Antifungal Guide for Use in Patients on Extracorporeal Membrane Oxygenation Circuit (ECMO)

Most of the current ECMO PK data exists in the neonatal/pediatric literature

Physicochemical Characteristics to Consider

- Lipophilicity
  - Described by the n-octanol/water partition coefficient (log P)
    - **High positive log P = higher degree of lipophilicity = greater drug sequestration**
- Plasma protein binding
  - Only free drug crosses membranes and has pharmacological effects
    - **Higher protein binding = greater drug sequestration**
- Volume of distribution (V_d), molecular size, & degree of ionization

Antifungal Agent	N-octanol/water partition coefficient (log P)	Protein binding	Anticipated/reported PK changes	Empiric Dosing Recommendations
Azoles				
Fluconazole	0.4-0.56	12%	Minimal drug sequestration; large Vd	No change
Itraconazole	5.7	99.8%	Significant drug sequestration; increased Vd	Recommend alternative agent
Voriconazole[1]	1	58%	Significant drug sequestration	No change due to limited data; recommend weekly TDM
Posaconazole	5.4	>98%	Significant drug sequestration; increased Vd	Recommend alternative agent
Isavuconazole[2]	3.4-4	>99%	Limited data; drug sequestration suspected	No change; consider TDM or 372mg twice daily in patients with suspected clinical failure
Echinocandins				
Micafungin[3]	-1.5	>99%	Drug sequestration may occur (AUC reduced by 23%); increased V_d and clearance	No change; consider micafungin 150mg daily in patients with invasive fungemia
Caspofungin	<0.17	97%	Minimal to moderate circuit drug sequestration	No change
Polyenes				
Amphotericin B (liposomal)[4]	0.8	>90%	Conflicting data; drug sequestration may occur	No change; consider 10 mg/kg/day in patients with suspected clinical failure

1. *Ex vivo* studies have demonstrated significant voriconazole losses up to 71%. A patient with invasive aspergillosis required up to 12 mg/kg q12h to reach therapeutic levels. However, increased voriconazole doses (6 mg/kg q12h) have also resulted in supratherapeutic levels. Voriconazole exhibits inter-patient variability. Additionally, it can fully saturate the ECMO membrane, exhibit non-linear kinetics, and eventually result in supratherapeutic levels. Recommend close TDM (weekly) while on voriconazole and ECMO.
2. Limited data with isavuconazole in ECMO. One case report utilized 372mg twice daily and achieved C_{min} levels of 4.1-4.7 mcg/mL whereas the 372mg daily dosing achieved a C_{min} = 1.9 mcg/mL. Mean plasma C_{min} on isavuconazole 372mg daily reported in phase III clinical trials: 3-4 mcg/mL when levels drawn < 21 days on therapy and ≥ 4 µg/ml when levels drawn at ≥ 21 days on therapy.
3. Micafungin has been studied mostly in neonates and children. Alternative doses have been recommended in infants (e.g. 2.5 mg/kg/day for prophylaxis and 5 mg/kg/day for treatment). Micafungin plasma levels at 24h were significantly reduced and ECMO was found to reduce the serum micafungin concentration and AUC by 23%.
4. Case reports exist utilizing liposomal amphotericin B (L-AMB) 10 mg/kg/day in ECMO. Patient PK parameters (e.g. C_{max}, $T_{1/2}$, V_d, and Cl) were similar between the ECMO 10 mg/kg/day case report and the L-AMB production information (non-ECMO) 5 mg/kg/day.

****Lung transplant patients on ECMO may transition from posaconazole to micafungin 100mg daily for fungal prophylaxis given the significant drug sequestration with posaconazole. If an invasive fungal infection is suspected, consider Transplant ID consultation for further drug and dosing recommendations.**

References:

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Connor Deri, PharmD
Gowri Satyanarayana, MD

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