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Candidemia following solid organ transplantation in the era of antifungal prophylaxis: the Australian experience

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Abstract: Solid organ transplant (SOT) recipients have high rates of invasive fungal infections, with *Candida* species the most commonly isolated fungi. The aim of this study was to identify differences between incidence rates, risk factors, clinical presentations, and outcomes of candidemia in SOT recipients and non-SOT patients. Data from the multicenter prospective Australian Candidaemia Study were examined. From August 2001 to July 2004, 24 episodes (2.2%; 24/1068) of candidemia were identified in SOT recipients. During this period, the numbers of transplanted organs included liver ($n = 455$), kidney ($n = 1605$), single lung ($n = 57$), bilateral lung ($n = 183$), heart and lung ($n = 18$), heart ($n = 157$), and pancreas ($n = 62$). The overall annual estimated incidence of candidemia in SOT recipients was higher (3 per 1000 transplant admissions) than in non-SOT patients (incidence 0.21 per 1000 admissions; $P < 0.001$). The incidence and timing of candidemia post transplant was influenced by the transplanted organ type, with the majority of episodes ($n = 14$, 54%) occurring > 6 months after renal transplantation. Risk factors for candidemia in the month preceding diagnosis were similar to non-SOT recipients except for corticosteroid therapy ($P < 0.001$). Antifungal prophylaxis did not select for more resistant or non-*albicans Candida* species in the SOT group. The 30-day all-cause mortality was similar to non-SOT patients with candidemia and remains high at 21%. All deaths in SOT recipients occurred early (within 5 days of diagnosis), underlining a need for better diagnostic tests, targeted prevention, and early treatment strategies.

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Candida species are the most common fungal pathogens in solid organ transplant (SOT) recipients and account for 35–90% of invasive fungal infections (1–5). Manifestations range from mucosal colonization to disseminated disease with most infections occurring in the early post-transplant period (within 30 days) (1, 6, 7). Invasive infections are associated with significant morbidity and reported mortality rates that range from 5–77% (4, 6). The epidemiology and outcome of invasive candidiasis in SOT recipients are influenced by the type of organ transplanted. Candidemia occurs most frequently in liver and pancreatic transplant recipients (1–32%) followed closely by heart and/or lung transplant recipients (1–16%) (8). In contrast, renal transplant recipients have among the lowest rates reported (2%) (7, 8). SOT recipients share many of the same risk factors for candidemia as non-transplanted patients. These include broad-spectrum antibiotic use, total parenteral nutrition, long-term central venous lines, and prolonged stay in intensive care. In addition, specific risk factors for candidemia in SOT recipients include immunosuppression and cytomegalovirus (CMV) infection (9–11).

Antifungal prophylaxis was introduced in SOT recipients in an attempt to reduce invasive fungal infection-associated mortality. The choice of antifungal agent is

dependent on the need for anti-mold activity, which, like the incidence of candidemia, differs between the types of solid organs transplanted. Although the use of antifungal prophylaxis together with improvements in surgery and post-transplant care has reduced overall rates of *Candida* infection in SOT recipients, breakthrough infections continue to occur (particularly with non-*albicans Candida* species) (2, 4). Further, it remains unknown whether antifungal prophylaxis in SOT recipients has influenced the burden of candidemia and/or the all-cause mortality rates in these patients compared with non-SOT patients. In this report, data from the multicenter prospective Australian Candidaemia Study were examined to determine and compare the incidence, clinical risk factors, and outcomes in SOT recipients and non-SOT patients.

Methods

The Australian Candidaemia Study methodology, data collection procedures, and microbiological methods are described in detail elsewhere (12). Cases were prospectively identified by blood culture surveillance from August 2001 to July 2004 in 50 of 52 participating microbiology laboratories. All transplants performed (renal [$n = 82$] and heart [$n = 17$]) at institutions serviced by the two non-participating laboratories were excluded from the study. Data including patient demographics, clinical risk factors within the preceding 30 days (including corticosteroid usage and/or antifungal prophylaxis), co-morbidities, likely portal of entry, disease manifestations, antifungal therapy, and all-cause mortality at 30 days were collected. The source of the candidemic episode was determined by the treating physician, except in patients with a vascular access device where the same *Candida* species had to be isolated from the device tip and the blood for the device to be considered the source. Outcomes were assessed at 30 days in all patients including those discharged from hospital. Mortality attributable to the candidemia was determined by the treating clinician.

A case was defined by the occurrence of one or more positive blood cultures yielding a *Candida* species. Recurrent episodes of candidemia were classified as a new episode if they occurred 30 days or more after the last negative blood culture. An inpatient healthcare-associated episode was defined as candidemia acquired ≥ 48 h after hospital admission, while outpatient episodes were diagnosed within 48 h of admission. Among outpatient-acquired episodes, the presence of healthcare-associated risk factors (an indwelling medical device or a surgical procedure within 30 days of candidemia) further categorized these episodes as outpatient healthcare-associated infection.

Phenotypic identification of *Candida* organisms and antifungal susceptibility testing (Sensititre® YeastOne® Y06, Trek Diagnostics, Cleveland, Ohio, USA) were performed at a reference laboratory (Women's and Children's Hospital, Adelaide) (12).

Statistical analysis

SOT denominator data were collated from transplant hospital queries using the following inpatient procedure codes – 3650300 (for renal transplants), 9031700 (for liver transplants), 9020501 (for heart and lung transplants), 9020500 (for heart transplants), 9017200/1 (for lung transplants), and 9032400 and 1420301 (pancreas transplants) according to the International Statistical Classification of Diseases and Related Health Problems, 10th revision, Australian modification (13). The subsequent calculated annual incidence in SOT recipients was the quotient of the pooled means of the numerators and the denominators from all sites. Similarly, the incidence in non-SOT patients was calculated using pooled mean denominator data based on completed admissions from individual hospitals.

Continuous variables were compared with the Student t test, and categorical variables were compared with the χ^2 or Fisher exact tests as appropriate using SPPS version 10.0 (SPSS Inc., Chicago, Illinois, USA). A P value of < 0.05 was considered statistically significant.

Results

A total of 1068 episodes of candidemia in 1068 patients were identified, of which 24 (2.2%) occurred in SOT recipients. Demographic, clinical, and outcome data were available for all 24 candidemia episodes in SOT recipients. In the episodes occurring in non-SOT patients, demographic and clinical data were available for 93% (981 patients) of the episodes and outcome data for 80% (833 patients). Fifty percent of SOT recipients were male with a median age of 52 years (range 7–74 years) compared with a male predominance of 54% with a median age of 56 years (0–98 years) in non-SOT patients (P = non-significant [NS]).

During the study period, 2536 patients underwent SOT. The transplanted organs included liver ($n = 455$), kidney ($n = 1605$), single lung ($n = 57$), bilateral lung ($n = 183$), heart and lung ($n = 18$), heart ($n = 157$), and pancreas ($n = 62$). The overall annual incidence of candidemia in SOT recipients was 3 per 1000 transplant admissions, with the highest rate found in lung (single or bilateral) trans-

plant recipients (7.0 per 1000 transplants per year) (see Table 1). There were no cases of candidemia in patients with pancreatic transplants. In general, SOT recipients were more likely to develop candidemia than the non-SOT patients (incidence of 0.21 per 1000 admissions; odds ratio [OR] 43, 95% confidence interval [CI] 29–65, $P<0.001$).

Comparison of the setting, source, and clinical risk factors for candidemia in SOT recipients and non-SOT patients are summarized in Table 2. Most patients, 81%, acquired their candidemia in hospital with 46% ($n=11$) of SOT recipients in the intensive care unit at the time of diagnosis (OR 1.9, 95% CI 0.8–4.4, $P=$ NS) (Table 2). Vascular access devices were the most commonly identified source for candidemia in both SOT and non-SOT groups. Risk factors for candidemia were similar, with the exception that SOT recipients were significantly more likely to have received corticosteroid therapy in the previous 30 days (OR 5.9, 95% CI 2.4–14.3, $P<0.001$).

Antifungal prophylaxis was significantly more likely to be given in the previous month to SOT recipients (12 of 24 SOT recipients OR 3.4, 95% CI 1.5–7.7, $P<0.001$). The distribution of *Candida* species was similar in both groups (Table 3). Drugs prescribed included voriconazole ($n=1$), liposomal amphotericin ($n=3$), fluconazole monotherapy ($n=3$), or fluconazole in combination with conventional amphotericin ($n=1$), and unspecified therapy ($n=4$). *C. albicans* was the most frequent isolate in both SOT and non-SOT patients. Use of fluconazole prophylaxis did not select for non-*albicans Candida* species in SOT recipients (OR 1.2, 95% CI 0.89–1.7), but was a risk factor in the overall group (SOT and non-SOT patients) (OR 2, 95% CI 1.26–3.2, $P<0.001$). However, the frequency of fluconazole-resistant (including fluconazole sensitive-dose dependent) *Candida* species (e.g., *C. glabrata* and *C. krusei*) was not influenced by antifungal prophylaxis use in either group.

Episodes of candidemia occurred within 1 month of transplantation in 38% ($n=9$) of patients, between 1 and 6 months in 8% ($n=1$), and $\geq$ 6 months post transplantation in the remaining 54% ($n=13$) of SOT recipients. Late-onset candidemia episodes ($\geq$ 6 months) occurred more often after renal transplantation, when compared with liver, lung, and heart transplantation (OR 16.5, 95% CI 2.3–121.2, $P<0.001$) (see Table 1).

All late-onset candidemia patients had at least one risk factor for candidemia in the month before diagnosis including 5 bacteremic episodes (3 renal, 2 liver); 1 surgical site infection (renal); 4 pneumonias (3 renal, 1 liver); indwelling urinary catheters in 10 patients (9 renal, 1 liver), and a confirmed urinary tract infection in 6 patients (4 renal, 2 liver). All patients had received broad-spectrum antibiotics in the 30 days preceding candidemia. Renal impairment (median creatinine 199 μmol/L [range 100–600 μmol/L]) was present in 8 patients (7 renal, 1 liver). Corticosteroid treatment and other immunosuppressive agents for treatment of graft rejection were administered to 10 (8 renal, 2 liver) and 3 (all renal) patients, respectively.

Metastatic complications of candidemia were noted in 25% ($n=6$) of SOT recipients (1 pericardial infection, 1 gallbladder infection, and 4 renal abscesses) compared with 15% (126/840) of non-SOT patients (OR 1.8, 95% CI 0.7–4.9, $P=$ NS). All SOT recipients had an echocardiogram. However, only a third underwent ophthalmologic examination. There were no cases of endocarditis or ophthalmic features consistent with ocular candidiasis detected.

The all-cause 30-day mortality for SOT recipients with candidemia was 21% (5/24) with 80% of all deaths (4 of 5) occurring in the SOT recipients >6 months post transplantation. Although the mortality rates were similar to

Timing and incidence of candidemia according to solid organ transplanted during the period August 2001 to July 2004

Transplant	Heart	Lung	Kidney	Pancreas	Liver
Number of episodes	1	5[1]	14[1]	0	5
Proportion taking antifungal prophylaxis (%)[2]	100	80	28	0	80
Timing of candidemia post SOT (months)					
<1		5	2[1]		3
1–6	1		1		
>6			11[3]		2
Annual incidence per 1000 SOT admissions	2.1	7.0	2.7	0	3.7

[1]One patient had a kidney and lung transplant.
[2]Proportion of patients taking antifungal prophylaxis at time of diagnosis with candidemia.
[3]Renal transplant patients were significantly more likely to acquire candidemia >6 months post transplant compared with any other SOT (OR 16.5; 95% CI 2.3–121.2; $P<0.01$).
SOT, solid organ transplant; OR, odds ratio; CI, confidence interval.

Table 1

Location, setting, and risk factors for candidemia in solid organ transplant (SOT) recipients and non-SOT patients

	SOT no. (%)	Non-SOT no. (%)	*P*-value
Setting for candidemia[1]			
Inpatient healthcare-associated	22 (92)	728 (81)	NS
Outpatient-acquired			
Healthcare-associated	2 (8)	104 (12)	NS
Outpatient	0	63 (7)	NS
Total	24	895	NS
Ward of diagnosis			
ICU	11 (46)	313 (32)	NS
Other	13 (54)	655 (67)	NS
Total	24	968	
Source of candidemia			
Vascular access device	10 (42)	424 (47)	NS
Urinary tract	1 (4)	57 (6)	NS
Gastrointestinal tract	1 (4)	53 (6)	NS
Other	1 (4)	53 (6)	NS
Unknown	11 (46)	308 (34)	NS
Total	24	895	
Risk factors present within the preceding 30 days of diagnosis[2]			
Antimicrobial use	20 (83)	754 (86)	NS
Sepsis present	16 (67)	689 (79)	NS
Neutropenia	3 (13)	161 (19)	NS
Steroid use	17 (71)	249 (29)	$P<0.01$
TPN	6 (25)	326 (38)	NS
Recent surgery	9 (38)	360 (42)	NS
Diabetes	7 (29)	130 (15)	NS

[1]Definitions can be found in the text.
[2]Total number of patients for which this parameter is known varies between categories. For each parameter in the SOT recipients data were available on all 24 patients.
no., number; ICU, intensive care unit; NS, non-significant; TPN, total parenteral nutrition.

Table 2

Species, sensitivity of *Candida* isolated, and mortality in solid organ transplant (SOT) patients separated by the use of antifungal prophylaxis at time of diagnosis

	Antifungal prophylaxis number (%)	No prophylaxis number (%)	*P*-value
SOT patients with candidemia	12 (50)	12 (50)	NS
Candida species			
C. albicans	6 (50)	5 (42)	NS
C. glabrata	3 (25)	2 (17)	NS
C. parapsilosis	1 (8)	2 (17)	NS
C. krusei	1 (8)	0	NS
C. dubliniensis	0	1 (8)	NS
C. tropicalis	1 (8)	1 (8)	NS
Other	0	1 (8)	NS
Fluconazole sensitivity of *Candida* species			
Sensitive[1]	8 (67)	10 (83)	NS
SDD or resistant[2]	4 (33)	2 (17)	NS
30 day all-cause mortality	3 (25)[3]	2 (17)[4]	NS

[1]All sensitive isolates MIC ≤ 1 μg/mL.
[2]All *C. glabrata* isolates in both groups SDD; 1 resistant isolate *C. krusei*.
[3]The deaths occurred in kidney ($n = 2$) and liver ($n = 1$) transplant recipients.
[4]The deaths occurred in kidney ($n = 2$) transplant recipients.
NS, non-significant; MIC, minimum inhibitory concentration; SDD, sensitive dose dependent.

Table 3

those seen in non-SOT patients with candidemia (28%; 236/853), all deaths in SOT recipients occurred within the first 5 days of diagnosis, compared with 43% (101/236) of non-SOT patients ($P<0.001$).

Discussion

This large prospective study provides an overview of candidemia in Australian SOT recipients and documents a higher rate of candidemia in these patients compared with non-SOT patients ($P<0.001$). Other key findings of the study include the identification of a high proportion of late-onset candidemia (occurring ≥ 6 months post transplantation) with a high early (within 5 days) overall mortality (100%).

The annual incidence of candidemia in the present study of 3 per 1000 transplant admissions is lower than previously reported rates (11, 14–16). Explanations for this difference include improvements in surgical techniques and post-transplant care with increasing use of targeted antifungal and CMV prophylaxis (1, 17).

Of note, late-onset candidemia occurred in over half of patients (54%). This differs substantially from other studies where late-onset candidemia occurred in <1% of blood stream infections with no documented cases in 1400 renal transplants over a 2-year period (18, 19). The reasons for this difference are unexplained. Although the epidemiology of late-onset candidemia is not well defined, the development of candidemia in SOT recipients in our study may be a marker of severe underlying illness, as 12 of the 13 late-onset episodes were hospital inpatients at the time of diagnosis and had multiple risk factors for candidemia. These risk factors included receipt of broad-spectrum antibiotics for concurrent bacterial infections, ongoing immunosuppression, and indwelling medical devices such as urinary catheters and vascular access devices.

It is not surprising that most cases of late-onset candidemia occurred in renal transplant recipients, as this is the most common type of transplant performed and is generally associated with the longest survival times (20). Although we found predisposing factors for candidemia in SOT recipients to be similar to those in non-SOT patients (with the exception of corticosteroid use), studies of large numbers of patients with SOT are required to identify specific risk factors for this group of individuals, especially in those with late-onset candidemia.

In the present study, the all-cause mortality was 21% in SOT recipients compared with 5–77% in published studies (5, 21, 22). Surprisingly, mortality rates were similar to non-SOT patients, despite the increased use of corticosteroids in the SOT group (Table 2), which has been documented as an independent factor for all-cause mortality in candidemia (12). However, compared with non-SOT patients, SOT recipients were more likely to die within the first 5 days of candidemia diagnosis. This may reflect a higher burden of disease in SOT recipients, contributed to by a poor inflammatory response leading to a lack of classic clinical and radiological signs of candidal infection (1). Thus, delays in the commencement of therapeutic antifungal agents result in rapid progression of infection. All these factors are further compounded by a reliance on a relatively insensitive 'gold standard' test (i.e., blood cultures) (23). These issues may be addressed in the future with non-culture-based diagnostic methods, although their sensitivity and specificity are highly variable and not well evaluated in SOT recipients (24, 25).

Antifungal prophylaxis has not been shown to reduce all-cause mortality in SOT recipients in randomized controlled trials (21). This may be secondary to unwanted consequences of azole antifungal prophylaxis, including drug–drug interactions resulting in toxicity-related morbidity or due to breakthrough fungal infections (26). Such breakthrough infections include non-*albicans Candida* species, which have been associated with higher attributable mortality rates compared with *C. albicans* infections (27). In our study, azole antifungal prophylaxis was not associated with selection of non-*albicans Candida* species in SOT recipients or increased mortality. This may reflect the small number of SOT recipients studied, because these associations were demonstrated in the total population (12).

Rates of invasive candidiasis in SOT recipients are probably underestimated in our study, as only blood culture positive patients were included. In addition, it remains unknown whether denominators for SOT recipients are complete because failure to code for 'organ transplantation' could have resulted in an underestimation of incidence. Similarly, the inclusion of 'high-risk' patients, such as hematopoietic stem cell transplantation (HSCT) recipients in the non-SOT patient population, may have skewed the results. However, associations did not change after the exclusion of HSCT recipients (17 allogeneic and 11 autologous HSCT patients) from the non-SOT group (data not shown). Finally, limitations of subgroup analysis should always be considered when applying these data to clinical practice.

In conclusion, SOT recipients continue to have a high incidence of candidemia compared with other patient groups. Rates vary according to the type of organ transplanted, with highest rates seen in lung transplant recipients. Similarly, the timing of candidemia post transplantation is influenced by the type of organ transplanted, with an unexplained high proportion of late-onset candidemias in renal transplant recipients. Apart from corticosteroid therapy in the preceding 30 days, risk factors were not dissimilar from those seen in non-SOT patients with candidemia, although a more detailed analysis of risk factors for late candidemia should be undertaken. Antifungal prophylaxis did not select for more resistant or non-*albicans Candida* species in the SOT group. The 30-day all-cause mortality was similar to non-SOT patients with candidemia and remains high at 21%. All deaths in SOT recipients occurred early (within 5 days of diagnosis), underlining the need for better diagnostic tests and earlier intervention strategies.

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