INTERNAL MEDICINE JOURNAL

Internal Medicine Journal **44** (2014)

Survey of antifungal prophylaxis and fungal diagnostic tests employed in malignant haematology and haemopoietic stem cell transplantation (HSCT) in Australia and New Zealand

S. J. van Hal,[1]* N. M. Gilroy,[2,3] C. O. Morrissey,[4,5] L. J. Worth,[6,7] J. Szer,[8.9] C. S. Tam,[9,10] S. C. Chen,[11,12,13] K. A. Thursky[6,14] and M. A. Slavin[6,9,14]

[1]Department of Microbiology and Infectious Diseases, Royal Prince Alfred Hospital, Camperdown, New South Wales, [2]Blood and Marrow Transplant (BMT) Network, Agency for Clinical Innovation, Chatswood, New South Wales, [3]Department of Infectious Diseases and Clinical Microbiology, St Vincent's Hospital, Darlinghurst, New South Wales, [4]Department of Infectious Diseases, Alfred Health and Monash University, Prahran, Victoria, [5]Department of Clinical Haematology, Alfred Health, Prahran, Victoria. [6]Department of Infectious Diseases and Infection Control, Peter MacCallum Cancer Centre, East Melbourne, Victoria, [7]Department of Medicine, The University of Melbourne, Melbourne, Victoria, [8]Department of Clinical Haematology and Bone Marrow Transplant Service, The Royal Melbourne Hospital, Parkville, Victoria, [9]School of Medicine, The University of Melbourne, Melbourne, Victoria, [10]Department of Haematology, Peter MacCallum Cancer Centre, East Melbourne, Victoria, [11]Centre for Infectious Diseases and Microbiology Laboratory Services, ICPMR – Pathology West, Westmead, New South Wales, [12]Department of Infectious Diseases, Westmead Hospital, Westmead, New South Wales, [13]Sydney Medical School, The University of Sydney, Sydney, New South Wales, [14]Victorian Infectious Diseases Service, The Doherty Institute for Infection and Immunity, Parkville, Victoria

Key words
haematological malignancy, antifungal, prophylaxis, haemopoietic stem cell transplantation, fungal diagnostic test, survey.

Correspondence
Sebastiaan J. van Hal, Department of Microbiology and Infectious Diseases, Royal Prince Alfred Hospital, PO Box M30 Missenden Road, Camperdown, NSW 2050, Australia.
Email: Sebastian.vanhal@sswahs.nsw.gov.au

doi:10.1111/imj.12594

Abstract

This article reports the findings of a survey developed to assess the current use of antifungal prophylaxis among haematology and infectious disease clinicians across Australia and New Zealand, and their alignment with existing consensus guidelines for the use of antifungal agents in the haematology/oncology setting (published 2008). Surveyed clinicians largely followed the current recommendations for prophylaxis in the setting of induction chemotherapy for acute myeloid leukaemia, as well as autologous and low-risk allogeneic haemopoietic stem cell transplantation (HSCT). In keeping with guideline recommendations, posaconazole was the agent used by most centres for high-risk allogeneic HSCT. However, its routine continuation for 75–100 days post-transplantation without de-escalation suggested use beyond those indications described in the 2008 guidelines, namely pre-engraftment neutropenia and graft-versus-host disease. Variations in practice were observed in other settings, such as acute lymphoblastic leukaemia and myelodysplastic syndrome, reflecting the general lack of evidence for antifungal prophylaxis in these patient populations and changing perceptions of risk. With regard to the availability of testing in cases of suspected breakthrough IFD, 40% of centres did not have access to investigative bronchoscopy within 48 h of referral, and results of *Aspergillus* galactomannan (GM), fungal polymerase chain reaction and therapeutic drug monitoring (TDM) were not available within 48 h in 83%, 90% and 85% of centres respectively. The survey's findings will influence the recommendations provided in the updated 2014 consensus guidelines for the use of antifungal agents in the haematology/oncology setting.

Introduction

Invasive fungal disease (IFD) remains a significant problem in patients undergoing chemotherapy for haematological malignancies and allogeneic haemopoietic stem cell transplant (HSCT) recipients.[1] These infections incur substantial morbidity and mortality.[2] Accordingly, a range of preventative approaches have been employed in clinical

*First author.

Funding: No funding was received for this project.

Conflict of interest: The following working group members 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: Sharon Chen, Gilead, Merck Sharp & Dohme, Pfizer; Nicole Gilroy, Gilead, Merck Sharp & Dohme, Pfizer, Schering Plough; Orla Morrissey, Gilead, Merck Sharp & Dohme, Pfizer; Monica Slavin, Gilead, Merck Sharp & Dohme, Pfizer, Schering Plough; Jeff Szer, Gilead, Pfizer; Constantine Tam, Gilead; Karin Thursky, Pfizer; Sebastiaan van Hal,Gilead, Merck Sharp & Dohme, Pfizer, Schering Plough.

haematology and transplant units to reduce the incidence of IFD and improve clinical outcomes. In Australia and New Zealand, antifungal prophylaxis remains the most common preventative strategy.

The Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting were first published in 2004 and updated in 2008.[3,4] These guidelines were developed to assist clinicians to identify and stratify patients at risk of IFD, and to provide evidence-based recommendations for the prophylactic and therapeutic use of antifungal agents. The current guidelines (see accompanying articles published elsewhere in this supplement for 2014 update) seek to keep clinicians abreast of best practice within the context of the evidence base now available.

Before updating these consensus recommendations, we first sought to survey clinicians to ascertain the current nature and scope of antifungal prophylaxis practice throughout Australia and New Zealand, and to assess the extent of alignment with the most recently published guidelines (2008). We also sought to identify the availability and timeliness of newer diagnostic tests and therapeutic drug monitoring (TDM). These findings were then used to help inform the recommendations provided in the 2014 consensus guidelines.

Methodology

Survey population

Haematologists, infectious disease specialists and pharmacists were invited to participate in this survey given that they represent the main providers of clinical support to patients with haematological malignancies and/or undergoing HSCT. These professionals also represent the key personnel involved in the development and application of hospital-based antifungal protocols and clinical decision support.

Survey tool

An online survey (using Survey Monkey®, Paulo Alto, CA, USA) was developed in consultation with members of the Australian-New Zealand Mycology Interest Group and the Australasian Leukaemia Lymphoma Group (ALLG). The membership base of both these organisations represent a range of disciplines involved in clinical research, supportive care and guideline development for patients with haematological malignancies. The final piloted survey consisted of 15 questions and took less than 10 minutes to complete. The survey was distributed electronically to those members of the ALLG (n = 340) and to approximately 800 members of the Australian Society of Infectious Diseases (ASID) who were registered subscribers of an online email discussion group ('OzBug').

Survey analysis

Participation in the survey was voluntary, and individual respondents and their affiliated institutions were de-identified. Survey responses were collated and analysed using IBM SPSS (version 22.0, Armonk, NY: IBM Corp.).[5] Given the aim of the survey, the number and percentage of respondents (and centres, where relevant) ascribing to a particular practice were sufficient for describing the current state of clinical practice throughout Australia and New Zealand.

Results

Survey response

A total of 50 clinicians from 31 institutions (30 adult and one paediatric hospital) completed the survey. All Australian state and territory jurisdictions except Tasmania were represented, including nine institutions from NSW, nine from Victoria, seven from Queensland, two from South Australia and one institution each from the Australian Capital Territory, Northern Territory and Western Australia. One institution from New Zealand was also represented. The majority of respondents were haematologists (61%; 31/50), with the remainder either infectious disease specialists (n = 17) or pharmacists (n = 2).

Several institutions had more than one respondent. Responses from the same institution varied between specialists and within the same specialty at these institutions. This variability was seen with respect to prophylaxis agent chosen, duration of prophylaxis and patient population requiring prophylaxis, especially in less well-defined risk groups, such as lymphoma. Results, however, were consistent when analysed by individual hospital.

Some respondents did not answer one or more questions. As such, the number of responses received per clinical topic is shown where relevant in the results following and taken into consideration when interpreting the survey's findings.

Use of existing guidelines

All respondents, except one, stated that the previously developed guidelines assisted in the formulation of local protocols. In contrast, local data were available and utilised in only 65% (20/31) of hospitals.

Current use of antifungal prophylaxis by patient population

Acute myeloid leukaemia

The majority of respondents (90%; 35/39 representing 22 hospitals) used posaconazole prophylaxis for induction chemotherapy. The other antifungal agents used included fluconazole (n = 2), itraconazole (n = 1) and liposomal amphotericin B (n = 1). Forty-one per cent (16/39) of respondents commenced prophylaxis on admission, while 44% (17/39) aligned the start of prophylaxis with the start of chemotherapy. Forty-three per cent of respondents (10/23) ceased prophylaxis upon resolution of neutropenia (neutrophil counts at least >500 cells/mm^3).

Most respondents (79%; 30/38) also preferred posaconazole for prophylaxis during consolidation chemotherapy with the timing of commencement and cessation similar to induction.

It is also worth noting that prophylaxis with fluconazole, which has no activity against moulds, was used during consolidation chemotherapy in three hospitals and during induction in one hospital.

Blood and marrow transplantation

Allogeneic HSCT was performed in 13 of the hospitals represented in the survey (22 respondents). Most respondents (68%; 15/22) prescribed fluconazole prophylaxis for those patients deemed to be at a low to moderate risk of IFD. Those respondents who used prophylaxis in this setting generally continued it for a period of 75–100 days (72%; 16/22). Respondents prescribed anti-mould prophylaxis with posaconazole (68%; 15/22), voriconazole (5%; 1/22) or itraconazole (14%; 3/22) for patients at high risk of IFD for a period of 75–100 days (64%; 14/22) following transplantation.

Multiple factors influenced the decision to commence antifungal prophylaxis in patients with graft-versus-host disease (GVHD) post-allogeneic HSCT, including the grading of GVHD, overall level of immunosuppression and steroid dose >20 mg/day. Severity of symptoms was considered important by less than half of the clinicians surveyed (40%; 9/22), while five respondents used additional unspecified criteria to inform their decision. Similarly, a composite endpoint informed the cessation of antifungal prophylaxis, including absence of symptoms for more than 3 months, cessation of immunosuppressant agents/modulators and a steroid dose requirement of <20 mg/day.

Autologous HSCT was performed in 18 of the hospitals represented by respondents and fluconazole prophylaxis used by all. Although the absolute indications for mould-active prophylaxis differed between hospitals, the most common indications were transplantation in the setting of relapsed or refractory disease, or the need for high-dose corticosteroids.

Acute lymphocytic leukaemia

Induction chemotherapy for acute lymphocytic leukaemia (ALL) was deemed to place patients at higher risk for IFD by clinicians with 53% (18/34) of respondents using anti-mould prophylaxis in this setting. Agents used included liposomal amphotericin B (n = 15) and posaconazole (n = 3). Two respondents did not use prophylaxis, with the remaining clinicians prescribing fluconazole (41%; 14/34). During maintenance chemotherapy for ALL, 34% (11/33) of respondents used no prophylaxis, while 52% (17/33) used fluconazole prophylaxis. Irrespective of cycle of chemotherapy, most respondents initiated prophylaxis around the commencement of chemotherapy and ceased prophylaxis upon resolution of neutropenia (neutrophil counts at least >500 cells/mm^3).

Other haematological malignancies

Table 1 shows the antifungal agent chosen and general indications for commencement of prophylaxis in the setting of Burkitt's lymphoma, non-Hodgkin lymphoma (NHL), Hodgkin lymphoma, chronic lymphocytic leukaemia, aplastic anaemia and myelodysplastic syndrome (MDS). Percentages did not change substantially when limited to hospital unit. Overall, fluconazole – rather than anti-mould prophylaxis – was the most common agent used, irrespective of malignancy. The perceived risk factors for IFD within the setting of a particular malignancy varied among respondents, with the exception of chemotherapy intensification for NHL, which was accepted by all as a definite requirement for antifungal prophylaxis.

Breakthrough IFD

There was a direct association between the antifungal agent chosen for prophylaxis and the agent subsequently chosen for empiric therapy of breakthrough IFD. Respondents switched patients receiving posaconazole or voriconazole prophylaxis to liposomal amphotericin B (60%; 19/32), an echinocandin (9%; 3/32) or combination therapy (16%; 5/32). In the setting of itraconazole or fluconazole prophylaxis, most respondents (73%; 22/30) switched patients to voriconazole, with the remaining opting for liposomal amphotericin B (n = 7) or posaconazole (n = 1).

Table 1 Respondents (%) using antifungal prophylaxis in various haematological malignancies and agent used

Indications for use of prophylaxis	BL *n* = 27 (%)	NHL *n* = 28 (%)	HL *n* = 24 (%)	CLL *n* = 21 (%)	AA *n* = 27 (%)	MDS *n* = 23 (%)
Refractory or relapsed disease	44	46	38	38	37	49
Chemotherapy intensification	78	100	50	48	26	49
T-cell depleting chemotherapy	30	43	25	62	63	22
High-dose corticosteroids	48	61	46	48	44	13
Other	11	7	13	24	34	49[†]
Agent used when prescribed						
Liposomal amphotericin B	4	0	0	0	0	0
Fluconazole	89	89	96	71	59	30
Itraconazole	0	0	0	0	4	4
Voriconazole	4	7	4	8	0	0
Posaconazole	4	4	0	19	37	65

[†]Other indications for antifungal prophylaxis in myelodysplastic syndrome were not specified. AA, aplastic anaemia; BL, Burkitt's lymphoma; CLL, chronic lymphocytic leukaemia; HL, Hodgkin's lymphoma; MDS, myelodysplastic syndrome; NHL, non-Hodgkin lymphoma.

Availability of testing

Respondents were able to provide information on the availability of testing in 20 hospitals around Australia and New Zealand. Respondents from all 20 hospitals reported that they were able to obtain a computed tomography (CT) scan within 48 h as part of their diagnostic work-up for suspected breakthrough IFD (Table 2). Although bronchoscopy was also available in all 20 hospitals, the procedure was generally not performed until 3–5 days after referral in eight (40%) of these sites. With respect to newer diagnostic and TDM modalities, only a minority of hospitals (35%; 7/20) had these available on-site. The direct consequence of this was longer turnaround times, with the majority of results only available after 3–5 days.

Table 2 Availability of tests for the investigation of patients with a suspected breakthrough fungal infection (number of hospitals (%))

Availability	Investigation				
	GM	PCR	CT	BAL	TDM
On-site	7 (35)	7 (35)	20 (100)	20 (100)	7 (35)
Send away	10 (50)	12 (60)	0 (0)	0 (0)	13 (65)
Not available	3 (15)	1 (5)	0 (0)	0 (0)	0 (0)
Timing of results availability	GM	PCR	CT	BAL	TDM
<48 h	3 (15)	2 (10)	20 (100)	12 (60)	3 (15)
3–5 days	6 (30)	11 (55)	0 (0)	8 (40)	15 (75)
>7 days	11 (55)	6 (30)	0 (0)	0 (0)	2 (10)
Not stated	0 (0)	1 (5)	0 (0)	0 (0)	0 (0)

BAL, bronchoalveolar lavage; CT, chest computer tomography; GM, *Aspergillus* galactomannan; PCR, *Aspergillus* polymerase chain reaction; TDM, azole therapeutic drug monitoring.

Discussion

A recognised strength of the 2008 consensus guidelines was the recommendation that clinicians use a risk stratification approach to identify which HSCT recipients and patients with haematological malignancies were at high, intermediate or low risk of IFD, and to inform the need for antifungal prophylaxis.[6] Within this schema, those ranked at highest risk of IFD include matched unrelated or mismatched allograft recipients, umbilical cord donor graft recipients, allogeneic HSCT recipients on immunosuppression for acute grade 2–4 or chronic extensive GVHD, and patients with acute myeloid leukaemia (AML) receiving cytarabine-based chemotherapy regimens for remission induction or re-induction.[7] Those AML patients receiving intensive consolidation treatment were also considered at high risk for IFD.

It was recommended that high-risk patients receive anti-mould prophylaxis, based on good levels of evidence generated from well-designed randomised controlled trials and meta-analyses in these populations over the last two decades.[8–10] Only two agents could be recommended in the 2008 guidelines (posaconazole or itraconazole) as no published data existed for voriconazole prophylaxis at that time. Survey responses indicate a high level of compliance with this recommendation, with posaconazole the predominant agent used. The use of voriconazole as primary prophylaxis remains low but was reported as the preferred agent for therapy in patients on a first-generation azole (fluconazole or itraconazole) with suspected breakthrough IFD.

Similar recommendations were made in 2008 for patients with MDS receiving anthracycline or cytarabine

chemotherapy based on a comparable IFD risk to AML.[11] However, unlike AML, indications for prophylaxis were not as well defined, which may explain why choice of agent is more varied among those surveyed. Alternatively, current prophylaxis usage may reflect changes in MDS patient care following the introduction of DNA hypomethylating agents (such as azacitidine) as frontline or salvage therapy.[12] IFD risk in these patients remain poorly defined but are perceived to be high.[13]

All survey respondents from centres performing autologous HSCT reported using fluconazole when prophylaxis was considered necessary. The majority of standard-risk and high-risk allogeneic HSCT received fluconazole (68%) and posaconazole (75%) prophylaxis as recommended and were routinely continued for 75–100 days post-transplant in most cases. The survey was unable to gauge whether further risk stratification or prophylaxis modification, as recommended in the 2008 guidelines, was followed. Improved local surveillance efforts should be encouraged as respondents reported that only two-thirds (65%) of hospitals use local data to inform the development of local protocols. This will also assist in defining IFD epidemiology in the post-transplant period and facilitate stewardship efforts to align day-to-day practice with the consensus guidelines.[14]

Evidence to guide the choice and duration of antifungal prophylaxis in settings other than AML and HSCT is limited, with no formal recommendations made based on malignancy type in 2008. Nevertheless, the survey identified that clinicians are currently prescribing prophylaxis for patients with lymphomas (Burkitt's, NHL and Hodgkin lymphomas), chronic lymphocytic leukaemia and aplastic anaemia. Chemotherapy intensification, refractory or relapsed disease, and therapy resulting in T-lymphocyte depletion were cited as the most common indications for antifungal prophylaxis. In all conditions, fluconazole was the preferred agent. These findings indicate the need for further research to define the epidemiology of IFD outside the standard risk groups to better inform the use of prophylaxis and choice of agent.

Patients with acute lymphoblastic leukaemia (ALL) have been under-represented in antifungal prophylaxis studies because it is a less common diagnosis in adults than AML/MDS. Potential drug–drug interactions and serious adverse events associated with azole antifungals and vinca alkaloids, which constitute the backbone of many ALL treatment protocols, have also limited the participation of patients with ALL in these kinds of trials.[15] Subsequent to the 2008 guidelines, two Australian studies identified patients with ALL to be at high risk of IFD, including mould infections.[16,17] Hence, it is not surprising to find that the majority of clinicians surveyed use mould-active prophylaxis during ALL treatment and that liposomal amphotericin B was the preferred agent in most cases (53%) with fluconazole an alternative. This variation in practice is reflective of the uncertainties that surround the duration of IFD risk and need for prophylaxis. A study comparing liposomal amphotericin B prophylaxis to no prophylaxis in this patient group (NCT01259713) was recently completed, but its findings are yet to be published.

The diagnostic work-up of patients with suspected IFD is important in guiding escalation of antifungal therapy, especially in the era of broad-spectrum azole prophylaxis.[18] CT imaging and directed invasive diagnostic procedures, such as bronchoalveolar lavage (BAL) with routine microbiology and histology, were available on-site at all hospitals. However, the >48 h delay reported between time of referral time of procedure in 40% of hospitals is considered suboptimal; yield from BAL is highest when performed within 24 h of new infiltrates and declines significantly by 5 days.[19] Inclusion of respiratory physicians within the multidisciplinary team providing care for these patients should be encouraged. In contrast, non-culture-based tests and TDM were generally available off-site. Consequently, turnaround times for results were typically greater than 3 days for these 'specialised' tests. This is likely to reduce the utility of these assays, especially drug levels. Ongoing efforts should be made to improve the timely reporting of results *and* the widespread availability of these critical tests to guide and optimise patient care.[18]

The main limitations of this study include potential response bias and the generalisability of the respondents' reported current practice and observations given the sample included multiple respondents from individual hospitals but no respondents at all from other hospitals. Ongoing periodic or point prevalence surveys could be used to inform and evaluate guideline uptake, as well as to assess new and emerging high-risk populations and to examine where new evidence or opinion is leading to changes in clinical practice.

Conclusion

The quality of the Australian 2008 guidelines has been independently evaluated across several domains and has ranked foremost in clarity and presentation when compared with other internationally published guidelines.[6] Furthermore, all but one respondent considered them useful in formulating local guidelines. The current survey has indicated high levels of adherence to the recommended guidelines for antifungal use, especially in high-risk AML patients. In haematological malignancies other than AML, a greater diversity of practice was noted, but reassuringly, when antifungals are used in this setting,

most survey respondents justified their use on the basis of recognised risk factors. Greater research efforts should be directed to these patient groups to enable the refinement of subsequent guidelines. Areas for further improvement include earlier access to bronchoscopy, diagnostic tests and therapeutic drug monitoring.

Acknowledgements

The authors would like to thank members of ALLG, ASID and ANZCHOG for their review of the draft document and Dr Candice O'Sullivan from Wellmark Pty Ltd for her assistance in preparing the manuscript for submission.

References

1 Ramana KV, Kandi S, P VB, Sharada CV, Rao R, Mani R *et al*. Invasive fungal infections: a comprehensive review. *Am J Infect Dis Microbiol* 2013; **1**: 64–9.
2 Prentice H, Kibbler C, Prentice A. Towards a targeted, risk-based, antifungal strategy in neutropenic patients. *Br J Haematol* 2000; **110**: 273–84.
3 Slavin MA, Szer J, Grigg AP, Roberts AW, Seymour JF, Sasadeusz J *et al*. Guidelines for the use of antifungal agents in the treatment of invasive Candida and mould infections. *Intern Med J* 2004; **34**: 192–200.
4 Slavin M, Heath C, Thursky K, Morrissey C, Szer J, Ling L *et al*. Antifungal prophylaxis in adult stem cell transplantation and haematological malignancy. *Intern Med J* 2008; **38**: 468–76.
5 IBM Corp. Released. *IBM SPSS Statistics for Windows, Version 22.0. Armonk*. NY: IBM Corp; 2013.
6 Agrawal S, Jones B, Barnes R, Kibbler C, Millen M, Ashcroft M *et al*. A practical critique of antifungal treatment guidelines for haemato-oncologists. *Crit Rev Microbiol* 2012; **38**: 203–16.
7 Slavin M. Introduction to the updated Australian and New Zealand consensus guidelines for the use of antifungal agents in the haematology/oncology setting, 2008. *Intern Med J* 2008; **38**: 457–67.
8 Robenshtok E, Gafter-Gvili A, Goldberg E, Weinberger M, Yeshurun M, Leibovici L *et al*. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. *J Clin Oncol* 2007; **25**: 5471–89.
9 Xu S-X, Shen J-L, Tang X-F, Feng B. Newer antifungal agents for fungal infection prevention during hematopoietic cell transplantation: a meta-analysis. *Transplant Proc* 2013; **45**: 407–14.
10 Pechlivanoglou P, Le H, Daenen S, Snowden J, Postma M. Mixed treatment comparison of prophylaxis against invasive fungal infections in neutropenic patients receiving therapy for haematological malignancies: a systematic review. *J Antimicrob Chemother* 2014; **69**: 1–11.
11 Cornely O, Maertens J, Winston D, Perfect J, Ullmann A, Walsh T *et al*. Posaconazole vs. Fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med* 2007; **356**: 348–59.
12 Tawfik B, Sliesoraitis S, Lyerly S, Klepin H, Lawrence J, Isom S *et al*. Efficacy of the hypomethylating agents as frontline, salvage, or consolidation therapy in adults with acute myeloid leukemia (AML). *Ann Hematol* 2014; **93**: 47–55.
13 Falantes J, Calderón C, Márquez-Malaver F, Aguilar-Guisado M, Martín-Pen˜a A, Martino M *et al*. Patterns of infection in patients with myelodysplastic syndromes and acute myeloid leukemia receiving azacitidine as salvage therapy. Implications for primary antifungal prophylaxis. *Clin Lymphoma Myeloma Leuk* 2014; **14**: 80–6.
14 Ananda-Rajah M, Slavin M, Thursky K. The case for antifungal stewardship. *Curr Opin Infect Dis* 2012; **25**: 107–15.
15 Moriyama B, Henning SA, Leung J, Falade-Nwulia O, Jarosinski P, Penzak SR *et al*. Adverse interactions between antifungal azoles and vincristine: review and analysis of cases. *Mycoses* 2012; **55**: 290–7.
16 Hale K, Shaw P, Dalla-Pozza L, Raina MacIntyre C, Isaacs D, Sorrell T. Epidemiology of paediatric invasive fungal infections and a case-control study of risk factors in acute leukaemia or post stem cell transplant. *Br J Haematol* 2010; **149**: 263–72.
17 Henden A, Morris K, Truloff N, Nakagaki M, Kennedy G. Incidence and outcomes of invasive fungal disease in adult patients with acute lymphoblastic leukemia treated with hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone: implications for prophylaxis. *Leuk Lymphoma* 2013; **54**: 1329–31.
18 Heng S, Chen S, Morrissey C, Thursky K, Manser R, De Silva H *et al*. Clinical utility of Aspergillus galactomannan and PCR in bronchoalveolar lavage fluid for the diagnosis of invasive pulmonary aspergillosis in patients with haematological malignancies. *Diagn Microbiol Infect Dis* 2014; **79**: 322–7.
19 Shannon V, Andersson B, Lei X, Champlin R, Kontoyiannis D. Utility of early versus late fiberoptic bronchoscopy in the evaluation of new pulmonary infiltrates following hematopoietic stem cell transplantation. *Bone Marrow Transplant* 2010; **45**: 647–55.