Critical care antifungal guidance

Candida infections and azoles/echinocandin dosing recommendations

For Haematology patients see Haematology guidance on intranet here.

For Transplant patients or immunosuppressed patients seek specialist advice.

Actual therapy may be modified after discussion with microbiology.

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

Indications:

- **PROVEN** - Invasive candidiasis caused by fluconazole-sensitive candida species.
- **PRE-EMPTIVE** - Gastrointestinal perforation or anastomotic leak with septic shock and multiple organ failure (and a positive serum beta-D-glucan assay if available) OR
- Multiple site growth/colonisation of fluconazole-sensitive candida.

- EMPIRIC - treatment of suspected invasive candidiasis AND septic shock with multiple organ failure AND fluconazole-resistance is unlikely, (i.e. no recent history of fluconazole/azole therapy or known recent colonisation with fluconazole-sensitive candida species).

Intravenous loading dose: 12mg/kg (rounded to the nearest 50mg).Typically, 800mg daily. *Maximum loading dose of 1200mg.*

then

Intravenous maintenance dose: 6mg/kg (rounded to the nearest 50mg) once daily (typically, fluconazole 400 mg once daily). *Maximum maintenance dose of 600mg.*

Increased exposure dose (e.g in candida galbrata infection): 12mg/kg (rounded to the nearest 50mg) once daily. Typically, 800mg once daily. *Maximum maintenance dose of 1200mg.*

Maximum infusion rate is 20milligrams/minute.

Duration of therapy – If candidaemia, 14 days from 1st negative blood culture.

- 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.
- It is associated with dysrhythmias, particularly prolonged QT interval on ECG, which may lead to torsades de pointes. Monitor ECG daily.

ECHINOCANDINS

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

- **PROVEN** - Invasive candidiasis caused by fluconazole-resistant candida species.
- **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.

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.

- No dose adjustment is required during hepatic or renal impairment. Does not interact with calcineurin inhibitors i.e. tacrolimus, ciclosporin
- Please note that echinocandins do not penetrate eye or CNS. If there is evidence that these organs are affected (Candida endophthalmitis), please discuss with microbiology to adjust treatment.
- For the treatment of candidaemia in neutropenic patients, consult the haematology guidelines on the intranet.

Mould infections and other antifungals dosing recommendations

EMPIRIC MOULD THERAPY (agents below will cover most *Candida* sp. as well).

(If suspecting Mucormycosis consult microbiologist)

If mould (e.g. Aspergillus) infection suspected:

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.**

Obesity: Use adjusted body weight and adjust the dose based on serum trough concentration to ensure efficacy and avoid toxicity.

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 day OR
- Toxicity is suspected OR
- The patient is on or initiated on a drug known to interact with voriconazole.

Please note this must be a **white cap blood tube** as other types of tubes can affect the result due to the chelating agents contained within them.

- Voriconazole may increase the plasma concentration of tacrolimus and ciclosporin.
- Cardiovascular effects are similar to fluconazole, please refer above.
- Voriconazole is associated with hepatotoxicity.

Pre-dose sample taken immediately before administration.

Voriconazole levels are a send away test. Please see Test Directory | Edinburgh and Lothians Laboratory Medicine (edinburghlabmed.co.uk) for further details. Reference ranges shown on the report.

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

SECOND LINE: LIPOSOMAL AMPHOTHERICIN: (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 minutes and then observe patient for at least 30 minutes. If no allergic/anaphylactic reactions, administer the rest of the infusion. Consider premedication with an anti-histamine or hydrocortisone.

(*10mg/Kg dosing can be used in cases of Mucormycosis in severe immunocompromise- consult Microbiology)*

Obesity: No dose adjustment necessary. Use actual body weight. Maximum dose of 600mg is recommended.

- Monitor electrolytes closely. Amphotericin is associated with hypocalcaemia, hypokalaemia, hypomagnesemia and hyponatraemia. It can also be associated with hypersensitivity reactions and nephrotoxicity.
- No dose adjustment required during renal impairment.
- Increased nephrotoxicity with calcineurin inhibitors (i.e. tacrolimus and ciclosporin).
- Please note that liposomal amphothericin does not penetrate into the kidney. For patients with proven fungal kidney disease resistant to fluconazole, please discuss with a microbiologist.

FLUCYTOSINE:

This 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 minutes.**

Cockroft and Gault Equation: CrCl (ml/min) = [(140- age) x weight (kg) x 1.04(female) or 1. 23 (male)] divided by serum creatinine (micromols/litre).

Creatinine clearance	Dose
>40mls/min	37.5mg/kg (capped at 2.5g/dose) 6 hourly.
20-40ml/min	37.5mg/kg (capped at 2.5g/dose) 12 hourly.
10-20ml/min	37.5mg/kg (capped at 2.5g/dose) 24 hourly.
<10ml/min	37.5mg/kg (capped at 2.5g/dose) as a single dose, then adjust regimen according to levels.
CVVHD	37.5mg/kg (capped at 2.5g/dose) 24 hourly.
Haemodialysis	2.5 g as a single dose, then no further doses should be given until after the patient is next dialysed. Monitor levels pre-dialysis, post dialysis and post dose. Levels may not be available immediately, 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

Peak – 30 - 60 minutes after end of infusion

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.

Flucytosine levels are a send away test. Please see Test Directory | Edinburgh and Lothians Laboratory Medicine (edinburghlabmed.co.uk) for further details. Reference ranges shown on the report.

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