with MRSA or MRSE and allergy or toxicity to vancomycin
	• Alternative oral therapy at discharge for documented non-bacteremic MRSA infection with plan for ≤ 14 days of therapy to avoid the need for intravenous access.

Liposomal Amphotericin B	• Treatment of Aspergillosis and Mucormycosis
	  ○ Alternative therapy for aspergillosis in patients unable to tolerate voriconazole
	  ○ Primary therapy in patients with proven or probable mucormycosis
	• Treatment of Candidemia
	  ○ Alternative to Micafungin in critically ill and neutropenic patients with recent exposure to echinocandins
	• Treatment of Candida Endophthalmitis
	  ○ Fluconazole and voriconazole resistant isolates, including C. glabrata isolates with elevated MICs (Fluconazole MIC > 4, Voriconazole MIC ≥ 0.125)

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Meropenem	• Treatment of Bacterial Meningitis
	  ○ Community-acquired, non-life threatening PCN/Cephalosporin allergy
	  ○ Basilar skull fracture, non-life threatening PCN/cephalosporin allergy
	  ○ Penetrating trauma, non-life threatening PCN/cephalosporin allergy
	  ○ Post neurosurgery, non-life threatening PCN/cephalosporin allergy
	  ○ CSF shunt, non-life threatening PCN/cephalosporin allergy
	• Treatment of Vertebral Osteomyelitis, Discitis, and Spinal Epidural Abscess
	  ○ Alternative in patients with Penicillin Allergy (non-anaphylaxis)

Meropenem-vaborbactam	• Treatment of highly suspected or documented extensively drug-resistant gram-negative pathogens where polymyxins, tigecycline, and aminoglycosides are the only susceptible agents (ex. KPC-producing carbapenamase-producing Enterobacteriaceae). • Meropenem-vaborbactam is the preferred treatment for infections caused by KPC-producing carbapenamase-producing Enterobacteriaceae

Micafungin	• Treatment of Neutropenic Fever in Hematology and BMT patients
	  ○ Alternative in patients with liver dysfunction or drug interactions prohibiting voriconazole use
	• Prophylaxis in Hematology and BMT patients
	  ○ Alternative to Fluconazole, Voriconazole, or Posaconazole in patients unable to tolerate or absorb oral azole antifungals, or in patients at risk of drug interactions/additive toxicity with azole antifungals
	• Treatment of Candidemia
	• Treatment of Aspergillosis
	  ○ Monotherapy should only be considered in possible disease

Minocycline IV	• Treatment of documented Acinetobacter infection resistant to all beta-lactam antibiotics and doxycycline, and the patient is unable to take oral minocycline
Omadacycline	• Nontuberculosis mycobacterial infection in patients who cannot tolerate or are resistant to formulary alternatives such as macrolides, clarithromycin, imipenem, cefoxitin, and linezolid • Treatment of non-urinary tract, vancomycin-resistant enterococci infections resistant to daptomycin and linezolid, or patient intolerance to daptomycin and linezolid • If started in the inpatient setting for outpatient use, ensure outpatient insurance coverage prior to discharge
Peramivir	• Inpatients with influenza in which drug delivery by a route other than IV is not feasible • Peramivir should be given for a maximum of 5 days

Restricted Medication	Approved Reasons for Use

Polymyxins (Colistin & Polymyxin B)	*Note: Polymyxin B is the preferred systemic polymyxin for extraurinary infections. Colistin use is restricted to urinary source infections and inhaled therapy*
	
	Systemic Therapy with Polymyxin B or Colistin
	• Treatment of infections due to *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Enterobacter* spp, *Escherichia coli*, *Klebsiella* spp, or *Citrobacter* spp resistant or intolerant to all beta-lactams, aminoglycosides, and fluoroquinolones.
	• Cystic fibrosis patients with minimal clinical response to standard therapy or cultures demonstrating multi-drug resistant gram-negative isolates, as defined above.
	• Treatment with systemic polymyxins (IV polymyxin B or IV colistin) must be in combination with one or more additional antibiotics with gram-negative activity for synergistic activity and to prevent treatment emergent resistance.[38,39]
	Inhaled Therapy with Colistin
	• Patients with cystic fibrosis or bronchiectasis receiving inhaled polymyxins as continuation of home therapy
	• Patients with cystic fibrosis or bronchiectasis who meet the clinical or microbiological criteria listed above for initiation of polymyxin therapy
	• For the adjunctive treatment of pneumonia, provided ALL the following criteria are met[40]
	  ○ Isolated pathogen is susceptible ONLY to polymyxins or aminoglycosides
	  ○ Inhaled therapy is used in addition to systemic therapy with a polymyxin or aminoglycoside in combination with another gram-negative antibiotic (usually a beta-lactam)

Posaconazole delayed-release tablets and PO suspension	• BMT and Hematology antifungal prophylaxis • Treatment of aspergillosis • Treatment of mucormycosis ○ Mucormycosis: in combination with LAmB in severe disease, after clinical improvement with LAmB, as salvage therapy, or in patients unable to take LAmB.

Posaconazole intravenous	• Treatment of aspergillosis and mucormycosis
	  ○ Aspergillosis: unable to tolerate oral posaconazole
	  ○ Mucormycosis: in combination with LAmB in severe disease, after clinical improvement with LAmB, as salvage therapy, or in patients unable to take LAmB. In call cases, must not be able to tolerate oral posaconazole.

Rezafungin	• Treatment of invasive candidiasis in the following scenarios:
	  ○ Patients unable to take oral azoles / oral therapy is not deemed appropriate
	  ○ 1x dose prior to discharge is an option for patient unable to take oral azoles that have ≤ 7 days of therapy remaining
	  ○ Patients unable to maintain IV access outpatient or when IV access weighs potential risk

Inhaled Ribavirin	• Restricted to UMHS guidelines for use entitled “Indications for the Use of Ribavirin for Treatment of Respiratory Viral Infections in Adult and Pediatric Patients” • ID consult is mandatory prior to starting therapy
Sulbactam-durlobactam	• Treatment of pneumonia due to Acineotbacter that is resistant to ampicillin-sulbactam and carbapenems.

Restricted Medication	Approved Reasons for Use

Tigecycline	• Treatment of gram-negative infections resistant to alternative agents, or for patient intolerance to alternative agents
	  ○ *Acinetobacter* or Enterobacteriaceae resistant to all beta-lactams and fluoroquinolones
	  ○ *Stenotrophomonas* resistant to trimethoprim-sulfamethoxazole, ceftazidime and levofloxacin
	• Treatment of vancomycin-resistant enterococci infections resistant to daptomycin and linezolid, or patient intolerance to daptomycin and linezolid
	• Empiric therapy for patients with significant allergies to all alternative agents

Tocilizumab	• Treatment of laboratory confirmed COVID-19 in patients on dexamethasone and newly on mechanical ventilation (<48 hours) or on HFNC/NIV

Voriconazole	• Treatment of Neutropenic Fever in Hematology and BMT patients
	• Prophylaxis in Hematology and BMT patients
	• Treatment of Candidemia
	  ○ Alternative if additional coverage of molds is indicated
	  ○ Step-down oral therapy in patients with *C. krusei* infection
	• Treatment of Ocular Infections
	  ○ Candida Endophthalmitis
	  ▪ Due to C. krusei
	  ▪ Due to C. glabrata only if fluconazole MIC > 4 and voriconazole MIC ≤ 0.125
	• Treatment of Aspergillosis

Antimicrobial Subcommittee Approval:	01/2019; 06/2020	Originated:	Unknown
P&T Approval:	12/2017; 07/2020, 04/2022	Last Revised:	03/2024

Revision History: 01/2020 - added eravacycline
08/2020 - added cifiderocol and imipenem-relebactam
11/2020 - added remdesivir
04/2022 - removed moxifloxacin, updated ertapenem
11/2022 - added omdacycline
06/2023 - updated posaconazole and isavuconazole
03/2024 - added rezafungin, sulbactam-durlobactam, baricitinib