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Hospital costs, length of stay and mortality attributable to invasive scedosporiosis in haematology patients

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Background: *Scedosporium* species are increasingly recognized as a cause of invasive mould disease in haematology patients, but little is known about the hospitalization costs and outcomes attributable to invasive scedosporiosis (SCEDO).

Methods: A retrospective case–control study was undertaken during 2002–10 to determine the attributable inpatient costs, length of stay (LOS) and mortality associated with SCEDO in haematology patients. Case patients with SCEDO ($n=30$) were matched 1:2 to controls ($n=60$) according to haematological diagnosis, admission year and age. Diagnostics, antifungal drugs, ward and other SCEDO-related costs were estimated using actual cost data. Median regression modelling was used to adjust for variables that were not accounted for in the matched-pairs analysis.

Results: The crude total median cost of treating SCEDO was AU$32 182 per patient versus AU$17 424 per control. In multivariable analysis, SCEDO was associated with median excess costs of AU$23 611 (95% CI = AU$17 992–AU$29 231; $P<0.001$), approximating US$15 509 at purchasing power parity, with prolonged LOS of 13 days (95% CI = 8.2–17.8 days; $P<0.001$). Exclusion of cases and matched pairs with early death further increased the median excess cost and LOS. The cost differential was driven by ward costs (64%, $P=0.005$) and antifungal treatment costs (29%, $P<0.001$). The all-cause inpatient mortality was 38 times higher for the SCEDO cases versus the control group (63.3% versus 1.7%; $P<0.001$).

Conclusions: SCEDO has substantial impact on hospital resource consumption, LOS and mortality in haematology patients. Risk factors and preventative measures for SCEDO should be further studied.

Keywords: *Scedosporium*, costs, outcome, fungal infection, haematology

Introduction

The emergence of *Scedosporium* species as an important pathogenic mould in patients with underlying haematological diseases,[1] particularly leukaemia patients receiving chemotherapy and stem cell transplant recipients, has triggered concern.[2–4] The prevalence of invasive fungal disease (IFD) caused by this mould is difficult to estimate. In the organ transplant population, invasive scedosporiosis (SCEDO) was reported to account for approximately 25%–29% of non-*Aspergillus* mould infections in the USA.[5,6] Most infections are due to *Scedosporium apiospermum*/*Pseudallescheria boydii* and *Scedosporium prolificans*, although geographic variation exists with regards to species distribution.[7–9] The management of SCEDO represents a significant challenge, given the innate resistance of *Scedosporium* species to many available antifungal agents[10] and high mortality rates (65%–100%).[3,4,11,12]

Treatment of SCEDO remains largely driven by anecdotal experience and observational case series. Multiple treatment modalities are commonly required, including treatment with combination antifungal therapy, aggressive surgical intervention and/or adjunctive immunomodulatory therapy.[6,13] Voriconazole,

as a single agent, represents the approved treatment of choice for infections caused by *S. apiospermum*, while combination therapy of voriconazole with another antifungal agent, most often terbinafine, is recommended for the more resistant *S. prolificans*.[14] Treatment responses to voriconazole have varied, with haematology patients demonstrating the poorest responses.[15] A 30% response rate was noted in a small study in 10 patients,[16] while a larger compassionate study involving 107 patients reported a success rate of 57%.[15]

Although several economic studies have analysed medical costs and excessive burden of hospitalization caused by more common fungal pathogens, such as *Candida* and *Aspergillus* species,[17–21] estimates related to the costs of treating SCEDO are sparse. Accurate estimates of the economic and clinical burden of SCEDO are important to justify potential benefits, in terms of cost savings and survival, of new treatments or SCEDO-specific preventative measures such as antifungal prophylaxis.[22] Compared with crude cost estimates, determination of attributable costs and a breakdown of cost components are of greater utility for cost-effectiveness analysis of such interventions. Accordingly, a retrospective case–control study of SCEDO in adult patients with haematological malignancies was undertaken to determine the inpatient costs, length of stay (LOS) and mortality directly attributable to SCEDO from that incurred by patients' underlying disease.

Materials and methods

Study design and setting

This is a multicentre, retrospective, case–control analysis of SCEDO in adult haematology patients. Cases were haematology patients with SCEDO, whereas controls were hospitalized patients with similar underlying haematology diseases but without SCEDO. The study was approved by the Human Ethics Committees of Royal Melbourne Hospital (RMH), Peter MacCallum Cancer Centre (PMCC) and Monash University.

Patients with invasive SCEDO (i.e. case patients) were identified from three sources: the Australian *Scedosporium* (AUSCEDO) Study database, which contains data from this prospective population-based survey for SCEDO in Australia during 2003–05,[23] and from the RMH and PMCC during 2002–10. The case patients were categorized into proven, probable or possible IFD according to the revised European Organization for Treatment of Cancer/Mycoses Study Group (EORTC/MSG) criteria.[24] SCEDO was defined as cases whereby tissue biopsy or sterile specimens showed fungal hyphae or from which the pathogen was grown.[23] The classification and attributable cause of inpatient death due to SCEDO was conducted by M. A. S. and S. C.-A. C. Control patients were recruited from the RMH and PMCC using a patient list maintained by M. A. S.

Each case patient was matched to two control patients according to the following hierarchy of criteria: the primary underlying haematological disease or type of stem cell transplantation, year of admission (±1 year) and age within ±15 years of a case patient. Exclusion criteria included age <18 years, LOS of <3 days and colonization with *Scedosporium* species.

Outcomes assessment

Three outcome measures were used: (i) attributable inpatient hospitalization costs; (ii) LOS in hospital; and (iii) inpatient mortality.

Clinical data collection

Patient-level data obtained from the AUSCEDO Study database and patient medical records included demographic characteristics, primary underlying disease, haematopoietic stem cell transplantation (HSCT) type, comorbidities, type of chemotherapy, duration of neutropenia (absolute neutrophil count <500 cells/mm^3), LOS, inpatient antifungal medications administered and the indications, radiological and microbiological results, adjunctive surgical interventions for SCEDO, inpatient mortality and cause of death.

The first day of *Scedosporium* species isolation was defined as the onset date of SCEDO. Neutropenia that persisted for ≥10 days was defined as prolonged neutropenia. Combination antifungal therapy was defined as administration of at least two antifungal drugs for ≥3 consecutive days at any point during a patient's hospital stay.[25]

Cost data, cost calculations and perspective

The study was performed from the hospital inpatient perspective. Only direct medical costs that were likely to be affected by the presence or absence of SCEDO and known to exert significant impact on total hospitalization costs were included. The costs of ward stays were based on general room rates, which included salaries of staff, food, linens and laundry service. For the medications used, only acquisition costs for antifungal drugs were included. Diagnostic costs to evaluate or identify infections included radiological imaging (X-ray, CT scan, magnetic resonance imaging and ultrasound) and pathological investigations (histopathological examination, microscopy and cultures). Costs related to adjunctive procedures for treating SCEDO included bronchoscopy with bronchoalveolar lavage, tissue biopsy, pulmonary wedge resection, debridement of localized lesions and sinus washout. Outpatient costs, medical supplies and consumables (e.g. needles, syringes and cotton) that were low in price, analgesics and anti-emetics that were low in volume were excluded. Indirect medical costs related to underlying diseases, indirect non-medical costs and intangible costs were not included.

The ward costs were obtained from the National Hospital Cost Data Collection for diagnosis-related groups;[26] costs for diagnostic tests and procedures were retrieved from the Medicare Benefits Schedule Book 2010;[27] and acquisition costs of antifungal medications were from Health Purchasing Victoria tender 2010–12.[28]

For each patient, the total cost of antifungal drug therapy was calculated by multiplying the daily drug cost by the number of therapy days, where daily drug costs were estimated by multiplying the total doses per day by the wholesale price for that drug. Drug costs were calculated based on actual doses administered to patients. Diagnostic and adjunctive procedure costs were determined by multiplying the cost unit for each test or procedure by the volumes used. Hospital stay was determined by multiplying the floor charge of a general ward by the number of inpatient bed days. Due to the 1:2 matching ratio for case and control patients, the total costs from two matched controls were averaged and the mean value was used as the reference for comparison with the respective case. Subtraction of the mean costs or LOS of control patients from the mean costs or LOS of case patients, respectively, afforded the crude attributable costs and LOS of SCEDO.

Actual cost data collected were expressed in Australian dollars for the financial year 2010–11. Discounting was not applied because of the short costing period of index hospitalization (maximum 3 months). Costs that were not available for the current financial year were adjusted according to the healthcare component of the Australian Consumer Price Index 2010.[29] To allow comparison of results with those from other studies, conversion to 2010 US dollars was performed using the purchasing power parity (PPP) method.[30]

Statistical analyses

Statistical analyses were conducted using PASW statistical software version 17.0 (IBM SPSS, Inc) and Stata version 11 statistical package (Stata Corp., College Station, TX, USA). Data were analysed for normality using the Kolmogorov–Smirnov test. In matched-pairs analysis, attributable costs and LOS were calculated by the median of the difference in costs between cases and controls, and compared using the Mann–Whitney *U*-test.

To control for residual confounding factors that were not accounted for by matched analysis, patient-level median regression models were developed to enable calculation of costs truly attributable to SCEDO. Potential variables were identified and their relationship with costs and LOS were analysed using univariable analyses. Selection of variables was governed by their impact on both cost and LOS outcomes. Only variables with a P value <0.25 for both costs and LOS were included in the multivariable models, where the independent effects of the variables on incremental median costs and LOS were analysed using backward stepwise regression. SCEDO case status (as the primary outcome variable of interest) and receipt of combination antifungal therapy were entered into two multivariable models through force-inclusion. The regression coefficient of SCEDO case status represents the adjusted excess median cost or LOS associated with the presence of SCEDO.

For subgroup analysis, the adjusted median excess costs and LOS were assessed by excluding those with early death (LOS <14 days) attributable to SCEDO and their matched controls.

All-cause inpatient mortality was compared between groups with the χ^2 test. Crude SCEDO-attributed mortality rate was estimated on the basis of the difference in survival between case and control patients.

Incomplete data for the pathology and radiological tests performed in the AUSCEDO Study database were managed using a simple imputation approach, where each missing value was replaced with the median observed values for that cost variable. In a one-way sensitivity analysis, we estimated the robustness of cost estimates when the number of laboratory tests was minimized or maximized in the observed range. Sensitivity analyses were also performed to evaluate the impact of variation (100% decrease to 100% increase) in the acquisition costs of the antifungal drug most commonly used in the case group, voriconazole, and ward cost. Table 1 shows the variation range for variables with missing data and key cost variables.

For all analyses, a two-sided *a priori* level of significance was set at 0.05.

Results

Study patients and features of SCEDO infection

There were a total of 28 proven, 1 probable and 1 possible infections. The probable and possible cases were differentiated from other moulds through repeated non-sterile cultures isolating *Scedosporium* species, where two separate toe wound swab cultures were positive for *S. apiospermum* in the probable case and the possible case had five separate sputum cultures yielding *S. prolificans*. The demographics and pre-specified characteristics were similar in both groups (Table 2); however, SCEDO cases were more likely to have neutropenia at baseline compared with control patients (80.0% versus 58.3%; $P=0.071$). Fluconazole was the antifungal agent that was most commonly used for universal prophylaxis, while the agents most frequently employed for mould-active prevention were itraconazole and voriconazole.

SCEDO appeared to have early onset, with 43% of cases having an LOS $\leq$12 days prior to diagnosis. Overall 88.8% (16/18) of leukaemia patients and 62.5% (5/8) of stem cell transplant patients were diagnosed with SCEDO within 30 days of admission. In 4 (13.3%) patients, isolation of *Scedosporium* species preceded hospital admission. Combination antifungal therapy was used mainly for the treatment of infection caused by *S. prolificans* (10/12), in which dual therapy with voriconazole plus terbinafine was the preferred regimen. The median duration of combination antifungal therapy was 5 days (range 3–17 days). For all cases that received antifungal treatment (26/30), the median duration of treatment during hospitalization (including single and combination therapies) was 11 days (range 1–50 days). After the diagnosis of SCEDO was made, definitive antifungal treatment was administered for a median of 5 days (mean 9 days, range 1–40 days) until death or discharge. Of these, 1 case was an outlier (40 days) and the remaining cases received $\leq$17 days of treatment.

Cost estimates and length of hospital stay

The median total hospitalization cost for a patient with SCEDO was significantly higher than that for a control patient (AU$32182 versus AU$17424; $P=0.001$), affording a crude median attributable inpatient cost of AU$17796 per patient (Table 3). Patients with SCEDO had a longer hospitalization compared with control patients (median 22 versus 14 days; $P=0.005$; Table 2). The major contributors to the differences in costs between the two patient groups were ward costs (64% of total cost; $P=0.005$) and antifungal drug costs (29% of total cost; $P<0.001$).

Table 1. Variation of range for variables in sensitivity analysis

		Variation range	
Variables	Base case	low	high
Hospitalization cost/day	AU$1133.0	AU$0.0	AU$2266.0
Voriconazole cost/vial	AU$187.1	AU$0.0	AU$375.0
Voriconazole cost/tablet	AU$45.2	AU$0.0	AU$90.0
Counting for the diagnostics costs	Yes	No	Yes
Counting for the procedures costs	Yes	No	Yes
Number of blood culture done	4	0	11
Number of sputum, skin and sinus tissue culture done	1	0	18
Number of urine culture done	2	0	10
Number of chest X-ray done	4	0	23
Number of chest CT done	1	0	6

Table 2. Characteristics of patients with and without SCEDO

Variable	SCEDO group $n=30$ (%)	Control group $n=60$ (%)
Age in years; mean, median (range)	53, 57 (22–77)	52, 56 (17–76)
Male sex	19/30 (63.3)	31/60 (51.7)
Haematological malignancy		
leukaemia	21/30 (70.0)	46/60 (76.7)
relapsed or refractory leukaemia	2/30 (6.7)	1/60 (1.7)
stem cell transplantation	8/30 (26.7)	16/60 (26.7)
allogeneic	7/30 (23.3)	14/60 (23.3)
lymphoma	4/30 (13.3)	5/60 (8.3)
transformed MDS	2/30 (6.7)	4/60 (6.7)
other[a]	3/30 (10.0)	5/60 (8.3)
Receipt of myelotoxic chemotherapy	18/30 (60.0)	25/60 (41.7)
Baseline neutropenia	24/30 (80.0)	35/60 (58.3)
Duration of neutropenia: days; median (range)	16 (1–32)	13 (3–36)
Prolonged neutropenia ≥10 days	15/27 (55.6)[b]	27/60 (45.0)
Receipt of systemic antifungal prophylaxis	19/30 (63.3)	49/60 (81.7)
Mould-active prophylaxis	17/30 (56.7)	35/60 (58.3)
Antifungal prophylaxis[c]		
fluconazole	3/30 (10.0)	13/60 (21.7)
itraconazole	8/30 (26.7)	1/60 (1.7)
voriconazole	7/30 (23.3)	30/60 (50.0)
posaconazole	2/30 (6.7)	4/60 (6.7)
LAmB	2/30 (6.7)	0/60 (0)
SCEDO classification		
proven SCEDO	28/30 (93.3)	NA
probable SCEDO	1/30 (3.3)	
possible SCEDO	1/30 (3.3)	
Site of infection[d]		
fungaemia	19/30 (63.3)	NA
sino-pulmonary	15/30 (50.0)	
CNS	2/30 (6.7)	
skin or soft tissue	4/30 (13.3)	
other[e]	5/30 (16.7)	
disseminated	22/30 (73.3)	
localised	8/30 (26.7)	
LOS prior to isolation of *Scedosporium* spp.; mean, median (range)	17.5, 17.0 (−4–69)[f]	NA
Species isolated		
S. apiospermum	8/30 (26.7)	NA
S. prolificans	22/30 (73.3)	
Receipt of antifungal treatment	26/30 (86.7)	NA
combination therapy[g]	12/30 (40.0)	
Initial antifungal treatment received[h]		
voriconazole	21/30 (70.0)	NA
terbinafine	14/30 (46.7)	
cAmB	1/30 (3.3)	
LAmB	5/30 (16.7)	
fluconazole	1/30 (3.3)	

Continued

Table 2. *Continued*

Variable	SCEDO group $n=30$ (%)	Control group $n=60$ (%)
Timing of antifungal drug initiation[i] in days; mean, median (range)	−1.4, 0 (−1–6)[j]	NA
Inpatient mortality	19/30 (63.3)	1/60 (1.7)
LOS in days; mean, median (range)	27.2, 22.0 (5–77)	16.4, 14.0 (5–46)

$P>0.05$ for all comparisons (by Mann–Whitney *U*-test for continuous variables and by χ^2 test for categorical variables). SCEDO, invasive scedosporiosis; MDS, myelodysplastic syndrome; LOS, length of stay; NA, not applicable; cAmB, conventional amphotericin B; LAmB, liposomal amphotericin B.
[a]Other includes aplastic anaemia and multiple myeloma.
[b]Missing data for three case patients.
[c]Four patients had a change in antifungal prophylactic regimen.
[d]Some patients had more than one site involved.
[e]Two hepatosplenic infections; plus one each for elbow, eye and ear.
[f]Missing data for one patient. Negative number denotes isolation of *Scedosporium* species prior to admission.
[g]Combination therapy refers to the administration of at least two antifungal drugs for ≥3 consecutive days at any point during a patient's hospital stay.
[h]Not mutually exclusive, as some patients may have more than one antifungal agent.
[i]Time of the earliest initiated antifungal drug, including empirical therapy, in relation to isolation date of *Scedosporium* species.
[j]Zero indicates initiation of antifungal therapy on the same day that *Scedosporium* species was isolated; negative number signifies empirical antifungal therapy before isolation of *Scedosporium* species.

After adjusting for prolonged neutropenia, receipt of combination antifungal therapy, chemotherapy and inpatient mortality in a multivariable model, SCEDO was significantly associated with an excess median cost of AU$23 611 (95% CI=AU$17 992–AU$29 231; $P<0.001$) and prolonged LOS of 13 days (95% CI=8.2–17.8 days; $P<0.001$) over the baseline control (Table 4). Prolonged neutropenia was strongly correlated with extended excess median LOS and higher adjusted excess median costs. Combination antifungal therapy was an independent predictor of excess costs ($P=0.001$), but not increased LOS ($P=0.679$). If the SCEDO case patient died during hospitalization, the adjusted median excess cost was reduced to AU$18 760 (95% CI=−AU$24 450 to −AU$13 070; $P<0.001$) and excess median LOS shortened to 10 days (95% CI=−14.7 to −5.3; $P<0.001$).

In a sub-analysis, adjusted excess costs and LOS were re-analysed after excluding seven cases with early inpatient death (<14 days) attributable to SCEDO and their matched controls ($n=14$). Under this circumstance, the median excess cost associated with SCEDO was further increased to AU$31 658 (95% CI=AU$21 097–AU$42 220; $P<0.001$) relative to baseline control, with a longer LOS (19 days; 95% CI=14.2–23.8 days; $P<0.001$). The results for prolonged neutropenia (excess median cost AU$19 478; 95% CI AU$12 723–AU$26 232; $P<0.001$ and LOS 16 days; 95% CI=13.0–19.0 days; $P<0.001$), receipt of chemotherapy (excess median cost AU$5409; 95% CI −AU$1146–AU$12 234; $P<0.118$ and LOS 3 days; 95% CI=0.04–5.9 days; $P=0.047$), inpatient death (reduced excess median cost −AU$14 528; 95% CI=−AU$25 353 to −AU$3702; $P<0.009$ and LOS −11 days; 95% CI=−15.9 to −6.1 days; $P<0.001$) and receipt of combination antifungal therapy (−4 days; 95% CI=−8.9–0.9 days; $P=0.112$) were largely unchanged. Receipt of combination antifungal therapy, however, lost its significant association with median excess costs in the subgroup analysis (−AU$1773; 95% CI=−AU$13 028–AU$9482; $P=0.754$).

The results of one-way sensitivity analysis showed that varying the number of pathology and radiological tests performed did not change the results (data not shown), and therefore there was minimal impact of incomplete pathology and radiological information (7/30, 23.3%) from the AUSCEDO Study database on the study outcomes. Baseline cost difference was also not sensitive to changes in the acquisition costs of voriconazole. Interestingly, if the ward cost was reduced to $0 (an unlikely scenario), the unadjusted mean cost difference between the SCEDO case and control groups would be increased to almost 7-fold compared with the base case difference of 2-fold. Doubling of ward cost did not change the magnitude of the cost difference observed.

Patient mortality

The all-cause inpatient mortality was approximately 38 times higher for those with SCEDO (19/30) versus the control group (1/60) (63.3% versus 1.7%; $P<0.001$). SCEDO was determined to be the cause of death in 17 of the 19 (89.5%) cases, translating into an overall SCEDO-attributable mortality rate of 56.7% (17/30). Seven of 12 case patients (58.3%) who were receiving combination antifungal treatment died, versus 9 of 14 patients (64.3%) on monotherapy.

Discussion

This study represents the first report of the combined attributable economic and clinical outcomes of SCEDO. Two different methods were used to determine SCEDO-attributable costs, where residual confounding factors were corrected in the

Table 3. Hospitalization costs per patient, inflated to 2010 AU$ for year of admission

Cost category	Cases (AU$)	Controls (AU$)	Difference between groups (%)	P^a
Diagnostics				
total	1406	270	1136 (6.0)	<0.001
radiology	981	166	815 (4.3)	<0.001
pathology	425	104	321 (1.7)	<0.001
Antifungal drugs	6356	903	5453 (28.6)	<0.001
Hospital stay				
ward	30817	18562	12255 (64.3)	0.005
Adjunctive procedures	197	8	189 (1.0)	<0.001
Operating room	22	0	22 (0.1)	0.044
Total costs				
mean	38798	19743	19055	
median	32182	17424	17796[b]	0.001
range	8315–101970	2301–56472		

SCEDO, invasive scedosporiosis.
Values are reported as means unless otherwise stated.
[a]Test of the difference between SCEDO case and control groups using the Mann–Whitney *U*-test.
[b]Median of the difference in costs between case–control pairs.

Table 4. Median regression analyses of the impact of clinical variables on total hospitalization costs and length of stay per patient

	Hospitalization costs (inflated to 2010 AU$)			Length of stay (days)		
Variable	Coefficient	95% CI	*P*	Coefficient	95% CI	*P*
Univariable analysis						
SCEDO infection	14750	4502–24997	0.005	9	−0.13–18.13	0.053
Length of stay	1249	1235–1263	<0.001	-[a]	—	—
Age	−205	−551–141	0.243	−0.1	−0.41–0.21	0.522
Allogeneic HSCT	3728	−9372–16829	0.573	6	−1.36–13.36	0.109
Prolonged neutropenia	20204	14928–25480	<0.001	17	12.67–21.33	<0.001
Receipt of combination therapy	14508	−1832–30848	0.081	6	−6.06–18.06	0.326
Receipt of chemotherapy	13544	3828–23261	0.007	9	1.43–16.56	0.020
Inpatient death	9794	−4318–23905	0.171	6	−4.23–16.23	0.247
Multivariable analysis[b]						
Baseline control[c]	8435	5570–11300	<0.001	7	4.7–9.3	<0.001
SCEDO infection	23611	17992–29231	<0.001	13	8.2–17.8	<0.001
Prolonged neutropenia	20313	16808–23818	<0.001	17	14.2–19.8	<0.001
Receipt of combination therapy	10505	4576–16435	0.001	1	−3.8–5.8	0.679
Receipt of chemotherapy	5409	1946–8872	0.003	3	0.19–5.8	0.036
Inpatient death	−18760	−24450 to −13070	<0.001	−10	−14.7 to −5.3	<0.001

[a]Variables not included in the model.
[b]Multivariable analysis involved force-inclusion of SCEDO case status and receipt of combination antifungal therapy and significant variables from univariable analysis ($P<0.25$).
[c]For the purpose of multivariable analysis, baseline control referred to a patient without SCEDO, with no prolonged neutropenia, who did not receive chemotherapy and/or combination antifungal therapy and was discharged from the hospital alive.

median regression models and additional predictors that can influence total costs were established. Our study showed that SCEDO was independently associated with increased median inpatient costs and LOS.

The unadjusted and adjusted median per hospitalization cost for treating SCEDO generated by case–control analysis and median regression methods were in good agreement, with a 32% disparity. The higher cost estimate obtained with median

regression could be partly explained by the adjustment for impact of neutropenia, given that patients with SCEDO had a greater likelihood of being neutropenic at baseline ($P=0.071$). Breakdown of cost components revealed that the major determinant of SCEDO-related hospitalization cost was increased LOS, with ward cost representing 65% of total costs. This is congruent with the findings of previous studies focusing on IFD caused by other organisms.[18,20,31] The cost of therapeutic drug monitoring (TDM) of antifungal drugs was not included, given the small volume of use, as the majority of cases (80%) were recruited from 2006 or earlier, during which antifungal TDM was uncommon.

Comparison of our findings with those from other studies is restricted by the lack of economic data for SCEDO and the discrepancy in the study methodologies employed. Using the cost:charge ratio, Tong and colleagues reported the incremental median cost of invasive aspergillosis (IA) to be US$41 379 in 2003 for non-HSCT haematology patients,[21] which was similar to Menzin *et al*.,[32] who found a mean IFD-attributable cost of US$37 046 in 2004 for patients affected by haematological malignancies. The median gross hospitalization cost reported by Kim *et al*.[25] was higher than for the previous two studies, at US$73 029 in 2006 using actual costs, but attributable costs could not be determined due to the absence of a control arm. Slobbe *et al*.[20] conducted a more detailed analysis of IA-related costs in leukaemia patients, in which the cost attributable to proven or probable IA after correcting for neutropenia duration was €15 280 in 2007. Conversion of this figure to 2007 US dollars using PPP yielded US$17 767, which appeared to be similar to our adjusted excess median costs of US$15 509 at the 2010 PPP rate. The apparently lower total hospitalization costs of SCEDO compared with IA may be influenced by the higher mortality rate and subsequently shorter inpatient LOS of patients with SCEDO.

The mortality rate attributable to SCEDO in our study cohort was substantial (56.7%), higher than the SCEDO-attributable mortality rate observed by Troke *et al*.[15] (30%) and Rodriguez-Tudela *et al*.[33] (47%), whose study groups comprised mixed populations with relatively low proportions (<45%) of haematology patients. Our higher mortality rate most likely reflects the general poor health of haematology patients and the higher proportion of disseminated infection in our cohort. Indeed, SCEDO patients with underlying haematological malignancies have been shown to have a higher overall mortality rate (76.8%) compared with other subgroups [HSCT (68%) and organ transplant recipients (57%)].[6] Disseminated SCEDO is rapidly fatal and patient mortality is usually higher than with other mould diseases in a similar population, e.g. 13%–31% due to IA.[20,21,25] Given the profound effect of inpatient mortality on median cost and LOS, a separate analysis was performed to re-examine the median cost and LOS attributable to SCEDO after excluding seven matched pairs ($n=21$) with an LOS <14 days. SCEDO-related median excess cost and LOS were increased significantly, denoting the true impact of SCEDO on median cost and LOS.

Combination antifungal therapy is of increasing interest. Unfortunately evidence for or against combination antifungal therapy is limited. Whether the use of combination antifungal therapy improved clinical outcome and allowed earlier discharge of SCEDO patients in the current study could not be determined in this observational study.

The high mortality rate observed in our study highlights several underlying problems with respect to the management of SCEDO in haematology patients, including the use of insensitive diagnostic methods and challenges in interpreting the findings; the lack of surveillance and specific treatment guidelines for SCEDO; and inadequate antifungal prophylaxis, where mould-active prophylaxis was only administered in roughly half of our study participants. Prompt and more systematic collection of tissue samples (e.g. bronchoalveolar lavage fluid) combined with better use of molecular techniques are several important factors that could potentially improve early diagnosis. More effective pharmacological interventions for SCEDO need to be sought in terms of a standardized treatment protocol or the optimal combination of antifungal drugs, and the potential role of adjunctive cytokines or disease-modifying agents that may expedite immune reconstitution. The high median excess costs and poor outcome attributable to SCEDO also reflect the importance of preventative measures, including mould-active antifungal prophylaxis. However, long-term prophylaxis with expensive antifungal agents (e.g. voriconazole and posaconazole) would be costly. A more cost-effective approach could be to identify those who are at risk of SCEDO among the general haematology patients and individualize the prophylactic regimen.

Our study had several limitations. First, the sample size was limited given the emerging nature of this uncommon infection. Second, the controls should ideally be obtained from the same hospital where SCEDO cases were identified, but the cases identified from the AUSCEDO Study database were from different regions in Australia and we were unable to access control patients from all the institutions where these cases originated. To mitigate the discrepancy in hospital charges between regions and institutions, costing of healthcare resources in this study was based on Australian national cost databases. This study has focused on inpatient medical costs and did not include physician clinic visits and outpatient pharmacy costs. The costs associated with managing SCEDO can extend beyond the initial hospitalization, and patients who survived the infection may require prolonged courses of antifungal treatment in the outpatient setting. Future analysis should include the outpatient costs, which could potentially add a further dimension to quantifying the total costs of SCEDO. However, given the high inpatient mortality rate attributable to SCEDO, most of the medical costs would be incurred during hospitalization. The cost of an intensive care unit (ICU) stay was not included in this study, primarily because very few patients with SCEDO in our study required an ICU stay (1.6% from the AUSCEDO Study database).[23] This is most probably due to the rapid progressive nature of SCEDO, resulting in many patients dying before they can be transferred to the ICU.

In conclusion, this study has demonstrated that SCEDO in haematology patients exerts a substantial impact on hospital resource consumption and patient mortality, with the total costs driven by ward stay and antifungal drug costs. Strategies to improve diagnostics and prevention of SCEDO may be critical for cost savings and improved survival.

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Transparency declaration

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