

## 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 1<sup>st</sup> 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 1<sup>st</sup> 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 to 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.**

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

**Creatinine clearance**

> 40 ml/min  
20-40 ml/min  
10-20 ml/min

**Dose**

37.5 mg/kg (capped at 2.5g/dose) 6 hourly,  
37.5mg/kg (capped at 2.5g/dose) 12 hourly,  
37.5mg/kg (capped at 2.5g/dose) 24 hourly,

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<10 ml/min

37.5mg/kg (capped at 2.5 g) as a single dose then adjust regimen according to levels.

**CVH**

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

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