Epidemiology of invasive fungal diseases among patients with haematological disorders in the Asia-Pacific: a prospective observational study

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Abstract

We conducted a 2-year multicentre prospective observational study to determine the epidemiology of and mortality associated with invasive fungal diseases (IFDs) among patients with haematological disorders in Asia. Eleven institutions from 8 countries/regions participated, with 412 subjects (28.2% possible, 38.3% probable and 33.5% proven IFDs) recruited. The epidemiology of IFDs in participating institutions was similar to Western centres, with *Aspergillus* spp. (65.9%) or *Candida* spp. (26.7%) causing the majority of probable and proven IFDs. The overall 30-day mortality was 22.1%. Progressive haematological disorder (odds ratio [OR] 5.192), invasive candidiasis (OR 3.679), and chronic renal disease (OR 6.677) were independently associated with mortality.

Keywords: Antifungal agents, Asia-Pacific, epidemiology, haematological diseases, invasive fungal disease
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Introduction

Invasive fungal diseases (IFDs) are a major cause of morbidity and mortality in patients with haematological disorders, especially in the setting of profound neutropenia and/or haematopoietic stem cell transplantation (HSCT) [1–3]. Local fungal epidemiology should be considered before deciding on antifungal prophylaxis or empirical antifungal therapy. Several large-scale multicentre haematology registries have shown the predominance of mold over yeast infections, especially invasive aspergillosis [4–6]. Underlying haematological disorders and the type of IFD are important determinants of mortality from IFDs, which averages 28% [7–9]. There are, however, few attempts to document the epidemiology of IFD and its associated mortality in the Asia-Pacific region [10].

Materials and methods

We performed a 2-year multicentre prospective cohort study from June 2012, recruiting consecutive adult patients with haematological disorders who fulfilled 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) definitions for possible, probable or proven IFD [11], treated at 11 participating centres from 8 regions in Asia (Table 1). The only individual outcome data collected were 30-day mortality from the diagnosis of IFD. Institutional data concerning availability of institutional protocols governing antifungal prophylaxis, number of patients treated for leukaemia or receiving HSCT, and number of patients diagnosed with IFD were obtained where available. One centre (National Taiwan University Hospital) recruited subjects only for the first year of the study. The ethics review boards of all participating institutions approved the study,

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TABLE 1. Participating institutes and types of invasive fungal diseases observed

Institute	Region/ country	Number of cases recruited	Type of invasive fungal disease			Type of fungus		
			Possible (%)	Probable (%)	Proven (%)	*Candida* spp. (%)	*Aspergillus* spp. (%)	Others (%)
Queen Mary Hospital	Hong Kong	31	11 (35.5)	7 (22.6)	13 (41.9)	7 (35.0)	7 (35.0)	6 (30.0)*
Maedanta Medicity Gurgaon	India	16	5 (31.3)	11 (68.8)	0 (0)	0	11 (100)	0 (0)
Rajiv Gandhi Cancer Institute	India	46	11 (23.9)	28 (60.9)	7 (15.2)	4 (11.4)	30 (85.7)	1 (2.9) †
Seoul St. Mary's Hospital	South Korea	111	2 (1.8)	73 (65.8)	36 (32.4)	13 (11.9)	91 (83.5)	5 (4.6)‡
National Kidney and Transplant Institute	Philippines	4	0 (0)	2 (50.0)	2 (50.0)	0 (0)	2 (50.0)	2 (50.0) §
National University Hospital	Singapore	15	1 (6.7)	5 (33.3)	9 (60.0)	7 (50.0)	7 (50.0)	0 (0)
Singapore General Hospital	Singapore	37	3 (8.1)	11 (29.7)	23 (62.2)	11 (32.3)	21 (67.8)	2 (5.9)‖
China Medical University Hospital	Taiwan	61	36 (59.0)	17 (27.9)	8 (13.1)	1 (4.0)	20 (80)	4 (16.0) ¶
National Taiwan University Hospital**	Taiwan	12	7 (58.3)	4 (33.3)	1 (8.3)	1 (20.0)	4 (80.0)	0 (0)
Maharaj Nakorn Chiang Mai Hospital	Thailand	33	30 (90.9)	0 (0)	3 (9.1)	0 (0)	1 (50.0)	2 (66.7)#
National Institute of Hematology and Blood Transfusion	Vietnam	46	10 (21.7)	0 (0)	36 (78.3)	35 (97.2)	1 (2.8)	0 (0)

*Four cases of *Cryptococcus neoformans*, one case of *Pencillium marneffei*.
†One case of mucormycosis.
‡One case of mucormycosis, three cases of fusariosis, one case of *Trichosporon asahii*.
§Two cases of mucormycosis.
‖One case of *Fusarium solani*.
¶Two cases of mucormycosis, one case of *Trichosporon asahii*.
#One case of *Cryptococcus neoformans*, one case of *Trichosporon* spp.
**This institute provided data for only 1 year.

and informed consent was obtained from all subjects prior to recruitment. A detailed description of the methodology is provided in the Supplementary Data file.

Results

Four hundred and twelve subjects (28.2% possible IFDs, 38.3% probable IFDs, and 33.5% proven IFDs) were recruited, with *Aspergillus* spp. (65.9%) and *Candida* spp. (26.7%) forming the bulk of probable and proven IFDs. The breakdown by subjects recruited, type of IFD and fungal aetiology according to participating centre is shown in Table 1. The most common sites of involvement were lung and bloodstream (Supplementary Table 1), with the lung also most commonly involved in possible IFDs (94.8%).

The demographic, clinical and environmental characteristics of the subjects are shown in Table 2. The majority were male, had AML, and had received chemotherapy within a month before developing IFD. At the point of IFD, the majority were neutropenic, had received antifungal prophylaxis, and were hospitalized in open general wards. Almost a quarter of cases had undergone HSCT, the majority being allogeneic HSCT. Comorbidities were present in a minority of subjects, the most prevalent being diabetes mellitus (10.2%). Nonstandard antifungal prophylaxis, defined as antifungals that are not recommended in international guidelines for prophylaxis in the haematology setting [1–3]. in the form of ketoconazole and nystatin was prescribed to 4.6% of the subjects.

Excluding HSCT recipients, subjects with AML were more likely to receive antifungal prophylaxis compared to others (63.7% vs. 40.9%, $p < 0.001$). Subjects on nonstandard antifungal prophylaxis had a higher proportion of invasive candidiasis, whereas invasive aspergillosis remained the most common aetiology of IFD for the rest, including subjects who were not on any prophylaxis (Supplementary Table 2). Voriconazole was the most common antifungal drug prescribed for treatment of invasive aspergillosis, whereas amphotericin was most commonly prescribed for invasive candidiasis (Supplementary Table 3). For subjects with possible IFD, the majority received voriconazole (57.8%) and/or amphotericin (43.1%).

The overall 30-day mortality was 22.1%. Univariate analysis of cohort characteristics showed that progressive haematological disorder, presence of chronic renal or liver disease, echinocandin prophylaxis, nonstandard antifungal prophylaxis, proven IFD, invasive candidiasis, and bloodstream fungal infection were associated with increased mortality, whereas pulmonary fungal disease was associated with a lower risk. On multivariate analysis, progressive haematological disorder (odds ratio [OR]: 5.192; 95% confidence interval [CI]: 2.376–11.345; $p < 0.001$), invasive candidiasis (OR: 3.679; 95% CI: 1.463–9.250; $p < 0.001$), and chronic renal disease (OR: 6.677; 95% CI: 1.481-30.100; p 0.022) was associated with increased mortality. The Hosmer-Lemeshow goodness-of-fit test p value for the multivariate model was 0.140.

Ten of 11 participating centres provided institutional data, and the proportion of IFDs recruited ranged from 8% to 100% (median = 78.6%). The number of patients treated at each institute varied greatly. Most participating centres had antifungal

TABLE 2. Demographic, clinical and environmental characteristics of subjects with IFDs

Characteristic	Number of subjects (n = 412)
Median age (interquartile range), years	49 (37–58)
Male sex (%)	232 (56.3)
Underlying haematological disorder	
• AML (%)	201 (48.8)
• ALL (%)	84 (20.4)
• Lymphoma, any (%)	53 (12.9)
• Myelodysplastic syndrome (%)	27 (6.6)
• Myeloma (%)	17 (4.1)
• Aplastic anaemia (%)	14 (3.4)
• Others	16 (3.9)
Chemotherapy	
• Received up to 1 month prior to IFD (%)	322 (78.2)
• Induction chemotherapy among subjects with AML or ALL (%)	149 (55.0)
• Consolidation chemotherapy among subjects with AML or ALL (%)	55 (20.3)
Neutropenia at the point of diagnosis of IFD (%)	294 (71.4)
• Profound neutropenia at the point of diagnosis of IFD (%)	189 (64.3)
HSCT prior to IFD (%)	95 (23.1)
• Autologous HSCT (percent of all HSCT)	16 (16.8)
• Allogeneic HSCT (percent of all HSCT)	75 (78.9)
• Cord blood HSCT (percent of all HSCT)	4 (4.2)
Subjects with allogeneic or cord blood HSCT and GVHD at the time of IFD (percent of all allogeneic or cord blood HSCT)	44 (55.7)
• Acute GVHD (percent of all subjects with GVHD)	24 (54.5)
Other comorbid conditions:	
• Diabetes mellitus (%)	42 (10.0)
• Chronic liver disease (%)	39 (9.3)
• Cardiac disease (%)	24 (5.7)
• Chronic renal disease (%)	13 (3.1)
• Solid cancer (%)	10 (2.4)
• Chronic pulmonary disease (%)	10 (2.4)
• Neurological disease (%)	4 (1.0)
Status of haematological disorder at the point of IFD	
• Progressive disease (%)	134 (32.5)
• Partial response (%)	40 (9.7)
• Remission (%)	92 (22.3)
• Unknown (%)	146 (35.4)
Receiving antifungal prophylaxis at the point of IFD (%)	239 (58.0)
• Fluconazole (percent of subjects on antifungal prophylaxis)	80 (36.2)
• Itraconazole (percent of subjects on antifungal prophylaxis)	48 (21.7)
• Posaconazole (percent of subjects on antifungal prophylaxis)	38 (17.2)
• Caspofungin (percent of subjects on antifungal prophylaxis)	13 (5.9)
• Micafungin (percent of subjects on antifungal prophylaxis)	13 (5.9)
• Voriconazole (percent of subjects on antifungal prophylaxis)	10 (4.5)
• Amphotericin B deoxycholate (percent of subjects on antifungal prophylaxis)	9 (4.1)
• Liposomal amphotericin (percent of subjects on antifungal prophylaxis)	9 (4.1)
• Nonstandard antifungal prophylaxis (percent of subjects on antifungal prophylaxis)	19 (8.6)
Ward setting at the point of IFD	
• Open general ward (%)	195 (47.3)
• High efficiency particulate air-filtered room (%)	138 (33.5)
• Isolation room (%)	45 (10.9)
• High dependency/intensive care unit (%)	34 (8.2)

IFD, invasive fungal disease; AML, acute myeloid leukaemia; ALL, acute lymphoblastic leukaemia; HSCT, haematopoietic stem cell transplantation; GVHD, graft-vs.-host disease.

prophylaxis protocols for leukaemia chemotherapy or allogeneic HSCT. Galactomannan testing was unavailable in the Thai and Vietnamese centres, and bronchoalveolar lavage galactomannan testing was available in only four centres (Supplementary Table 4).

Discussion

Our study provided a snapshot of the epidemiology of IFDs in patients with haematological disorders in Asian institutions. Although the majority of IFDs occurred in high-risk subjects [1,2,12], a significant minority did not have these risk factors (146 subjects, 43.8%). Unfortunately, the complete baseline demographic data were unavailable; hence the actual incidence of IFDs in these non–high-risk groups could not be determined. However, the results suggest that subjects with acute lymphoblastic leukaemia might be at a higher risk of IFDs [12].

The fungal epidemiology was similar to what had been reported from non-Asian centres [4,6,7]. *Aspergillus* spp. was not the major fungal pathogen in the Thailand and Vietnam centres, probably because galactomannan testing was unavailable. Mucormycosis was rare, even from the Indian centres [10]. The overall mortality was lower than previous reports [7–9], but this is likely due to our cut-off of 30 days. The factors independently associated with mortality in our cohort are consistent with the published literature [12–16].

The major limitation is that involvement of participating centres with varied sizes, capabilities and treatment/diagnostic resources has resulted in the recruitment of a heterogeneous cohort managed with differing protocols. This complexity has enhanced the study, but also limits the meaningful conclusions that can be drawn. In order to facilitate the participation of centres where resources are limited, the extent of data collection was restricted. Therefore the rates of IFDs for each major haematological disorder and the impact of antifungal therapy on mortality could not be determined.

In conclusion, the epidemiology of IFDs in participating Asian centres was similar to that in other international centres, as was the risk of mortality. Further studies to determine the risk–benefit of antifungal prophylaxis for certain haematological disorders, especially acute lymphoblastic leukaemia, are necessary. The heterogeneity of diagnostic, prophylactic and therapeutic approaches for IFD in the region highlighted in this study may be a first step toward standardizing such protocols in the future (i.e. better antifungal guidance in the treatment of invasive candidiasis) to improve patient outcomes.

Transparency declaration

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cmi.2015.02.019

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