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Epidemiology of invasive fungal infections in immunocompromised children; and Australian national 10-year review.

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Article Summary Line

Epidemiology of invasive fungal (IFI) infections in immunocompromised children has changed over time and varies by location, challenging traditional criteria for characterising burden of disease.

Abbreviation key

Abbreviation	Full term
IFI	Invasive fungal infection
ALL	acute lymphoblastic leukaemia
AML	acute myeloid leukaemia
TERIFIC	The Epidemiology and Risk factors for Invasive Fungal Infections in immunocompromised Children
HSCT	haematopoietic stem cell transplant
PID	primary immunodeficiency
EORTC	European Organisation for Research and Treatment of Cancer
BAL	bronchoalveolar lavage
SD	standard deviation
IQR	interquartile range
OR	odds ratios
CI	95% confidence intervals
OS	Overall survival
HR	hazard ratios
aHR	adjusted hazard ratios
CHR	adjusted cause-specific hazard ratios
CNS	Central Nervous System
SCID	Severe Combined Immune deficiency
CGD	Chronic Granulomatous Disease

HLH	Haemophagocytic lymphohistiocytosis

ABSTRACT

Background: A thorough understanding of local and contemporary invasive fungal infection (IFI) epidemiology in immunocompromised children is required to provide rationale for targeted prevention and treatment strategies.

Methods: Retrospective data over 10 years from four tertiary paediatric oncology and haematopoietic stem cell transplant (HSCT) units across Australia was analysed to report demographic, clinical, and mycological characteristics of IFI episodes, and crude IFI prevalence in select oncology/HSCT groups. Kaplan-Meier survival analyses were used to calculate 180-day overall survival.

Results: A total 337 IFI episodes occurred in 320 children, of which 149 (44.2%), 51 (15.1%), and 110 (32.6%) met a modified European Organization for Research and Treatment of Cancer (mEORTC) criteria for proven, probable, and possible IFI respectively. There were a further 27 (8.0%) that met a 'modified possible IFI' criteria. Median age at IFI diagnosis was 8.4 years. Crude mEORTC IFI prevalence in acute lymphoblastic leukaemia, acute myeloid leukaemia, solid tumour, and allogeneic HSCT cohorts was 10.6%, 28.2%, 4.4%, and 11.7% respectively. Non-*Aspergillus* species represented 48/102 (47.1%) moulds identified, and non-*albicans Candida* represented 66/93 (71.0%) yeasts identified. There were 56 deaths among 297 children who met mEORTC criteria, with 180-day overall survival for proven, probable, and possible IFIs of 79.7%, 76.2%, and 84.4% respectively.

Conclusion: Non-*Aspergillus* moulds and non-albicans *Candida* contributed substantially to paediatric IFI in our study, with high IFI prevalence in leukaemia and allogeneic HSCT cohorts. Inclusion of IFIs outside of EORTC criteria revealed an IFI burden that would go otherwise unrecognised in published reports.

INTRODUCTION

The epidemiology of invasive fungal infections (IFI) in immunocompromised children continues to evolve alongside cancer treatment regimens and haematopoietic stem cell transplant (HSCT) protocols in conjunction with selective pressure from antifungal prophylaxis strategies and environmental influences.[1-7] As such, the morbidity and mortality associated with IFIs in immunocompromised children remains a major concern.[8]

Despite it being recognised that IFIs represent a significant disease burden, much of the international literature on IFI epidemiology and outcomes in children are single-centre studies,[2,9,10] studies focused on either *Candida*[11] or mould infections,[12-16] studies which examined specific oncology or HSCT cohorts,[17,18] or those which are limited to microbiologically-confirmed IFIs.[19] In Australia, analysis of a 10-year national acute myeloid leukaemia (AML) cohort demonstrated 20% with a microbiologically confirmed IFI,[18] and a 4-year single centre study found 13% of children with AML and 24% of children with acute lymphoblastic leukaemia (ALL) experienced an IFI.[9] Further collaborative research to capture IFIs across a broad oncology and HSCT cohort is required to provide a comprehensive understanding of IFI epidemiology and outcomes to guide IFI diagnostic strategies as well as targeted prevention and treatment strategies.

The Epidemiology and Risk factors for Invasive Fungal Infections in immunocompromised Children (TERIFIC) study is a retrospective multicentre study evaluating risk factors, microbiology, treatment, and outcomes associated with IFIs in immunocompromised children in Australian. This article presents the first data from the TERIFIC study and describes the epidemiology and mortality in one of the larger published cohorts of IFIs in immunocompromised children to date.

METHODS

Study design and population

The TERIFIC study comprises four tertiary paediatric oncology and HSCT centres in Australia (Brisbane, Melbourne, Perth, and Sydney) that collected retrospective data from patients with an IFI who were managed over 10 years (2004-2013) for Brisbane, Melbourne, and Perth centres; and one year (2012-2013) for the Sydney centre. Eligible patients were identified by screening pharmacy records (receipt of systemic antifungal therapy for at least seven days), microbiology laboratory records, oncology and HSCT databases, and hospital diagnostic coding (with IFI coded as either primary or secondary discharge diagnosis; codes B35-39, *The International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification*).[20] The information collected included demographics; primary haematology, oncology or immunodeficiency diagnosis; chemotherapy treatment regimen and HSCT protocol; IFI diagnosis (including radiology, histopathology, culture, PCR, and galactomannan results); antifungal prophylaxis (in the preceding 90 days of IFI diagnosis); antifungal therapy; and outcomes at one, two, and six months following IFI diagnosis. Data was entered by study centres into a centralised web-based database (*Webspirit, Paediatric Trials Network Australia*). Human

research ethics approval was granted at each study centre prior to study commencement.

Definitions

Episodes of IFI were defined as possible, probable, and proven according to European Organization for Research and Treatment of Cancer (EORTC) criteria,[21] with a recommended modification to include *Aspergillus* polymerase chain reaction (PCR) as part of the mycological criteria (modified EORTC criteria; mEORTC).[22] A further category, 'modified possible IFI', was additionally included to reflect real-world practice where children are diagnosed with and treated for IFI based on history, risk factors, and clinico-radiological features, but with limited capacity for invasive diagnostic procedures (e.g., bronchoalveolar lavage (BAL)) or radiology (e.g., computed tomography (CT) scan) due to general anaesthetic requirements or clinical acuity that dictates limited invasive investigations. A 'modified possible IFI' episode was defined as the presence of EORTC recognized host factors[21] in conjunction with a chest x-ray appearance consistent with an IFI where CT unavailable, or multiple liver or splenic lesions identified without documented candidemia. Disseminated IFI was defined as either microbiological or radiological findings consistent with an IFI in two or more sites. Final IFI classification was determined by the principal investigator at each centre (JEC, CCB, GMH, BJM), including clarifications on whether multiple IFIs in any one patient represented a new IFI or was a relapse or recrudescence of a previously diagnosed IFI. Any ambiguities were discussed with principal investigators at two other centres and resolved once a consensus was reached. A positive galactomannan was defined as an optical density index of at least 0.5 in serum and at least 1.0 in a BAL specimen.[8,23] Identification of fungal pathogens was determined

via standard culture and PCR practices within the laboratories that serviced the study centres. Outcomes at one, two, and six months were characterized as complete response, partial response, stable, progression of IFI, or death.[24] Mortality attributed to an IFI was determined by the documented opinion of the treating physician and review by the principal investigator at the respective study centre.

Statistical analyses

Descriptive analyses were used to report demographic, clinical, and mycological characteristics of the entire study population. Crude IFI prevalence calculations were calculated for children diagnosed with an IFI episode meeting mEORTC criteria and were limited to study centres with ten years of data (Brisbane, Melbourne, and Perth). Oncology subtypes were grouped as per the International Classification of Childhood Cancer,[25] and leukaemia further categorized as ALL or AML. Denominator data regarding non-oncology diagnoses was not available. Crude IFI prevalence with 95% confidence intervals (CI) were calculated by dividing the number of children with an IFI by the total number of new children seen for each oncology or HSCT category. Chi-square tests were used to determine any significant differences in IFI prevalence within specific sub-groups across the study centres.

Overall survival probability was calculated for those who met mEORTC IFI criteria using the Kaplan-Meier method for: (i) the entire mEORTC IFI cohort; (ii) proven, probable, and possible IFI cohorts; (iii) ALL, AML, and solid tumour cohorts who did not undergo a HSCT; (iii) those who underwent a HSCT; and (iv) invasive aspergillosis and invasive candidiasis. For children who had multiple IFI episodes during the study period, only the last reported IFI episode was used for the analysis. Follow-up began at date of IFI diagnosis through to 180 days following IFI diagnosis.

All statistical analyses were performed using Stata, version 14.2 (StataCorp LP, College Station, Texas, US).

RESULTS

Demographic and clinical characteristics

Data on a total of 337 IFI episodes reported in 320 children at a median age of 8.4 [interquartile range (IQR) 3.9, 13.4] years were collected. Of these, 310 (92.0%) episodes met mEORTC IFI criteria, with 149 (44.2%) proven IFI episodes, 51 (15.1%) probable IFI episodes, and 110 (32.6%) possible IFI episodes. The addition of *Aspergillus* PCR to the mycological criteria changed 3 IFI episodes from possible to probable IFI categories. There were an additional 27 (8.0%) episodes that met the criteria for 'modified possible IFI'. Yeast were identified in 89/337 (26.4%) IFI episodes, at a median age of 5.0 [IQR 2.7, 9.1] years; and moulds were identified in 91/337 (27.0%) IFI episodes, at a median age of 8.6 [IQR 3.8, 13.1] years. Table 1 summarises the demographic and clinical characteristics of the study population. Across all IFI episodes reported, sites of infection included pulmonary in 245, bloodstream in 98, hepatosplenic in 36, skin/soft tissue in 22, central nervous system (CNS) in 22, renal in 20, sinonasal in 16, and bone in 5. There were 105/337 (31.2%) episodes with disseminated invasive fungal infection. For IFI episodes occurring following HSCT (n=70), the median time to IFI diagnosis post HSCT was 58 [IQR 15, 247] days.

Antifungal prophylaxis was administered in the preceding 90 days in 207/337 (61.4%) IFI episodes. A mould active prophylactic agent was used in 94/337 (27.9%) episodes, and a non-mould active agent used exclusively in 113/337 (33.5%) episodes. Specifically, fluconazole was used in 142/337 (42.1%) episodes,

itraconazole in 43/337 (12.8%), liposomal amphotericin in 33/337 (9.8%), posaconazole 15/337 (4.5%), voriconazole in 12/337 (3.6%), and caspofungin in 2/337 (0.6%).

Prevalence

For the three centres with ten years of data (Brisbane, Melbourne, Perth), overall IFI prevalence was 28.2% [95%CI 22.3, 34.2] in AML, 10.6% [95%CI 8.9, 12.4] in ALL, and 4.4% [95%CI 3.2, 9.4] in solid tumours. Within the solid tumour group, the IFI prevalence was 6.3% [95%CI 3.2, 9.4] in neuroblastoma and 2.2% [95%CI 1.3, 3.1] in CNS tumours. The IFI prevalence in HSCT cohorts was 11.7% [95%CI 8.7, 14.7] in allogeneic HSCT and 3.1% [95%CI 1.2, 4.9] in autologous HSCT. There were no significant differences in IFI prevalence across the study centres for AML, HSCT, and solid tumour cohorts, however IFI prevalence in ALL was higher for the Brisbane centre compared to the Melbourne and Perth centres (Chi-square p=0.02) (additional information on request through corresponding author).

Microbiology

There were 195 fungal pathogens (102 moulds and 93 yeasts) identified via culture or PCR in 177/337 (52.5%) IFI episodes (Table 2). In 93 episodes a mould was identified, in 88 episodes a yeast was identified, and in 3 both mould and yeast were identified. Polymicrobial infection was seen with two or more moulds in 8 episodes and with two or more yeasts in 4 episodes.

Aspergillus species represented 54/102 (52.9%) of moulds identified, with *A. fumigatus* the most frequently identified *Aspergillus* species (31/54, 57.4%). Of the non-*Aspergillus* species (n=48), *Lomentospora (*formerly *Scedosporium) prolificans*

was the most commonly identified (13/48, 27.1%). Mucormycosis was uncommon, with Mucorales species identified in four episodes. *Candida* represented 84/93 (90.3%) yeasts isolated, with *C. parapsilosis* the most common *Candida* detected (28/84, 33.3%). Across the centres with ten years of data, the Melbourne centre reported more yeasts (33/48, 68.8%) than moulds (15/48, 31.2%), while moulds were more frequently detected for the Brisbane and Perth centres, representing 56/93 (60.2%) and 29/51 (56.9%) of fungal pathogens isolated respectively.

Survival

Of 297 children who met mEORTC IFI criteria, there were 56 (18.9%) deaths within 180 days of IFI diagnosis, including 18 (6.1%) deaths attributed to IFI (Table 3). The 180-day overall survival probability for children who met mEORTC IFI criteria was 80.8% [95%CI 75.8, 84.9]. Figure 1 demonstrates the 180-day overall survival probability for children who met mEORTC criteria for proven, probable, and possible IFI, which was 79.7% [95%CI 71.9, 85.5], 76.2% [95%CI 61.9, 85.7], and 84.4% [95%CI 75.7, 90.2] respectively. For the ALL, AML, and solid tumour cohorts that did not receive a HSCT, the 180-day overall survival was 87.4% [95%CI 79.6, 92.3], 84.2% [95%CI 70.8, 91.8], and 82.1% [95%CI 62.3, 92.2] respectively (Fig. 2). For those who underwent a HSCT, the 180-day overall survival probability was 68.1% [95%CI 54.6, 78.3] (Fig. 2). The 180-day overall survival probability for invasive aspergillosis was 79.6% [95%CI 64.4, 88.8] and for invasive candidiasis was 83.7% [95%CI 73.0, 90.4]. Interestingly, 2/3 (66.7%) of children with *Fusarium* infection and 4/4 (100%) of children with mucormycosis survived to the end of the follow-up period (Table 3). Central nervous system involvement had the highest proportion of deaths

across all sites of disease, with 40.9% and 31.8% for all cause and IFI-attributed mortality respectively (Table 3).

DISCUSSION

This national multi-centre study, involving one of the larger IFI datasets to date, provides valuable insights into IFI epidemiology and outcomes in Australian immunocompromised children. Fungal pathogens were identified in over half of IFI episodes, demonstrating a broad range of mould and yeast species, with *Aspergillus* species representing approximately 50% of invasive moulds identified and *Candida* representing 90% of invasive yeasts identified. In keeping with previous studies *A. fumigatus* was the most common mould isolated,[6,19] however the epidemiology of the non-*Aspergillus* moulds identified in our study differs from other reports. *Lomentospora prolificans* was the most commonly encountered non-*Aspergillus* mould in our study, and although reported in previous predominantly adult Australian studies,[26] rarely features in paediatric series.[19] There is also a striking paucity of mucormycosis, which is in contrast to other international paediatric[10,12] and local adult[26] studies. Variations in the prevalence and epidemiology of non-*Aspergillus* mould infections, may reflect selective antifungal pressure through antifungal prophylaxis strategies and local environmental influences such as agricultural antifungal use and construction works;[7] and highlights the importance of ongoing evaluations of local IFI epidemiology and outcomes in specific diagnostic and HSCT cohorts to optimise prevention and treatment strategies to minimise IFI morbidity and mortality. The impact of antifungal prophylaxis on IFI epidemiology in our cohort will be separately explored in depth.

Epidemiology of *Candida* infections is changing worldwide with increasing prevalence of non-*albicans* species.[1,27,28] Of the *Candida* identified in our study, 70% were non-*albicans*, with *C. parapsilosis* the most frequently isolated *Candida* overall. The high proportion of *C. parapsilosis* in children with acute leukaemia is in keeping with other international paediatric cohorts,[19] which likely reflects the recognised affinity for this organism for central venous access devices.[29] *C. parapsilosis* also accounted for almost 50% of fungal pathogens isolated in our solid tumour cohort. This association has not been reported elsewhere.

Overall survival for our IFI cohort meeting mEORTC criteria is in keeping with previous paediatric reports.[2,30,31] Overall survival for our proven and probable IFIs is better than that recently reported in an Italian cohort,[19] which demonstrated an overall survival probability of 68% at 90-days. However, this study only included patients with acute leukaemia, non-Hodgkin lymphoma, or who underwent HSCT, and thus exclusively represented a higher risk cohort, whereas children in our study encompassed a more complete spectrum of haematological malignancies and solid tumours. The mortality associated with invasive aspergillosis and invasive candidiasis in our cohort is also better than previously reported,[32-34] which again may reflect our broader oncology and HSCT cohort, but also reflect developments in supportive care, and improved diagnostic and therapeutic strategies.

Throughout the study period we identified an additional 27 cases that did not meet EORTC criteria but were suggestive of an IFI and managed as such, representing 8% of our overall IFI cohort. This reflects limitations in applying current EORTC IFI criteria in clinical settings where patient acuity may restrict diagnostic investigations that require general anaesthesia and provides scope for a pragmatic approach to managing IFIs. Further studies involving suspected IFIs that do not meet the EORTC

criteria would provide valuable contributions to further understanding the burden of IFIs in immunocompromised children that would otherwise go unrecognised.

Limitations to this study include its retrospective nature, which lends itself to incomplete capture of all IFI episodes despite the use of multiple department and hospital data sources as well as incomplete demographic, clinical, mycological, and outcome data. Our IFI-attributed mortality was reliant on treating physician opinion, and even though study investigators reviewed each IFI-attributed death for accuracy, we were not able to apply guidelines *a priori* in determining an IFI-attributed death. Calculation of IFI rates within specific oncology/HSCT cohorts is limited by the lack of time at-risk data for the denominator population, as well as the possibility of those being diagnosed with an IFI within the study period having had their oncology diagnosis or HSCT prior to the study period and therefore are not included in the denominator population. Our addition of 'modified possible IFI' to the inclusion criteria may limit compatibility with other studies, but for this reason we also provided information on key outcomes in a comparable fashion, using the standard EORTC criteria modified to include *Aspergillus* PCR as part of the mycological criteria, which minimally changed IFI categorisation. In addition, we believe further modifications such as ours are helpful for paediatric studies to optimise inclusion of real-world IFI detection and management.

This study identifies the burden of IFIs in Australia across a broad range of immunocompromised children, with around half of all moulds species identified as non-*Aspergillus* and a predominance of *C. parapsilosis* among yeast identified, particularly in the solid tumour cohort. There is further scope for improving local IFI detection, prevention and survival, and a need to capture IFI burden outside of the

EORTC criteria that would go otherwise unrecognised to better inform local targeted treatment and prevention strategies.

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Access to data*:* All authors have full access to the data and Julia E Clark is the guarantor for the data.

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Figure Legends

FIGURE 1 Overall survival for proven, probable, and possible invasive fungal infection

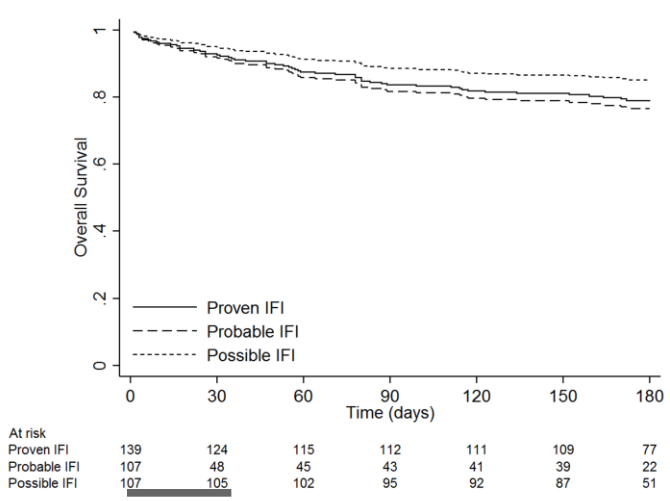

FIGURE 2 Overall survival for acute lymphoblastic leukaemia[a], acute myeloid leukaemia[a], solid tumour[a], and haematopoietic stem cell transplant groups

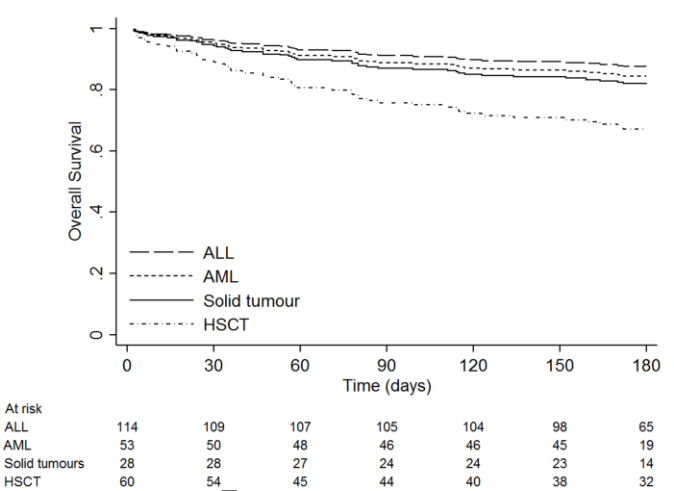

TABLE 1 Characteristics of study population

	Patients (n=320)
Centre	
Brisbane	115 (35.9)
Melbourne	122 (38.1)
Perth	69 (21.6)
Sydney	14 (4.4)
Sex	
Male	177 (55.3)
Ethnicity	
Caucasian	223 (69.7)
Indigenous, Māori and South Pacific Islander	16 (5.0)
Other	45 (14.1)
Unknown/missing	36 (11.3)
Primary diagnosis	
Haematological	254 (79.4)

B-cell ALL	126 (39.4)
T-cell ALL	17 (5.3)
AML	69 (31.6)
Lymphoma	14 (4.4)
Aplastic anaemia	1 (0.3)
Other	27 (8.4)
Solid tumour	40 (12.5)
Neuroblastoma	17 (5.3)
Sarcoma	8 (2.5)
CNS tumour	5 (1.6)
Other	10 (3.1)
Primary immunodeficiency	15 (4.7)
SCID	5 (1.6)
CGD	8 (2.5)
Other	2 (0.6)
HLH	7 (2.2)
Autoimmune disease	4 (1.3)
HSCT	64 (20)

Autologous	11 (17.2)
Allogeneic	53 (82.8)

Values n (%). ALL = acute lymphoblastic leukaemia. AML = acute myeloid leukaemia. SCID = severe combined immune deficiency CGD = chronic granulomatous disease. CNS = central nervous system. HLH = haemophagocytic lymphohistiocytosis. HSCT = haematopoietic stem cell transplant.

TABLE 2 Fungal pathogens identified in select primary diagnostic and haematopoietic stem cell transplant cohorts

	All episodes	HSCT	ALL	AML	Solid tumours[a]	Neuroblastoma
Total fungal pathogens identified	195	44	82	36	31	18
Moulds	102 (52.3)	23 (52.3)	46 (56.1)	22 (61.1)	7 (22.6)	2 (11.1)
Aspergillus species	54 (27.7)	11 (25.0)	25 (30.5)	9 (25.0)	4 (12.9)	0
A. fumigatus	31 (15.9)	3 (6.8)	13 (15.9)	4 (11.1)	3 (9.7)	
A. flavus	7 (3.6)	1 (2.3)	6 (7.3)	1 (2.8)		
A. niger	5 (2.6)	3 (6.8)	3 (3.7)	2 (5.6)		
A. terreus	4 (2.1)	2	1			

		(4.5)	(1.2)			
A. nidulans	1 (0.5)					
Aspergillus spp. NOS	6 (3.1)	2 (4.5)	2 (2.4)	2 (5.6)	1 (3.2)	
Non-*Aspergillus* moulds	48 (24.6)	12 (27.3)	21 (25.6)	13 (36.1)	3 (9.7)	2 (11.1)
Lomentospora (Scedosporium) prolificans	13 (6.7)	3 (6.8)	5 (6.1)	7 (19.4)		
Penicillium spp.	6 (3.1)	2 (4.5)	2 (2.4)	2 (5.6)	1 (3.2)	1 (5.6)
Fusarium spp.	3 (1.5)	2 (4.5)	2 (2.4)			
Exserohilum spp.	4 (2.1)		4 (4.9)			
Mucorales[b]	4 (2.1)		2 (2.4)	2 (5.6)		
Curvularia spp.	2 (1.0)					
Acremonium spp.	2 (1.0)	1	1		1 (3.2)	

		(2.3)	(1.2)			
Basidiomycetes	2 (1.0)		1 (1.2)			
Paecilomyces spp.	2 (1.0)		1 (1.2)			
Other[c]	10 (5.1)	4 (9.1)	3 (3.7)	2 (5.6)	1 (3.2)	1 (5.6)
Yeasts	93 (47.7)	21(46.7)	36 (43.9)	14 (38.9)	24 (77.4)	16 (88.9)
Candida species	84 (43.1)	20 (45.5)	34 (41.5)	14 (38.9)	20 (64.5)	12 (66.7)
C. parapsilosis	28 (14.4)	6 (13.6)	7 (8.5)	2 (5.6)	15 (48.4)	8 (44.4)
C. albicans	22 (11.3)	3 (6.8)	12 (14.6)	2 (5.6)	1 (3.2)	
Pichia kudriavzevii (Candida krusei)	13 (6.7)	4 (9.1)	5 (6.1)	5 (13.9	1 (3.2)	1 (5.6)

				)		
C. glabrata	7 (3.6)	4 (9.1)	3 (3.7)	2 (5.6)		
C. guillermondii	5 (2.6)	1 (2.3)	2 (2.4)	2 (5.6)		
C. tropicalis	3 (1.5)		2 (2.4)		1 (3.2)	1 (5.6)
C. lusitaniae	2 (1.0)	1 (2.3)			2 (6.5)	2 (11.1)
Other[d]	4 (2.1)	1 (2.3)	2 (2.4)	1 (2.8)		
Non-Candida yeasts	9 (4.6)	1 (2.3)	3 (3.7)	0	4 (12.9)	4 (22.2)
Cryptococcus spp.[e]	4 (2.1)	1 (2.3)	1 (1.2)		3 (9.7)	3 (16.7)
Rhodotorula spp.	3 (1.5)		1 (1.2)		1 (3.2)	1 (5.6)
Trichosporon asahii	1 (0.5)		1 (1.2)			
Zygosaccharomyc	1 (0.5)					

es spp.						

Values n (%). [a]Includes sarcomas, central nervous system tumours, and neuroblastomas. [b]One each of *Lichtheimia ramosa*, *Mucor ramosissimus*, *Mucor* spp. NOS, *Rhizopus microsporus*. [c]One each of *Aureobasidium pullulans, Cladosporium* spp.*, Engyodontium album*, *Malbranchea* spp., *Pesotum* spp.*, Phanerochaete sordida*, and four Mould spp. NOS.[d] One each of *Candida famata, Candida rugosa, Candida lipolytica,* and *Candida* spp. NOS. [e]Two *Cryptococcus neoformans*, one *Crytpococcus laurentii*, one *Cryptococcus* spp. NOS, 1. ALL = acute lymphoblastic leukaemia. AML = acute myeloid leukaemia. HSCT = haematopoietic stem cell transplant. NOS = not otherwise specified

TABLE 3 Mortality associated fungal pathogens identified and site of infection

	All EORTC IFI episodes[a]	All deaths	IFI-attributed deaths
Total	310	56 (18.1)	18 (5.8)
Moulds[b]	86	18 (20.9)	15 (17.4)
Aspergillus species	47	9 (19.1)	6 (12.8)
A. fumigatus	28	3 (10.7)	3 (10.7)
Other	19	6 (31.6)	3 (15.8)
Non-*Aspergillus* species	42	9 (21.4)	9 (21.4)
Lomentospora (Scedosporium) prolificans	13	7 (53.8)	7 (53.8)
Fusarium spp.	3	1 (33.3)	0
Exserohilum spp.	4	0	0
Mucorales	4	0	0
Other	18	1 (5.6)	2 (11.1)
Yeast[b]	85	13 (15.3)	4 (4.7)
Candida species	78	11 (14.1)	3 (3.8)
C. albicans	19	4 (21.1)	1 (5.3)

Pichia kudriavzevii (Candida krusei)	13	2 (15.4)	0
C. glabrata	6	3 (50.0)	1 (16.7)
C. parapsilosis	28	1 (3.6)	0
Other	12	1 (25.0)	1 (8.3)
Non-*Candida* yeasts	8	2 (25.0)	1 (12.5)
Cryptococcus spp.	4	1 (25.0)	0
Other	4	1 (25.0)	1 (25.0)
Site of infection[c]			
Pulmonary	224	47 (21.0)	16 (7.1)
Bloodstream	98	24 (24.5)	9 (9.2)
CNS	22	9 (40.9)	7 (31.8)
Hepatosplenic	29	9 (31.0)	5 (17.2)
Renal	20	8 (40.0)	5 (25.0)
Bone	5	1 (20.0)	1 (20.0)
Skin / soft tissue	22	5 (22.7)	2 (9.1)
Sinonasal	15	3 (20.0)	1 (6.7)
Disseminated disease	100	30 (30.0)	14 (14.0)

Values n (%) calculated across rows. [a]Meeting the modified EORTC criteria. [b]Mould and yeast co-infection in three episodes. [c]Data for individual sites of infection include involvement in disseminated disease. CNS = central nervous system. EORTC = European Organization for Research and Treatment of Cancer. IFI = invasive fungal infection.