Medical Mycology, 2017, 55, 705–712
doi: 10.1093/mmy/myw141
Advance Access Publication Date: 28 January 2017
Original Article

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Is a biomarker-based diagnostic strategy for invasive aspergillosis cost effective in high-risk haematology patients?

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Received 5 September 2016; Revised 6 November 2016; Accepted 2 December 2016; Editorial Decision 20 November 2016

Abstract

Empirical antifungal therapy is frequently used in hematology patients at high risk of invasive aspergillosis (IA), with substantial cost and toxicity. Biomarkers for IA aim for earlier and more accurate diagnosis and targeted treatment. However, data on the cost-effectiveness of a biomarker-based diagnostic strategy (BDS) are limited. We evaluated the cost effectiveness of BDS using results from a randomized controlled trial (RCT) and individual patient costing data. Data inputs derived from a published RCT were used to construct a decision-analytic model to compare BDS (*Aspergillus* galactomannan and PCR on blood) with standard diagnostic strategy (SDS) of culture and histology in terms of total costs, length of stay, IA incidence, mortality, and years of life saved. Costs were estimated for each patient using hospital costing data to day 180 and follow-up for survival was modeled to five years using a Gompertz survival model. Treatment costs

were determined for 137 adults undergoing allogeneic hematopoietic stem cell transplant or receiving chemotherapy for acute leukemia in four Australian centers (2005–2009). Median total costs at 180 days were similar between groups (US$78,774 for SDS [IQR US$50,808–123,476] and US$81,279 for BDS [IQR US$59,221–123,242], $P = .49$). All-cause mortality was 14.7% (10/68) for SDS and 10.1% (7/69) for BDS, ($P = .573$). The costs per life-year saved were US$325,448, US$81,966, and US$3,670 at 180 days, one year and five years, respectively. BDS is not cost-sparing but is cost-effective if a survival benefit is maintained over several years. An individualized institutional approach to diagnostic strategies may maximize utility and cost-effectiveness.

Key words: aspergillosis, diagnosis, cost analysis, galactomannan, polymerase chain reaction (PCR), antifungal therapy.

Introduction

Invasive fungal disease (IFD) contributes to significant morbidity and mortality in haematology patients at high risk for IFD such as those undergoing allogeneic stem cell transplantation (SCT) and induction-consolidation chemotherapy for acute leukemia.[1,2] Because culture and histology are not sensitive for the diagnosis of IFD, empiric antifungal therapy (EAFT) is commonly given in patients with persistent neutropenic fevers despite broad-spectrum antibiotics. However, such widespread use of EAFT is associated with overtreatment, toxicity and excess cost. Biomarker-based diagnostic strategies (BDS) that aim to diagnose IFD at an early stage and avoid unnecessary antifungal use have good potential to improve patient survival. A BDS typically includes regular use of galactomannan (GM) and/or *Aspergillus* polymerase chain reaction (A-PCR) in conjunction with use of high-resolution computerized tomography scan of the chest (HRCT) in the setting of persistent fevers.[3] We had performed a randomised controlled trial (RCT) comparing a strategy comprising GM and A-PCR with a culture- and histology-based directed strategy and found that BDS reduced EAFT use.[4]

Treatment of IFD is associated with significantly increased costs,[5] primarily due to expensive drugs.[6] Trials utilizing BDS have demonstrated decreased EAFT use and an observational study found cost savings using this approach.[4,7–9] However, data on the cost effectiveness of this approach have been limited to modelling analyses and have not previously been evaluated using individual patient costing data from an RCT.[10] We aimed to determine the cost and cost-effectiveness of a BDS compared with a standard diagnostic strategy (SDS) using outcome and individual patient costing data generated from hospital finance departments and the results of a trial conducted by our research group.[4]

Patients and methods:

Perspective

The economic modelling was conducted from an Australian public hospital perspective, encompassing all costs from time of enrolment in a recently published RCT until 180 days.[4] Original data were collected from September 2005 to November 2009.

Study design and model inputs

A decision analytic model was developed to compare the costs of a BDS with the costs of a SDS of culture and histology (Fig. 1). Chance nodes represented the probability of mortality at each time point.

Outcomes

Clinical data regarding the diagnostic strategy, diagnosis of IFD and outcomes were taken from patient-level data obtained in the aforementioned RCT that compared the efficacy and safety of BDS with SDS in patients undergoing allogeneic SCT or intensive combination induction-consolidation chemotherapy for acute myeloid or lymphoblastic leukaemia.[4] Costing data were available for four of the six trial sites (see below). Mortality was determined at 180 days for both the BDS and SDS study arms and the data were extrapolated to 360 days, as well as each of one to five years based on the findings of Lee et al.[11] A Gompertz survival function was fitted to allow for a proportional hazards specification of mortality on the basis of inputs from the RCT conducted by our group and Lee et al.[4,11] To validate our assumptions, we compared our fit Gompertz model with Weibull, log-logistic and exponential models (see Supplemental Fig. 1).[12] Life-years saved were calculated on the basis of this mathematical model of mortality.

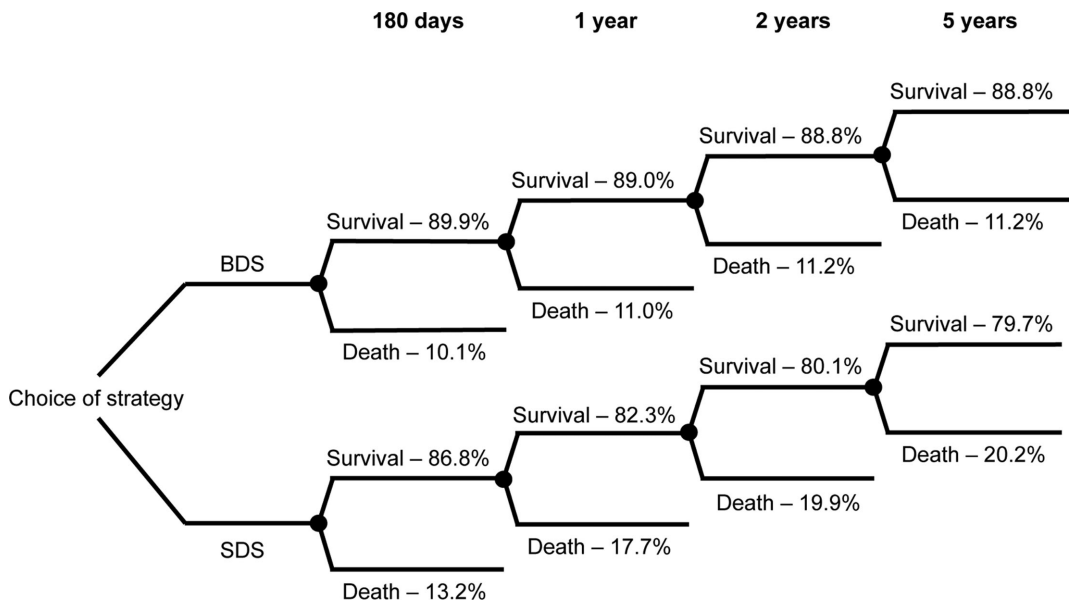

Figure 1. Decision analytic model. BDS, Biomarker-based diagnostic strategy. SDS, Standard diagnostic strategy.

Standard diagnostic strategy (SDS) pathway

In brief, SDS was based on 2002 guidelines for antimicrobial use in neutropenic patients with cancer.[13] If IFD was suspected, patients would undergo diagnostic evaluation that included HRCT scan of chest. EAFT was given while patients underwent evaluation and was continued, de-escalated, or changed depending on whether definite, probable, or possible invasive aspergillosis (IA) or other IFD were diagnosed as per European Organisation for Research and Treatment of Cancer / Mycoses Studies Group (EORTC/MSG) definitions.[14]

Biomarker-based diagnostic (BDS) strategy

BDS consisted of GM and A-PCR testing twice weekly on blood while inpatients and once weekly while outpatients for 26 weeks or until death, if earlier. The galactomannan enzyme-linked immunosorbent assay (ELISA; Platelia Aspergillus Ag Kit, Bio-Rad, Marnes-la-Coquette, France) was done in accordance with the manufacturer's instructions and an optical density of 0.5 or higher was regarded as a positive result.[14] A nested PCR assay that targeted an *Aspergillus* genus-specific region of the multicopy 18S ribosomal RNA gene was used. Amplification of a 249-base-pair band was taken as a positive PCR result. This assay was subsequently adapted to a qualitative real-time PCR format that incorporated an *Aspergillus*-genus-specific TaqMan probe, which had excellent reproducibility with the nested assay. For the qualitative real-time PCR assay, an exponential increase in fluorescence during the first 30 cycles of PCR amplification was regarded as a positive result. All positive results were verified by repeat testing.

A single positive GM or A-PCR, or serially negative results for both tests in patients with persistent neutropenic fevers, prompted HRCT scan of chest. IFD was likewise defined according to modified EORTC/MSG criteria. Briefly, we assigned the same weight for PCR as GM in the EORTC/MSG criteria; adopted stricter criteria for possible invasive aspergillosis, which required mycological evidence in addition to clinical factors; interpreted intermittently positive results as recommended by Halliday and colleagues and classified a single positive result with no clinical features as not indicative of invasive aspergillosis.[4,14] Antifungal treatment was recommended when the criteria for probable or possible IA or other IFD were met.[4]

Cost calculations

Costing data were obtained from the clinical costing units of four sites (Alfred Health, Royal Melbourne Hospital, Westmead Hospital, and St. Vincent's Hospital Sydney). These data included ward, pharmacy, pathology, and imaging costs that were calculated for each patient per hospital admission. All costs are expressed in 2015 US dollars adjusted for exchange rates at the time of the service being provided. GM cost was US$14.80, and A-PCR cost was US$23.40 per sample, based on data from our previous trial.[4] Itemized costs of hospital admissions were not available, and costs of outpatient clinic visits were not included. Patients with missing costing data for their enrolment admission were excluded (Fig. 2). Cost effectiveness was measured in quality-adjusted life years (QALYs).

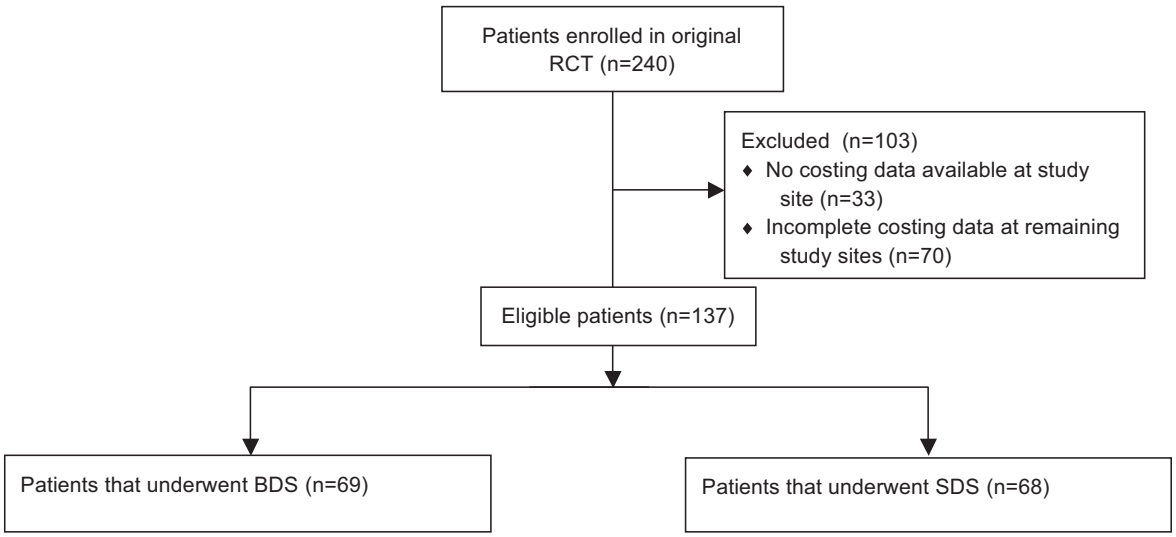

Figure 2. Trial profile. BDS, Biomarker-based diagnostic strategy. SDS, Standard diagnostic strategy.

Statistical analysis

Statistical analysis was performed using Stata/IC 12.1 (StataCorp, College Station, Texas). A χ^2 or Fisher's exact test were used for comparison of categorical variables, and the Student's *t* test or Wilcoxon ranked-sum test were used for continuous variables, as appropriate.

Results

Clinical outcomes

A total of 137 patients were included in the analysis, 68 (49%) in SDS and 69 in BDS arms. Table 1 summarizes their demographic and clinical features. Nine patients (6.5%) had proven or probable IA (1/68 [1.5%] in SDS and 8/69 [11.6%] in BDS, $P = .033$). All-cause mortality was 14.7% (10/68) for SDS and 10.1% (7/69) for BDS ($P = .573$).

Costs of diagnostic strategies and diagnosis of invasive aspergillosis

The median costs of SDS and BDS were comparable (US$78,774 for SDS [IQR US$50,808 – 123,476] and US$80,439 for BDS [IQR US$59,221–123,242], $P = .49$). Length of stay was also similar between the two groups (SDS median length of stay 47 days [IQR 29 – 75 days] and BDS 52 days [IQR 37–72 days], $P = .75$). The median total cost of GM and A-PCR samples in the BDS arm was US$1,069 (IQR $US801–1,146). Patients with probable or proven IA had median total costs of US$110,779 (IQR US$65,113–136,899), compared with remaining patients having median total cost US$79,544 (IQR US$52,741–122,270, $P = .21$).

Detailed costing data were available for three of four sites (n = 112) and are summarized in Figure 3. Clinical care was the biggest contributor to costs for both SDS and BDS (median cost SDS US$40,135 [IQR US$30,103–55,557] and BDS US$44,902 [IQR US$33,322–63,872], $P = .40$), followed by pharmacy costs (median cost SDS US$19,058 [IQR US$9,912–34,237] and BDS US$20,898 [IQR US$12,497–40,747], $P = .41$). Total median costs at sites varied, with one centre having a significantly higher total median cost (US$102,438 [IQR US$66,504–167,268]) compared with other hospitals' total median cost (US$68,418 [IQR US$48,140–109,171], $P = .0001$)—see Supplementary Table 1. This appeared to be driven by EAFT (center A 15/48 vs. centers B, C, and D 13/89, $P = .021$) and pharmacy costs (center A US$40,173 [IQR US$21,184–77,055 compared with centers B, C and D US$19,925 [IQR US$15,280–27,535], $P < .0001$).

Cost effectiveness analysis

The results of the cost effectiveness analysis are summarized in Table 2. A Gompertz model was selected over other models as it had the most clinical plausibility (Supplemental Fig. 1). With the costs being similar between the two arms, evidence of cost-effectiveness for BDS was dependent on this strategy being associated with a mortality benefit. In our model using data from Lee et al.,[11] BDS was not cost effective in the short term but proved cost effective in the longer-term (approximately 1.5 years) assuming a cost-effectiveness threshold of US$50,000 (see Table 2).[15] Use of different pricing for GM and A-PCR did not change the final outcome of the analysis as these investigations

Table 1. Demographic and clinical features of patients in standard diagnostic strategy and biomarker-based diagnostic strategy.

	SDS (n = 68)	BDS (n = 69)	*P*
Median age, years (IQR)	50.5 (39.5–56.5)	48 (35 – 54)	
Men	43 (63%)	38 (55%)	.331
Patients undergoing allogeneic stem-cell transplantation	50 (74%)	57 (82.6%)	.199
Initial antifungal prophylaxis			
None	1 (1.5%)	2 (3%)	
Fluconazole	20 (29%)	18 (26%)	
Itraconazole	29 (43%)	36 (52%)	
Voriconazole	6 (9%)	7 (10%)	
Posaconazole	8 (12%)	4 (6%)	
Liposomal amphotericin B	4 (6%)	2 (3%)	
Probable or proven invasive aspergillosis	1 (1.5%)	8 (11.6%)	.033
Received empirical antifungal therapy	16 (24%)	12 (17%)	.373
Median total hospital stay (days)	47 (range 6–208)	52 (range 2–128)	.7465
All-cause mortality	10 (14.7%)	7 (10.1%)	.573
Invasive aspergillosis-related death	2 (3%)	1 (1%)	
Other IFD	0	1 (1%)	
Death due to non-IFD related cause	7 (10.3%)	5 (7%)	

IFD, Invasive fungal disease.

constituted a small proportion of total cost per patient (data not shown).

Discussion

Several previous trials have noted decreased EAFT use when a BDS was employed for managing IA.[4,7,8] Due to the high cost of antifungal drugs, this has led to speculation about possible cost savings through use of BDS, but this has not been studied systematically in a real-world setting. We evaluated the cost-effectiveness of BDS across four hematology and transplant tertiary centers in Australia using patient-specific costing data from patients enrolled in a pragmatic, randomised controlled trial.

Our key finding was that BDS was cost-effective, but this was dependent on a survival benefit and was only apparent after several years of follow-up. We found similar costs regardless of which strategy was used, despite a lower rate of EAFT in the BDS group. These data are valuable as they represent 'real-world' findings from a randomized controlled trial that included outcome data and matched individual patient costing records, thus minimizing the assumptions inherent to modelling studies. This may account for the difference between our findings and those of a recent study reported cost reduction through a BDS strategy.[10] Moreover, costs may have varied due to (i) differences in patient population since the study by Barnes et al. did not include patients undergoing allogeneic SCT;[10] (ii) prophylactic regimens (absence of mould-active prophylaxis in the study of Barnes et al.), and (iii) background incidence of IA. An improved diagnostic strategy is likely to lead to more diagnoses of IA with subsequent increase in use of directed antifungal therapy and possibly longer length of stay. These increased costs may offset the savings in EAFT, as noted in our study where there was a significantly higher rate of probable or proven IA with BDS.[4]

As BDS was not cost saving per se, BDS must have a survival benefit to be cost-effective. It has been postulated that earlier diagnosis of IA offered by BDS may improve survival. This has been difficult to demonstrate in previous trials as frequently they were not powered for mortality.[3] Our trial also noted a trend towards improved survival that was not statistically significant.[4] A recent study by Aguado et al. showed an increase in IA-free survival when GM and A-PCR were used concurrently as opposed to GM alone but both arms could be considered to be BDS as they incorporated the use of biomarkers.[16] Similar to our study, a meta-analysis and cost comparison of empirical versus BDS found 'economic equipoise' between empirical and preemptive therapy where the decreased antifungal treatment rates and duration were offset by the costs of BDS-increased IFD detection.[17] This analysis, however, did not look at cost-effectiveness and incorporated studies that used heterogeneous approaches to the diagnosis and treatment of IFD, highlighting the difficulties in extrapolating the results from one setting to another. Indeed, in our study, differences in cost and practice even existed between different centers within one healthcare system (see Supplementary Table 1).

The total costs in our study were in keeping with previous data and incorporated findings from multiple sites.[5,18–22] Importantly, the costs of performing GM and A-PCR comprised only a small proportion of total costs (Fig. 2). Improvements in biomarker technology and decreased costs of new technology are therefore unlikely to

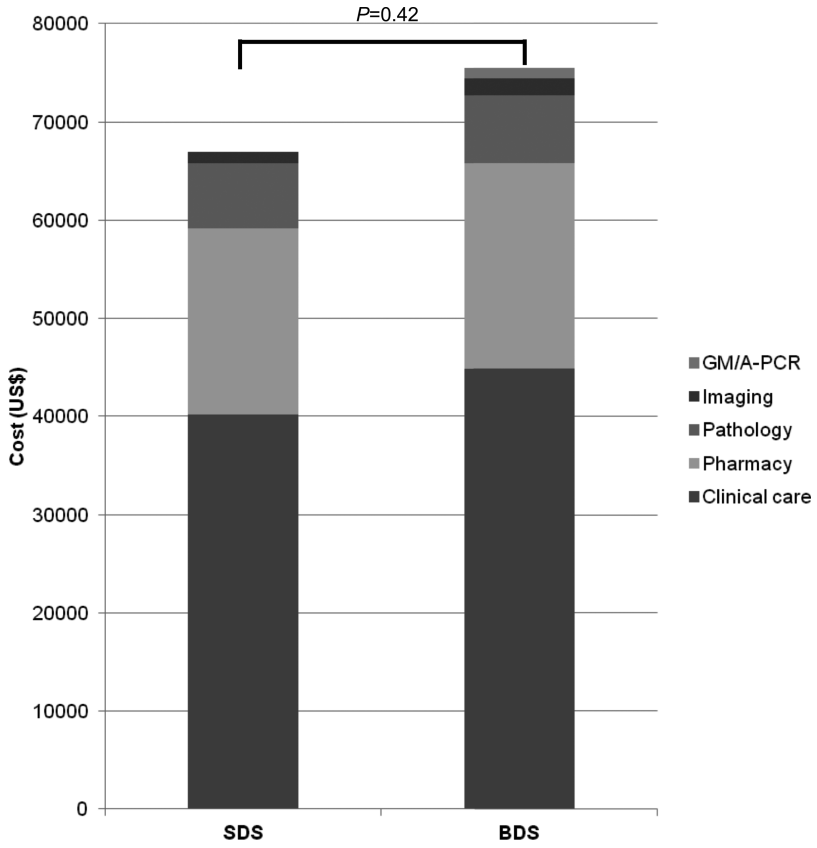

Figure 3. Proportional contribution of each costing category to overall costs*. *Three of four sites had detailed costing data available. A-PCR, *Aspergillus* PCR BDS; Biomarker-based diagnostic strategy; GM, galactomannan, SDS, Standard diagnostic strategy.

Table 2. Years of life saved and cost-effectiveness analysis.

	Life-years saved	Cost per life year saved (US$)
180 days	0.008	$325,448
360 days	0.023	$81,966
2 years	0.057	$28,583
3 years	0.130	$11,497
4 years	0.199	$6,011
5 years	0.266	$3,670

BDS, Biomarker-based diagnostic strategy; SDS, Standard diagnostic strategy.

alter the findings of this study. Although individual data regarding other items contributing to costs were limited to three sites, it was interesting to note that clinical care cost was the highest contributor, as opposed to pharmacy costs. This has been noted in several studies[5,18–22] but is different to previous findings from Ananda-Rajah et al.[6] This is possibly due to use of coding for quantitating IFD diagnoses in that study and underscores the importance of prospective data collection.[6]

Cost-effectiveness is one of many factors that impact on the feasibility of implementing a BDS. Each institution needs to assess if BDS is appropriate by taking into consideration additional factors such as institutional choice of antifungal prophylaxis, incidence of IA and availability and turn-around-time for investigations, including GM and A-PCR. For example, our original trial found that a surveillance (i.e., twice weekly testing) BDS may have limited utility in a population receiving mould-active prophylaxis. This may have impacted our cost-effectiveness findings in the present study. However, there are also numerous 'moving targets': changing definitions of IFD,[23] changing drug costs (e.g., voriconazole and caspofungin becoming generic in 2016 in many countries), changing prophylaxis practice (e.g., increasing use of posaconazole and therapeutic drug monitoring), changing diagnostics (e.g., new imaging techniques[24] and use of GM to 'rule in' IFD vs. 'rule out' IFD[25]) and changing hematology practice (e.g., different transplant techniques and the emerging use of molecularly-targeted therapies for acute myeloid leukemia). This will impact on the future performance and cost-effectiveness of diagnostic strategies.

Our study had limitations. First, BDS being cost-effective was contingent on a survival benefit. Although we noted a trend, this was not statistically significant. Nonetheless using "real-world" costing data we have demonstrated that

BDS may not be cost-saving, which impacts upon design of future studies in this field by demonstrating the need for using a mortality benefit as the primary endpoint. It should also be noted that treatment approaches to IA diagnosed by A-PCR need further study and may change with more experience of its use in clinical practice. Second, our data pertain to the period of 2005–2009, hence limiting generalizability to current practice. Third, the evaluation of cost-effectiveness is based on projections from mortality data published by Lee et al.,[11] which pertains specifically to AML patients undergoing allogeneic SCT. However, it should be noted that 78% of patients studied were hematology patients undergoing SCT, and it does provide a reasonable estimate of future survival for this group. Finally, more comprehensive data collection that itemizes costs per patient (e.g., outpatient visits, day-care center visits) would have been more informative and may have helped refine conclusions about in which population a BDS is most cost-effective. Cost-effectiveness should therefore be incorporated into the design of future prospective trials as was the case in the RCT previously conducted by our group.[4] In addition, robust cost-effectiveness analyses are likely to be more feasible as we enter the era of 'Big Data' and improved costing systems.

In conclusion, we found that BDS is not cost saving but is cost-effective if associated with a survival benefit. Galactomannan and A-PCR test costs make up only a small proportion of the costs associated with a BDS, with clinical care contributing to most of costs regardless of management strategy. BDS has not as yet been widely adopted and defining the period and patient population at highest risk for IA may maximise its utility and cost-effectiveness.[26] Future implementation of BDS will require an institutional-specific approach that takes into account local incidence of IA, patterns of antifungal prophylaxis and turn-around time of tests.

Supplementary material

Supplementary data are available at *MMYCOL* online.

Funding

This work was supported by the Australian National Health and Medical Research Council, Cancer Council New South Wales, Pfizer, Merck and Gilead Sciences.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

References

1. Neofytos D, Horn D, Anaissie E et al. Epidemiology and outcome of invasive fungal infection in adult hematopoietic stem cell transplant recipients: analysis of Multicenter Prospective Antifungal Therapy (PATH) Alliance registry. *Clin Infect Dis*. 2009; **48**: 265–273.
2. Maertens JA, Nucci M, Donnelly JP. The role of antifungal treatment in hematology. *Haematologica*. 2012; **97**: 325–327.
3. Cordonnier C, Robin C, Alanio A et al. Antifungal pre-emptive strategy for high-risk neutropenic patients: why the story is still ongoing. *Clin Microbiol Infect*. 2014; **20** Suppl 6: 27–35.
4. Morrissey CO, Chen SC-A, Sorrell TC et al. Galactomannan and PCR versus culture and histology for directing use of antifungal treatment for invasive aspergillosis in high-risk haematology patients: a randomised controlled trial. *Lancet Infect Dis*. 2013; **13**: 1–10.
5. Ceesay MM, Sadique Z, Harris R et al. Prospective evaluation of the cost of diagnosis and treatment of invasive fungal disease in a cohort of adult haematology patients in the UK. *J Antimicrob Chemother*. 2015; **70**: 1175–1181.
6. Ananda-Rajah MR, Cheng A, Morrissey CO et al. Attributable hospital cost and antifungal treatment of invasive fungal diseases in high-risk hematology patients: an economic modeling approach. *Antimicrob Agents Chemother*. 2011; **55**: 1953–1960.
7. Cordonnier C, Pautas C, Maury S et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis*. 2009; **48**: 1042–1051.
8. Maertens J, Theunissen K, Verhoef G et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis*. 2005; **41**: 1242–1250.
9. Barnes RA, White PL, Bygrave C et al. Clinical impact of enhanced diagnosis of invasive fungal disease in high-risk haematology and stem cell transplant patients. *J Clin Pathol*. 2009; **62**: 64–69.
10. Barnes R, Earnshaw S, Herbrecht R et al. Economic comparison of an empirical versus diagnostic-driven strategy for treating invasive fungal disease in immunocompromised patients. *Clin Ther*. 2015; **37**: 1317–1328 e2.
11. Lee SJ, Storer B, Wang H et al. Providing personalized prognostic information for adult leukemia survivors. *Biol Blood Marrow Transplant*. 2013; **19**: 1600–1607.
12. Collett D. *Modelling Survival Data in Medical Research*. 3rd edn. Boca Raton, CA: CRC Press, 2015.
13. Hughes WT, Armstrong D, Bodey GP et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis*. 2002; **34**: 730–751
14. De Pauw B, Walsh TJ, Donnelly JP et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis*. 2008; **46**:1813–1821.
15. Owens DK. Interpretation of cost-effectiveness analyses. *J Gen Intern Med*. 1998; **13**: 716–717.

16. Aguado JM, Vazquez L, Fernandez-Ruiz M et al. Serum galactomannan versus a combination of galactomannan and polymerase chain reaction-based Aspergillus DNA detection for early therapy of invasive aspergillosis in high-risk hematological patients: a randomized controlled trial. *Clin Infect Dis*. 2015; **60**: 405–414.
17. Fung M, Kim J, Marty FM et al. Meta-analysis and cost comparison of empirical versus pre-emptive antifungal strategies in hematologic malignancy patients with high-risk febrile neutropenia. *PLoS One*. 2015; **10**: e0140930.
18. Wilson LS, Reyes CM, Stolpman M et al. The direct cost and incidence of systemic fungal infections. *Value Health*. 2002; **5**: 26–34.
19. Dasbach EJ, Davies GM, Teutsch SM. Burden of aspergillosis-related hospitalizations in the United States. *Clin Infect Dis*. 2000; **31**: 1524–1528.
20. Rentz AM, Halpern MT, Bowden R. The impact of candidemia on length of hospital stay, outcome, and overall cost of illness. *Clin Infect Dis*. 1998; **27**: 781–788.
21. Slobbe L, Polinder S, Doorduijn JK et al. Outcome and medical costs of patients with invasive aspergillosis and acute myelogenous leukemia-myelodysplastic syndrome treated with intensive chemotherapy: an observational study. *Clin Infect Dis*. 2008; **47**: 1507–1512.
22. Dodds Ashley E, Drew R, Johnson M et al. Cost of invasive fungal infections in the era of new diagnostics and expanded treatment options. *Pharmacotherapy*. 2012; **32**: 890–901.
23. White PL, Wingard JR, Bretagne S et al. *Aspergillus* polymerase chain reaction: systematic review of evidence for clinical use in comparison with antigen testing. *Clin Infect Dis*. 2015; **61**: 1293–1303.
24. Stanzani M, Sassi C, Lewis RE et al. High resolution computed tomography angiography improves the radiographic diagnosis of invasive mold disease in patients with hematological malignancies. *Clin Infect Dis*. 2015; **60**: 1603–1610.
25. Duarte RF, Sánchez-Ortega I, Cuesta I et al. Serum galactomannan-based early detection of invasive aspergillosis in hematology patients receiving effective antimold prophylaxis. *Clin Infect Dis*. 2014; **59**: 1696–1702.
26. van Hal SJ, Gilroy NM, Morrissey CO et al. Survey of antifungal prophylaxis and fungal diagnostic tests employed in malignant haematology and haemopoietic stem cell transplantation (HSCT) in Australia and New Zealand. *Intern Med J*. 2014; **44**: 1277–1282.