



# Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2014

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## Key words

antifungal therapy, invasive fungal disease, *Candida*, *Aspergillus*, mould, *Pneumocystis jirovecii*.

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## Abstract

This article introduces the second revision of the *Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting*. The current update occurs within the context of a growing population at risk of invasive fungal disease, improved understanding of risk factors, availability of new diagnostic tests, a much-expanded evidence base and changing clinical paradigms. Here, we provide an overview of the history and purpose of the guidelines, including changes in scope since the last clinical update was published in 2008. The process for development, and for enabling review of draft recommendations by end-users and other relevant stakeholders, is described. The approach to assigning levels of evidence and grades of recommendation is also provided, along with a comparison to international grading systems.

## Introduction

Invasive fungal disease (IFD) remains a major cause of mortality in patients with haematological and other malignancies.<sup>1</sup> With the availability of newer diagnostic tests, as well as an improved understanding of risk factors, clinical paradigms for antifungal prophylaxis and therapy are changing.<sup>2</sup> These evidence-based guidelines

aim to keep clinicians abreast of current best practice for the prevention, diagnosis and treatment of IFD within the haematology/oncology setting.

The current guidelines represent the second revision of the *Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting*. These guidelines were first published in 2004 as a stand-alone paper<sup>3</sup> and updated in 2008 as a supplement

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**Conflicts of interest:** The following authors are consultants or advisory committee members or receive honoraria, fees for service, or travel assistance from, or have research or other associations with the organisations listed: Christopher C. Blyth – Pfizer, Merck Sharp & Dohme (investigator on investigator-initiated research projects funded by these companies); Sharon Chen – Gilead, Merck Sharp & Dohme, Pfizer; C. Orla Morrissey – Gilead, Merck Sharp & Dohme, Pfizer; Monica Slavin – Gilead, Merck Sharp & Dohme, Pfizer, Schering Plough; Jeff Szer – Gilead, Pfizer; Karin Thursky – Pfizer.

consisting of six separate articles.<sup>4-9</sup> When recently compared with other international antifungal treatment guidelines, the 2008 guidelines ranked the highest overall when the Appraisal of Guidelines Research and Evaluation criteria for assessing the quality and methodological rigour of guidelines was applied.<sup>10</sup>

A recent survey of antifungal drug prescribers also highlighted the clinical relevance and applicability of the previous guidelines.<sup>11</sup> The majority of survey respondents indicated that they had found the 2008 guidelines useful for formulating local institutional guidelines – a key requirement for antifungal stewardship and hospital accreditation.<sup>11</sup> While adherence to the guidelines by respondents was generally good, the survey also identified areas for improvement. This included the need for more discipline around reassessing IFD risk over time, particularly following haemopoietic stem cell transplant. The selection of a prophylactic agent in patient groups where data are currently lacking could also be more judicious.<sup>11</sup>

The utility of the previous guidelines is further supported by metrics from the *Internal Medicine Journal's* website, with the number of full text downloads since publication approaching 8500. Although the peak number of downloads occurred in 2008 and 2009, the guidelines have been downloaded over 950 times within the current year (2014), indicating that they are still regularly being referred to. All six articles comprising the 2008 guidelines have been accessed online. The guidelines have also been cited in other peer-reviewed publications 143 times since 2008.

### Scope and purpose of current guidelines

As per its previous iterations, the current guidelines primarily focus on the haematology/oncology setting, given that this patient population represents the largest consumers of antifungal agents within our hospitals.<sup>11</sup> Data specific to other immunocompromised host settings, such as human immunodeficiency virus infection, critically ill patients in intensive care units (e.g. candidiasis) and solid organ transplantation, are included only when pertinent.

The purpose of these guidelines is to provide clinicians with a robust, evidence-based framework for:

- Stratifying patients at risk of IFD
- Prescribing antifungal prophylaxis and therapy
- Ordering diagnostic tests
- Understanding potential antifungal drug interactions and toxicities
- Employing therapeutic drug monitoring, and
- Planning and implementing quality processes and surveillance strategies to monitor and prevent IFD

The guidelines also provide a basis for laboratories and clinicians to assess and agree which diagnostic and therapeutic drug monitoring tests should be made available within their institution, including optimal turnaround times for clinical utility. The guidelines also encourage specific consideration of IFD prevention within broader hospital-led antimicrobial stewardship programs.<sup>11</sup>

### Expanded scope of 2014 guidelines

For the first time, the guidelines provide recommendations for antifungal drug use in paediatric patients. The guidelines now also include a discrete article on the management of *Pneumocystis jirovecii* infections. Further, the article that previously related to the treatment of fungal infections has been divided into two articles, to separately address the treatment of yeast and mould infections. The article pertaining to the treatment of yeast infections includes a substantial focus on *Cryptococcus gattii* and the related complexities of management that clinicians face in the setting of this endemic Australian pathogen.<sup>12,13</sup> Much new information has also become available since 2008 regarding the optimal use of diagnostic tests for invasive aspergillosis (IA) and therapeutic drug monitoring. Evidence and strategies for both are discussed and incorporated into clinical pathways for diagnosis and management (see empiric and diagnostic-driven treatment guidelines by Morrissey *et al.*, 2014 appearing elsewhere in this supplement).<sup>14</sup>

### Process for guideline development

The process of updating the 2008 guidelines commenced with a survey of antifungal practice within Australia and New Zealand, with the aim of understanding clinicians' current use of prophylaxis, as well as the availability of key diagnostic tests within centres, and general attitudes and adherence to the existing guidelines. The survey's findings are reported in full in the article by van Hal *et al.*, 2014,<sup>15</sup> appearing elsewhere in this supplement, and were used to help inform the scope of recommendations provided in the 2014 guidelines. For example, the survey revealed that many centres do not currently receive results from non-culture based tests for IA within an optimal timeframe, and thus would benefit from evidence-based recommendations to guide the use of empiric antifungal therapy.

A steering committee for the guidelines was formed (see Appendix I) with each committee member responsible for leading and overseeing the editorial development of at least one topic section of the guidelines (with the exception of Christopher C. Blyth who was responsible for overseeing all paediatric recommendations). The

**Table 1** NHMRC body of evidence matrix<sup>†</sup>

Component	A Excellent	B Good	C Satisfactory	D Poor
Evidence base	One or more level I studies with a low risk of bias or several level II studies with a low risk of bias	One or two level II studies with a low risk of bias or a SR/several level III studies with a low risk of bias	One or two level III studies with a low risk of bias, or level I or II studies with a moderate risk of bias	Level IV studies, or level I to III studies/SRs with a high risk of bias
Consistency	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	Population/s studied in body of evidence are the same as the target population for the guideline	Population/s studied in the body of evidence are similar to the target population for the guideline	Population/s studied in body of evidence differ to target population for guideline but it is clinically sensible to apply this evidence to target population	Population/s studied in body of evidence differ to target population and hard to judge whether it is sensible to generalise to target population
Applicability	Directly applicable to Australian healthcare context	Applicable to Australian healthcare context with few caveats	Probably applicable to Australian healthcare context with some caveats	Not applicable to Australian healthcare context

<sup>†</sup>Adapted from National Health and Medical Research Council (NHMRC).<sup>23</sup> SR, systematic review; several, more than two studies.

steering committee was also responsible for reviewing the grades assigned to recommendations, and for liaising with Therapeutic Guidelines Limited to ensure that recommendations cited in the guidelines and the current national prescribing manual (*Therapeutic Guidelines: Antibiotic, version 14, 2010*)<sup>16</sup> were aligned. Links to the 2014 guidelines will be provided in the revised edition of *Therapeutic Guidelines: Antibiotic, version 15*.

A core writing group was established for each topic section of the guidelines (see Appendix I for author lists): antifungal prophylaxis (Fleming *et al.*, 2014);<sup>17</sup> empiric and diagnostic-driven treatment strategies (Morrissey *et al.*, 2014); treatment of yeasts (Chen *et al.*, 2014);<sup>18</sup> treatment of moulds (Blyth *et al.*, 2014);<sup>19</sup> diagnosis and treatment of *Pneumocystis jirovecii* (Cooley *et al.*, 2014);<sup>20</sup> optimising drug therapy and monitoring to avoid toxicity and improve outcomes (Chau *et al.*, 2014);<sup>21</sup> and quality processes for infection prevention and enhanced surveillance during building works (Chang *et al.*, 2014).<sup>22</sup> Each of these topic areas is presented as a discrete article in the current supplement along with the survey of current clinical practice (van Hal *et al.*, 2014).

All relevant areas of practice were represented among the writing groups, with contributing authors including infectious diseases physicians (adult and paediatric), haematologists (adult), hospital pharmacists, microbiologists, infection prevention consultants and building project managers. Participants were drawn from the cohort of clinicians who had contributed to earlier versions of the guidelines (2004 and 2008), as well as from

clinicians who responded to a national call for expressions of interest from the Australasian Society for Infectious Diseases (ASID).

Writing commenced in August 2013 with each group identifying the key clinical questions that needed to be addressed in the updated guidelines and the required search strategy. Following a review of evidence published since 2007, draft guidelines were developed and circulated to all members of the writing group for review and comment. The draft guidelines were then made available to the ASID, the Australasian Leukaemia and Lymphoma Study Group (ALLG) and the Australian and New Zealand Children's Haematology/Oncology Group (ANZCHOG) for distribution to their member networks for feedback and commentary prior to publication. The ASID has a network of 800 members, including all infectious diseases physicians and trainees in Australia and New Zealand, as well as specialist pharmacists, infection prevention nurses, microbiologists and medical scientists. The ALLG has a national network of 340 haematologists, stem cell transplant physicians, research nurses, study coordinators and supportive care experts. The ANZCHOG also has a multidisciplinary membership comprising 82 healthcare professionals working in, or with an interest in, the fields of paediatric blood diseases and cancer throughout Australia and New Zealand. One or more experts from these groups were also selected to independently review each section of the guidelines. Following this wider review process, the feedback received was collated and incorporated into the guidelines, as

**Table 2** Comparison of evidence and recommendation grading systems used by various bodies in recent publications

Grading system	Evidence grading					Recommendation grading				Comments
	I	II	III	IV	A	B	C	D		
NHMRC <sup>23</sup>	Systematic review of RCTs	RCT	Non-RCT studies	Case series	Excellent: trusted to guide practice	Good: trusted to guide practice in most situations	Satisfactory: some support for recommendation but take care with application	Poor: apply with caution	Subgrades for strength of category III evidence (1–3)	
IDSA <sup>24</sup>	Evidence from ≥1 RCT	Non-RCT studies	Expert opinion or case series	Not applicable	Good evidence for or against	Moderate evidence for or against	Poor evidence	Not used	Used pre-October 2008	
ESCMID <sup>25</sup>					Strongly supports use	Moderately supports use	Marginally supports use	Supports a recommendation against use	Subgrades for category II evidence based on comparator group and publication status	
ECIL <sup>26</sup>					Strong evidence for efficacy and benefit; strong recommendation	Strong or moderate evidence for efficacy but only limited clinical benefit; generally recommended	Insufficient evidence for efficacy or efficacy does not outweigh potential adverse consequences; optional	Moderate evidence against efficacy or for adverse outcome. Generally not recommended	Also 'E': strong evidence against efficacy or of adverse outcome, never recommended	
GRADE <sup>27</sup>	High	Moderate	Low	Very low	Strong: if evidence quality is high or moderate	Weak: if evidence quality is low or very low			Quality of evidence determined by confidence in estimating an effect for a specific question	

ECIL, European Conference on Infections in Leukemia; ESCMID, European Society for Clinical Microbiology and Infectious Diseases; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IDSA, Infectious Diseases Society of North America; NHMRC, National Health and Medical Research Council; RCT, randomised control trial.

appropriate. Key recommendations from the draft guidelines were also presented at ASID's annual meeting in April 2014 and ALLG's bi-annual scientific meeting in May 2014 and feedback invited.

### Grading of evidence and recommendations

These guidelines use the grading system endorsed by the Australian National Health and Medical Research Council (NHMRC). Within this system, studies are assessed according to strength of evidence (based on level, quality and statistical precision of study), size of effect and the relevance of the evidence to the patient population to which the recommendations are to be applied. The hierarchy of evidence is:

- Level I: a systematic review of level II studies
- Level II: a randomised control trial
- Level III: comparative studies (e.g. a pseudo-randomised controlled trial, a comparative study with concurrent controls)
- Level IV: a case series

The strength of evidence for a recommendation is graded A (excellent) to D (poor), based on five criteria: the evidence base, the consistency of study results, the potential clinical impact of the recommendation, the generalisability of the body of evidence to the target population and the applicability of the evidence to the Australian healthcare context (see Table 1). Within this system, a recommendation can only be graded 'AI' if systematic reviews with consistent findings – and in the same patient population to which the guideline applies – support the benefit and is deemed adequately relevant to the Australian healthcare system.<sup>23</sup>

The NHMRC grading system differs from those appearing in guidelines produced by the Infectious Diseases Society of North America, European Conference on Infections in Leukemia and European Society for Clinical Microbiology and Infectious Diseases. Indeed, numerous differences between the various grading systems used here and internationally (see Table 2 for a comparison)

make it impossible to directly compare any of these guidelines. However, there is a shift towards using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system in international guidelines due to its transparency; within this system, each question addressed within a guideline must be evaluated separately and the assigned grade of recommendation supported by a summary of evidence table.<sup>28</sup> It is worth noting that the NHMRC and GRADE evaluation systems use a similar approach to assess quality of evidence.

### Conclusion

The 2008 consensus guidelines for the use of antifungal agents in the haematology/oncology setting were well accepted and widely used throughout Australia and New Zealand. The 2014 update of these guidelines (see collection of articles published in the current supplement) were developed following a rigorous and independent writing and consensus process. The guidelines were also subject to wide end-user review prior to publication and have been endorsed by ASID, ALLG and ANZCHOG. The NHMRC grading system was used to assess the evidence upon which all recommendations are based. This system differs from that used in other guidelines but incorporates similar criteria to the internationally accepted GRADE system of evaluation. The authors welcome feedback and suggestions for improvement from users of these guidelines and look forward to further data and research to strengthen and inform future versions of these guidelines.

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## Appendix I

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### Treatment of yeasts

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### Treatment of moulds

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**Diagnosis and treatment of *Pneumocystis jirovecii***

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