

# Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2008

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## Key words

antifungal therapy, invasive fungal infection, *Candida*, *Aspergillus*, moulds, prophylaxis.

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## Abstract

The process for development of these consensus Australasian antifungal guidelines for use in adult patients with haematological malignancy is described. New features included, how the guidelines should be applied, the risk assessment tool used and the grading system for evidence and strength of recommendation are discussed.

## Introduction

Guidelines for the use of antifungal agents in the treatment of invasive *Candida* and mould infections were previously published in this journal in 2004. While these guidelines have been widely used and adapted throughout Australasia, it was recognized that they could benefit from a more transparent writing process and wider consultation prior to publication. The current guidelines aim to update our recommendations, based on a more recent review of the evidence and expand on the topics covered previously.

The updated guidelines focus on the most commonly occurring fungal infections due to yeasts (with the exception of *Pneumocystis jirovecii* (*P. carinii*)) and moulds in adult haematology and oncology patients – the highest users of systemic antifungal drugs among hospitalized patients. An online survey of current practice was made available on the websites of the Australasian Leukaemia and Lymphoma Study Group (ALLG), Australasian Society for Infectious Diseases (ASID) and NSW Cancer Institute prior to our first consensus meeting. Responses to the survey revealed significant variability in practice between institutions and confirmed an overall need (and desire) for clinical guidance in this particular setting.

Further consensus meetings may be organized in the future to generate recommendations for the use of antifungal agents in other clinical settings such as intensive care, solid organ transplant, dermatology and ophthalmology.

The salient differences between the current guidelines and those published in 2004 are summarized in Box 1.

## Process for development of guidelines

The process for developing these guidelines was modelled on a successful European consensus meeting held in September 2005 involving the European Bone Marrow Transplant Society, European Organisation for Research and Treatment of Cancer, International Immunocompromised Host Society and the Supportive Care Group of the European Leukemia Network. Three working groups were formed to review the literature and formulate evidence-based guidelines on antifungal prophylaxis, empirical antifungal treatment and the treatment of proven fungal infections. An initial consensus meeting revealed that there was sufficient interest and questions from clinicians to warrant the formation of two further working groups – one to discuss drug–drug interactions, drug toxicity and the role of therapeutic drug monitoring

**Box 1**

Updated guidelines – additional features

The new guidelines:

- have a broader scope; recommendations are provided for and beyond the treatment of established fungal infections
- provide pathogen-based treatment recommendations
- incorporate newer antifungal agents, i.e. licensed for use in Australia since 2004, e.g. posaconazole
- adopt a specific patient risk stratification tool
- include additional topics:
  - ancillary treatment decisions
  - treatment of infections in special/difficult sites, e.g. central nervous system (CNS), eye
  - non-culture based diagnostic tests
  - infection control issues
- address antifungal drug interactions, toxicity and the role of therapeutic dose monitoring in greater detail
- no longer recommend using serum creatinine and creatinine clearance to guide the use of lipid amphotericin B products
- incorporate clinical pathways (see Appendix II of electronic appendix).

(TDM); the other to provide guidance on how to prevent and reduce the risk of invasive fungal infections (IFIs) during hospital building works.

Representatives from haematology, infectious diseases, microbiology and pharmacy were appointed to each working group. Each group presented their findings at a one-day consensus meeting in November 2006, to which all ASID and ALLG members were invited (see Appendix I for a list of attendees). All discussion points were subject to debate. Where there was significant contention, a group vote was employed to reach a consensus. The draft guidelines were revised accordingly and presented at an ALLG meeting in May 2007. Over the intervening months, each group chair facilitated round-robin reviews to oversee the writing process. The final manuscript was made available to all ASID and ALLG members for comment prior to publication.

## Application of guidelines

The updated guidelines provide a general framework for best practice. Regard should be given to local fungal epidemiology and the incidence of IFI in your institution when applying the recommendations presented herein. As always, clinical judgement and local experience should govern how you implement these guidelines in each individual case.

The risk stratification tool used throughout these guidelines was adapted from Prentice *et al.*, which assigns patients at risk of developing an IFI to one of four risk groups: low, intermediate low, intermediate high and high (see Table 1).<sup>1</sup> It was chosen for ease of use and

**Table 1** Invasive fungal infection risk groups

### Low risk

Peripheral blood stem cell autologous bone marrow transplant  
 Childhood acute lymphoblastic leukaemia except for *Pneumocystis jiroveci* (*P. carinii*) pneumonia  
 Lymphoma

### Intermediate risk

#### Low

Moderate neutropenia  $0.1\text{--}0.5 \times 10^9/\text{L}$  for <3 weeks, lymphocytes  $<0.5 \times 10^9/\text{L}$  + antibiotics, e.g. trimethoprim and sulfamethoxazole (Septrin®)  
 Older age  
 Central venous catheter

#### High

Colonized >1 site or heavy at one site, neutropenia  $<0.5$  to  $>0.1 \times 10^9/\text{L}$  for >3 to <5 weeks  
 Acute myeloid leukaemia  
 Total body irradiation  
 Allogeneic matched sibling donor bone marrow transplant

### High risk

Neutrophils  $<0.1 \times 10^9/\text{L}$  for >3 weeks  
 Colonized by *Candida tropicalis*, allogeneic unrelated or mismatched donor bone marrow transplant  
 Graft-versus-host disease  
 Neutropenia  $<0.5 \times 10^9/\text{L}$  for >5 weeks  
 Prednisolone >1 mg/kg and neutrophils  $<1 \times 10^9/\text{L}$  for >1 week  
 Prednisolone >2 mg/kg for >2 weeks  
 High-dose cytosine arabinoside (Ara-C)  
 Fludarabine (uncertain)

Adapted from Prentice *et al.* (2000).<sup>1</sup>

**Table 2** Levels of evidence and grades of recommendations – clinical intervention†

Level of evidence	Study design	Grade of recommendation
I	A systematic review of level II studies	A Body of evidence can be trusted to guide practice
II	Evidence obtained from at least one properly designed randomized controlled trial (RCT)	B Body of evidence can be trusted to guide practice in most situations
III-1	Evidence obtained from well designed pseudo-RCTs (alternate allocation or some other method)	B
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomized (cohort studies), case-control studies, or interrupted time series without a control group	B
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series with a parallel control group	C Body of evidence provides some support for recommendations but care should be taken in its application
IV	Evidence obtained from case series, either post-test or pre-test and post-test	C D Body of evidence is weak and recommendation must be applied with caution

†National Health and Medical Research Council. NHMRC additional levels of evidence and grades for recommendations for developers of guidelines. Pilot program 2005–2007. Canberra: NHMRC, 2005.

because it has been validated in a prospective study.<sup>2</sup> However, it does have limitations; it does not account for some factors known to determine IFI risk such as (dynamic) net state of immunosuppression due to prior therapy, disease status (e.g. relapse), presence of organ dysfunction (e.g. renal failure, mucositis, severe graft-versus-host disease (GVHD)) and likely exposure to fungal pathogens.<sup>3</sup>

Where relevant, these guidelines use the probability-based definitions for IFI ('proven', 'probable' and 'possible') developed by Ascioğlu *et al.*, 2002<sup>4</sup> but these should not form the basis of treatment decisions.

The availability of rapid diagnostic tests, computed tomography (CT) scanning, biopsy and bronchoscopy, along with a centre's experience with these modalities, will determine how these guidelines are applied. Without robust diagnostic support, some centres have become increasingly reliant on antifungal prophylaxis and empirical therapy.<sup>5</sup>

The role of new non-culture based tests (e.g. high-resolution computed tomography (HRCT) scans and serological assays) in diagnosing IFI and guiding therapy is currently undergoing extensive investigation; as such, it is likely that paradigms will shift over the next several years. To accommodate these likely changes, non-culture-based diagnostic tests are discussed and referred to in the clinical pathways presented by Morrissey *et al.* in the section on diagnostic and therapeutic approach to persistent or recurrent fevers of uncertain origin of these guidelines.

Studies examining the impact of combination drug therapies on patient outcomes may also influence future treatment algorithms. The guidelines will require modification over the next few years to keep pace of these and other new developments.<sup>6</sup>

## Levels of evidence and grades of recommendations

The levels of evidence and grades of recommendations used in these guidelines (see Table 2) are adapted from the National Health and Medical Research Council (NHMRC) levels of evidence for clinical intervention. The NHMRC's proposed criteria allow us to differentiate between the strengths of our recommendations by taking into account the volume, consistency, clinical impact, generalizability and applicability of the supporting evidence.

## References

- 1 Prentice HG, Kibbler CC, Prentice AG. Towards a targeted, risk-based, antifungal strategy in neutropenic patients. *Br J Haematol* 2000; **110**: 273–84.
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## Conflicts of interest

The following working group members are consultants or advisory committee members or receive honoraria, fees for service, or travel assistance (independent of research-related meetings) from; or have research or other associations with the organizations listed: Sharon Chen – Gilead Sciences; Jody Chu – Society of Hospital Pharmacists; David Ellis – Gilead Sciences, Merck Sharp & Dohme, Novartis, Pfizer, Schering Plough; Nicole Gilroy – Gilead Sciences, Pfizer, Schering Plough; Andrew Grigg – Schering Plough; Stephen Guy – AstraZeneca, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Pfizer, Roche, Schering Plough; Chris Heath – Boehringer Ingelheim, Gilead Sciences, Merck Sharp & Dohme, Pfizer; Sue Kirska

– Amgen, Mayne, Novartis, Roche, Society of Hospital Pharmacists; Debbie Marriott – Merck Sharp & Dohme, Pfizer, Schering Plough; Orla Morrissey – Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering Plough; Geoffrey Playford – Merck Sharp & Dohme, Pfizer, Schering Plough; David Shaw – Gilead Sciences, Merck Sharp & Dohme, Tibotec; Monica Slavin – Bristol-Myers Squibb, Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering Plough; Tania Sorrell – Gilead Sciences, Merck Sharp & Dohme, Pfizer, Schering Plough; Jeff Szer – Abbott, Actelion, Amgen, Bristol-Myers Squibb, Celgene, CSL, Genzyme, Gilead Sciences, Janssen-Cilag, KaloBios, Merck Sharp & Dohme, MGI Pharma, Novartis, Pfizer, Pharmion, Roche, Schering Plough; Julie Wilkes – Amgen, Pfizer, Pharmion, Roche.

## Appendix I

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Orla Morrissey, Co-chair (Empirical therapy)  
Peter Bardy, Co-chair (Empirical therapy)  
Karin Thursky, Co-chair (Treatment)  
John Seymour, Co-chair (Treatment)  
Leon Worth, Co-chair (Optimizing antifungal drug dosage, avoiding toxicity and improving outcomes)  
Christopher Blyth, Co-chair (Optimizing antifungal drug dosage, avoiding toxicity and improving outcomes)  
*On behalf of the Antifungal Guidelines Working Group*

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### Consensus meeting attendees

In addition to the Antifungal Guidelines Working Group members, the following individuals attended the consensus meeting:

Anthony Allworth – Royal Brisbane Hospital, Qld; David Andresen – The Children's Hospital, Westmead, NSW; Minyon Avent – Royal Adelaide Hospital, SA; Angela Booth – Cancer Institute, NSW; Ken Bradstock – Westmead Hospital, NSW; Philip Campbell – Andrew

Love Cancer Centre, Geelong, Vic.; Steve Chambers – Christchurch Hospital, NZ; Celia Cooper – Women's and Children's Hospital, SA; Chris Coulter – The Prince Charles Hospital, Qld; Mark Dean – Gosford Hospital, NSW; Petra Derrington – Gold Coast Hospital, Qld; Maria Downey – Royal Melbourne Hospital, Vic.; Alwyn D'Souza – Wellington Hospital, NZ; Jane Estell – Sydney Cancer Centre, NSW; Joan Faoagali – Princess Alexandra Hospital, Qld; Liam Fernyhough – Christchurch Hospital, NZ; Paul Georghiou – Wesley Hospital, Qld; David Gottlieb – Westmead Hospital, NSW; Tom Gottlieb – Concord Hospital, NSW; Kate Hale – The Children's Hospital at Westmead, NSW; Jock Harkness – St Vincent's Hospital, NSW; Derek Hart – Mater Hospital, Qld; Mark Hertzberg – Westmead Hospital, NSW; Noemi Horvath – Royal Adelaide Hospital, SA; Simon Iles – Alfred Hospital, Vic.; Ian Irving – Townsville Hospital, Qld; Glen Kennedy – Royal Brisbane and Women's Hospital, Qld; David Looke – Princess Alexandra Hospital, Qld; Joe McCormack – Mater Hospital, Qld; Peter Mollee – Princess Alexandra Hospital, Qld; Michael Nissen – Royal Children's Hospital, Qld; Clare Nourse – Mater Children's Hospital, Qld; Tracey O'Brien – Sydney Children's Hospital, NSW; Nigel Patton – Royal Adelaide Hospital, SA; Miles Prince – Peter MacCallum Cancer Centre, Vic.; Humphrey Pullon – Waikato Hospital, NZ; Andrew Roberts – Royal Melbourne Hospital, Vic.; Joe Sasadeusz – Royal Melbourne Hospital, Vic.; Peter Shaw – The Children's Hospital at Westmead, NSW; Ruth Spearing – Christchurch Hospital, NZ; Bryan Speed – Austin Hospital, Vic.; Ferenc Szabo – Royal Darwin Hospital, NT; Judith Trotman – Concord Hospital, NSW; Robyn Ward – St Vincent's Hospital, NSW.

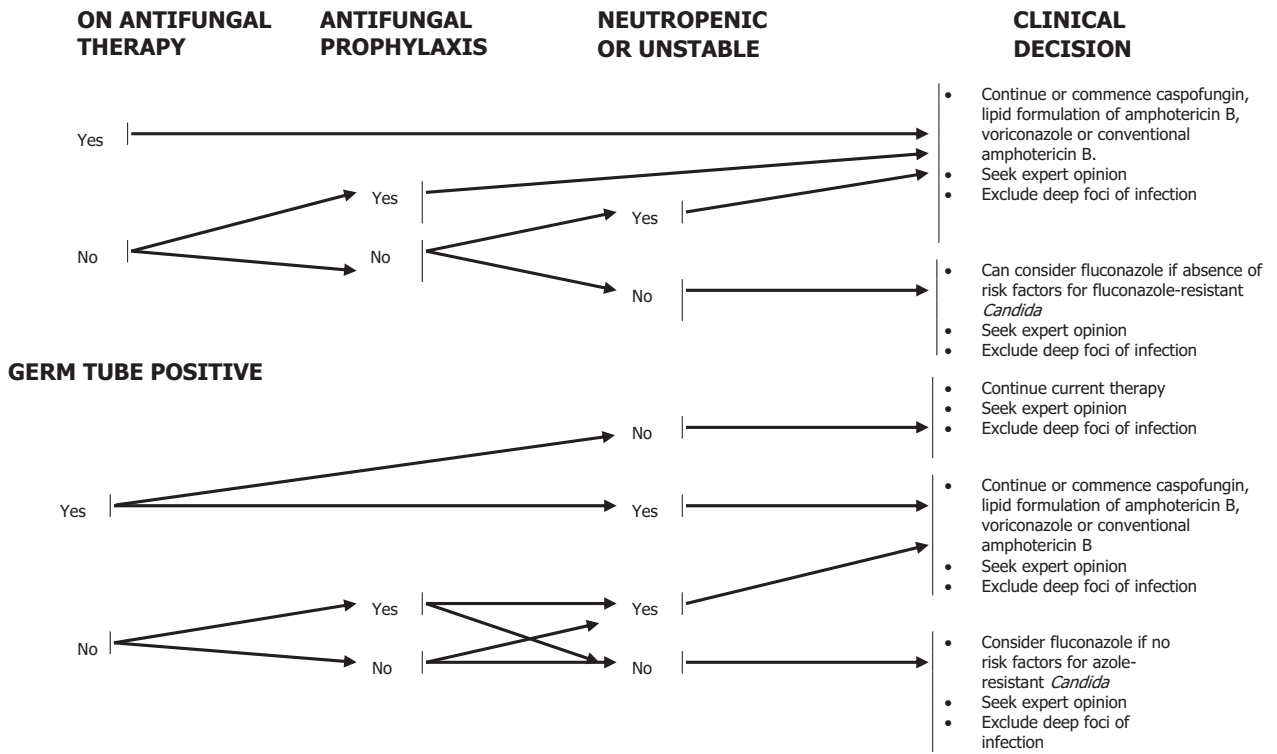
## Appendix II

### Summary of clinical pathways

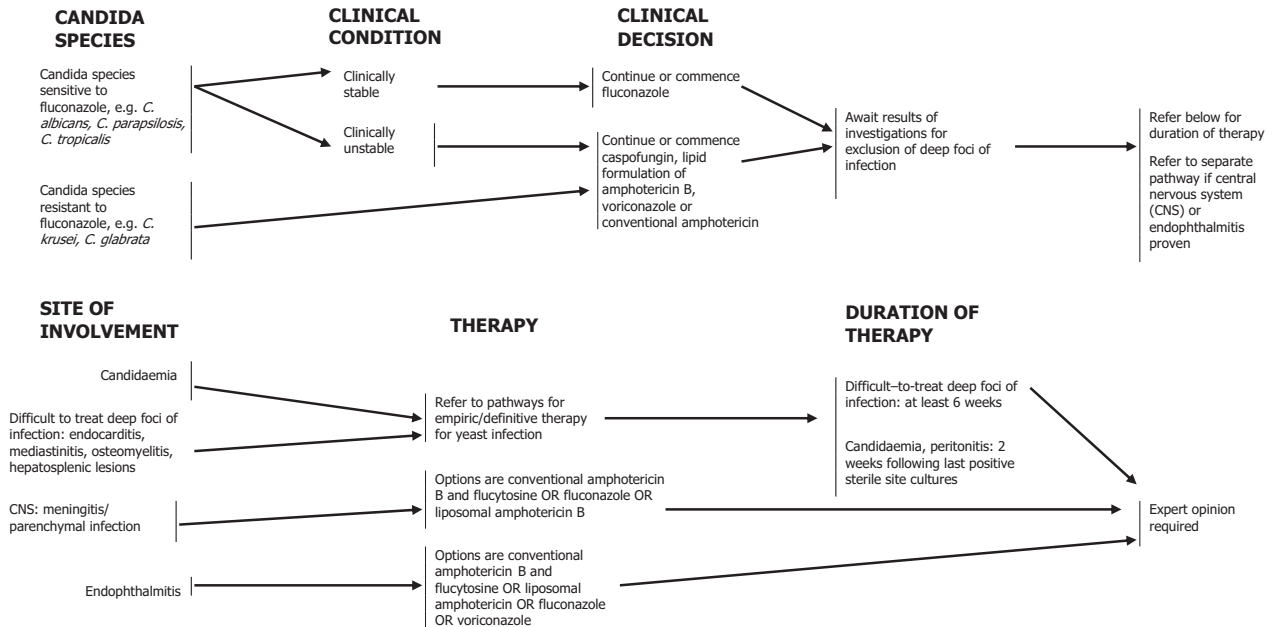
<b>HIGHER-RISK PATIENT</b>		
<ul style="list-style-type: none"> <li>Intensive chemotherapy of AML: induction, re-induction, consolidation with high-dose therapy</li> </ul>	→	Posaconazole solution 200 mg tds (with fatty food/drink). Start 24 hours after last anthracycline or on day of chemotherapy in patients not receiving anthracycline. Continue until neutropenia has resolved and patient in complete remission
<ul style="list-style-type: none"> <li>Higher risk allogeneic SCT, pre-engraftment, e.g. cord blood, unrelated donor transplant with bone marrow stem cell source or likely delayed engraftment</li> </ul>	→	Posaconazole solution 200 mg tds (with fatty food/drink). Other options: voriconazole 200 mg bd or itraconazole 200 mg bd or lipid formulation amphotericin 50 mg/day 3 times a week. Start after conditioning. Continue until neutropenia resolves. If no GVHD develops, use fluconazole through to day 75
<ul style="list-style-type: none"> <li>Allogeneic SCT with grade 2–4 GVHD</li> </ul>	→	Posaconazole solution 200 mg tds until day 112 post-onset GVHD or resolution
<b>LOWER-RISK PATIENT</b>		
<ul style="list-style-type: none"> <li>Less intensive chemotherapy AML or standard consolidation</li> </ul>	→	Fluconazole 200 mg/day. Start on admission and continue until neutropenia resolved
<ul style="list-style-type: none"> <li>Autologous SCT</li> </ul>	→	Fluconazole 200–400 mg/day. Start on admission and continue until neutropenia resolved
<ul style="list-style-type: none"> <li>Standard allogeneic SCT, pre-engraftment eg: sibling, matched, peripheral blood stem cell source</li> </ul>	→	Fluconazole 400 mg daily from admission to day 75
<ul style="list-style-type: none"> <li>Autologous SCT with non-mucositic regimen, chemotherapy for solid organ tumours</li> </ul>	→	No prophylaxis needed

**Figure A1** Prophylaxis in patients with haematological malignancy or profound neutropenia ( $ANC < 0.5/mm^3$ ). Note: Check posaconazole level if severe mucositis, diarrhoea. Use with caution or consider with holding posaconazole, voriconazole and itraconazole during treatment with cyclophosphamide. Monitor cyclosporin, tacrolimus levels if using voriconazole, itraconazole or posaconazole concomitantly. AML, acute myeloid leukaemia; SCT, stem cell transplant; GVHD, graft-versus-host disease.

**GERM TUBE NEGATIVE**



**Figure A2** Empirical therapy of yeast infection, species unknown. Note: If species identified, refer to specific pathway.

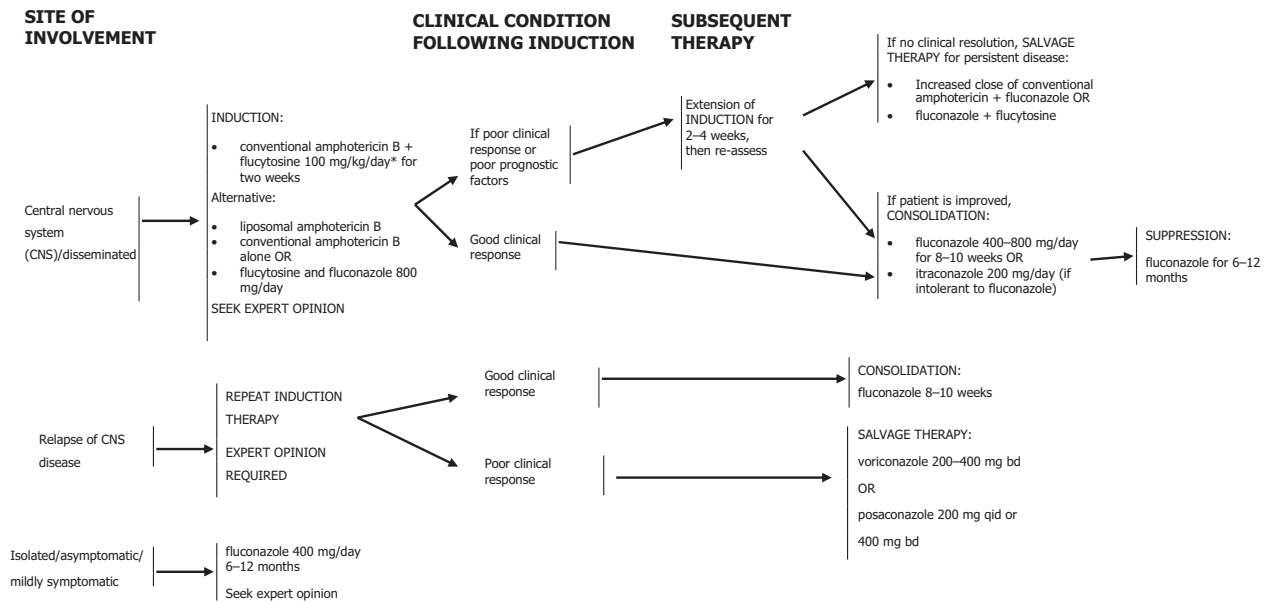


**Figure A3** Definitive therapy of *Candida* infection, species known. Note: In the above pathways, the antifungal agents are listed in descending order of preference, i.e. the first agent listed is the preferred drug of choice. See Table A1 in guidelines for drug doses.

**Table A1** Recommended doses of licensed antifungal agents for *Candida*†

Agent	Preparation	Recommended dose
Amphotericin B deoxycholate	IV	0.6–1.0 mg/kg daily
Liposomal amphotericin	IV	3–5 mg/kg daily
Amphotericin B lipid complex	IV	3–5 mg/kg daily
Fluconazole	Oral, IV	400 mg (6–12 mg/kg) daily
Voriconazole	Oral, IV	6 mg/kg every 12 h for 24 h, then 4 mg/kg every 12 h
Caspofungin	IV	70 mg daily for 24 h, then 50 mg daily

†Also see full Product Information. IV, intravenous.

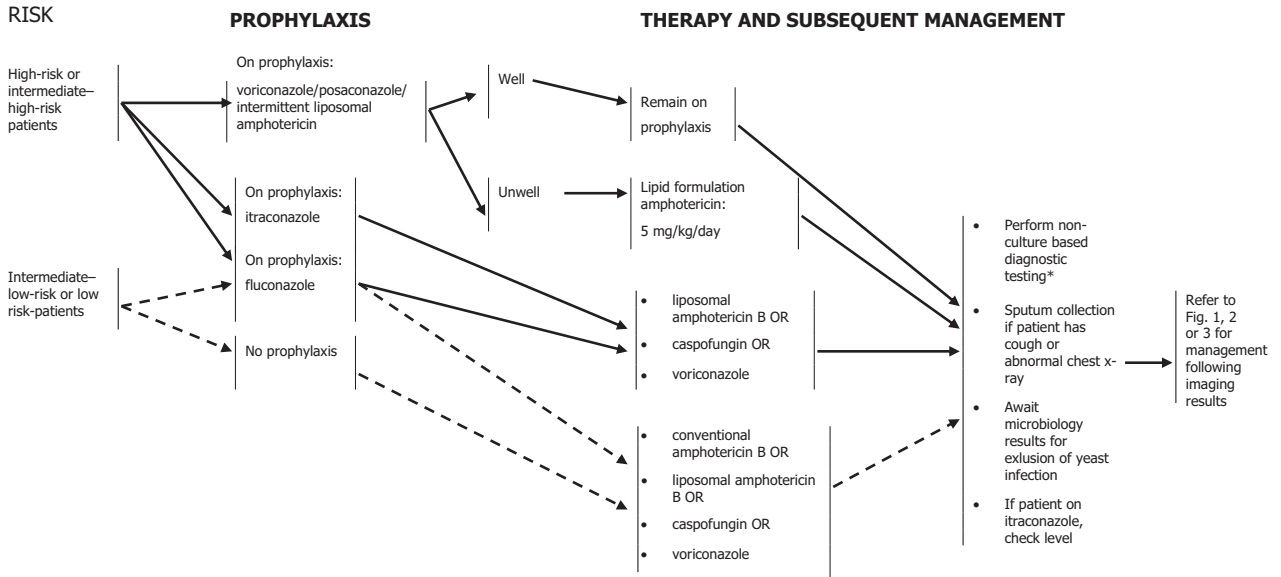


**Figure A4** Yeast infection (Indian Ink positive): *Cryptococcus*. \*Monitor electrolyte creatinine, liver function tests and full blood count if patient receives flucytosine for >2 weeks. Measure serum flucytosine levels 2 h post-dose. Adjust dose to maintain serum level between 30–80 mg/L.

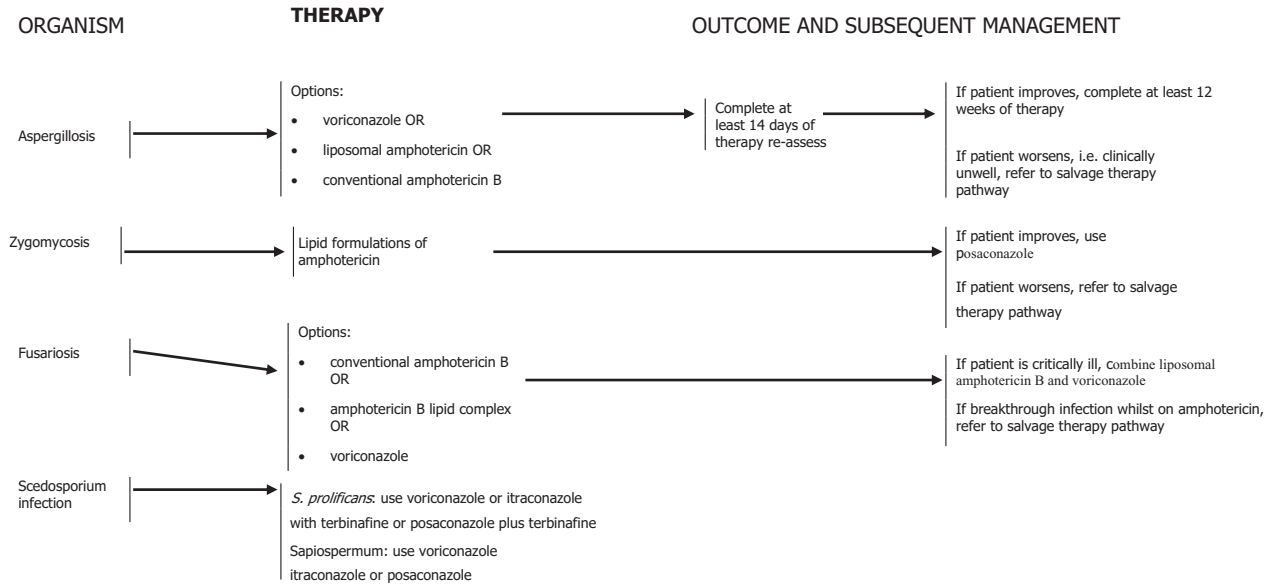
**Table A2** Recommended doses of antifungal agents for cryptococcal infections

Agent	Preparation	Recommended dose
Conventional Amphotericin B		
Induction	Intravenous	At least 0.7 mg/kg/day
Relapse of central nervous system (CNS) disease		Consider using increased dose: 1 mg/kg/day
Fluconazole	Oral, intravenous	
Consolidation		400 mg/day
Suppressive therapy		200 mg/day
Consolidation for relapse of CNS disease		600–800 mg/day
Liposomal amphotericin B†	Intravenous	
Induction		3–4 mg/kg
Relapse of CNS disease		5 mg/kg

†This agent can be used in place of conventional amphotericin B in cases of renal impairment.



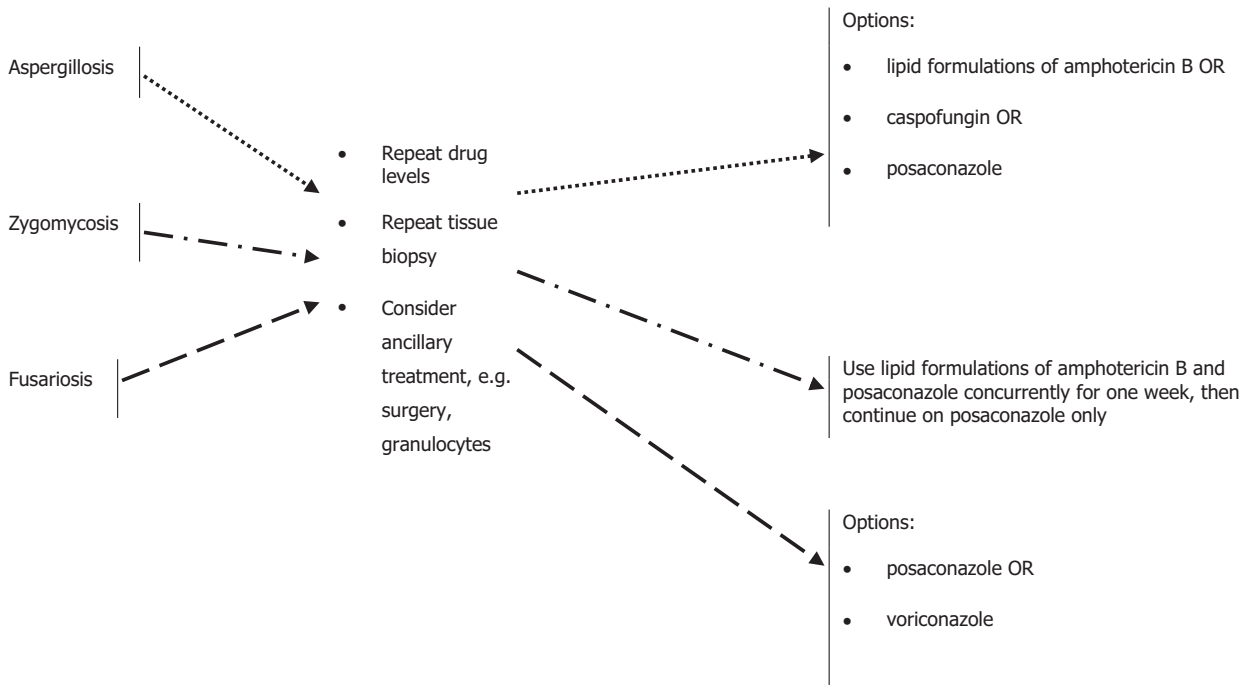
**Figure A5** Empirical therapy for mould infections. Note: expert opinion is required early in treatment and should be sought from empirical therapy onwards. ---- = empirical therapy for patients at low risk or intermediate low risk of invasive mould infection; \*Non-culture based diagnostic tests include: high-resolution computed tomography, galactomannan assay, polymerase chain reaction.



**Figure A6** Definitive therapy of proven mould infections. Note: expert opinion is required early in treatment and should be sought from empirical therapy onwards. Exact duration of therapy for zygomycosis, fusariosis and scedosporium infection is unknown.

ORGANISM

THERAPY



**Figure A7** Salvage therapy of mould infections (clinical progression despite 14 days of antifungal therapy). Note: expert opinion is required early in treatment and should be sought from empirical therapy onwards. .... = salvage therapy for aspergillosis; -.- = salvage therapy for zygomycosis; --- = salvage therapy for fusariosis.

**Table A3** Doses of antifungals for invasive mould infection

Agent	Preparation	Recommended dose
Amphotericin B deoxycholate	Intravenous	1–1.5 mg/kg/day
Liposomal amphotericin B/ Amphotericin B lipid complex	Intravenous	3–5 mg/kg/day; if concerned about non-aspergillus mould infection, start with 5 mg/kg/day
Voriconazole	Intravenous	6 mg/kg every 12 h for 24 h then 4 mg/kg every 12 h
	Oral (maintenance)	200–300 mg bd; for non-aspergillus mould infection, start with 400 mg bd on Day 1 then 300 mg bd thereafter
Caspofungin	Intravenous	70 mg daily for 24 h, then 50 mg daily
Posaconazole	Oral	200 mg qid, after 7–10 days can be dosed at 400 mg bd (aspergillosis)
		200 mg qid (zygomycosis)
		400 mg bd (fusariosis, scedosporium infection)
Itraconazole	Oral, intravenous	200 mg bd
Terbinafine	Oral	250 mg daily