Candidemia at selected Canadian sites: results from the Fungal Disease Registry, 1992–1994

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Abstract

Background: *Candida* species are important bloodstream pathogens that are being isolated with increasing frequency. Despite the availability of effective antifungal therapy, the mortality rate associated with *Candida* infection remains high. With the objective of describing the epidemiology of candidemia, the Canadian Infectious Disease Society conducted a study of candidemia in Canada.

Methods: Fourteen medical centres across Canada identified all patients with candidemia from March 1992 to February 1994 through blood culture surveillance for *Candida* spp. Patient-related data for invasive fungal infection were compiled retrospectively by chart review using a standardized data-recording form developed for the Fungal Disease Registry of the Canadian Infectious Disease Society. Cases of candidemia were studied in relation to underlying medical conditions, predisposing factors, concurrent infection, antimicrobial agents, antifungal treatment and deaths.

Results: In total, 415 cases of candidemia were identified, 48 (11.6%) in children and 367 (88.4%) in adults. The causative pathogens were *C. albicans* in 286 cases (68.9%), *C. parapsilosis* in 43 (10.4%), *C. glabrata* in 34 (8.2%), *C. tropicalis* in 27 (6.5%) and other *Candida* species in 18 (4.3%); polymicrobial candidemia occurred in 7 cases (1.7%). The overall mortality rate was 46%, and the rate of deaths clinically related to candidemia was 19%. However, only 13 (27%) of the children died. A univariate analysis indicated that significant risk factors for death were age greater than 60 years, therapy for concomitant bacterial infection, stay in an intensive care unit, concurrent malignant disease, cytotoxic chemotherapy and granulocytopenia, although only age and stay in an intensive care unit emerged as significant risk factors in the multivariate analysis. After adjustment for other predictors of death, only infection with *C. parapsilosis* was associated with a lower mortality rate than infection with *C. albicans*. Treatment was given in 352 (84.8%) of cases. Amphotericin B was the preferred agent in 244 cases (69.3% of those treated); fluconazole was used in 101 cases (28.7%) and ketoconazole in 5 cases (1.4%).

Interpretation: Candidemia in Canada is caused predominantly by *C. albicans*. The mortality rate associated with candidemia is high, but it varies with the species of *Candida* and is lower in children than in adults. Age greater than 60 years and stay in an intensive care unit were the most significant risk factors for overall mortality.

Résumé

Contexte : Les espèces de *Candida* sont d'importants agents pathogènes présents dans la circulation sanguine qu'on isole de plus en plus souvent. En dépit de la disponibilité de traitements antifongiques efficaces, le taux de mortalité associé à l'infection par *Candida* demeure élevé. Cherchant à décrire l'épidémiologie de la candidémie, la Société canadienne des maladies infectieuses a réalisé une étude sur la candidémie au Canada.

Méthodes : Quatorze centres médicaux de toutes les régions du Canada ont identifié tous les patients atteints de candidémie entre mars 1992 et février 1994 en surveillant les cultures sanguines analysées en laboratoire pour le dépistage de *Candida* spp. On a compilé rétrospectivement les données sur les infections fongiques envahissantes au moyen d'une étude des dossiers des patients et d'une formule normalisée de consignation des données créée pour le Registre des infections fongiques de la Société canadienne des maladies infectieuses. On a établi des liens entre des cas de candidémie et des problèmes médicaux sous-jacents, des facteurs prédisposants, une infection simultanée, des agents antimicrobiens, un traitement antifongique et des décès.

Résultats : Au total, on a repéré 415 cas de candidémie, dont 48 (11,6 %) chez des enfants et 367 (88,4 %) chez des adultes. Les agents pathogènes étaient les suivants : *C. albicans* dans 286 cas (68,9 %), *C. parapsilosis* dans 43 (10,4 %), *C. glabrata* dans 34 (8,2 %), *C. tropicalis* dans 27 (6,5 %) et autres espèces de *Candida* dans 18 (4,3 %) cas. Il y a eu sept cas (1,7 %) de candidémie polymicrobienne. Le taux de mortalité total a atteint 46 % et l'on a établi un lien clinique entre le décès et la candidémie dans 19 % des cas. Seulement 13 (27 %) des patients en pédiatrie sont décédés. Une analyse à une variable a indiqué que les facteurs importants de risque de décès sont l'âge de plus de 60 ans, un traitement contre une infection bactérienne concomitante, un séjour aux soins intensifs, une affection maligne simultanée, une chimiothérapie cytotoxique et une granulocytopénie, même si l'âge et le séjour aux soins intensifs sont les seuls facteurs que l'analyse à variables multiples a dégagés comme facteurs de risque importants. Après rajustement en fonction d'autres prédicteurs de décès, seul l'infection par *C. parapsilosis* est associé à un taux de mortalité moins élevé que l'infection par *C. albicans*. On a administré un traitement dans 352 (84,8 %) des cas. L'amphotéricine B était l'agent privilégié dans 244 cas (69,3 % des cas traités) et l'on a utilisé le fluconazole dans 101 cas (28,7 %) et le kétoconazole dans 5 cas (1,4 %).

Interprétation : La candidémie au Canada est causée surtout par *C. albicans*. Le taux de mortalité associé à la candidémie est élevé, mais il varie en fonction des espèces de *Candida* et est moins élevé chez les enfants que chez les adultes. L'âge de plus de 60 ans et le séjour aux soins intensifs sont les facteurs de risque les plus significatifs de mortalité globale.

Species of the genus *Candida* have emerged as important pathogens. *Candida* infections are increasing in frequency and are now the fourth most common cause of nosocomial bloodstream infection in the United States.[1,2] The impact of nosocomial *Candida* infections of the bloodstream may be most significant in certain clinical populations, such as patients in the intensive care unit (ICU)[3] and those with underlying malignant disease.[4,5] Despite effective therapy for candidemia, the mortality rate remains high, ranging from 27% to 79%,[6-9] and the mortality rate attributable to *Candida* is significant, at 38%.[10] Moreover, non-*albicans* species of *Candida* are an important and frequent cause of candidemia,[11] and they may make successful treatment more difficult.

Because the epidemiology of candidemia due to *C. albicans* and other *Candida* species has not been previously documented in Canada, a large multicentre study was conducted under the auspices of the Canadian Infectious Disease Society. Differences in mortality rate associated with different species of *Candida*, risk factors for death and treatment strategies were also assessed.

Methods

Data were collected on all cases of candidemia identified by laboratory blood culture surveillance between March 1992 and February 1994 at medical referral centres in 14 major metropolitan areas across Canada. Study coordinators appointed by the Canadian Infectious Disease Society, who formed the Fungal Disease Registry, were responsible for identifying all cases of candidemia in their respective geographic areas by scrutinizing microbiology laboratory reports and reviewing patients' medical records; they recorded the pertinent data and then forwarded this information to a central site for collation and analysis.

Children and adults were included in the study if *Candida* organisms were isolated from a single blood culture. The isolated microorganisms were identified at each medical centre

by routine methods.[12] Patient-related data were compiled from chart reviews and recorded on a standard form developed for the Fungal Disease Registry. The following information was extracted: age, sex, geographic location, underlying conditions, predisposing factors, concurrent bacterial infection, antimicrobial agents received, pretreatment signs and symptoms of infection, diagnostic studies, laboratory evidence of infection, antifungal treatment, adverse reactions to antifungal treatment, assessment of effectiveness of treatment and infection-related death. The study was observational, and treatment was at the discretion of the attending physician.

Statistical analyses were performed by SciAn Clinical (Etobicoke, Ont.) with SAS 6.11 software (SAS Institute, Cary, NC). Relations between categorical variables were analysed by χ^2 tests. A 2-sided p value of less than 0.05 was used to determine statistical significance. The relation between mortality rate and various patient characteristics and clinical features was examined by multiple logistic regression. Population counts for each metropolitan area were obtained from the 1991 census data of Statistics Canada.

Results

Patient characteristics

A total of 415 cases of candidemia were identified during the study period. The mean age of the patients was 52 years (range 1 month to 93 years). Forty-eight cases of candidemia (11.6%) were documented in patients less than 18 years of age. Twenty-two episodes of candidemia occurred in infants less than 1 year old, of whom 13 were less than 1 month old. Of the 415 patients, 215 (51.8%) were male. Malignant disease, which affected 145 (34.9%) of the patients, was the most common major underlying condition, and diabetes mellitus was the second most common underlying condition (58 patients [14.0%]). Prematurity accounted for another 16 patients overall (3.8%); this represented 33% of the infected children.

Most patients had an identifiable risk factor for candidemia, including previous antimicrobial therapy, presence of a central vascular line, stay in an ICU, total parenteral feeding and major surgery (Table 1). These risk factors were identified in comparable proportions of infected children. The patients exhibited a range of symptoms and signs at the time of diagnosis. The most common presenting symptoms were fever (in 333 [80.2%]), malaise (in 251 [60.5%]), anorexia (in 187 [45.1%]), chills (in 176 [42.4%]), weight loss (in 152 [36.6%]), cough (in 94 [22.6%]), night sweats (in 69 [16.6%]), lethargy (in 67 [16.1%]), hepatomegaly (in 53 [12.8%]), skin lesions (in 49 [11.8%]) and confusion (in 47 [11.3%]). A total of 84% of the patients had a concurrent infection with another organism.

Candidemia developed a mean of 35.2 days after admission to hospital. The mean duration of hospital stay after *Candida* was identified by blood culture was 32 (range 1 to 213) days; this average includes the patients who died in hospital.

The incidence rates for candidemia were well characterized in 3 regions: metropolitan Hamilton and Burlington in Ontario (population 448 075), the metropolitan Ottawa area (population 678 147) and the province of Manitoba (population 1 091 942). There were 46 cases of candidemia in Hamilton and Burlington over the study period, for an annual incidence rate of 5.14 cases per 100 000 population (95% confidence interval [CI] 3.75–6.85), whereas 77 cases were documented in Manitoba for an annual rate of 3.53 per 100 000 population

Table 1: Characteristics of 415 patients with candidemia, as reported from 14 Canadian sites, 1992–1994

Characteristic	No. (and %) of patients
Age group	
Adults (≥ 18 yr)	367 (88.4)
Children (< 18 yr)	48 (11.6)
Major underlying condition	
Present*	257 (61.9)
Absent	158 (38.1)
Risk factors	
Antimicrobial therapy	361 (87.0)
Central line	307 (74.0)
Stay in intensive care unit	217 (52.3)
Parenteral nutrition	209 (50.4)
Major surgery	192 (46.3)
Steroid therapy	104 (25.1)
Cytotoxic therapy	92 (22.2)
Neutropenia	81 (19.5)
Radiation therapy	21 (5.1)
Dialysis	14 (3.4)
Intravenous drug use	9 (2.2)

*Malignant disease in 145 (34.9% of all 415 patients), diabetes in 58 (14.0%), prematurity in 16 (3.8%), transplantation in 15 (3.6%), trauma in 9 (2.2%), burn in 7 (1.7%), alcohol abuse in 4 (1.0%) and HIV infection in 3 (0.7%).

Table 2: Prevalence of *Candida* isolates

	Age group; no. (and %) of patients		
Species	Children $n = 48$	Adults $n = 367$	Total
C. albicans	27 (56)	259 (70.6)	286 (68.9)
C. parapsilosis	15 (31)	28 (7.6)	43 (10.4)
C. glabrata	1 (2)	33 (9.0)	34 (8.2)
C. tropicalis	3 (6)	24 (6.5)	27 (6.5)
C. krusei	NR	4 (1.1)	4 (1.0)
C. lusitaniae	1 (2)	2 (0.5)	3 (0.7)
C. pseudotropicalis	NR	2 (0.5)	2 (0.5)
C. guilliermondii	NR	1 (0.3)	1 (0.2)
C. humicola	NR	1 (0.3)	1 (0.2)
Other species	NR	7 (1.9)	7 (1.7)
Polymicrobial infection	1 (2)	6 (1.6)	7 (1.7)

Note: NR = none reported.

(95% CI 2.73–4.32). The annual incidence rate was lowest in metropolitan Ottawa (1.18 per 100 000 population [95% CI 0.89–1.92]), where only 16 cases of candidemia were recorded.

Epidemiology of Candida isolates

The distribution of various species of *Candida* among the 415 bloodstream isolates is shown in Table 2. *C. albicans* (identified in 286 isolates [68.9%]) was the most common species recovered. Of the non-*albicans* species, *C. parapsilosis* was isolated most frequently, followed by *C. glabrata* and *C. tropicalis* (Table 2). *C. krusei, C. lusitaniae, C. pseudotropicalis, C. guilliermondii, C. humicola*, and other species each accounted for less than 2.0% of cases. Polymicrobial candidemia was observed in 7 (1.7%) of cases. The most frequent combination was *C. albicans* and *C. glabrata* (in 4 cases).

There were differences between children and adults in the frequencies of the *Candida* species isolated. Although *C. albicans* isolates predominated in both age groups, they constituted only 56% (95% CI 4l% to 71%) of the pediatric isolates but 71% (95% CI 66% to 75%) of the adult isolates (*p* = 0.048). The second most frequent species was *C. parapsilosis* in children (in 31%) and *C. glabrata* in adults (in 9%).

In assessing the distribution of *Candida* isolates according to major underlying medical conditions, we found that *C. albicans* was the most frequent isolate for all conditions. However, *C. tropicalis* was the second most common isolate in patients with malignant disease (18/145 cases [12.4%]), whereas *C. glabrata* was second in order of frequency in the diabetic patients (8/58 cases [14%]). In patients with none of the underlying medical conditions mentioned in Table 1, *C. parapsilosis* (15/158 cases [9.5%]) was the second most commonly isolated organism, and it also accounted for 15 (10.3%) of the 145 cases in patients with malignant disease. We also evaluated the identifiable risk factors associated with the most common *Candida* species isolated (*C. albicans, C. parapsilosis, C. glabrata* and *C. tropicalis*). Prior antimicrobial therapy was a factor in 82% of *C. glabrata* cases and 96% of *C. tropicalis* cases. ICU stay was a factor in 57%, 42%, 41% and 37% and a central vascular line was a factor in 76%, 86%, 53% and 70% of *C. albicans, C. parapsilosis, C. glabrata* and *C. tropicalis* cases respectively.

Treatment strategies

A total of 352 (84.8%) patients were treated with antifungal agents, 42 (88%) of the children and 310 (84.5%) of the adults. Among those treated, the initial antifungal treatment was amphotericin B in 244 (69.3%), flucona-

zole in 101 (28.7%) and ketoconazole in 5 (1.4%). Amphotericin B was initially given to 38 (91%) of the 42 children who were treated and 206 (66.5%) of the 310 adults who were treated (*p* = 0.11). The initial therapy was amended in 60 (24.6%) of those initially receiving amphotericin B; the drug was changed to fluconazole in 97% of these cases. Initial treatment with fluconazole was amended in 43 cases (43%), most often to amphotericin B (in 95% of these cases). The mean duration of therapy was 15.4 days for amphotericin B, 12.2 days for fluconazole and 14.8 days for ketoconazole.

Mortality rate

The overall mortality rate was 46% (95% CI 41% to 51%), and the rate of death judged clinically by the attending physician as due to candidemia was 19%. The mortality rate associated with infection with various species of *Candida* is shown in Table 3. The χ^2 test for differences among the mortality rates for the various *Candida* species resulted in a *p* value of 0.095.

The mortality rate was only slightly lower in the treated patients than in the untreated patients (45% v. 56%; *p* = 0.11). No significant differences in mortality rate were observed between treated and untreated patients for each species of *Candida*. In addition, the mortality rate was lower for children (27% [95% CI 15% to 42%]) than for adults (49% [95% CI 44% to 54%]) (*p* = 0.005).

An analysis of mortality rate by major underlying medical condition revealed that patients with malignant disease were more likely to die (87/145 [60.0%; 95% CI 52% to 68%]) than patients with diabetes (26/58 [44.8%; 95% CI 32% to 58%]) or those with no major underlying medical condition (59/158 (37.3%; 95% CI 30% to 45%]) (*p* < 0.001).

Univariate analysis showed that the mortality rate was much higher for patients treated with cytotoxic drugs, those treated for concomitant bacterial infection, those

Table 3: Mortality rate for patients infected with various species of *Candida*

Species	No. of patients	% (and 95% CI)
C. albicans	141/286	49 (43–55)
C. parapsilosis	11/43	26 (14–41)
C. glabrata	15/34	44 (27–62)
C. tropicalis	12/27	44 (25–65)
Other species	9/18	50 (26–74)
Polymicrobial infection	4/7	57 (18–90)
All species	192/415	46 (41–51)

Note: CI = confidence interval.
*Global test of difference in mortality rate: *p* = 0.095.

admitted to the ICU, those who had neutropenia, those who were older and those who had malignant disease (Table 4). Logistic regression of the effect of these risk factors and major underlying medical conditions on mortality rate showed that only advanced age and ICU stay were significant predictors of death.

Because imbalances in these risk factors may have caused apparent differences in mortality rate among the various *Candida* species, we used logistic regression to evaluate the mortality rate associated with each *Candida* species after adjustment for the risk factors displayed in Table 4. Table 5 shows the mortality rate associated with each species of *Candida* (relative to *C. albicans*) and the corresponding odds ratio after adjustment for important risk factors. Infection with *C. parapsilosis* was associated

with a lower mortality rate than infection with *C. albicans* (odds ratio 0.38 [95% CI 0.17–0.85]).

Interpretation

Candidemia is becoming an increasingly important bloodstream infection in non-immunocompromised people as well as in patients with major underlying medical conditions. Numerous studies have evaluated risk factors for the development of candidemia through case–control studies.[4,13,14] Neutropenia, a central vascular access device, colonization of various anatomic sites with *Candida* spp. and receipt of vancomycin have been identified as predisposing risk factors for candidemia in patients with malignant disease.[4,13] In the general population, however, the

Table 4: Risk factors for death associated with candidemia

Risk factor	Observed mortality rate, no. (and %)	Univariate analysis		Multivariate analysis	
		Odds ratio (and 95% CI)	p	Odds ratio (and 95% CI)	p
Age, yr*					
< 18	13/48 (27)	1.00 —		1.00 —	
18–60	73/181 (40)	1.82 (0.90–3.68)		2.13 (0.85–5.33)	
> 60	106/185 (57)	3.57 (1.77–7.20)	< 0.001	4.66 (1.80–12.00)	< 0.001
Therapy for concomitant bacterial infection					
No	16/51 (31)	1.00 —		1.00 —	
Yes	176/364 (48)	2.05 (1.09–3.84)	0.023	1.98 (0.99–3.99)	0.062
Steroid therapy					
No	137/311 (44)	1.00 —		1.00 —	
Yes	55/104 (53)	1.43 (0.91–2.23)	0.12	1.48 (0.89–2.45)	0.14
Cytotoxic therapy					
No	136/323 (42)	1.00 —		1.00 —	
Yes	56/92 (61)	2.14 (1.33–3.44)	< 0.001	1.74 (0.82–3.70)	0.16
ICU stay					
No	81/198 (41)	1.00 —		1.00 —	
Yes	111/217 (51)	1.51 (1.02–2.23)	0.037	1.91 (1.18–3.11)	0.011
Central line					
No	50/108 (46)	1.00 —		1.00 —	
Yes	142/307 (46)	1.00 (0.64–1.55)	0.99	0.92 (0.56–1.54)	0.77
Neutropenia					
No	145/334 (43)	1.00 —		1.00 —	
Yes	47/81 (58)	1.80 (1.10–2.95)	0.018	1.47 (0.72–3.02)	0.33
Underlying condition					
Malignant disease	87/145 (60)	1.00 —		1.00 —	
Diabetes	26/58 (45)	0.54 (0.29–1.00)		0.66 (0.32–1.37)	
Prematurity	4/16 (25)	0.22 (0.07–0.73)		0.74 (0.16–3.44)	
Transplantation	8/15 (53)	0.76 (0.26–2.22)	< 0.001	0.73 (0.23–2.31)	0.16
Burn	1/7 (14)	0.11 (0.01–0.95)		0.18 (0.02–1.69)	
Alcohol abuse	3/4 (75)	2.00 (0.20–19.80)		1.90 (0.18–20.70)	
Others	63/170 (37)	0.39 (0.25–0.62)		0.45 (0.25–0.80)	
Antifungal treatment					
No	35/63 (56)	1.00 —		1.00 —	
Yes	157/352 (45)	0.64 (0.38–1.11)	0.108	0.64 (0.35–1.17)	0.16

*Age missing for one patient.

number of antibiotics prescribed, hemodialysis, the presence of a central vascular access device and the presence of *Candida* spp. from other anatomic sites have emerged as significant risk factors.[14] In our study, only 35% of patients affected by candidemia had an underlying malignant condition. Our results show that candidemia affects an increasing proportion of patients who are not affected by malignancy, that is, those who are older than 60 years of age, have received prior antimicrobial therapy or have received care in an ICU.

In our study *C. albicans* was the *Candida* species most frequently isolated from the bloodstream, as has occurred in numerous other studies.[1,5–9] However, non-*albicans* species have recently surpassed *C. albicans* as a cause of candidemia elsewhere.[11] *C. parapsilosis* is now the most common cause of candidemia in patients with hematological malignant disease in Italy.[15] The role of non-*albicans* species as bloodstream pathogens is increasing, and their intrinsic properties may contribute to this change. In our study *C. parapsilosis* surpassed *C. tropicalis* as the second most commonly isolated species of *Candida*. This may be related to the association of *C. parapsilosis* with central vascular access devices.[16] However, *C. tropicalis* infection was more frequent than *C. parapsilosis* infection among patients with cancer (12% v. 10%). There were also differences in the frequencies of bloodstream isolates between age groups.

The overall mortality rate was 46% and is consistent with previously reported rates.[6–8,9] Polymicrobial candidemia was associated with a mortality rate of 57%, which is consistent with the mortality rate of 59% reported in a review of polymicrobial fungemia.[18] In addition, the mortality rate among children was lower than that among adults (27% v. 49%, p = 0.005) and was similar to the 19% mortality rate reported by Stamos and Rowley.[17]

The mortality rate was lower for *C. parapsilosis* infections than for other *Candida* fungemias in this survey. In a review of catheter-related candidemia in non-neutropenic patients, the overall mortality rate and the mortality rate attributable to the infection were lower for *C. parapsilosis* than for *C. albicans* infections,[19] whereas a low mortality rate has also been found in neutropenic patients infected with this pathogen.[15] Differences between and within species in virulence factors and invasiveness may explain the differences in mortality rates.

There were several limitations to our study. Treatment for candidemia was at the discretion of the attending physician and was affected by the patients' underlying condition and severity of illness. Moreover, the reasons for witholding antifungal therapy were not documented. Second, no data were formally collected to assess the severity of illness of the patients. Thus, severity of illness could not be used as a risk factor for death. Our findings are further limited by the fact that other treatments such as the removal of central venous catheters were not captured consistently and, therefore, information on the possible cause of candidemia and the therapeutic effect of catheter removal are lacking. Furthermore, it was not possible to assess the long-term mortality rates in those patients who appeared to survive the candidemia. Finally, because of sporadic reporting of candidemia cases from some centres and poor documentation of the patients' area of residence, precise incidence estimates across Canada could not be obtained.

In summary, candidemia in Canada is caused predominantly by *C. albicans*. Although the mortality rate associated with candidemia is high, interspecies differences in mortality rate exist. We also found that the mortality rate was lower in children than in adults. Age greater than 60 years and ICU stay were significant risk factors for death from candidemia. Further study is warranted to optimize prevention and pharmacological treatment strategies for candidemia.

Table 5: Adjusted mortality rates for patients infected with various *Candida* species

Species	Odds ratio (and 95% CI)		Adjusted odds ratio (and 95% CI)	
C. albicans	1.00	—	1.00	—
C. parapsilosis	0.35	(0.17–0.73)	0.38	(0.17–0.85)
C. glabrata	0.82	(0.37–1.82)	0.62	(0.26–1.46)
C. tropicalis	0.81	(0.40–1.66)	0.92	(0.42–2.03)
Other species	1.03	(0.40–2.67)	0.79	(0.28–2.23)
Polymicrobial infection	1.37	(0.30–6.24)	1.60	(0.32–7.95)
Global test of any difference, *p* value	0.095		0.216	

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