Guidelines for use of Anti-fungal agents on Adult patients with viral pneumonitis requiring Extracorporeal Membrane Oxygenation (ECMO) - ITAPS	University Hospitals of Leicester NHS NHS Trust **Trust Reference: B44/2024**

1. Introduction and Who Guideline applies to

Glenfield Hospital is one of the national severe respiratory centres which provides ECMO as part of a bundle of care for adult (> 18 years) patients who develop respiratory failure from numerous causes who fail conventional support. It is established that patients with viral pneumonitis requiring ECMO are at increased risk of fungal infections and this is associated with increased mortality.[1,2]

The fungal organisms commonly encountered are Aspergillus and Candida spp.

This guideline is for the benefit of ICU consultants, microbiologists and critical care pharmacists looking after these patients to facilitate a rationalised approach to the management of fungal infections on patients requiring ECMO support.

2. Guideline Standards and Procedures

a. Patients with a diagnosis of viral pneumonitis admitted requiring ECMO support should be commenced empirically on IV voriconazole at an appropriate dose. This should be continued pending the results of microbiological samples and serological markers of fungal infection taken on admission, i.e. respiratory sample (ideally BAL or NBL) for culture and galactomannan, serum beta-D-glucan (BDG), serum galactomannan,

Patients >20% above ideal body weight should use adjusted body weight to calculate doses of voriconazole

Formula: Adjusted body weight = 0.4 x (Actual BW – IBW) + IBW

Ideal Body Weight
and Overweight Chart

Height		MEN		WOMEN	
ft. inches	cm	IBW (kg)	Overweight if >kg	IBW (kg)	Overweight if >kg
5.0	152.40	50	60	45.5	54.5
5.1	154.94	52.3	62.5	47.8	57
5.2	157.48	54.6	65.5	50.1	60
5.3	160.02	56.9	68	52.4	63
5.4	162.56	59.2	71	54.7	65.5
5.5	165.10	61.5	74	57.0	68.5
5.6	167.64	63.8	76.5	59.3	71
5.7	170.18	66.1	79	61.6	74
5.8	172.72	68.4	82	63.9	76.5
5.9	175.26	70.7	85	66.2	79.5
5.10	177.80	73.0	87.5	68.5	82.2
5.11	180.34	75.3	90	70.8	85
6.0	182.88	77.6	93	73.1	87.5
6.1	185.42	79.9	96	75.4	90
6.2	187.96	82.2	98.5	77.7	93
6.3	190.50	84.5	101.5	80.0	96
6.4	193.04	86.8	104	82.3	98.5
6.5	195.58	89.1	107	84.6	101.5

b. Patients without any microbiological or serological evidence of fungal infection who are deemed to be in a stable well-supported state on ECMO should be de-escalated to oral voriconazole if absorbing through their gastro-intestinal tract (GIT). In patients who are not absorbing through their GIT, a judgement should be made amongst the MDT to either remain on IV voriconazole or switch to another intravenous anti-fungal agent (e.g. caspofungin, AmBisome). Oral voriconazole (or appropriate alternative) should be continued until the patients are liberated from ECMO.

c. Patients with microbiological or serological evidence of fungal infection or who continue to deteriorate despite maximal support should be discussed with a microbiologist. Note that Candida spp. isolated from a non-sterile site such as the respiratory tract normally represents colonisation rather than infection. In cases of viral-associated pulmonary aspergillosis, the patient should ideally remain on IV voriconazole except where it is contra-indicated (e.g. interaction with other drugs, side effects or evidence of azole resistance). Where IV voriconazole is considered contraindicated, other alternatives should be considered (AmBisome, caspofungin) first and isavuconazole should only be considered if all the other options have either been considered or judged not effective.

d. Patients who have previously been diagnosed with a fungal infection and have become negative (microbiologically and serologically) should be discussed with a microbiologist and considered for de-escalation to oral voriconazole (if not contra-indicated and good GIT absorption) which should continue at least until they are liberated from ECMO. Patients who are partway through a treatment course for invasive fungal infection (such as candidaemia or viral-associated pulmonary aspergillosis) may need to continue treatment beyond their duration of ECMO.

e. All ECMO patients with viral pneumonitis should have weekly microbiological surveillance for breakthrough fungal infections. The most useful weekly surveillance sample to detect viral-associated pulmonary aspergillosis is a deep respiratory sample (BAL or NBL) for culture and galactomannan. Surveillance serum fungal biomarkers should not be sent routinely – serum galactomannan has inadequate sensitivity to detect COVID-associated pulmonary aspergillosis, but may be useful if influenza is the underlying viral pathogen. Serum BDG can be considered if there is additional clinical concern.

f. The dosing and route considerations for voriconazole should be guided by regular assessment of plasma voriconazole levels.

3. Education and Training

None.

4. Monitoring Compliance

What will be measured to monitor compliance	How will compliance be monitored	Monitoring Lead	Frequency	Reporting arrangements
Quantity of IV Voriconazole used on ECMO patients per month	Assessment of stock	Corrine Ashton	6 monthly	

5. Supporting References (maximum of 3)

1. Cavayas, Y.A., Yusuff, H. & Porter, R. Fungal infections in adult patients on extracorporeal life support. *Crit Care* **22,** 98 (2018). https://doi.org/10.1186/s13054-018-2023-zCavayas, Y.A.,

Yusuff, H. & Porter, R. Fungal infections in adult patients on extracorporeal life support. *Crit Care* **22,** 98 (2018). https://doi.org/10.1186/s13054-018-2023-z

2. Pluim T, Halasa N, Phillips SE, Fleming G. The morbidity and mortality of patients with fungal infections before and during extracorporeal membrane oxygenation support. *Pediatr Crit Care Med*. 2012;13(5):e288-e293. doi:10.1097/PCC.0b013e31824fbaf7

6. Key Words

: Anti-fungal, Voriconazole, ECMO, pneumonitis

CONTACT AND REVIEW DETAILS	
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Details of Changes made during review:	

Appendix 1

Overview of pharmacokinetics of antifungals in patients with renal or liver failure.

Notes:

- If renal function declines with AmBisome or LFTs rise with azoles or echinocandins antifungal treatment may need adjusting as these may be a contributing cause. Please discuss with Microbiology, Antifungal stewardship team or Pharmacy team.
- For doses in CVVHDF see separate trust guidance.

Drug	Renal Impairment	Chronic Liver Impairment	Suggestions
AmBisome ♠ (Liposomal Amphotericin)	If possible use alternative due to nephrotoxicity. Unless benefit outweighs risk. No dosage adjustment	No dosage adjustment	Test dose of 1mg over 10 minutes required due to potential for anaphylactoid reactions. Monitor patient for 30 minutes and if no reaction proceed to give full dose – see Medusa for additional information.
Fluconazole	Dose reduction by 50% for GFR 11–50 ml/min	No dosage adjustment but may choose alternative agent if LFTs markedly raised. Discuss with microbiologist in this case.	• Obese critically ill: actual body weight • ICU patient: enhanced doses • Strong inhibitor of CYP3A4 and 2C9
Voriconazole ♠	No dose adjustment Consider Sulfobutylether-β-Cyclodextrin (SBECD) accumulation during intravenous infusion	Mild to moderate hepatic impairment: Normal loading doses then 50% dose reduction Severe impairment: Not been studied. Caution advised. Discuss with microbiology for alternatives	• Strong inhibitor of CYP2C0 and 2C19 • Moderate inhibitor of CYP3A4 • TDM recommended, see antimicrobial website for further information
Isavuconazole ♠	No dose adjustment	Enhanced serum levels, no dosage reduction required	• Moderate inhibitor of CYP3A4, P-glycoprotein, and BRCP • Blueteq approval needed for IFI
Posaconazole ♠	No dose adjustment for oral route	No dose adjustment. Potential for enhanced serum levels. TDM essential.	• Strong inhibitor of CYP3A4 causing drug–drug interactions. • TDM recommended, see antimicrobial website for further information

			• Oral suspension is **not** interchangeable with the tablet form (milligram for milligram). Please contact the ICU pharmacist for further advice
Caspofungin ♠	No dose adjustment	Enhanced exposure in moderate hepatic impairment: dosage reduction, discuss with pharmacy to ensure dose reduction does not cause underexposure in critically ill patients	
Anidulafungin ♦	No dose adjustment	Slightly lowered serum concentrations but no dosage adjustment recommended	Not stocked at UHL, patients from other NHS trusts will need discussion with Microbiology for alternatives
Micafungin ♠	No dose adjustment	Slightly lowered serum concentrations	Potential risk for liver tumours: use only if other antifungals are not appropriate

Reference/Adapted from: Chatelon et al (2019). Choosing the right antifungal agent in ICU patients. *Advances in Therapy*. Volume: 36, Pages: 3308-3320
Key: ♠= microcode required, ♦ = not stocked at UHL