



Good Practice Recommendations for treatment of candidaemia and the use of antifungal agents

Introduction

The purpose of this document is to provide guidance on empirical and targeted use of antifungal agents in the treatment of uncomplicated candidaemia in **non-solid organ transplant recipients, non-neutropenic, non haemato-oncology patients**. It is based upon national surveillance data on candidaemia, in addition to the current (at the time of writing) published evidence-based IDSA¹ (*Infectious Diseases Society of America*) and ESCMID² (*European Society of Clinical Microbiology and Infectious Diseases*) recommendations.

This guidance is intended to assist healthcare professionals in the choice of antifungal treatments. It is not intended to be a comprehensive clinical pathway or a substitute for consultation with a Microbiologist or an Infection Specialist.

Clinical judgement as always should be exercised on the applicability of this guideline, influenced by individual patient risk factors. Clinicians should be mindful of the potential for harmful polypharmacy and increased risk to adverse drug reactions in patients with multiple co-morbidities or frailty.

These recommendations have been developed by the Scottish Antimicrobial Prescribing Group (SAPG) antifungal stewardship group through consultation with clinical specialists to provide practical advice for Antimicrobial Management Teams and Infection Specialists.

The aims are to:

1. **Support** clinical management of invasive candidiasis
2. **Reduce** emergence/ development of antifungal resistance
3. **Promote** more judicious use of antifungal agents
4. **Protect and preserve** antifungal agents

Definitions

Candidaemia- describes the presence of *Candida* species in the blood (a blood culture that yields a *Candida* species). Candidemia is the most common manifestation of invasive candidiasis. Acute disseminated invasive candidiasis occurs when visceral sites are infected as a result of haematogenous spread.

Neutropenia - Neutropenia is typically defined as an absolute neutrophil count of less than $1 \times 10^9/L$ (severe neutropenia is defined as an absolute neutrophil count of less than $0.5 \times 10^9/L$). Prolonged neutropenia (> 7 days) most likely occurs in the pre-engraftment phase of hematopoietic cell transplantation (most frequently allogeneic) and in patients undergoing induction chemotherapy for acute leukemia.

1 Candidaemia

Invasive infection due to *Candida* species remains a major cause of morbidity and mortality, with candidaemia becoming an increasingly important nosocomial infection in the modern healthcare setting¹⁻². Based on the 2017 national surveillance data, candidaemia was the eighth most common cause of blood stream infection in Scotland³.

Important risk factors for the development of candidaemia include¹⁻²:

- Presence of Central venous catheters and other intravascular devices, long-term intravascular lines such as patients receiving parenteral nutrition (TPN), dialysis.
- Compromised Gastrointestinal tract/breach in integument; recent abdominal surgery, anastomotic leaks, or necrotizing pancreatitis
- Exposure to broad-spectrum antibiotic therapy
- Severe systemic illness or burns
- Patients with prolonged neutropenia or sustained immunosuppression, corticosteroid therapy

Currently there are no prospective clinical studies to support a risk-based treatment algorithm to guide the management of candidaemia.

Diagnosis

The gold standard for the diagnosis of candidaemia is a positive blood culture, which should be sent in all patients where there is a clinical suspicion of invasive *Candida* infection. The overall sensitivity of blood cultures in diagnosing invasive candidiasis is approximately 50%. As such blood cultures may be negative in cases of low-level level candidaemia, intermittent candidaemia or deep-seated *Candida* infection¹.

A potential adjunct to blood cultures is the beta-D-glucan assay. This non-culture diagnostic antigen assay is based upon the detection of beta-D-glucan, a cell wall constituent of many fungi. The assay despite having limited sensitivity (high false positivity rate) has excellent negative predictive value. Its role in the diagnosis and management of candidaemia however remains unclear¹. Optimal timing and frequency of testing has not yet been established, with there being limited data and no prospective clinical trials supporting its routine use.

The decision on utility of beta-D-glucan testing should be individualised for each patient in consultation with a Microbiologist or an Infection Specialist.

In patients with focal clinical manifestations in the context of haematogenous spread (e.g. skin lesions or parenchymal involvement), a biopsy should also be performed and sent for microscopy, culture, and histopathologic evaluation.

2 Treatment Recommendations¹⁻⁹

Initial antifungal therapy: Positive blood culture with a *Candida* species prior to antifungal sensitivities being available.

Note no single trial to date has demonstrated the clear superiority of an echinocandin over fluconazole in the management of candidaemia.

First Line therapy*: IV fluconazole

(Consult with a Pharmacist/ the BNF for detailed prescribing advice- see Table 1 for guidance)

*In patients who are not critically ill; not on vasopressors for resuscitation of septic shock and no evidence of sepsis-associated organ dysfunction.

Based on the 2017 national surveillance candidaemia data; $\geq 85\%$ of *Candida* species tested were fluconazole susceptible. Fluconazole as such is considered a reasonable first line empirical agent based on an appropriate patient risk assessment and no evidence of:

- Recent exposure, within 4 weeks, to azoles (risk of non-*albicans Candida* species)
- Prolonged exposure to azoles (risk of fluconazole and azole class resistance)
- Recent failure, within 4 weeks, of fluconazole (defined as either clinical failure or failure of bloodstream clearance)
- Previous positive blood culture/invasive infection due to an azole-resistant isolate
- Current colonisation with fluconazole-resistant *Candida* species (infection with *C. krusei* or *C. glabrata* of unknown fluconazole susceptibility)
- Intolerance of/contraindication (e.g. drug interaction) to fluconazole

Alternative therapy:

Echinocandin e.g. IV Caspofungin

May be considered in patients who are critically ill; on vasopressors for resuscitation of septic shock and evidence of sepsis-associated organ dysfunction. Note that echinocandins have a higher cost than azoles (Consult with a Pharmacist/ the BNF for detailed prescribing advice- see Table 1 below for guidance)

An echinocandin is considered a reasonable alternative empirical agent based on an appropriate patient risk assessment and no evidence of:

- Renal candidiasis
- CNS involvement
- Previous positive blood culture/invasive infection due to *C. parapsilosis*
- Recent, within 4 weeks, failure of an echinocandin (defined as either clinical failure or failure of bloodstream clearance)
- Intolerance of/contraindication (e.g. drug interaction)

OR

AmBisome® IV lipid formulation amphotericin B

(Consult with a Pharmacist/ the BNF for detailed prescribing advice- see Table 1 below for guidance; note initial test dose of 1mg over 10 minutes is advised after which the infusion should be stopped with the patient being observed for at least 30 minutes. Continuation of therapy advised only if no anaphylactoid/allergic reactions). Lipid formulation amphotericin B is a reasonable effective alternative empirical agent if there is intolerance, severe hepatic impairment or resistance to other antifungal agents.

The choice of antifungal agent and dose should always be discussed with a Microbiologist (or an infection specialist) and Pharmacist. Antifungal dosing is frequently suboptimal in the treatment of candidaemia, particularly in critically ill patients due to inappropriate under dosing in organ dysfunction. Through an understanding of relevant pharmacokinetic properties antifungal therapy can be optimized, improving efficacy.

Table 1 Antifungal dosing guidance ¹⁰⁻¹¹

Drug	Standard Dose	Extremes of body weight	Hepatic Impairment	Renal Impairment	CRRT [§]
Fluconazole	IV 800mg stat then 400mg daily	12mg/kg stat then 6mg/kg daily Dose according to total body weight	No change	200mg daily if creatinine clearance (CrCL) < 50ml/min	400mg twice daily
Caspofungin	IV 70mg stat then 50mg daily (70mg daily if > 80kg)	If weight > 110kg give 105mg daily	If Child-Pugh B or C, maintenance dose 35mg daily*	No change	No change
Liposomal Amphotericin B	IV 3mg/kg	Dose on lean body weight	No change	No change	No change

*If Child Pugh score is driven by hypoalbuminaemia in a critically ill patient, use normal dosing.

§ Continuous Renal Replacement Therapies

Targeted antifungal therapy: Positive blood culture with a *Candida* species with confirmed antifungal sensitivities (typically available at 48-72 hours)

Rationalisation of anti-fungal therapy is recommended once the *Candida* species and anti-fungal susceptibilities are confirmed.

Transition from an echinocandin (or Lipid formulation amphotericin B) to fluconazole is recommended if the isolate is confirmed susceptible to fluconazole (e.g. *C. albicans*) and the patient is clinically stable, responding.

For infection due to *C. glabrata*, transition to higher-dose fluconazole 800 mg daily (or 12mg/kg) should be considered in patients with fluconazole-susceptible isolates.

Prophylactic, empirical and pre-emptive antifungal treatment

There are no current multicentre randomised controlled clinical trials in adult patients to support the use of prophylactic, empirical or pre-emptive antifungal therapy in non-neutropenic patients¹⁻².

The role of antifungal prophylaxis in high-risk patients may be considered, in consultation with a Microbiologist or an Infection Specialist, in ICU settings with a high rate (>5%) of invasive candidiasis.

The use of empirical antifungal therapy in high risk patients (in the absence of proven/confirmed invasive candidiasis) may be justified and should be discussed with a Microbiologist or an Infection Specialist.

Note that **endotracheal colonisation alone is not an indication for empirical antifungal therapy.**

3 Important considerations- General management recommendations ¹⁻²

- Always consult with a Pharmacist/ the BNF for detailed prescribing advice for neonates/paediatrics, patients with hepatic or renal impairment and to check possible drug interactions.
- All patients with a candidemia should be assessed for metastatic complications/dissemination. Early removal of central venous catheters should be considered in all patients with candidaemia where infection of the catheter is possible.

- Endocarditis should be considered when blood cultures are persistently positive in a patient with persistent fever despite appropriate treatment, or when there is evidence of a new heart murmur, heart failure, or embolic phenomena.
- An ophthalmological evaluation should always be considered and is recommended in all patients who are unable to report ocular symptoms.
- The recommended minimum duration of antifungal therapy for the management of candidaemia with source control and without metastatic complications is 2 weeks from documented clearance of *Candida* species from the bloodstream (first negative blood culture).
- IV antifungal therapy should be reviewed daily to confirm the need for continuation and to assess whether an alternative antifungal (oral or systemic) is appropriate.
- Transition to oral therapy can be considered for uncomplicated candidaemia with source control if the isolate is confirmed susceptible to an appropriate agent, the patient is clinically stable and can tolerate/absorb oral therapy.
- The antifungal management of localised syndromes associated with candidaemia such as infective endocarditis, meningitis, septic arthritis, osteomyelitis, prosthetic device infections, renal tract candidiasis or retinitis/endophthalmitis should always be carried out in consultation with a Microbiologist or an Infection Specialist.
- There is currently no evidence that therapeutic drug monitoring is routinely indicated for the use of fluconazole, caspofungin or amphotericin.
- TDM for itraconazole, voriconazole, posaconazole and flucytosine however has been shown to be useful and should be considered in patients to limit toxicity and allow optimization of dosing.
- The role of combination antifungal therapy for invasive candidiasis has not yet been established. Currently there is limited evidence to support combination therapy for the treatment of uncomplicated candidaemia, as such this is not generally recommended.

4 Use of biomarker diagnostics

The clinical and cost effectiveness of diagnostic strategies incorporating Beta-D-glucan (BDG) tests to reduce unnecessary use of empirical antifungal therapies for invasive *Candida* infection in the critical care setting were assessed by the Scottish Health Technologies Group [Pre-emptive compared with empirical antifungal strategies for invasive *Aspergillus* infection \(shtg.scot\)](https://www.shtg.scot.nhs.uk/pre-emptive-compared-with-empirical-antifungal-strategies-for-invasive-Aspergillus-infection)

Conclusions of this assessment include:

- Preliminary clinical evidence and economic modelling suggests there is potential for the Fungitell® Beta-D glucan (BDG) test to reduce empirical antifungal overuse with minimal direct cost impact, however, caution should be exercised in relation to the imperfect nature of the test and the potential risk involved in withholding or discontinuing empirical treatment in false negative cases.
- Evidence from a small number of published studies indicates that BDG tests can be used as part of strategies to increase the rate of early discontinuation of empirical antifungal therapies in the adult critical care setting, although studies were not large enough to inform the safety of this approach.
- No evidence was identified on the use of BDG testing to withhold empirical antifungal therapy in this setting. Several relevant trials are in progress.

It should be noted that optimum cost-effectiveness of BDG testing is only seen in units with very high antifungal use and high lab throughput. Good clinical microbiology liaison remains pivotal.

5 Good practice recommendation for the use of antifungal therapy out with candidaemia and deep-seated *Candida* infection

The following table provides practical advice on the clinical interpretation and management recommendations for the treatment of *Candida* species isolated from non-sterile sites.

Candida species isolated from sputum/respiratory tract specimen
<p>Growth of <i>Candida</i> from sputum/respiratory tract secretions without clinical signs of oral thrush commonly indicates colonisation and does not warrant treatment.</p> <p><i>Candida</i> in the sputum/ respiratory tract secretions is not an indicator of <i>Candida</i> pneumonia, which is considered an extremely rare infection. If suspected, discussion with a Microbiologist or an Infection Specialist is advised.</p>
Candida species isolated from throat swab/sputum/upper respiratory tract specimen indicative of oropharyngeal candidiasis
<p>Refer to local guidelines/policy for empirical antifungal treatment options. HIV testing should be considered in all patients with unexplained oropharyngeal candidiasis.</p> <p>For mild <i>Candida</i> infection, nystatin oral suspension is a reasonable empirical agent. For moderate to severe disease, oral fluconazole for 7–14 days is recommended. For denture-related candidiasis, appropriate disinfection of the denture, in addition to antifungal therapy is advised.</p> <p>Treatment of fluconazole-refractory infection or infection with fluconazole-resistant <i>Candida</i> species or at risk patients should always be discussed with a Microbiologist or an Infection Specialist.</p>
Candida species isolated from urinary tract specimen (mid-stream urine, catheter specimen)
<p>Growth of <i>Candida</i> is commonly encountered, particularly in patients with an indwelling urinary catheter. Elimination of predisposing factors, such as removal/change of urinary catheters when feasible and repeat sampling is advised.</p> <p>Antifungal treatment is not recommended in asymptomatic patients who are not high risk for dissemination. High-risk patients include neutropenic patients, very low-birth-weight infants (<1500 g), and patients undergoing urologic manipulation or instrumentation.</p> <p>Treatment of such high-risk patients should always be carried out in consultation with a Microbiologist or an Infection Specialist.</p>
Candida species isolated from genital tract specimens indicative of vulvo-vaginal candidiasis
<p>Refer to local guidelines/policy for empirical antifungal treatment options.</p> <p>For the treatment of uncomplicated candida vulvo-vaginitis, topical antifungal therapy is recommended. No one agent has been shown have superiority to another.</p> <p>For severe acute <i>Candida</i> vulvo-vaginitis, fluconazole-refractory infection/ relapse or infection with fluconazole-resistant <i>Candida</i> species consultation with a Microbiologist or an Infection Specialist is advised.</p>

6 References

1. Pappas, P.G., Kauffman, C.A., Andes, D.R., et al. 2015/2016, Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America, *Clinical Infectious Diseases* 62: e1-e50.: an official publication of the Infectious Diseases Society of America
[Available at: https://academic.oup.com/cid/article-abstract/62/4/e1/2462830](https://academic.oup.com/cid/article-abstract/62/4/e1/2462830)
2. Cornely, O.A., Bassetti, M., Calandra, T., et al., al & ESCMID Fungal Infection Study Group, 2012, ESCMID* guideline for the diagnosis and management of Candida diseases 2012: non-neutropenic adult patients, *Clinical Microbiology and Infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, 18 Suppl 7:, pp. 19-37. Available at:
https://www.escmid.org/fileadmin/src/media/PDFs/4ESCMID_Library/2Medical_Guidelines/ESCMID_Guidelines/ESCMID_Candida_Guidelines_CMI_Dec2012_summary.pdf
3. Scottish One Health Antimicrobial Use and Antimicrobial Resistance in 2017
Health Protection Scotland 2018 <https://www.hps.scot.nhs.uk/pubs/detail.aspx?id=3604>
4. Andes DR ,Safdar N, Baddley JW et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials.
Clin Infect Dis 2012; 54:1110–22.
5. Rex JH , Bennett JE, Sugar AM et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia.Candidemia Study Group and the National Institute. *N Engl J Med* 1994; 331:1325–30.
6. Reboli AC ,Shorr AF, Rotstein C et al. Anidulafungin compared with fluconazole for treatment of candidemia and other forms of invasive candidiasis caused by *Candida albicans*: a multivariate analysis of factors associated with improved outcome. *BMC Infect Dis* 2011; 11:261.
7. Betts RF ,Nucci M, Talwar D et al. A Multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. *Clin Infect Dis* 2009; 48:1676–84.
8. NucciM , Colombo AL, Petti M et al. An open-label study of anidulafungin for the treatment of candidaemia/invasive candidiasis in Latin America. *Mycoses* 2014; 57:12–8.
9. Vazquez J ,Reboli AC, Pappas PG et al. Evaluation of an early step-down strategy from intravenous anidulafungin to oral azole therapy for the treatment of candidemia and other forms of invasive candidiasis: results from an open-label trial. *BMC Infect Dis* 2014; 14:97.
10. Overview of antifungal dosing in invasive candidiasis. Pea F, Lewis R. *J Antimicrob Chemother* 2018;73 S33-s43
11. Therapeutic Drug Monitoring (TDM) of antifungal agents: guidelines from the British Society for Medical Mycology. Ashbee HR, Barnes RA, Johnson EA et al. *J Antimicrobial Chemother* 2014; 69 (5) 1162-1176