NHS
Greater Glasgow and Clyde

CLINICAL GUIDELINE

Invasive Candidiasis in non haemato oncology adult patients

A guideline is intended to assist healthcare professionals in the choice of disease-specific treatments.

Clinical judgement should be exercised on the applicability of any guideline, influenced by individual patient characteristics. Clinicians should be mindful of the potential for harmful polypharmacy and increased susceptibility to adverse drug reactions in patients with multiple morbidities or frailty.

If, after discussion with the patient or carer, there are good reasons for not following a guideline, it is good practice to record these and communicate them to others involved in the care of the patient.

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Important Note:

The Intranet version of this document is the only version that is maintained.
Any printed copies should therefore be viewed as 'Uncontrolled' and as such, may not necessarily contain the latest updates and amendments.

Good Practice Recommendations for the Treatment of Invasive Candidiasis In Non-Haemato-Oncology Adult Patients

Proven invasive candidiasis OR Yeast seen on Gram stain of blood culture or sterile fluid

CONSIDER SOURCE AND COMPLICATIONS OF CANDIDAEMIA

Consider source: remove central venous catheters and other implicated prosthetic material (e.g. ureteric stent, biliary stent, V-P shunt). If this is not possible discuss management **with microbiology/ID** as this may affect primary therapy (an alternative first line antifungal agent /higher doses may be required).

If the patient has <u>new</u> visual symptoms or if the patient is unable to report visual symptoms, such as ICU patients, referral to Ophthalmology is advised. [1]

Consider **metastatic complications** (e.g. endocarditis) particularly if persistent fever or persistent positive blood cultures.

CNS infection discuss with microbiology /ID.

ONGOING MONITORING

Follow-up blood cultures should be performed every other day until negative to establish the time point at which candidaemia has been cleared.

DO ANY OF THE FOLLOWING APPLY?

- Previous (within 4 weeks) positive blood culture/invasive candida infection due to an azole-resistant isolate.
- Recent (within 4 weeks) treatment failure of fluconazole.
- Known recent colonisation with a fluconazole-resistant Candida species (e.g. *C. krusei*)
- Contraindication e.g. QTc prolongation or significant drug interaction with fluconazole (see below).

YES

Urinary/ Renal Source

YES

Discuss with microbiology/ ID
Fungizone (non-lipid formulation amphotericin B).
Not available out of hours – discuss with microbiology.

NO

NO

Caspofungin IV

See table below for dosing and monitoring advice **If Echinocandin unsuitable or advised by microbiology/ID then -**

Liposomal Amphotericin B (Tillomed) or AmBisome IV

See table below for dosing and monitoring advice

Rezafungin

For weekly OPAT use only.

Fluconazole Oral/ IV

See table below for dosing and monitoring advice

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Notes

1. **Good practice recommendations** are based on local expert consensus opinion and review of published guidance. More detailed investigation for deep source/metastatic infective complications may be warranted in individual cases depending on the clinical situation and level of concern. Management of candidaemia should always be discussed with an infection specialist and with pharmacy.
2. **Empirical Therapy – discuss with microbiology/ID** May be justified in patients with continuing fever or sepsis despite > 72 hours of broad spectrum antibiotics and no obvious source of infection. Risk factors to consider include: CVC/TPN; length of stay > 3 days; multiple broad spectrum antibiotics; haemodialysis; GI perforation/surgery; *Candida* colonisation at > 1 site. Endotracheal colonisation alone is not an indication for empiric therapy. If treating empirically use IV fluconazole, see table below for IV fluconazole dosing advice.
3. **IV to Oral switch: Discuss timing, antifungal choice and dosing with microbiology/ID**. Oral fluconazole can be dosed as per IV dose (90% oral bioavailability) for fluconazole susceptible candida isolates. Echinocandins (Caspofungin & Anidulafungin) and Liposomal Amphotericin B (Tillomed) or AmBisome are not available for oral administration – discuss with microbiology/ID.
4. **Duration of Therapy.** Assuming complete clinical/microbiological resolution and absence of localised syndromes, continue antifungal therapy for 14 days after last negative blood culture (if negative blood cultures not available – then 14 days from last positive blood culture [2]). Where candidiasis arises from a removable source (*e.g.* vascular catheter, ureteric stent) continue treatment for 14 days after removal of the source. If recovery is delayed/evidence of refractory disease, choice of antifungal therapy and its duration should be discussed with microbiology/ID. If source control is not possible, discuss with microbiology/ ID.
5. **Antifungal Prescribing and Monitoring Guidance:** Always discuss with pharmacy – see table below

Antifungal Agents Dosing and Monitoring Advice

Oral/IV Fluconazole [3-9]	Standard dosing	**Loading dose**, all patients: 800mg on day 1 Oral / IV (as a single dose over 40 min). **Maintenance dose** (From day 2 onwards if Cr Cl > 50 ml/min) • Fluconazole susceptibility (S): Oral /IV 400 mg as a single daily dose
	Oral Bioavailability	Fluconazole is well absorbed and plasma concentrations are **>90%** of the concentrations achieved after intravenous administration. Consider oral therapy first line unless oral route is compromised
	I sensitivity (*susceptible at Increased dose*)	I Fluconazole susceptibility (I): 800 mg oral as single daily dose (or IV infusion over 40 min if oral route note available)
	Endocarditis Dosing	This is not first line therapy – initial monotherapy with fluconazole associated with high relapse rate – discuss with microbiology/ ID. Long term suppressive therapy or step down therapy for patients who have susceptible *Candida* isolates, have demonstrated clinical stability, and have cleared *Candida* from the bloodstream • Oral fluconazole 400mg -800mg (6-12mg/kg) daily.
	Preparation & administration	see BNF/ SPC/ Medusa
	Obesity	**BMI >30 kg/m^2** **Loading dose** 12 mg/kg (actual body weight) **Maintenance dose** (from day 2 onwards): 6mg/kg (actual body weight) once daily. If I sensitivity discuss dosing with microbiology. **BMI ≥40 kg/m^2** Doses > 800mg may be required, discuss dosing with microbiology. TDM may be required in some patients, discuss with antimicrobial pharmacist
	Hepatic impairment	No change. (SPC states caution –may be associated with hepatotoxicity – monitor LFTs)
	Renal impairment	**Loading dose** oral or IV Fluconazole 800mg (as a single dose over 40 min)

		Then if Creatinine Clearance (CrCl) ≥ 10-50 ml/min Dose fluconazole as 50-100% of normal dose, discuss dosing with infection specialist. **CrCl < 10 ml/min** Reduce fluconazole dose by 50% **CAPD** dialysis - Dose as in GFR<10 mL/min. **HD (Haemodialysis)** - 50% of normal dose daily, or 100% of normal dose 3 times a week after dialysis. Patients on daily dialysis should have 100% of dose after each haemodialysis session. **CVVHDF** dialysis - 400–800 mg every 24 hours If unclear about which form of dialysis applies, discuss with renal pharmacist. In patients with unstable renal function there is risk of inappropriate dosing. Ensure discussion of maintenance dosing with antimicrobial pharmacist/ microbiology/ ID. **To calculate CrCl** see GGC medicines App or Clinical Information tab in StaffNet, the Cr Cl calculator is listed under quick links. TDM may be required in some patients, discuss with antimicrobial pharmacist.
	Drug interactions/ other	**See BNF/ SPC** Fluconazole interacts with numerous other medicines. Pharmacy can advise on the significance & management of these. May prolong QTc. Contra-indicated in acute porphyria
	Monitoring	LFTs, UEs, Creatinine, K^+, Mg^{2+}, FBC, ECG QTc
IV Caspofungin [3-7 9-11,]	Standard dosing	**Loading dose:** Weight ≤ 110 kg: 70 mg on day 1 **Maintenance dose (from day 2 onwards):** Weight ≤ 80 kg: 50 mg once daily Weight > 80 kg to: ≤ 110 kg: 70 mg once daily.
	I sensitivity	Contact microbiology / ID
	Endocarditis Dosing	IV Caspofungin 150 mg once daily. Discuss with microbiology/ ID.
	Preparation & Administration	Preparation see BNF/ SPC/ Medusa
	Obesity	**BMI >30 kg/m²** **Loading dose** Weight > 110 kg**:** 100 mg (2x50 mg) on day 1 **Maintenance dose (from day 2 onwards):** Weight > 80 kg to: ≤ 110 kg: 70 mg once daily. Weight >110 kg: 100 mg (2x50 mg) once daily. Excludes endocarditis
	Hepatic	**Mild hepatic impairment** (Child-Pugh score 5 to 6), no dosage

	impairment	adjustment is needed **Moderate & Severe hepatic impairment** Child-Pugh score ≥ 7 use ANIDULAFUNGIN (refer to product literature and discuss with pharmacy, also see below).
	Renal impairment	Dose as normal renal function. Not Dialysed: dose as normal renal function
	Drug interactions/ other	**See BNF/ SPC** Maintenance dose may need increased if caspofungin is co-administered with enzyme inducers e.g. rifampicin (see SPC).
	Monitoring	LFTs, FBC, Creatinine, K^+, Ca^{2+},Mg^{2+}, Glucose, BP
Liposomal Amphotericin B (Tillomed) or IV AmBisome [3-7, 9,12,13, 15] (prescribe by brand name) Tillomed liposomal amphotericin is considered to be bioequivalent to AmBisome. Tillomed liposomal amphotericin is the preferred product in GGC.	Standard dosing	3mg/kg once daily, maximum dose 5mg/kg once daily.
	I sensitivity	Not Applicable
	Endocarditis Dosing	Doses of 3-5 mg/kg once daily. Discuss with microbiology / ID.
	Preparation & Administration	Preparation see BNF/ SPC/ Medusa Every dose of liposomal amphotericin B should be infused over 30-60 minutes and the patient closely monitored every time. If a severe allergic or anaphylactic reaction occurs, the infusion should be immediately discontinued and the patient should not receive further infusion of liposomal amphotericin B.
	Obesity	**In obese** patients (BMI > 30 kg/m^2) starting dose 3 mg/kg/day dosing based on lean body weight (**LBW**). **LBW calculation;** Males: **LBW**= (9270 x TBW) / (6680 + (216 x BMI)) Female: **LBW**= (9270 x TBW) / (8780 + (244 x BMI)) TBW= Total (actual) Body Weight (kg). Max recommended dose of 300 mg once daily for 3 mg/kg and 500 mg for 5 mg/kg
	Hepatic impairment	No information available on dose recommendation. SAPG guidance states no dose change.
	Renal impairment	No change in dose. Not dialysed. Avoid administration of IV Liposomal Amphotericin B (Tillomed) or AmBisome, during dialysis or filtration procedure.
	Drug interactions/ other	**See BNF/SPC**
	Monitoring	LFTs, UEs, Creatinine, K^+, Mg^{2+}, FBC
IV Fungizone [3,9,14,15] (prescribe by brand name)	Standard dosing	(Test dose 1mg, then) 0.25 mg/kg daily gradually increased over 2-4 days to 1mg/kg once daily, max 1.5mg/kg once daily or on alternate days. If treatment is interrupted for longer than 7 days recommence at 0.25 mg/kg once daily and increase dose gradually.

	I sensitivity	Not applicable
	Endocarditis Dosing	Not applicable
	Preparation & Administration	Preparation see BNF/ SPC/ Medusa. Nephrotoxicity may be reduced by giving an IV infusion of sodium chloride 0.9% 250–500 mL over 30–45 minutes immediately before administering IV Fungizone.
	Obesity	**BMI >30 kg/m^2** Use LBW for dosing (See standard dosing – above) **LBW calculation;** Males: **LBW**= (9270 x TBW) / (6680 + (216 x BMI)) Female: **LBW**= (9270 x TBW) / (8780 + (244 x BMI)) TBW= Total (actual) Body Weight (kg).
	Hepatic impairment	Dosing – no change Monitoring -Therapy should be discontinued if liver function test results (elevated alkaline phosphatase and bilirubin) are abnormal.
	Renal impairment	CrCL <10-50 ml/min Dose as normal renal function. CAPD, Haemodialysis, CVVHD – not dialysed, dose as normal renal function. Serum creatinine > 260 micromol/L **stop** IV Fungizone or reduce dosage markedly until renal function is improved. Cumulative doses of > 5g are associated with permanent renal impairment.
	Drug interactions/ other	**See BNF/ SPC** Concomitant administration of nephrotoxic drugs or anti-neoplastics should be avoided if at all possible. The hypokalaemia following amphotericin B therapy may potentiate the toxicity of digitalis glycosides or enhance the curariform actions of skeletal muscle relaxants. Corticosteroids and Corticotrophin (ACTH) may increase the potassium loss due to amphotericin B. Flucytosine toxicity may be enhanced during concomitant administration, possibly due to an increase in its cellular uptake and/or impairment of its renal excretion. Acute pulmonary reactions have occasionally been observed in patients given amphotericin B during or shortly after leukocyte transfusions. It is advisable to separate these infusions as far as possible and to monitor pulmonary function.
	Monitoring	LFTs, UEs, Creatinine, K^+, Mg^{2+}, FBC
IV Anidulafungin [3,4,16]	Standard dosing	**Loading dose** 200mg once daily for 1 day **Maintenance dose** (from day 2 onwards): 100mg once daily There are insufficient data to support the 100 mg dose for longer than 35 days of treatment.
	I sensitivity	Contact microbiology / ID
	Endocarditis Dosing	200mg once daily

	Preparation & Administration	Preparation see BNF/ SPC/ Medusa
	Obesity	**Weight > 140 kg** **Loading dose** 250 mg once daily for 1 day **Maintenance dose** (from day 2 onwards): 125 mg once daily **Weight ≥ 200 kg** **Loading dose** 300 mg once daily for 1 day **Maintenance dose** (from day 2 onwards): 150 mg once daily
	Hepatic impairment	Dosing – no change
	Renal impairment	No dosing adjustments are required for patients with any degree of renal insufficiency, including those on dialysis. Anidulafungin can be given without regard to the timing of haemodialysis.
	Drug interactions/ other	**See BNF/SPC**
	Monitoring	LFTs, FBC, Creatinine, K^+, Glucose, BP
IV Rezafungin [17]	Standard Dosing	Loading dose 400 mg for 1 dose on day 1, then maintenance 200 mg on day 8 and **weekly** thereafter**.** Use via the OPAT service only.
	I sensitivity	Contact microbiology / ID
	Endocarditis Dosing	Doses as above in Standard dosing, once weekly. Discuss with microbiology / ID.
	Preparation & Administration	**Preparation** see BNF/ SPC/ Medusa. **Administration** After reconstitution and dilution, the solution should be administered by slow intravenous infusion over approximately 1 hour, infusion time may be increased up to 180 minutes to manage any evolving symptoms of infusion related reaction. Transient infusion-related reactions have occurred with rezafungin, characterised by flushing, sensation of warmth, nausea, and chest tightness. In clinical trials, infusion reactions resolved within minutes, some without interruption or discontinuation of the infusion. Patients should be monitored during the infusion. If the infusion is stopped due to a reaction, consideration may be given to restarting the infusion at a slower rate after the symptoms have resolved.
	Obesity	In simulation studies Body mass index (BMI) ≥ 30 showed that exposure was reduced in these subjects, but the reduction is not considered clinically meaningful.
	Hepatic impairment	Hepatic impairment does not have a clinically meaningful effect on rezafungin pharmacokinetics.
	Renal impairment	No dosing adjustments are required for patients with any degree of renal insufficiency
	Drug interactions/ other	**See BNF/SPC**
	Monitoring	Patients should be advised to avoid unprotected exposure to sunlight and other UV radiation during treatment and for 7 days after last treatment. FBC, LFTs, U&Es, Mg, phosphate, BP

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