Northwestern Medicine Antimicrobial ECMO Dosing Guidance

** ADSP is available for assistance for agent/dose selection. Consider engagement when exceeding normal max doses.

Antimicrobials High Impact – Likely Requires Dose Adjustment			
Amphotericin	Itraconazole	Posaconazole	
Isavuconazole	Micafungin	Voriconazole	
Antimicrobials Potential Impact – Potentially Requires Dose Adjustment			
Ampicillin	Ceftaroline	Linezolid	Penicillin G
Aztreonam	Ceftriaxone	Meropenem	Piperacillin-Tazobactam
Cefazolin	Ertapenem	Nafcillin	Vancomycin
Cefepime	Fluconazole	Oxacillin	
Antimicrobials Minimal Impact – Standard Dosing is Most Likely Appropriate			
Amikacin	Ceftolozane-tazobactam	Gentamicin	Tobramycin
Azithromycin	Ciprofloxacin	Levofloxacin	Trimethoprim-Sulfamethoxazole
Cefiderocol	Daptomycin	Metronidazole	
Ceftazidime	Doxycycline	Oseltamivir	
Ceftazidime-avibactam	Ganciclovir	Tigecycline	

General Considerations

The following recommendations are for adults on extracorporeal membrane oxygenation (ECMO) and only consider the effects of ECMO. Other scenarios that impact pharmacokinetic (PK) parameters may simultaneously exist and should also be considered when dosing antimicrobials (eg, obesity, critical illness, sepsis, impaired hepatic function, impaired renal function).

- Please refer to Renal and CRRT dosing guidance.
- PK parameters that enhance drug clearance in ECMO include increasing protein binding and lipophilicity
  - Protein binding is the degree to which drugs reversibly bind plasma proteins and is expressed as a percentage.
  - Lipophilicity is how fat-soluble a drug is and is expressed as LogPoctanol/water with increasingly positive values representing lipophilic drugs and increasingly negative values representing hydrophilic drugs. These values may be found on PubChem.
  - See table below for expected impact of PK parameters on ECMO sequestration (binding/drug loss in components of ECMO circuit)

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Recommended Dose Adjustments Based on Physiochemical Properties[1]

If published data regarding experience using medications in ECMO are lacking, the following principles can be applied to help guide initial dosing if dose adjustments are indicated.

Volume of Distribution			
Vd	**Expected change in Vd**	**Increase loading dose?**	
≤ 1 L/kg	Moderate-large increase	Yes	
> 1 L/kg	Minimal increase	No	
Drug Sequestration*			
Octanol/Water Partition Coefficient (log P)	**Protein Binding**		
	< 30%	**30-70%**	**> 70%**
< 1	Minimal	Minimal-Moderate	Moderate
1 – 2	Minimal-Moderate	Moderate	Moderate-High
> 2	Moderate	Moderate-High	High

*Dosing considerations based on interpretation of drug sequestration:

Minimal sequestration = No maintenance dose adjustment

Moderate sequestration = May require increased maintenance dose/frequency/rate

High sequestration = Increased maintenance dose/frequency/rate likely required

Drug	PK Properties	Anticipated Sequestration	Evidence	Recommendation
Amikacin	Protein binding: <10% LogP = <-1	Minimal	Increased Vd, potential failure to achieve target Cmax and attainment of goal levels[2–4]	Standard dose Recommend TDM
Amphotericin liposomal	Protein binding: NA Lipophilicity: High / exact LogP NA	Moderate to high	Mixed reports of no effect[5,6] to high sequestration requiring 7.5-10 mg/kg q 24hr[7–9] One case circuit failure potentially related to drug[10]	Dose on aggressive end 7-8 mg/kg/day or consider alternative Can consider 10 mg/kg if concern clinical failure
Amphotericin deoxycholate	Protein binding: >90% Log P: 0.8	Moderate	Case report achieved therapeutic level on 1 mg/kg/day [11]	Dose on aggressive end 1 mg/kg/day
Ampicillin	Protein binding: 15-18% Log P: 1.35	Minimal to moderate	Significant drug sequestration ex vivo circuit models [12]	Dose on aggressive end for ampicillin and ampicillin-sulbactam
Azithromycin	Protein binding: 7-51% LogP = 3-4	Moderate	Minimal PK changes compared to non-ECMO[13]	Standard dose
Aztreonam	Protein binding: 56% Log P: -0.66	Minimal to moderate	No data	Dose on aggressive end
Cefazolin	Protein binding: 74-86% Log P: -0.6	Minimal to moderate	Significant drug sequestration ex vivo circuit models [12] Minimal PK change[14]	Dose on aggressive end
Cefepime	Protein binding: 20% Log P: -1.6	Minimal	Increased Vd and reduced clearance[15]	Standard dose Consider TDM especially in cases of documented infections, renal dysfunction or CRRT on ECMO, prolonged duration
Cefiderocol	Protein binding: 40%-60% Log P: <-1	Minimal to moderate	Minimal change ex vivo circuit model[16]	Standard dose

Drug	PK Properties	Anticipated Sequestration	Evidence	Recommendation
Ceftaroline	Protein binding: 20% Log P: <-1	Minimal	Significant drug sequestration in ex vivo model[17] Case report use of 600 mg q 8hrs successful treatment on ECMO[18]	Dose on aggressive end
Ceftazidime	Protein binding: <10% Log P: < -1	Minimal	Minimal change ex vivo circuit model[19]	Standard dose
Ceftazidime-avibactam	Protein binding: <10/<10% Log P: < -1 /<-1	Minimal	Minimal change ex vivo circuit model[19] ECMO not significant factor avibactam Cmin[20]	Standard dose
Ceftolozane-tazobactam	Protein binding: 16-21%/ 30% LogP = <-1 / <-1	Minimal	Achievement of acceptable drug levels with standard dosing[21]	Standard dose
Ceftriaxone	Protein binding: >90% Log P: <-1	Moderate	Moderate sequestration in ex vivo model[22] ECMO not significant factor in drug clearance[23]	Standard dose May consider 2 g q 12 hours if concern clinical failure
Ciprofloxacin	Protein binding: 20-40% Log P: 0.28-0.65	Minimal to moderate	Minimal change ex vivo circuit model[22] ECMO not significant factor drug dosing[24,25]	Standard dose
Daptomycin	Protein binding: >90% Log P: < -1	Moderate	Minimal change ex vivo circuit model[26]	Standard dose
Doxycycline	Protein binding: >90% Log P: -0.54	Moderate	Minimal change[27]	Standard dose
Ertapenem	Protein binding: 85-95% Log P: 0.3	Moderate to high	No data	Consider alternative such as meropenem
Fluconazole	Protein binding: 12% Log P: 0.5	Minimal	Minimal change ex vivo circuit model[22,28] Higher Vd with minimal change clearance[29–31] PK model recommends weight based dosing 12 mg/kg LD with 6 mg/kg q24hr[32]	Consider increased LD Standard MD

Drug	PK Properties	Anticipated Sequestration	Evidence	Recommendation
Ganciclovir	Protein binding: <5% Log P: < -1	Minimal	Similar PK non-ECMO patient case[31]	Standard dose
Gentamicin	Protein binding: <30% Log P: < -1	Minimal	Increased Vd in pediatrics with minimal adult data[33]	Standard dose Recommend TDM
Isavuconazole	Protein binding: >90% Log P: 3.4 – 4	High	Significantly lower trough levels than non-ECMO patients[7,34] with other studies finding no change Overall critically ill at high risk lower levels than obtained in phase III clinical trials[35,36]	Recommend TDM for surveillance of ECMO impact* Consider alternative or 372 mg BID if concern clinical failure
Itraconazole	Protein binding: >90% Log P: 5.7	High	No data	Recommend TDM or consider alternative
Levofloxacin	Protein binding: 24-38% Log P: 0.65-2	Minimal to moderate	Minimal change ex vivo circuit model[37]	Standard dose
Linezolid	Protein binding: 31% Log P: 0.9	Minimal to moderate	PK model standard dosing favorable if MRSA MIC ≤ 1[38] Case report failure to attain AUC goal with 600 mg q8hrs dosing if MRSA MIC ≥ 2[18]	Standard dose Consider alternative or 600 mg q 8hrs if concern higher MIC (>2). Consider TDM if renal dysfunction or prolonged q 8 hr duration
Meropenem	Protein binding: <10% Log P: -0.6	Minimal	PK models suggest no impact[39–41] Drug inherently unstable/degrades quickly in ex vivo models making interpretation difficult	Dose on aggressive end Use extended infusions Consider TDM especially in cases of documented infections, renal dysfunction or CRRT on ECMO, prolonged duration
Metronidazole	Protein binding: <20% Log P: 0	Minimal	No data	Standard dose
Micafungin	Protein binding: >90%	Moderate	Significant circuit sequestration ex vivo model[28]	200 mg q24h

Drug	PK Properties	Anticipated Sequestration	Evidence	Recommendation
	Log P: -1.5		AUC reduced on ECMO[42] Report successful treatment using 150 mg q24hr[43]	
Nafcillin	Protein binding: 90% LogP: 3.3	High	No data	Dose on aggressive end or consider alternative with less protein binding
Oseltamivir	Protein binding: 42% LogP: 1.3	Moderate	Similar PK non-ECMO[44–46]	Standard dose
Oxacillin	Protein binding: >90% LogP: 2.4	High	Similar PK non-ECMO and successful treatment with standard dosing case report[47] Minimal change ex vivo circuit model[48]	Dose on aggressive end
Penicillin G	Protein binding: 45-68% Log P: 1.8	Moderate	No data	Dose on aggressive end
Piperacillin-Tazobactam	Protein binding: 26% / 30% Log P: 0.3 / <1	Minimal	Potential sequestration ex vivo circuit model[40] Similar PK non-ECMO[49] May require extended/continuous infusion less susceptible pathogens[50]	Dose on aggressive end Use extended infusions Consider TDM especially in cases of documented infections, renal dysfunction or CRRT on ECMO, prolonged duration
Posaconazole	Protein binding: >90% Log P: 5.5	High	Significant sequestration ex vivo models[12,28,51] Similar PK non-ECMO although overall critically ill at high risk subtherapeutic levels[52]	Standard dose Recommend TDM
Tigecyline	Protein binding: 71-89% Log P: 0.8	Moderate	Similar PK non-ECMO[53]	Standard dose
Tobramycin	Protein binding: LogP:	Minimal	No data	Standard dose Recommend TDM
Trimethoprim-Sulfamethoxazole	Protein binding: 44/70% Log P: 0.9 / 0.9	Minimal to moderate	Similar PK non-ECMO[54]	Standard dose

Drug	PK Properties	Anticipated Sequestration	Evidence	Recommendation
Vancomycin	Protein binding: 55% Log P: <-1	Minimal to moderate	Similar PK non-ECMO utilizing high LD 25-35 mg/kg[55] PK model suggests high probability achieve goal levels 25 mg/kg LD and standard MD[56] Failure to achieve goal trough levels critically ill using standard dosing[57]	**Treatment:** LD 20 mg/kg (max 2000 mg) **Prophylaxis:** LD not indicated Standard MD Recommend TDM
Voriconazole	Protein binding: 58% Log P: 1	Moderate	Mixed findings mostly suggestive significant sequestration ex vivo circuit models[12,51,58] Mixed findings on extent ECMO impact[59–61] Overall critically ill at high risk of subtherapeutic levels[8] If dose increased on ECMO may require reduction after decannulation	If considering extended LD duration, use early TDM after 3 days Standard MD Recommend frequent TDM if new start ECMO, circuit exchange, and if ECMO stopped

Abbreviations: PK, pharmacokinetics; Log P, octanol/water coefficient (retrieved from PubChem/ChemSpider); Vd, volume distribution; Cmax, Concentration max; LD, loading dose ; MD, maintenance dose; TDM, therapeutic drug monitoring; MRSA, Methicillin Resistant Staphylococcus aureus; MIC, minimum inhibitory concentration

*Definitive therapeutic ranges that correlate with efficacy/toxicity for isavuconazole have not been established in SECURE, a phase III clinical trial. It is reasonable to advocate for a trough level >1- 2mg/L in critically ill patients receiving treatment for invasive fungal infections supported on ECMO to obtain similar mean exposure as the SECURE trial where clinical efficacy against invasive mold infections was demonstrated. TDM may be helpful to compare pre/post-ECMO levels to determine impact of ECMO on need for dose escalation[35]

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