C.S. MOTT CHILDREN'S HOSPITAL
MICHIGAN MEDICINE

RESTRICTED ANTIMICORBIALS REQUIRING AST APPROVAL IN PATIENTS ON PEDIATRIC 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

Providers must obtain Antimicrobial Stewardship Team (AST) approval prior to prescribing the following agents. For patients with an active ID consult, contact the ID fellow or attending on call. For patients without an active ID consult, contact the pediatric antimicrobial approval pager (36149). Overnight (between 2300 and 0700) approval is not required, but approval must be obtained the following morning to continue use. The following are typical uses to guide prescribers.

UMHHC Policy 07-01-015 ("Use of Infectious Diseases Restricted Antimicrobials")

All treatment guidelines are available on the Antimicrobial Stewardship page

Restricted Antimicrobials		
Amphotericin B	Ertapenem	Palivizumab
Baloxavir	Fidaxomicin	Peramivir
Ceftazidime-avibactam	Imipenem	Polymixin B
Cefiderocol	Imipenem-relebactam	Posaconazole
Ceftaroline	Isavuconazole	Quinupristin-dalfopristin
Ceftolozane-tazobactam	Linezolid	Remdesivir
CMV-IGIV	Meropenem	Inhaled Ribavirin
Colistin	Meropenem-vaborbactam	Tigecycline
Daptomycin	Micafungin	Voriconazole
Eravacycline	Moxifloxacin	

Restricted Antimicrobial	Typical Reasons for Use
Amphotericin B	Deoxycholate: • Neonatal candidiasis Liposomal: • Invasive mold infection awaiting identification and susceptibilities • Documented or suspected mucormycosis • Moderate-to-severe infection with endemic mycoses
Baloxavir	• Influenza A or B infection with neuraminidase inhibitor-resistant strains • Indicated for patients ≥12 years of age who weigh ≥40 kg

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	• Documented carbapenamase-producing gram-negative infection requiring intravenous therapy AND resistance or intolerance to all other β-lactams, fluoroquinolones, and aztreonam
Ceftaroline	• Documented MRSA infection requiring intravenous therapy in patients with vancomycin intolerance (not vancomycin infusion reaction) AND pneumonia OR daptomycin/linezolid intolerance • In combination with daptomycin for persistent MRSA bacteremia (vancomycin failure) after 7 days
Ceftolozane-tazobactam	• Documented ceftolozane-tazobactam-susceptible *Pseudomonas* infection requiring intravenous therapy AND resistance or intolerance to all other β-lactams, fluoroquinolones, and aztreonam
CMV-IGIV	• Documented CMV pneumonitis in combination with antiviral agent against CMV • Severe, life-threatening or progressive CMV 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 donor +/recipient - lung transplant patients

Restricted Antimicrobial	Typical Reasons for Use
Colistin	Note: colistin is the preferred polymyxin for infections involving the urinary tract and inhaled therapy, for systemic infections see polymyxin B IV: • Documented gram-negative infections resistant or intermediate to all β-lactams, aminoglycosides, fluoroquinolones, and aztreonam, or allergies or intolerance to all β-lactams, aminoglycosides, fluoroquinolones, and aztreonam; treatment should be in combination with another non-aminoglycoside gram-negative antibiotic • Empiric therapy for up to 72 hours for history of gram-negative infections or gram-negative infections in patients with allergy or intolerance to all beta-lactams, fluoroquinolones, and aminoglycosides; treatment should be in combination with another gram-negative antibiotic • Cystic fibrosis patients with minimal clinical response to standard treatment or cultures that warrant colistin therapy Inhaled: • Cystic fibrosis or bronchiectasis patients receiving colistin inhaled therapy as continuation of home regimen or initiation based on above criteria o Inhaled therapy should be used in combination with systemic therapy in combination with another gram negative antibiotic (usually β-lactam)
Daptomycin	• Empiric broad-spectrum gram-positive coverage in patients with vancomycin allergy (not vancomycin infusion reaction) • Documented MRSA or MRSE infection requiring intravenous therapy in patients with vancomycin allergy (not vancomycin infusion reaction) • Documented vancomycin intermediate or resistant *Staphylococcus aureus* (MIC ≥4 mg/L) • Bacteremia/endocarditis: documented MRSA/MRSE with failure to clear blood cultures after 7 days despite vancomycin troughs 10-15 mg/L with vancomycin MIC ≤2 mg/L • Documented or suspected VRE infections in patients requiring intravenous therapy who are unable to receive linezolid • Empiric therapy for patients with *E. faecium* from blood positive for vanA or vanB on Verigene in patients unable to receive linezolid • Empiric therapy for pre-engrafted BMT patients with gram + cocci in pairs/chains from blood or other sterile sites <u>Unacceptable uses for daptomycin:</u> • Pneumonia (due to inactivation of drug by lung surfactant) • Prophylaxis • Initial therapy for staphylococcal infections, unless severe vancomycin allergy • VRE colonization of the urine, respiratory tract, wounds, or drains
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	• Empiric therapy for *E. coli* bacteremia positive for CTX-M on Verigene • Documented ESBL-producing gram-negative infection requiring intravenous therapy (excluding lower urinary tract infection or CNS infections) that is susceptible to ertapenem and for which non-fermenter coverage is not needed (Pseudomonas, Acinetobacter, Achromobacter)

Restricted Antimicrobial	Typical Reasons for Use
Fidaxomicin	• Considered in *C. difficile* infection in patients with documented recurrent disease who failed a recent oral vancomycin taper
Imipenem	• Documented gram-negative infection requiring intravenous therapy AND resistance or intolerance to aztreonam and all other β-lactam antibiotics including meropenem, but susceptible to imipenem
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	• Documented or suspected aspergillosis in patients intolerant to voriconazole (preferred over posaconazole), specifically in regards to hepatotoxicity and QT prolongation
	• Documented or suspected 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; isavuconazole is variably active against Mucorales; liposomal amphotericin B is first-line therapy for treatment of these infections

Linezolid	• Documented vancomycin intermediate or resistant *Staph aureus* (MIC ≥4 mg/L) • Infection at any site with MRSA or MRSE AND vancomycin allergy (not vancomycin infusion reaction) • Suspected VRE infections: cultures with gram-positive cocci in chains pending identification/susceptibilities in patients at high risk for VRE infection (e.g., post-engraftment BMT, Hem/Onc, liver transplant, on vancomycin at time of culture, VRE colonization) • Empiric therapy for patients with *E. faecium* from blood pending susceptibilities • Infection at any non-urinary site with VRE ○ Uncomplicated urinary tract infections with VRE that are susceptible to ampicillin, doxycycline, nitrofurantoin, or fosfomycin should not be treated with linezolid Risk of serotonin syndrome: • Due to the risk of serotonin syndrome, linezolid should generally not be given to patients taking drugs with seratonergic activity; however, if linezolid is the only treatment option for severe infection or the benefit of linezolid is felt to outweigh the risk, patients should be carefully observed for signs and/or symptoms of serotonin syndrome. When possible, the seratonergic drug should be stopped or tapered when linezolid is initiated. • www.fda.gov/drugs/drugsafety/ucm276251.htm • Michigan Medicine Serotonin Syndrome and Linezolid Guidelines

Restricted Antimicrobial	Typical Reasons for Use

Meropenem	• Documented infection with gram negative infections resistant to all other β-lactam antibiotics, including ertapenem
	• Empirical therapy for up to 72 hours for healthcare-associated infections with one of the following:
	  ○ Patients with a recent history of document pathogen(s) resistant to first line-agents, such as piperacillin-tazobactam and cefepime
	  ○ Critically ill patients with clinical failure or significant recent exposure to anti-pseudomonal β-lactams (e.g., piperacillin-tazobactam and cefepime)
	  ○ Patients with allergies or intolerances to first line-agents, such as piperacillin/tazobactam or cefepime, AND aztreonam

Meropenem-vaborbactam	• Treatment of highly suspected or documented extensively drug-resistant gram-negative pathogens where polymyxins, tigecycline, and aminoglycosides are the only susceptible agents (e.g., KPC-producing carbapenamase-producing Enterobacteriaceae). • Meropenem-vaborbactam is the preferred treatment for infections caused by KPC-producing carbapenamase-producing Enterobacteriaceae
Micafungin	• BMT and Hem/Onc empirically for persistent febrile neutropenia (>4 days) in patients who cannot tolerate voriconazole • Prophylaxis of invasive fungal infections in high-risk Hem/Onc patients receiving chemotherapy or HSCT recipients per BMT and Hem/Onc protocols in patients unable to tolerate voriconazole • Prophylaxis of invasive fungal infections in HSCT recipients with GVHD on steroids or etanercept in patients who cannot tolerate voriconazole • Documented aspergillosis when unable to tolerate voriconazole, isavuconazole, or posaconazole • Invasive candidiasis/candidemia based on UMHS guidelines
Moxifloxacin	• Nocardia in patients with sulfa allergy • Atypical mycobacteria infections • Endophthalmitis prophylaxis in patients with penetrating trauma to globe of the eye (open globe) for up to 48 hours
Palivizumab	• RSV prophylaxis in accordance with Michigan Medicine guidelines
Peramivir	• Inpatients with influenza in which drug delivery by a route other than IV is not feasible
Polymixin B	Note: polymyxin B is the preferred polymyxin for system infections not involving the urinary tract. For urinary tract infections and inhaled therapy, see colistin) IV: • Documented gram-negative infections resistant or intermediate to all β-lactams, aminoglycosides, fluoroquinolones, and aztreonam, or allergies or intolerance to all β-lactams, aminoglycosides, fluoroquinolones, and aztreonam; treatment should be in combination with another non-aminoglycoside gram-negative antibiotic • Empiric therapy for up to 72 hours for history of gram-negative infections or gram-negative infections in patients with allergy or intolerance to all beta-lactams, fluoroquinolones, and aminoglycosides; treatment should be in combination with another gram-negative antibiotic

Restricted Antimicrobial	Typical Reasons for Use

Posaconazole	• BMT and Hem/Onc antifungal prophylaxis in patients unable to receive voriconazole or isavuconazole
	• Documented aspergillosis in patients unable to receive voriconazole or isavuconazole
	• Documented 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; posaconazole is variably active against Mucorales; liposomal amphotericin B is first-line therapy for treatment of these infections
	• IV use is only appropriate in patients in which drug delivery by a route other than IV is not feasible

Quinupristin-dalfopristin	• Gram-positive infections resistant to all beta-lactams in patients who are unable to receive vancomycin, daptomycin, and linezolid
Remdesivir	• Treatment of laboratory confirmed COVID-19 in patients with ≤14 days of symptoms with SpO_2 ≤94% on room air or supplemental oxygen, HFNC, or non-invasive mechanical ventilation

Inhaled Ribavirin	• Inhaled ribavirin should be reserved for patients with LRTI who are deemed to be at exceptional risk for impending respiratory failure AND who are unable to receive oral ribavirin in the following circumstances:
	  ○ Autologous bone marrow transplant recipient:
	  ▪ RSV infections pre-engraftment
	  ▪ LRTI in the first three months post-transplant
	  ○ Allogeneic bone marrow transplant recipient:
	  ▪ URI/LRTI pre-engraftment
	  ▪ LRTI with GVHD and immunosuppression
	  ▪ URI patients on significant immunosuppression can be considered on a case by case basis:
	  • Examples of potentially appropriate patients would include GVHD patients on >1 mg/kg prednisone or have received thymoglobulin or alemtuzumab (Campath) in past 3 months, or on 3 or more immunosuppressant medications
	  • Special consideration for cord blood recipients <6 months post-transplant
	  • LRTI during the first two years after transplantation
	  ○ AML/ALL:
	  ▪ LRTI in patients who are neutropenic after re-induction chemotherapy for relapsed/refractory disease
	  ○ Lung transplant:
	  ▪ Aerosolized ribavirin should be reserved for patients with LRTI who are deemed to be at exceptional risk for impending respiratory failure by the Infectious Diseases physician

Tigecycline	• Documented gram-negative infections resistant to alternative agents, or for patient intolerance to alternative agents • Documented 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 <u>Tigecycline should be avoided in the following situations:</u> • Moderate-severe infections where alternative options are available • Empiric therapy, unless the patient has a documented history of infection consistent with above criteria • Infections involving *Pseudomonas*, *Morganella*, *Proteus* or *Providencia* • Bacteremia: tigecycline yields very low serum concentrations

Restricted Antimicrobial	Typical Reasons for Use
Voriconazole	• First-line therapy for treatment of aspergillosis • BMT and Hem/Onc empirically for persistent febrile neutropenia (>4 days) • Prophylaxis of invasive fungal infections in high-risk Hem/Onc patients receiving chemotherapy or HSCT recipients per BMT and Hem/Onc protocols • Prophylaxis of invasive fungal infections in HSCT recipients with GVHD on steroids or etanercept

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11/2020 - added remdesivir
09/2021 - Updated vancomycin infusion reaction terminology