Primary antifungal prophylaxis in adult patients with acute lymphoblastic leukaemia: a multicentre audit

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Objectives: The primary objectives were to investigate the prescribing practices of primary antifungal prophylaxis (PAP) and incidence of invasive fungal disease (IFD) in adult patients with ALL receiving induction-consolidation chemotherapy. Secondary objectives were to determine risk factors for IFD and resource utilization associated with IFD.

Methods: A retrospective chart review of adult patients with ALL from commencement of induction until completion of consolidation chemotherapy was undertaken from January 2008 to June 2013 in four hospitals in Melbourne, Australia. IFD was classified according to the revised European Organisation for Research and Treatment of Cancer criteria. Cost analysis was performed from an Australian public hospital perspective.

Results: Ninety-eight patients were included in the audit; 83 (85%) received PAP. Most patients (49/83, 59%) switched between two different antifungal agents, predominantly between liposomal amphotericin B and an azole. Five proven/probable and six possible IFD cases were identified. Proven/probable IFD was most common in patients receiving the BFM95 chemotherapy protocol. The incidence of proven/probable IFD was significantly lower in patients receiving PAP compared with those who did not (2/78, 2.6% versus 3/14, 21.4%; P = 0.024). For every five patients receiving PAP, one proven/probable IFD case would be prevented. Proven/probable IFD was associated with an additional median cost of 121,520 Australian dollars (95% CI: 90,781–180,141 Australian dollars; P < 0.001) compared with patients without IFD.

Conclusions: This is the first multicentre study evaluating PAP use in patients with ALL. With the caveats of interpretation of retrospective, non-randomized data, PAP was associated with a reduced IFD risk.

Introduction

Patients with ALL undergoing induction-consolidation chemotherapy are at high risk of developing invasive fungal disease (IFD) with considerable resultant morbidity and mortality.1–3 Consequently, primary antifungal prophylaxis (PAP) is frequently administered in these patients. However, patients with ALL are under-represented in clinical studies involving PAP because ALL is relatively uncommon in adults.4 Moreover, clinically significant drug interactions between azole antifungal agents and vinca alkaloids commonly used in the treatment of ALL (e.g. vincristine), which may result in increased incidence of neurotoxicity, have excluded the participation of adult patients with ALL in clinical studies.5 Consequently, data on PAP use, i.e. administered agents,
dose, duration and clinical outcomes, in the adult setting are limited and the optimal approach for PAP in these patients remains to be elucidated. Given the paucity of information, we investigated PAP prescribing practices and the clinical and economic consequences of PAP use in adult patients with ALL undergoing induction-consolidation chemotherapy in four major tertiary hospitals in Melbourne, Australia.

Methods

Study design and patients

We performed a retrospective chart review of adult patients (aged ≥18 years) with newly diagnosed ALL and receiving a first course of induction chemotherapy in four tertiary hospitals (Alfred Health, Royal Melbourne Hospital, Peter MacCallum Cancer Centre and Austin Health) in Melbourne, Australia between January 2008 and June 2013. Patients with a prior history of IFD were excluded. Each patient was followed from commencement of the first course of induction chemotherapy until resolution of neutropenia after the final course of consolidation chemotherapy. Patients were censored at the commencement of salvage chemotherapy or palliative care for refractory or relapsed ALL or, haematopoietic stem cell transplantation.

A data collection form was developed and piloted on a sample of patients before being refined to ensure consistency and accuracy in the data collected across all study sites. Data were extracted from patients’ medical records. The prescribing patterns of PAP, i.e. timing of initiation, administered agents, frequency, dose and duration, were recorded. For each patient, the following characteristics were collected: age, gender, subtype of ALL, Philadelphia chromosome status, remission status of ALL, chemotherapy regimen, duration of chemotherapy, presence of neutropenia at diagnosis, duration of neutropenia, duration of corticosteroid use and use of granulocyte colony-stimulating factor (and polyethylene glycol granulocyte colony-stimulating factor) across the follow-up period (see below for definitions). Microbiological, histopathological and radiological data relevant for the diagnosis of IFD were also collected.

To investigate the effectiveness of PAP, the incidence of IFD and the probability of being IFD-free over time were compared between patients who received PAP and those not receiving PAP. The demographic and clinical characteristics of patients with and without IFD were compared to identify potential risk factors for IFD. The average number of patients who needed to be prescribed PAP to prevent one IFD case (i.e. number needed to treat, NNT) was calculated. To evaluate whether one chemotherapy regimen was associated with increased risk of neutropenia, immunosuppression and thereby IFD, we compared the incidence of IFD, duration of neutropenia and duration of corticosteroid use between patients receiving different chemotherapy regimens. Cost analysis was performed to evaluate the economic burden of IFD. The study was approved by Monash University (approval number CF13/3687-20133001902) and the ethics committees of each participating hospital. Written informed consent was waived.

Definitions

PAP was defined as the administration of any systemic antifungal agent for two or more consecutive days to a patient without any evidence or history of IFD. Antifungal agent switching was defined as changing between two different antifungal agents irrespective of antifungal class. For the analysis comparing the incidence of IFD between patients with and without PAP, patients who received PAP and developed IFD >15 days after PAP cessation were classified as not having had PAP because the effects of antifungal agents were considered to no longer be active after this period. Neutropenia was defined as absolute neutrophil count (ANC) <0.5×10⁹/L. The duration of neutropenia of each patient was defined as the cumulative number of days during which the ANC was <0.5×10⁹/L across the follow-up period. Resolution of neutropenia was defined as ANC ≥0.5×10⁹/L for at least two consecutive days. Prolonged use of corticosteroids was defined as ≥1 mg/kg/day of prednisolone equivalent for ≥21 days across the follow-up period.

Diagnostic work-up for IFD

The diagnostic work-up for suspected IFD was similar across all participating hospitals. This included the routine collection of blood and urine cultures, high-resolution chest CT and, where clinically feasible, lung sampling (bronchoalveolar lavage or tissue biopsy) in the event of documented radiological abnormalities. Additional diagnostic evaluations included serological and molecular tests for IFD, CT sinus.brain, skin biopsy and abdominal ultrasound as clinically indicated.

IFD cases were classified as proven, probable or possible, according to the 2008 European Organisation for Research and Treatment of Cancer/Mycoses Study Group consensus criteria by a panel of infectious diseases physicians (M. A. S., M. R. A.-R. and C. O. M.). Consensus was reached for all IFD cases. Breakthrough IFD was defined as occurrence of IFD during PAP or within 7 days of PAP cessation. The date of IFD onset was considered as the first date of clinical, microbiological or radiological diagnosis.

Cost analysis

A cost analysis was undertaken from an Australian public hospital perspective in Australian dollars (AUS). The analysis included the costs of hospitalization, outpatient visits, IFD diagnostic tests (e.g. cultures, radiological examinations, histopathological examinations, serological examinations, microbiological tests and fungal PCR), diagnostic procedures (e.g. bronchoscopy, tissue biopsy and lumbar puncture), antifungal drugs (both PAP and treatment) and surgical procedures for IFD treatment (e.g. lung wedge resection). Drug acquisition costs were the wholesale prices paid by public hospitals in the state of Victoria, as per the Australian Medicare Benefits Schedule Book (2014). Antifungal drug costs were calculated based on the total doses prescribed to patients.

Total hospitalization costs were calculated by multiplying the total number of days in each ward/unit by the daily unit cost of either a general ward or ICU admission. This unit cost value was obtained from the Australian Refined Diagnostic Related Group (2011–12). Unit hospitalization costs were specifically for patients with acute leukaemia and excluded pharmacy, pathology and imaging costs to avoid double counting. Unit costs of diagnostic tests, diagnostic procedures, surgery procedures for IFD and outpatient clinic visits were obtained directly from the Australian Medicare Benefits Schedule Book (2014). Hospitalization costs were inflated to 2014 using the healthcare component of the Australian consumer price index. Discounting was not performed because of the short time horizon. The total cost incurred for each patient across the follow-up period was calculated and the median (IQR) of total costs for all patients was calculated.

Statistical analysis

Categorical variables were compared using Fisher’s exact test. Continuous variables were compared using the Wilcoxon rank-sum test (for comparison between two groups) or the Kruskal–Wallis test (for comparison between more than two groups). Associations between patient characteristics and IFD status were first investigated in a univariate analysis using Fisher’s exact test or the Wilcoxon rank-sum test. All variables with a P value of <0.2 in the univariate analysis were then included in a multivariate logistic regression model to assess their independent associations with IFD. Kaplan–Meier curves and the log-rank test were used to estimate and compare the probability of being IFD-free between patients who received PAP and those not receiving PAP. The NNT to prevent one IFD
case was calculated as the inverse of the absolute risk reduction associated with the use of PAP. All analyses were performed using Stata 12.0 (Stata Corp, College Station, TX, USA).

Results

A total of 98 patients were included in the audit. Table 1 summarizes the baseline clinical and demographic characteristics and chemotherapy details of these patients. Patients received chemotherapy (induction and consolidation) for a median (IQR) duration of 110 (67–175) days. Ninety-eight percent of patients developed neutropenia during induction and consolidation chemotherapy. The median (IQR) duration of neutropenia was 31 (18–45) days. Four (4/98, 4%) patients died after a median (IQR) of 42 (31–72) days since commencement of chemotherapy; none had IFD.

PAP was administered to 83/98 (85%) patients for a median (IQR) duration of 53 (32–91) days. Of these, 74/83 (89%) had PAP initiated during induction chemotherapy with the remaining 9 (11%) commencing PAP during consolidation chemotherapy. Liposomal amphotericin B (L-AMB) was initially administered as PAP in the majority of patients (54/83, 65%), followed by posaconazole (15/83, 18%), fluconazole (7/83, 8%), caspofungin (4/83, 5%) and voriconazole (3/83, 4%). The intravenous formulations of voriconazole and fluconazole were used in one patient each. The median (range) doses of L-AMB, posaconazole, fluconazole, voriconazole and caspofungin were 100 (50–200) mg three times a week, 200 (200–200) mg three times daily, 200 (100–200) mg daily, 200 (150–250) mg twice daily and 50 (50–70) mg daily, respectively.

Figure 1 summarizes the use of various prophylactic antifungal agents over the course of chemotherapy. The majority of patients (49/83, 59%) switched between two antifungal agents, predominantly from L-AMB for chemotherapy cycles with vincristine to posaconazole or voriconazole for chemotherapy cycles without vincristine (28/83, 33.7% of patients receiving PAP), or from L-AMB for the first cycle of chemotherapy to fluconazole for the remaining cycles of chemotherapy (13/83, 15.7% of patients receiving PAP).

Table 2 summarizes the 11 IFD cases (5 proven/probable and 6 possible) identified during the study. Of these, five (two proven/probable and three possible) cases were breakthrough IFD and four (one proven/probable and three possible) occurred in patients who did not receive PAP. The remaining two cases (both proven/probable) developed IFD 18 and 29 days after PAP cessation. Of the five breakthrough IFD cases, three (two proven/probable and one possible) were on L-AMB and one each (possible) on fluconazole or posaconazole at the time of IFD diagnosis. Moulds were responsible for the majority (4/5) of proven/probable IFD cases. Possible IFD and proven/probable IFD occurred at a median (IQR) of 31 (18–42) and 114 (111–125) days, respectively, after the commencement of chemotherapy. Five IFD cases (one proven/probable and four possible) were diagnosed during induction and six cases (four proven/probable and two possible) during consolidation chemotherapy.

The distribution of IFD incidence according to chemotherapy regimens is shown in Figure 2. Proven/probable IFD was most frequently observed in patients receiving the BFM95 regimen18 compared with other chemotherapy regimens; however, this association was not statistically significant (2/13, 15% versus 3/85, 3.5%; P = 0.129). These patients had a longer median duration of corticosteroid use (31 versus 20 days; P = 0.003) and longer duration of induction-consolidation chemotherapy (167 versus 104 days; P = 0.019) compared with patients receiving other chemotherapy regimens.

The only significant difference in characteristics between patients who developed IFD and those who did not was the use of PAP (Table 3). Patients who received PAP had a lower incidence...
of proven/probable IFD as compared with those not receiving PAP (2/78, 2.6% versus 3/14, 21.4%; P = 0.024). This association remains statistically significant (adjusted OR 0.06; 95% CI: 0.01–0.54; P = 0.013) in multivariate logistic regression analysis including PAP use status, duration of neutropenia, duration of corticosteroid use and duration of chemotherapy. All other variables included in the multivariate analysis were not statistically associated with the incidence of IFD. The NNT to prevent one proven/probable IFD case was calculated to be five patients.

Figure 3 gives the probability of being IFD-free after the commencement of chemotherapy between patients with and without PAP. The probability of being IFD-free was significantly higher among patients who received PAP than those not receiving PAP.

Treatment of IFD

All IFD cases were treated with antifungal therapy. L-AMB was initiated in most patients (8/11, 73%), followed by voriconazole (2/11, 18%) and caspofungin (1/11, 9%). Patients with possible and proven/probable IFD received antifungal treatment for a median (IQR) of 42 (21–49) and 50 (34–52) days, respectively (P = 0.410). Seven of 11 patients switched between two different antifungal agents during IFD treatment, most often from L-AMB to oral/intravenous voriconazole (n = 5). Median costs of PAP were comparable between the two groups (AUS$7735 versus AUS$6034; P = 0.890). When only PAP recipients (n = 83) were considered, the additional median costs were AUS$78376 (95% CI: AUS$26127–115301; P = 0.003) for patients with proven, probable or possible IFD and AUS$115427 (95% CI: AUS$76460–146310; P < 0.001) for patients with proven/probable IFD compared with patients without IFD.

Discussion

This multicentre study is the first to investigate the prescribing patterns and clinical and economic consequences of PAP in adult patients with ALL. We observed that 11% of our patients developed possible, proven or probable IFD (5% for the proven/probable IFD subset) during the period of induction and consolidation chemotherapy. To date, there are limited data on the rate of IFD in adults with ALL to compare our results with. In a retrospective cohort study conducted in Italy between 1999 and 2003, Pagano et al. reported an incidence of proven/probable IFD of 6.5%, consistent with our findings. Although the number of IFD cases and the sample size were small, in our study PAP was associated with a significantly reduced risk of IFD, suggesting that PAP may be effective in preventing IFD in patients with ALL undergoing chemotherapy. However, our study had insufficient statistical power to determine whether PAP is justified in all patients for the whole duration of induction and consolidation chemotherapy.

If PAP is deemed appropriate in selected adult patients with ALL, the optimal antifungal agent for this purpose remains uncertain. In the current study, L-AMB was the predominant prophylactic antifungal agent used, despite the lack of evidence supporting its use in this context. This observation could be due to concerns regarding increased incidence of neurotoxicity associated with the combination of vincristine and the azoles. Subsequent switching to other oral prophylactic antifungal agents during chemotherapy is not uncommon in this patient group. Indeed, the majority of

Figure 1. Distribution of patients receiving the same antifungal agent or switching between two or three different antifungal agents as prophylaxis during induction-consolidation chemotherapy (n = 83). Others include fluconazole/posaconazole (3.6%), L-AMB/caspofungin (2.4%), caspofungin/posaconazole (2.4%) and caspofungin/voriconazole (1.2%). CAS, caspofungin; FLC, fluconazole; POS, posaconazole; VRC, voriconazole.

Table 4 shows the distribution of cost components according to IFD categories in all patients (n = 98). The presence of IFD (proven, probable or possible) increased the median cost by AUS$66425 (95% CI: AUS$22572–107856; P = 0.002) compared with patients without IFD. The difference in median costs was more substantial when only patients with proven/probable IFD were compared with those without IFD (AUS$121520; 95% CI: AUS$90781–180141; P < 0.001). Hospitalization and antifungal treatment costs were the main cost drivers, responsible for 58% and 38% of the difference in median costs, respectively, between the two groups.
Table 2. Characteristics of IFD cases

<table>
<thead>
<tr>
<th>Patient</th>
<th>IFD category</th>
<th>Pathogen identified</th>
<th>Age (years)</th>
<th>Chemotherapy regimen and stage at IFD onset</th>
<th>PAP and sequence</th>
<th>Days from cessation of PAP to IFD onset</th>
<th>Days from start of chemotherapy to IFD</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>proven</td>
<td>Candida albicans</td>
<td>53</td>
<td>HyperCVAD, consolidation 2B</td>
<td>none</td>
<td>not applicable</td>
<td>111</td>
</tr>
<tr>
<td>2</td>
<td>proven</td>
<td>Aspergillus spp.</td>
<td>32</td>
<td>BFM95, intensified consolidation</td>
<td>L-AMB 100 mg 3 times/week (31 days) → oral voriconazole 200 mg twice daily (30 days) then 250 mg twice daily (29 days) → L-AMB 100 mg 3 times/week (16 days)</td>
<td>not applicable during PAP</td>
<td>114</td>
</tr>
<tr>
<td>3</td>
<td>probable</td>
<td>Rhizopus oryzae</td>
<td>62</td>
<td>Hoelzer, induction</td>
<td>none</td>
<td>not applicable</td>
<td>70</td>
</tr>
<tr>
<td>4</td>
<td>probable</td>
<td>Aspergillus flavus</td>
<td>26</td>
<td>BFM95, intensified consolidation</td>
<td>L-AMB 100 mg 3 times/week (22 days) → oral voriconazole 200 mg twice daily (24 days) → L-AMB 100 mg 3 times/week (52 days)</td>
<td>5</td>
<td>125</td>
</tr>
<tr>
<td>5</td>
<td>probable</td>
<td>Aspergillus spp.</td>
<td>29</td>
<td>HyperCVAD, consolidation 4B</td>
<td>none</td>
<td>not applicable</td>
<td>201</td>
</tr>
<tr>
<td>6</td>
<td>possible</td>
<td>none</td>
<td>47</td>
<td>HyperCVAD, induction 1A</td>
<td>L-AMB 50 mg 3 times/week (2 days) then 200 mg 3 times/week (5 days)</td>
<td>2</td>
<td>13</td>
</tr>
<tr>
<td>7</td>
<td>possible</td>
<td>none</td>
<td>65</td>
<td>LALA94, induction</td>
<td>none</td>
<td>not applicable</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>possible</td>
<td>none</td>
<td>38</td>
<td>BFM95, induction</td>
<td>none</td>
<td>not applicable</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>possible</td>
<td>unspecified yeast</td>
<td>52</td>
<td>LALA94, induction</td>
<td>none</td>
<td>not applicable</td>
<td>32</td>
</tr>
<tr>
<td>10</td>
<td>possible</td>
<td>none</td>
<td>53</td>
<td>HyperCVAD, consolidation 1B</td>
<td>oral fluconazole 200 mg daily (37 days) → posaconazole 200 mg 3 times/day (42 days) → L-AMB 100 mg 3 times/week (15 days) → posaconazole 200 mg 3 times/day (7 days)</td>
<td>1</td>
<td>45</td>
</tr>
<tr>
<td>11</td>
<td>possible</td>
<td>none</td>
<td>29</td>
<td>HyperCVAD, consolidation 2B</td>
<td>posaconazole 200 mg 3 times/day (45 days) during PAP</td>
<td>142</td>
<td></td>
</tr>
</tbody>
</table>

BFM95, Berlin-Frankfurt-Münster trial 95;17 HyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone;23 LALA, Leucémie Aiguës Lymphoblastique de l'Adulte.22
patients in our study switched between two prophylactic antifungal agents. Historically, prophylactic voriconazole has been used in patients with AML/myelodysplastic syndrome receiving remission-induction chemotherapy due to its antimould activity and the availability of both intravenous and oral formulations, despite its limited evidence as a prophylactic agent in patients with acute leukaemia.25 However, since the licensing of posaconazole for patients with AML/myelodysplastic syndrome,26 we have observed an increase in the use of posaconazole over the study period (data not shown) despite its lack of prophylaxis studies specifically in patients with ALL. Although it is 2 years since study completion, our findings are likely to be representative of current practice because international and institutional guidelines for PAP in the acute leukaemic setting have not changed since completion of our study.27 While the optimal duration of PAP in the ALL setting is undefined, it is often administered during periods of neutropenia,26,28,29 In our study, we noted that most patients who did not receive PAP were neutropenic. Four such patients developed IFD during periods of neutropenia, highlighting the need to consider PAP during these high-risk periods.

We observed that patients receiving the BFM95 chemotherapy regimen had the highest incidence of proven/probable IFD. This chemotherapy regimen is usually used in paediatric and adolescent patients with ALL with high-risk cytogenetics and is more dose intensive than adult protocols.17 Indeed, patients in our study receiving this regimen had significantly higher median duration of corticosteroid use and received chemotherapy for a longer period of time. It should be noted that these patients were from the same institution; therefore, institution-specific epidemiological factors cannot be ruled out. The incidence of proven/probable IFD among patients receiving the HyperCVAD (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone) regimen is lower (4% versus 13%) than that reported in a study of adult patients with ALL receiving this regimen with fluconazole prophylaxis.1 This may be due to differences in clinical practice, environmental factors and patient characteristics between institutions.

The epidemiology of IFD in patients with haematological malignancies has changed over the last decade with moulds becoming the most important cause of IFD in AML.30-32 We found that moulds (especially Aspergillus spp.) were responsible for 80% of the proven/probable IFD cases, in accordance with

![Figure 2. Incidence of IFD according to chemotherapy regimens.](image)

**Figure 2.** Incidence of IFD according to chemotherapy regimens. 68Other chemotherapy regimens include LALA94 (n = 5), ALL6 (n = 3), ANZCHOG Study 8 (n = 3), FRALLE93 (n = 2), R-CHOP (n = 1), CODOX-M (n = 1), COG AALL0232 (n = 1) and CALGB protocols (n = 1). ANZCHOG Study 8, Australia and New Zealand Children’s Haematology and Oncology Group Study 8 protocol;18 BFM95, Berlin-Frankfurt-Münster trial 95;17 CALGB, Cancer and Leukemia Group B;19 CODOX-M, cyclophosphamide, vincristine, doxorubicin and methotrexate;20 COG AALL0232, Children’s Oncology Group protocol AALL0232;21 FRALLE93, French group for childhood ALL-93 protocol;22 HyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone;23 LALA, Leucémie Lymphoblastique de l’Adulre;24 R-CHOP, rituximab, cyclophosphamide, doxorubicin, vincristine and prednisolone.25

**Table 3.** Comparison of the characteristics between patients with and without IFD

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Without IFD</th>
<th>Proven/probable/possible IFD</th>
<th>Proven/probable IFD</th>
<th>P value for A versus B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 87 A</td>
<td>N = 11 B</td>
<td>N = 5 C</td>
<td></td>
</tr>
<tr>
<td>Median age, years</td>
<td>43</td>
<td>47</td>
<td>32</td>
<td>0.860 (0.740)</td>
</tr>
<tr>
<td>Complete remission, n (%)</td>
<td>59 (68)</td>
<td>8 (73)</td>
<td>5 (100)</td>
<td>1 (0.320)</td>
</tr>
<tr>
<td>Philadelphia chromosome positive, n (%)</td>
<td>23 (26)</td>
<td>3 (27)</td>
<td>1 (20)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Median duration of neutropenia, days</td>
<td>30</td>
<td>36</td>
<td>39</td>
<td>0.740 (0.150)</td>
</tr>
<tr>
<td>Neutropenia at ALL diagnosis, n (%)</td>
<td>21 (24)</td>
<td>6 (55)</td>
<td>2 (40)</td>
<td>0.070 (0.600)</td>
</tr>
<tr>
<td>Median duration of corticosteroid use, days</td>
<td>21</td>
<td>22</td>
<td>30</td>
<td>0.900 (0.060)</td>
</tr>
<tr>
<td>Median duration of chemotherapy, days</td>
<td>110</td>
<td>96</td>
<td>221</td>
<td>0.770 (0.170)</td>
</tr>
<tr>
<td>PAP, n (%)</td>
<td>76 (87)</td>
<td>5 (45)</td>
<td>2 (40)</td>
<td><strong>0.003 (0.024)</strong></td>
</tr>
<tr>
<td>Median duration from start of chemotherapy to commencement of PAP, days</td>
<td>1</td>
<td>6</td>
<td>7</td>
<td>0.160 (0.490)</td>
</tr>
<tr>
<td>Use of granulocyte colony-stimulating factor, n (%)</td>
<td>74 (85)</td>
<td>7 (64)</td>
<td>4 (80)</td>
<td>0.090 (0.570)</td>
</tr>
</tbody>
</table>

*a* Determined by a Fisher’s exact test or the Wilcoxon rank-sum test when appropriate. Bold formatting indicates statistical significance.

*b* Only patients who received PAP were included in this analysis.

*c* Granulocyte colony-stimulating factor and polyethylene glycol granulocyte colony-stimulating factor.
previous observations.\textsuperscript{3,6,30–32} Previous studies reported an increasing incidence of mucormycosis in patients with haematological malignancies, particularly among those exposed to voriconazole.\textsuperscript{33–35} In our study, mucormycosis was only identified in one patient, who was not receiving PAP.

This study provides estimates of resource utilization associated with managing IFD in patients with ALL. We have found that the cost was substantially higher in patients with IFD than those without IFD (additional median cost AU$66 425 for proven, probable or possible IFD and AU$121 520 when possible IFD was excluded), although patient, disease and treatment characteristics also varied between these groups. Our results suggest that for every five patients newly diagnosed with ALL and prescribed PAP, one proven/probable IFD would be prevented, resulting in a potential cost saving of AU$121 520. Our costing is a conservative estimate of the true economic burden of IFD in patients with ALL because we did not take into consideration the costs associated with lost productivity. To date, data on the economic burden of IFD specifically in patients with ALL are lacking. A number of studies have estimated the costs associated with IFD in patients with haematological malignancies (any type including ALL) with variable results. Ananda-Rajah et al.\textsuperscript{36} reported an additional median cost of AU$30 957 for IFD (proven, probable or possible) in patients with haematological malignancies. In another study, Kim et al.\textsuperscript{37} estimated a median hospitalization cost of US$73 029 in patients with haematological malignancies and aspergillosis. It should be noted that differences in methodologies, settings and patient populations limit comparisons between our study and others.

In summary, this is the largest study to date on PAP use in patients with ALL. While the findings suggest that PAP may be effective in preventing IFD in this patient group, larger studies are needed to identify both the characteristics of high-risk patients with ALL in whom the expense of targeted antifungal prophylaxis is justified and the optimal antifungal agent in this setting.

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Transparency declarations
C. M. J. K. has undertaken collaborative research projects unrelated to the current work with Roche, Pfizer, CSL and d3 Medicine. M. A. S. has sat on antifungal advisory boards of Gilead Sciences, Merck Sharp & Dohme and Pfizer, and has received funding in the form of untied grants from Gilead Sciences and Merck Sharp & Dohme. M. R. A.-R. has received honoraria from Merck Sharp & Dohme, Gilead Sciences and Schering-Plough for educational activities and unrestricted research funding from Merck Sharp & Dohme, and has participated in advisory boards for Merck Sharp & Dohme. C. O. M. has received honoraria from, has participated in advisory board meetings for and has received unrestricted research funds for investigator-initiated studies from Gilead Sciences, Merck Sharp & Dohme and Pfizer, all monies have been paid directly to her employing institution. K. F. U. has sat on antifungal advisory boards of Merck Sharp & Dohme. A. G. has sat on antifungal advisory boards of Merck Sharp & Dohme. D. C. M. K. has sat on advisory boards of Pfizer and Merck Sharp & Dohme, and receives financial/travel support (unrelated to the current work) from Pfizer, Roche, Merck Sharp & Dohme, Novartis and Gilead Sciences. All other authors: none to declare.

References
Primary antifungal prophylaxis in ALL patients


