The Prospective Antifungal Therapy Alliance® registry: A two-centre Canadian experience

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BACKGROUND: The Prospective Antifungal Therapy Alliance® registry is a prospective surveillance study that collected data on the diagnosis, management and outcomes of invasive fungal infections (IFIs) from 25 centres in North America from 2004 to 2008.
OBJECTIVE: To evaluate surveillance data on IFIs obtained from study centres located in Canada.
METHODS: Patients with proven or probable IFIs at two Canadian medical centres were enrolled in the registry. Information regarding patient demographics, fungal species, infection sites, diagnosis techniques, therapy and survival were analyzed.
RESULTS: A total of 347 patients from Canada with documented IFIs were enrolled in the Prospective Antifungal Therapy Alliance registry. Infections occurred most commonly in general medicine (71.8%), nontransplant surgery (32.6%) and patients with hematological malignancies (21.0%). There were 287 proven IFIs, including 248 *Candida* infections. Forty-six patients had invasive aspergillosis (IA); all of these were probable infections. Most cases of invasive candidiasis were confirmed using blood culture (90.5%), while IA was most frequently diagnosed using computed tomography scan (82.6%) and serological methods (82.6%). Fluconazole was the most common therapy used for *Candida* infections, followed by the echinocandins. Voriconazole therapy was most commonly prescribed for IA.
CONCLUSIONS: The present study demonstrated that general medicine, surgery and hematological malignancy patients in Canada are susceptible to developing IFIs. In contrast to the United States, *Candida albicans* remains responsible for most IFIs in these Canadian centres. Surrogate serum markers are commonly being used for the diagnosis of IA, while therapy for both IFIs has shifted to broader-spectrum azoles and echinocandins.

Key Words: *Epidemiology; Invasive fungal infections; Prospective Antifungal Therapy (PATH) Alliance registry*

Le registre PATH : une expérience dans deux centres canadiens

HISTORIQUE : Le registre PATH de la *Prospective Antifungal Therapy Alliance* est une étude de surveillance prospective qui a permis de colliger des données sur le diagnostic, la prise en charge et les issues des infections fongiques invasives (IFI) provenant de 25 centres d'Amérique du Nord entre 2004 et 2008.
OBJECTIF : Évaluer les données de surveillance sur les IFI provenant de centres d'études situés au Canada.
MÉTHODOLOGIE : Les patients ayant une IFI démontrée ou probable provenant de deux centres médicaux canadiens ont été inscrits au registre. Les chercheurs ont analysé l'information portant sur la démographie des patients, les espèces fongiques, les foyers d'infection, les techniques diagnostiques, la thérapie et la survie.
RÉSULTATS : Au total, 347 patients du Canada ayant une IFI vérifiée ont été inscrits au registre PATH. Les infections se produisaient surtout en médecine générale (71,8 %), en chirurgie pour autre chose que des transplantations (32,6 %) et chez les patients ayant une tumeur hématologique maligne (21,0 %). Ainsi, 287 IFI ont été démontrées, y compris 248 infections à *Candida*. Quarante-six patients avaient une aspergillose invasive (AI), qui étaient toutes des infections probables. La plupart des candidoses invasives ont été confirmées par des prélèvements sanguins (90,5 %), tandis que les AI étaient surtout diagnostiquées par tomodensitométrie (82,6 %) et méthodes sérologiques (82,6 %). Le fluconazole était le traitement le plus utilisé pour traiter les infections à *Candida*, suivi des échinocandines. Quant au traitement au voriconazole, c'était le plus prescrit pour l'AI.
CONCLUSIONS : La présente étude a démontré qu'au Canada, les patients en médecine générale, en chirurgie et ayant une tumeur hématologique maligne sont susceptibles de contracter une IFI. Contrairement aux États-Unis, le *Candida albicans* demeure responsable de la plupart des IFI dans ces centres canadiens. Des marqueurs sériques de remplacement sont souvent utilisés pour diagnostiquer l'AI, tandis que le traitement des deux IFI est désormais assuré par des aux azoles et des échinocandines à large spectre.

Invasive fungal infections (IFIs) remain a formidable challenge for clinicians because their diagnosis can be elusive and their management requires early, and often prolonged, antifungal therapy. Rates of IFIs have continued to rise, mainly due to increasing numbers of high-risk patients and, to a lesser extent, because of the impact of the increased use of both antibacterial and antifungal agents for prophylaxis and empirical therapy (1). IFIs can be caused by yeasts (eg, *Candida* species, *Cryptococcus* species), molds (eg, *Aspergillus* species, Mucorales) or endemic fungi (eg, *Blastomyces dermatitidis*, *Histoplasma capsulatum* and *Coccidioides* species).

Candida species, the most common yeasts, are the fourth leading cause of hospital-acquired bloodstream infections and account for 80% of IFIs in the United States (2), but for only 66% of IFIs in Canada (3). A single population-based study of candidemia in Canada estimated a rate of 2.9 per 100,000 population (4). Based on a retrospective cohort study using matched propensity analyses, 8949 *Candida* bloodstream infections in adults were associated with an excess length of stay of 10.1 days, a crude mortality rate of approximately 31%, and an attributable mortality rate of approximately 15% compared with patients without candidemia (5). *Aspergillus* species are the leading cause of invasive mold infections, and patients with invasive aspergillosis (IA) reportedly experience an overall mortality rate of up to 60% (6). However, advances in early diagnosis and more potent directed antifungal therapy have reduced the 12-week mortality rate to 30% for IA (7).

Epidemiological studies of IFIs, including population-based studies, sentinel surveillance and single-centre experiences, have

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TABLE 1
Patient demographics

Characteristic	
Total	347 (100)
Age, years, mean (range)	57 (0–92)
Age group, years	
<18	13 (3.7)
18–65	222 (64.0)
>65	112 (32.3)
Sex	
Female	150 (43.2)
Male	196 (56.5)
Missing	1 (0.3)
Ethnicity	
Caucasian	177 (51.0)
African American (black)	3 (0.9)
Asian	8 (2.3)
Hispanic or Latino	3 (0.9)
American Indian or Alaska Native (Aboriginal)	1 (0.3)
Other	5 (1.4)
Unknown	150 (43.2)
Certainty of diagnosis	
Proven	287 (82.7)
Probable	60 (17.3)

Data presented as n (%) unless otherwise indicated

highlighted the differences in rates of IFIs (2,8-12); however, there is a paucity of surveillance studies that link microbiological data with detailed clinical surveillance data in Canada. The most comprehensive assessment of IFI cases to date was performed across Canada from 1992 to 1994 and largely focused on three geographical areas: the province of Manitoba, and the cities of Hamilton and Ottawa (Ontario) (3). In this study, a total of 787 IFIs were assessed: *Candida* species accounted for 66% of the reported cases, with *Cryptococcus neoformans*, *Aspergillus* species, *H capsulatum* and *B dermatitidis* accounting for 10%, 7.6%, 6.7% and 3.1% of the IFIs, respectively. In contrast, most other existing studies in Canada have been organism specific (*C neoformans*) (13), body-site specific (eg, *Candida* bloodstream infections) (14) and/or representative of specific locales, thus limiting the generalizability of these observations (15). A surveillance assessment of IFIs in Canada to provide relative frequency, diagnostic modalities, and a comparison of trends in mortality and management has not been undertaken for some time. These data, collected from 2004 to 2008, are the most current available epidemiological Canadian data, and we believe that this accurately represents the current demographics in Canada.

The Prospective Antifungal Therapy (PATH) Alliance® registry is a comprehensive North American registry focused on data collection and monitoring trends in patients with IFIs with respect to diagnosis, management and outcomes of these infections. The PATH Alliance registry has previously published aggregate data representing sites in both Canada and the United States (16-19). In the present analysis, we report data exclusively from the Canadian centres extracted from the original pooled database, highlighting unique aspects of microbiology, diagnosis, management and outcomes of IFIs.

METHODS

The PATH Alliance registry collected data from two medical centres in Canada and 23 centres in the United States (including Northeast, Midwest, West and Southern states, but with a predominance of centres in the Northeast and South) and monitored trends in epidemiology, diagnosis, treatment and patient outcomes. The details of registry design, inclusion criteria and data collection procedures have been described previously (16).

TABLE 2
Patient category

Category*	n (%)
Total	347 (100.0)
General medicine	249 (71.8)
Surgical (nontransplant)	113 (32.6)
Hematological malignancy	73 (21.0)
Solid tumour	49 (14.1)
Hematopoietic stem cell transplant	32 (9.2)
Solid organ transplant	15 (4.3)
HIV/AIDS	8 (2.3)
Neonatal intensive care unit	5 (1.4)
Other	2 (0.6)

**Patient categories are not mutually exclusive*

Patients with proven or probable IFIs were enrolled in the registry between July 1, 2004 and December 31, 2008, and prospectively evaluated for 12 weeks after diagnosis, or until they died or were lost to follow-up. Categorization of IFIs into proven or probable groups was based on the previously published European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) consensus definitions (20). Data from patients in the Canadian centres were extracted from the PATH registry, including information on patient demographics, underlying disease, type of IFI, causative organism, site of infection, diagnostic techniques and antifungal therapy. Survival rates were also evaluated.

Analyses

Descriptive statistics were used to summarize baseline demographic characteristics, type of IFI, site of infection and antifungal therapy. Day 1 was defined as the day of diagnosis. Descriptive survival analyses were performed for the entire patient group and subpopulations. The survival distribution functions for overall mortality by type of IFI were assessed using the Kaplan-Meier method. Patients were censored on the day of their last activity documented in the database. Statistical analyses were performed using SAS 9.2/Enterprise Guide 4.2 (SAS Institute Inc, USA).

RESULTS

Patient demographics and baseline clinical characteristics

A total of 347 patients with IFIs were enrolled in the PATH Alliance registry from 2004 to 2008 at two Canadian sites (Hamilton Health Sciences, Hamilton, Ontario [C Rotstein and S Haider] and *Hôpital Maisonneuve Rosemont*, Montreal, Quebec [M Laverdiere]).The Canadian cohort was separated from the total PATH Alliance cohort of 6845 patients. Patient demographic characteristics are listed in Table 1. The mean age of these patients was 57 years (range 0 to 92 years). Predominantly, patients were in the 18 to 65 years age group (64.0%), and 56.5% were male. Most of these patients originated from the general medical services (71.8%) and 32.6% of the patients had surgical (nontransplant) interventions (Table 2). Twenty-one percent of patients had an underlying hematologic malignancy, while 14.1% were diagnosed with solid tumours and 9.2% had undergone a hematopoietic stem cell transplant. Only 4.3% of patients were solid organ transplant recipients and 2.3% had HIV/AIDS.

Based on the EORTC/MSG criteria for the diagnosis of IFIs, there were 287 (82.7%) patients with proven IFIs, which included 275 patients with *Candida* infections. In contrast, all *Aspergillus* infections were classified as probable. *Candida* species was the most common fungal infection, accounting for 295 (85.0%) isolates. Within the *Candida* group, *C albicans* accounted for 51.2% of infections; *C glabrata*, *C parapsilosis* and *C tropicalis* were detected in 19.7%, 12.5% and 9.5% of cases, respectively (Table 3). A total of 232 (84.4%) patients had *Candida* bloodstream infections (Table 4). Abdominal candidiasis was detected in 19 (6.9%)

TABLE 3
Frequency of fungal species

Pathogens*	
Total	347 (100.0)
Candida	295 (85.0)
C albicans	151 (51.2)
C glabrata	58 (19.7)
C parapsilosis	37 (12.5)
C tropicalis	28 (9.5)
C krusei	13 (4.4)
C lusitaniae	2 (0.7)
C dubliniensis	1 (0.3)
Other *Candida* species	1 (0.3)
Unknown *Candida* species	4 (1.4)
Aspergillus	50 (14.4)
A fumigatus	23 (46.0)
A flavus	6 (12.0)
A niger	4 (8.0)
A terreus	1 (2.0)
Unknown *Aspergillus* species	16 (32.0)
Cryptococcus	7 (2.0)
Cryptococcus	7 (100.0)
Mucorales	3 (0.9)
Rhizopus	3 (100.0)
Endemic fungi	2 (0.6)
Histoplasma capsulatum	2 (100.0)
Other fungi	18 (5.2)
Pneumocystis jirovecii	17 (94.4)
Unidentified yeast	1 (5.6)
Other mold	1 (0.3)
Fusarium	1 (100.0)

*Data presented as n (%). *Categories are not mutually exclusive*

TABLE 4
Sites of infection

Infection site*	
Total	347 (100)
Candida	275 (79.3)
Blood	232 (84.4)
Abdominal	19 (6.9)
Skeleton	3 (1.1)
Lung	2 (0.7)
Central nervous system	2 (0.7)
Endopthalmitis	1 (0.4)
Tracheobronchial	1 (0.4)
Multisite†	15 (5.5)
Aspergillus	46 (13.3)
Lung	43 (93.5)
Tracheobronchial	2 (4.3)
Sinus	1 (2.2)
Cryptococcus	7 (2.0)
Lung	3 (42.9)
Blood	1 (14.3)
Multisite‡	3 (42.9)
Mucorales	3 (0.9)
Lung	2 (66.7)
Sinus/skin/orbital	1 (33.3)
Endemic fungi	2 (0.6)
Lung	1 (50)
Blood/lung	1 (50)
Other fungi	18 (5.2)
Lung	17 (94.4)
Blood	1 (5.6)
Other mold	1 (0.3)
Abdominal	1 (100)

*Data presented as n (%). *Categories are not mutually exclusive; †Multisite* Candida *infections were identified from the following number of sites: four blood/abdominal, three blood/skin, two blood/endophthalmitis, and one each from blood/heart, blood/lung, blood/other, blood/skin/other, skin/skeleton/abdominal and tracheobronchial/abdominal; ‡Multisite* Cryptococcus *infections were identified from the following number of sites: one each from blood/central nervous system, blood/lung and blood/tracheobronchial*

patients, while multifocal invasive candidiasis was noted in 15 (5.5%) patients. The other body sites involved are presented in Table 4.

Aspergillus was the second most common pathogen (50 infections; Table 3). In these infections, *A fumigatus* accounted for 46%, *A flavus* for 12%, *A niger* for 8% and *A terreus* for 2% of infections (Table 3), with lung involvement predominating (93.5%; Table 4).

Only seven cases of cryptococcal infection were identified. Of these, three individuals had multiorgan involvement (one blood and central nervous system, one blood and lung, and one blood and tracheobronchial tree). Mucorales were identified in only three patients, two of whom had lung involvement while one had sinus and orbital involvement. All three infections were caused by *Rhizopus* species. There were only two cases of endemic mycoses, both caused by *H capsulatum*; both infections involved the lung and one also involved the bloodstream. There were also 17 cases of *Pneumocystis jirovecii* infection (Table 4).

Diagnosis of IFIs

Diagnostic techniques used to establish the proven and probable IFIs are presented in Table 5. Invasive candidiasis was diagnosed via culture in 274 patients, with blood culture confirming the diagnosis in 248 (90.5%) patients. The second most common site from which *Candida* species were isolated was the peritoneal fluid in 19 (6.9%) patients and the third most common site was the skin/soft tissue in 10 (3.6%) patients (Table 6). Ancillary investigations used to diagnose invasive candidiasis included computed tomography (CT) scans, chest radiographs and histopathological examination. In contrast, IA was most frequently diagnosed using CT scanning and serological means (serum galactomannan antigen assays). Isolation of *Aspergillus* via culture from bronchoalveolar fluid occurred commonly (n=19), but histopathological confirmation was uncommon.

Antifungal treatment regimens

Because *Candida* species were the most common pathogens detected, it is not surprising that on day 3 of antifungal therapy, fluconazole was the most common antifungal agent used (Table 7), followed by echinocandins. Of note, 59 patients were not receiving any therapy for invasive candidiasis; these included patients who had died before day 3 (n=34), had received treatment before day 3 that was discontinued (n=14), had missing treatment information or were lost to follow-up (n=8), or had received no treatment on/before day 3 (n=3).

The therapy that was administered on day 3 for IA was primarily voriconazole (n=25/39 patients; 64.1%), with seven patients receiving echinocandins and one itraconazole. Five patients received no therapy for IA; of these, two patients had received treatment before day 3, which was discontinued, and one patient each had died, had received no treatment information or had missing treatment information on day 3.

Therapy for invasive candidiasis on day 10 revealed changes compared with the therapy used on day 3. The number of patients with invasive candidiasis treated with fluconazole declined, while more patients received therapy with echinocandins and amphotericin B (AmB) deoxycholate. A higher number of patients were recorded as not receiving therapy on day 10 compared with day 3. A comparable increase in the number not receiving therapy occurred as well in patients with IA; one patient with IA died between day 3 and day 10 of therapy (Table 8).

TABLE 5
Diagnostic tests*

Test	All	*Candida*	*Aspergillus*	*Cryptococcus*	Mucorales	Endemic fungi	Other fungi	Other mold
Culture	317	274	30	6	3	2	1	1
Computed tomography scan	66	16	38	3	2	1		0
Galactomannan antigen assay	38		38					
Chest x-ray	32	1	17		1			
Histopathological/cytopathological examination	29	1	7	3	1			
Magnetic resonance imaging	2	1	1					
Antigen test	1					1		
Other	9	5	1	3				

**A patient could have been diagnosed using more than one test*

TABLE 6
Source of culture*

Culture source	*Candida*	*Aspergillus*	*Cryptococcus*	Mucorales	Endemic fungi	Other mold	Other fungi
Blood	248		4		1		1
Broncheoalveolar fluid	3	19	1	1	1		
Central nervous system	1						
Cerebrospinal fluid	1		1				
Gastrointestinal	2						
Genitourinary	5						
Heart	1						
Lung	5			1			
Peritoneal fluid	19					1	
Sinus		1					
Skeleton	3						
Skin/soft tissue	10						
Sputum	1	14			2		
Urine	5				1		
Other	16	2	2	1			

**A patient could have had a pathogen isolated from more than one source*

TABLE 7
Day 3 treatment regimens

Parameter	All	*Candida*	*Aspergillus*	*Pneumocystis*	Multiple	Others
n	347	248	39	17	32	11
Monotherapy						
Echinocandins	52	43	7		2	
AmB deoxycholate	4	3				1
AmB lipids	10	8				2
Fluconazole	126	107			15	4
Voriconazole	32	3	25		4	
Posaconazole	1	1				
Itraconazole	2		1		1	
Blinded	22	19			3	
Combination therapy						
Voriconazole/echinocandins	1		1			
AmB lipids/fluconazole	2				2	
AmB lipids/posaconazole	1					1
Echinocandins/fluconazole	5	4			1	
Fluconazole/blinded	1				1	
Fluconazole/voriconazole	1	1				
No treatment*	87	59	5	17	3	3

**The no treatment category includes patients who had died, or for whom treatment records were incomplete due to missing data and loss to follow-up. AmB Amphotericin B*

Survival

The Kaplan-Meier survival probabilities of patients with invasive candidiasis and IA at 90 days after diagnosis were 0.59 and 0.66, respectively (Figure 1).

DISCUSSION

Notwithstanding the aforementioned pathogen, body site and locale-specific IFI surveillance studies undertaken in Canada (13-15), the PATH Alliance registry from 2004 to 2008 is the first comprehensive

TABLE 8
Day 10 treatment regimens

Parameter	All	*Candida*	*Aspergillus*	*Pneumocystis*	Multiple	Other
n	347	248	39	17	32	11
Monotherapy						
Echinocandins	41	32	4		5	
AmB deoxycholate	6	5				1
AmB lipids	8	5			1	2
Fluconazole	98	90			5	3
Voriconazole	32	4	24		3	1
Posaconazole	1	1				
Itraconazole	2		1		1	
Blinded	21	18			3	
Combination therapy						
Voriconazole/echinocandins	2		1		1	
AmB/echinocandins	2	1	1			
AmB lipids/fluconazole	2				2	
AmB lipids/posaconazole	1					1
Echinocandins/fluconazole	5	4			1	
Fluconazole/blinded	1				1	
Fluconazole/voriconazole	1	1				
No treatment*	125	89	8	17	9	2

**The no treatment category includes patients who had died, or for whom treatment records were incomplete due to missing data and loss to follow-up. AmB Amphotericin B*

surveillance of all types of IFIs in Canada in more than a decade, albeit in two specific centres. A total of 347 patients with IFIs were recorded. In contrast to the larger study by Nicolle et al (3) (787 infections), the pathogens producing IFIs in the PATH Alliance registry in descending order were: *Candida* species, *Aspergillus* species, *P jirovecii*, *Cryptococcus* species, Mucorales and *H capsulatum*. The Canadian Infectious Disease Society Invasive Fungal Registry noted that the incidence of *Cryptococcus* superseded that of *Aspergillus* and Mucorales (3). Similarly, recent data have also noted the emergence of nosocomial mold infections (8,9).

Geographical population coverage among the two participating centres likely explains the limited number of reported endemic fungi (only two) observed in our registry, compared with 94 endemic mycoses reported in the Canadian Infectious Diseases Society Fungal Registry (3).

One may also reflect on the patient demographics in our study that differ significantly from the aforementioned Invasive Fungal Registry – there were a higher proportion of IFIs in general medical and surgical patients in our study that was noteworthy. This may attest to the changing epidemiology of IFIs, particularly those infections caused by *Candida* species (21). In addition, the robustness of our study is underscored by the incorporation of the EORTC/MSG criteria for proven and probable IFIs. We categorized 82.7% of the infections as proven and 17.3% as probable.

Because *Candida* species were the most common fungal pathogens isolated, the differences in the microbiology found in Canada compared with the United States requires further comment. Previously, Yamamura et al (22), as part of the Canadian Infectious Disease Society Invasive Fungal Registry, conducted a cross-Canadian surveillance study of bloodstream infections caused by *Candida* in 14 Canadian centres, supported by clinical data of underlying disease, predisposing factors, antifungal treatment, and mortality. They reported *C albicans* in 68.9%, *C parapsilosis* in 10.4%, *C glabrata* in 8.2%, *C tropicalis* in 6.5% and other *Candida* species in 4.3% of patients. Crude mortality was 46% and attributable mortality was 19%. This was followed by a more recent single-centre, 10-year review of candidemia at *Hôpital Maisonneuve-Rosemont* from 1996 to 2006, again demonstrating the predominance of *C albicans* (57%), followed by *C glabrata* (15%), *C parapsilosis* (11%) and *C krusei* (9%) (14). This contrasts sharply with rates of candidemia in the United States, where higher rates of non-*albicans Candida* species were reported in the recent PATH Alliance registry for all of North America (17,18). In 2019 episodes of candidemia, *C albicans* accounted for only 45.6% of cases and non-*albicans* isolates produced the majority of cases. A one-day point-prevalence study of *Candida* colonization/infection across 35 Canadian intensive care units reported that *C albicans* predominated in 72%, *C glabrata* in 16%, *C parapsilosis* in 5% and *C krusei* in 3% of patients (23). A single population-based study of invasive candidiasis over five years (1999 to 2004) in the Calgary region reported a rate of 2.9 per 100,000 compared with a rate of six to 10 per 100,000 in population-based studies in the United States, further highlighting the differences in epidemiology between the two countries (4). Canadian population-based studies investigating rates of IA are lacking.

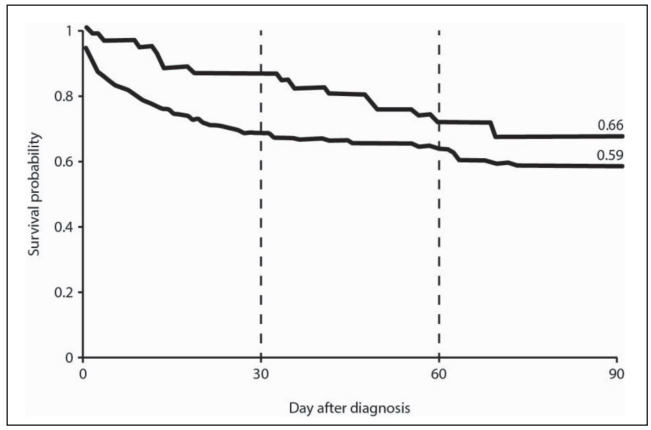

Figure 1) *Kaplan-Meier survival plot of* Candida *and* Aspergillus *patients from two Canadian sites*

One must be cognizant that there have been advances in the diagnosis of IFIs. Surrogate markers in serum and other body fluids, such as bronchoalveolar lavage fluid, have facilitated the diagnosis of IA (24). *Aspergillus* galactomannan antigen testing has become commonplace, enhancing clinicians' ability to detect IA, and is part of the microbiological criteria included in the EORTC/MSG criteria for the diagnosis of probable IA (25). Moreover, CT diagnostic imaging of the chest has promoted earlier diagnosis of pulmonary IFIs (26).

Focusing on therapeutics, differences were observed between Canada and the United States in the areas of prophylaxis, empirical and directed therapy, driven by differences in the epidemiology of IFIs, and availability and use of diagnostics, as highlighted in the recently published Canadian guidelines on invasive candidiasis (27). In earlier studies of invasive candidiasis, AmB was the treatment of choice in 69.3% of cases, followed by fluconazole in 28.7% of cases (22). In our study, fluconazole was the most commonly used therapy, followed by echinocandins, on day 3. Relatively few patients were treated with AmB deoxycholate or its lipid formulations. By day 10 of therapy, there was a reduction in the use of most antifungals and an increase in the number of patients for whom no treatment was recorded (owing to discontinued therapy, patient death, and incomplete data records due to missing data and loss to follow-up).

Therapy for IA has been revolutionized by the broad-spectrum azoles such as voriconazole. It was not surprising that voriconazole was the mainstay of antifungal therapy for IA on day 3 in the enrolled patients. The next most common therapeutic agents used were echinocandins.

Survival probabilities for both invasive candidiasis and IA at 90 days (0.59 and 0.66, respectively) were comparable with those noted in other reports of these IFIs (5,7).

The present study had several limitations. Only two academic referral centres accrued data, limiting the generalizability of our findings to other settings. The overall numbers of patients at each centre at risk of fungal infection were not collected and the variety of patient categories did not permit collection of denominator data, which, in turn, did not allow for evaluation of risk or calculation of incidence rates. Few children with IFIs enrolled in the registry, limiting assessment of epidemiological trends in pediatric patients in Canada. Data regarding treatments were captured; however, it was not possible to differentiate between prophylactic versus empirical/pre-emptive and concomitant versus sequential therapy. Moreover, data were lost due to early discharge from the hospital. We could not discern whether the IFIs were of nosocomial nature or community onset. Finally, survival data were limited to 90 days, which did not allow for the calculation of long-term survival of the patients. Other limitations to the PATH Alliance registry, including variability in diagnostic techniques and the heterogeneity of the case capture, have been commented on by Azie et al (18) in a recent publication. Despite these limitations, the present analysis provides meaningful results from the Canadian perspective.

CONCLUSION

The PATH Alliance registry in Canada is a comprehensive evaluation of all types of IFIs at two specific Canadian centres, and has provided an insight into the trends in the epidemiology of these infections. In addition, there has been a notable evolution in the diagnostic modalities for IFIs with the utilization of surrogate serum markers. Finally, there has also been a transformation in therapies from the traditional polyene compounds to oral azoles and the echinocandins for invasive candidiasis and IA.

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