Antifungal Guidelines for non-neutropaenic non-transplant adult patients

For Haematology patients see Haematology guidance on intranet at
http://intranet.lothian.scot.nhs.uk/NHSLothian/Healthcare/A-Z/Haematology/policy/Pages/default.aspx

For Transplant patients or immunosuppressed patients seek specialist advice

Actual therapy may be modified after discussion with microbiology.

1. FLUCONAZOLE: Fluconazole is the 1st line treatment for invasive candidiasis where fluconazole resistance is unlikely

Indications for fluconazole:

a) **PROVEN** - Invasive candidiasis caused by fluconazole-sensitive candida species.
b) **PRE-EMPTIVE** - Gastrointestinal perforation or anastomotic leak with
   i. Septic Shock and Multiple Organ Failure OR
   ii. Multiple site growth/colonisation of fluconazole-sensitive candida
c) **EMPIRIC** - treatment of suspected invasive candidiasis AND Septic Shock with M.O.F. AND fluconazole-resistance is unlikely, (i.e. no recent history of fluconazole/azole therapy or known recent colonisation with fluconazole-sensitive candida species).

Loading dose - fluconazole 800 mg i.v. (single dose over 40 mins) then
Maintenance dose – fluconazole 400 mg i.v. daily (single dose over 20 mins)
Duration of therapy – If candidaemia, 14 days from 1st negative blood culture.
If severe sepsis, consider a loading dose of 12mg/kg, followed by a daily maintenance dose of 6mg/kg.

Caution: If creatinine clearance < 10ml/min – 50% of daily i.v. fluconazole dose.
Fluconazole is removed by CVVHD, therefore dose as for normal renal function.

Fluconazole may increase the plasma concentration of tacrolimus

2. ECHINOCANDINS (ANIDULAFUNGIN & CASPOFUNGIN)

Indications for Echinocandins (NB ***Echinocandins do not reach therapeutic concentrations in urine***, hence are not suitable for treatment of urinary tract candidiasis):

a) **PROVEN** - Invasive candidiasis caused by fluconazole-resistant candida species.
b) **EMPIRIC** - treatment of suspected invasive candidiasis when severely unwell and fluconazole resistance is probable, (i.e. recent fluconazole prophylaxis/treatment or known colonisation with fluconazole-resistant candida species).
De-escalate to fluconazole if appropriate when culture results available.

CHOICE OF ECHINOCANDIN

ANIDULAFUNGIN

Day 1 Loading dose – anidulafungin 200mg i.v. (over 3 hours) then
Day 2 onwards – anidulafungin 100mg i.v. daily (over 1.5 hours) thereafter.

For the treatment of candidaemia in neutropenic patients, consult the haematology guidelines on the intranet.

3. **EMPIRIC "MOULD" THERAPY** (agents below will cover most *Candida* sp. as well)
   If mould (e.g . Aspergillus) infection suspected: (If suspecting Mucormycosis, consult microbiologist)

   First line : Voriconazole 6 mg/kg i.v. every 12 hour for 2 doses, then 4 mg/kg i.v. every 12 hours. Dilute in glucose 5% or sodium chloride 0.9% to a concentration of 0.5-5mg/ml and give at a rate **not exceeding 3 mg/kg/hour.**

   NB. In patients with creatinine clearance <50 ml/min accumulation of the voriconazole intravenous vehicle, (SBECD) can occur. Intravenous voriconazole should only be given to these patients if benefit outweighs risk and consider changing to oral therapy as soon as possible.

   Voriconazole trough levels should be measured if
   - The patient has been on voriconazole for >5 days

   OR
   - Toxicity is suspected

   OR
   - The patient is on or initiated on a drug known t o interact with Voriconazole

     Voriconazole may increase the plasma concentration of tacrolimus.

   If patient is intolerant of voriconazole, consider second line therapy.

   Second line: Liposomal amphotericin (Ambisome®) 3 mg/kg/day i.v. (single dose over 60 mins). Dilute in glucose 5% to a concentration of 0. 2 – 2mg/ml.

   Give a test dose of Ambisome® before a new course of treatment to exclude anaphylaxis.
   Administer 1mg over 10 mins and then observe patient for at least 30 mins. If no allergic/anaphylactic reactions, administer the rest of the infusion.

FLUCYTOSINE
- Should only be given on microbiological advice and always in combination with another antifungal agent.
- Possible indications include cryptococcal infection, intracranial yeast infection or complex renal tract yeast infection.
- Requires monitoring of serum levels.

Dosing depends on renal function calculated using Cockcroft and Gault. DO NOT USE eGFR. Renal function should be assessed daily in unstable patients and dose adjustments made accordingly. The standard dose is 150 mg/kg/day in 4 divided doses. **For patients of 70 kg or greater, doses of flucytosine are "capped" at 2.5 g. Administer each infusion over 40 mins.**

Cockroft and Gault Equation: $CrCl\ (ml/min) = \frac{(140 - age) \times weight\ (kg) \times 1.04 (female)\ or\ 1.23\ (male)}{Serum\ creatinine\ (micromols/litre)}$

Creatinine clearance	**Dose**
> 40 ml/min	37.5 mg/kg (capped at 2. 5g/dose) 6 hourly,
20-40 ml/min	37.5mg/kg (capped at 2. 5g/dose) 12 hourly,
10-20 ml/min	37.5mg/kg (capped at 2. 5g/dose) 24 hourly,

<10 ml/min	37.5mg/kg (capped at 2. 5 g) as a single dose then adjust regimen according to levels.
CVVH	37.5mg/kg (capped at 2. 5g/dose) every 24 hours
Haemodialysis	2. 5 g as a single dose and then no further doses should be given until after the patient is next dialysed. Monitor level pre-dialysis, post-dialysis and post dose. Levels may not be available immediately and therefore a clinical decision should be made as to whether to wait for the post dialysis level or to administer a further dose. Adjust regimen according to levels. (Flucytosine is dialysed).

FLUCYTOSINE SERUM LEVELS

- **Trough** – immediately pre dose (25-50 micrograms/ml)
- **Peak** – 30 mins after end of infusion (should not exceed 80 micrograms/ml)
- **When?**
  - 3-4 days after therapy commences, or sooner if patient has renal impairment.
  - It takes at least 24 hours for serum levels to reach steady state. Therefore serum levels should only be taken after a minimum of 24 hours of therapy.

  How?
  - Liaise with microbiology, Mon-Thurs. Arrange 24 hours in advance
  - Levels now sent away and done rapidly by HPLC.

References

1. Ashley C, Currie A. Eds. The Renal Drug Handbook. 4th ed. Radcliffe Medical Press. 2014
2. Flucytosine Summary of Product Characteristics (SmPC) https://www.medicines.org.uk/emc/product/1398 Accessed 07/07/2019
3. Amphotericin (Ambisome®). SmPC. https://www.medicines.org.uk/emc/product/1022 Accessed 07/07/2019
4. Anidulafungin (Ecalta®). SmPC. https://www.medicines.org.uk/emc/product/454 Accessed 07/07/2019
5. Voriconazole (Vfend®). SmPC. https://www.medicines.org.uk/emc/product/7976/smpc Accessed 07/07/2019
6. Pappas P, Kauffman C A et al. Clinical Practice guidelines for the Management of Candidiasis. Clinical Infectious Diseases 2009;48:503-35
7. Walsh T J, Anaissie E J et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Disease Society of America. Clinical Infectious Diseases 2008;46:327-60
8. Bailly S, Bouadma L et al. Failure of Empirical Systemic Antifungal Therapy in Mechanically Ventilated Critically ill Patients. American Journal of Critical Care Medicine. 2015;191:10:1139-1146
9. Martin-Loeches I et al ESICM/ESCMID task force on practical management of invasive candidiasis in critically ill patients. Intensive Care Medicine 2019;45(6):789-805
10. SAPG & HIS. Good Practice Recommendations for treatment of candidaemia and the use of antifungal agents. https://www.sapg.scot/media/4267/candidaemia-and-fungal-agents.pdf Accessed 07/07/2019.

Title: Antifungal Guidelines	
ID: AGFNNNTAP v4.20190707	**Authors:**C Hannah, Dr I Laurenson, D Inverarity, O Moncayo, Dr P Kalima, M Dunn
Category: 1	**Document Version; 4**
Status Draft/Final: Final	**Review Date :** July 2021
Authoriser; QIT, Infection Group	**Date Authorisation:** July 2019
Date added to intranet	
Key Words; Antifungal, Infection	
Comments;	