Invasive Candida species infections: a 5 year population-based assessment

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Received 11 May 2005; returned 6 June 2005; revised 9 June 2005; accepted 23 June 2005

Objectives: Candida species have emerged as important causes of invasive infections and rates of resistance to standard antifungal therapies are rising. The objective of this study was to define the occurrence of, risk factors for, and antifungal susceptibilities of invasive Candida species infections in a large Canadian health region.

Methods: Population-based surveillance was conducted for invasive Candida species infections in the Calgary Health Region during a 5 year period and susceptibility testing was performed.

Results: The annual incidence of invasive Candida species infection was 2.9 per 100,000 population (0.2 and 2.8 per 100,000 for central nervous system and bloodstream infection, respectively). The very young and elderly were at highest risk for invasive Candida species infections. Several risk factors for developing invasive Candida species infection were identified with chronic haemodialysis, organ transplant recipient, and cancer patients at highest risk. Thirty percent (56/184; 43 susceptible, dose-dependent and 13 resistant) of isolates demonstrated reduced susceptibility to fluconazole. Only one (1%) isolate had reduced susceptibility to amphotericin B and six (3%) and three (2%) isolates had minimum inhibitory concentrations of ≥1 mg/L to voriconazole and caspofungin, respectively. Overall, 40% of patients died in-hospital for an annual mortality rate of 1.2 per 100,000.

Conclusions: Candida species are an important cause of invasive infection and patients with co-morbidities and extremes of age are at highest risk. Alternatives to fluconazole should be considered for initial empiric therapy in patients with severe invasive Candida species infections.

Keywords: candidaemia, mortality, susceptibility

Introduction

Candida species are among the most common causes of invasive nosocomial infections and are associated with significant attributable mortality particularly in intensive care units (ICU).¹⁻⁶ With increasing use of medical devices, immunosuppression, and broad spectrum antibacterials over recent decades, there has been a dramatic increase in invasive Candida species infections.⁵⁻⁷ Concomitantly, there have been rising rates of resistance to azoles, the current standard therapeutic agents for these infections.⁵⁻⁹ In response, there has been a requirement to return to the use of the conventional agent amphotericin B, or the newer agents including echinocandins such as caspofungin and triazoles including voriconazole.⁵⁻¹³ Conventional amphotericin B is limited by its significant side effects profile, and lipid formulations of this agent, echinocandins, and triazoles by their dramatically higher cost.

Despite the importance of invasive Candida species infections, few reported studies have utilized a population-based methodology.

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and none have been from Canada. In addition, previously reported population-based studies have not quantified actual risk factors for development of invasive Candida species infections and antifungal susceptibility testing has been limited. The objective of this study was to establish the burden associated with invasive Candida species infections, determine risk factors for their acquisition, and assess trends in resistance rates to both standard and newer chemotherapeutic agents in a large unselected population over a 5 year period.

Methods

Study population

The Calgary Health Region (CHR) provides all publicly funded healthcare services to the more than one million population of the cities of Calgary and Airdre and numerous adjacent surrounding communities covering an area of 37 000 km². Acute care is provided principally through one paediatric and three large adult hospitals. Nearly all (>95%) standard microbiology testing from both community and hospital sites in the CHR is performed by Calgary Laboratory Services (CLS). All patients with culture-proven invasive Candida species infections as identified by CLS during the period 1 July 1999 and 30 June 2004 were included in this study. The ethics review board at the University of Calgary and Calgary Health Region approved the study prior to commencement.

Protocol

An active population-based laboratory surveillance design was utilized. Sterile site Candida species isolates were prospectively identified and frozen for later testing. An electronic search of all microbiology tests performed at CLS during the surveillance period was also conducted to ensure completeness of case ascertainment. Further clinical and demographic information was then obtained through a linkage with the Calgary Health Region Data Warehouse. This database maintains detailed information on all patients who receive care through any of the four major acute care sites within the CHR. Data obtained included patient demographics (dates of birth, gender, regional residency), hospital assessment (emergency department assessment or hospital dates of admission and discharge, and discharge status as alive or dead), and clinical information (admitting diagnosis and pre-existing co-morbid illnesses). Survival status at hospital discharge was used to establish mortality rates. Data regarding ICU admissions were only available for adults. Individual patient’s hardcopy medical charts were not reviewed. The source databases were linked based on a unique patient hospital number to make the final study database using Access 2003 (Microsoft Corp., Redmond, WA, USA).

Definitions

Invasive Candida species infection was defined by the isolation of Candida species from either blood or cerebrospinal fluid (CSF). Bloodstream infection and central nervous system infection were defined by positive cultures from blood or CSF, respectively. Community-onset disease was deemed to be present if a patient had an initial invasive culture diagnosed within 2 days of admission to hospital. Repeat episodes of invasive disease were diagnosed if a second Candida species was isolated ≥2 days after the first or with the same species if the second isolation was 2 months or more following the last positive culture. The presence of diabetes mellitus, heart disease, lung disease, HIV infection, cancer and alcoholism were deemed to be present if recorded by medical records based on ICD-9-CM/10 codes. A CHR resident was defined using the 1 April 2003 boundaries. Homeless individuals and outpatients who did not access acute care at some point during surveillance were classified as CHR residents as long as they had Alberta Healthcare numbers and samples were submitted at CHR-based collection sites.

Laboratory testing

Speciation of invasive yeast isolates was accomplished using germ tube testing, morphology on Commeal Blue agar, and by the API-20C AUX System (bioMérieux Inc., Durham, NC, USA). Sterile site Candida species isolates were frozen and batch susceptibility tested. Sensitivity YeastOne Y-05 colorimetric broth microdilution panels (Trek Diagnostic Systems Inc, Cleveland, OH, USA) were used for testing isolates against amphotericin B, fluconazole, 5-fluorocytosine, itraconazole, voriconazole, and caspofungin, according to the manufacturer’s instructions and interpreted based on current CLSI (formerly NCCLS) guidelines. A 24 h incubation period was used and MICs were determined by prominent growth reduction (for azoles and echinocandins) or complete growth inhibition (for amphotericin B and 5-fluorocytosine), facilitated by the presence of Alamar Blue dye within the colorimetric panels. Candida parapsilosis (ATCC 22019) was used as the quality control strain for testing.

Statistical analysis

Analysis was performed using Stata version 8.0 (Stata Corp, College Station, TX, USA). Normally or near-normally distributed variables were reported as means ± standard deviations (SD) and non-normally distributed variables as medians with inter-quartile ranges (IQR). Means were compared using the Student’s t-test and medians using the Mann–Whitney U-test. Differences in proportions among categorical data were assessed using Fisher’s exact test. Category-specific relative risks (RR) were calculated and reported with exact 95% confidence intervals (CI) as previously described. For determination of incidence rates, denominator data from Statistics Canada 2001 census were used with 2% annual adjustment for population growth. Estimates of the prevalence of co-morbid conditions were based on regional database or North American survey data. Rates of nosocomial and ICU-associated infections were based on estimated 475 000 total hospital and 17 000 adult ICU admissions during the study period.

Results

During the 5 year study period, 207 patients had 209 episodes of invasive Candida species infection; two patients had second incident infection episodes with different Candida species. Ninety-eight percent (203) of the patients were admitted to an acute care institution in the CHR and detailed data were available for all but two patients. The median length of hospital stay was 32 (IQR 14, 56) days and 76 adults required admission to ICU. Of the total 207 patients, 155 (75%) were classified as CHR residents. Overall 82 (40%) patients died during hospitalization for an annual mortality rate of 1.2 per 100 000 CHR residents.

Incidence

The overall annual incidence of invasive Candida species infection among residents of the CHR was 2.9 per 100 000 population. The incidence of central nervous system infection was 0.2 per 100 000 and 2.8 per 100 000 for bloodstream infection. There was a dramatic difference in the yearly incidence observed with a higher rate in the latter 3 years of the study (3.7 per 100 000 population)
compared with the first two (1.6 per 100,000 population; $P < 0.0001$) as shown in Figure 1. No significant monthly or seasonal variation in incidence was observed. Forty-two percent (169/207) of invasive Candida species infections were classified as nosocomial onset for a rate of 0.4 per 1000 acute care hospital admissions.

**Risk factors for acquisition**

The median age of the overall patient cohort (207) was 57.8 (IQR: 40.2–72.9) years and 107 (52%) were male. Among adults (≥18 years) admitted to hospital, admission to an ICU was associated with a dramatically increased risk for development of a nosocomial invasive Candida species infection (RR, 23.7; 95% CI, 16.82–33.59; $P < 0.0001$). Co-morbid/underlying conditions were common with malignancy in 66 (32%); 37 patients with solid organ tumours, 21 patients with leukaemia, five with lymphoma, and three with multiple myeloma) patients, heart disease in 60 (29%), diabetes in 37 (18%), chronic renal failure in 27 (13%); dialysis dependence in 10 patients), chronic lung disease in 16 (8%), transplant recipients in 13 (6%; eight patients with solid organ transplants and five with bone marrow transplants), alcoholism in 10 (5%), previous stroke in six (3%), and four (2%) patients had rheumatoid arthritis. Eleven of the children in the study were prematurely born. None of the patients had HIV infection.

In the population-based cohort (restricted to CHR residents), a significant relationship between age and the risk for development of invasive Candida species infection was observed as shown in Figure 2. Overall, the incidence rates were not significantly different between males and females (3.3 versus 2.6 per 100,000, respectively; $P = 0.15$). However, in the highest risk age groups of the very young (<1 year) and the elderly (≥75 years; Figure 2), males were at significantly increased risk compared with females (28.7 versus 10.6 per 100,000; RR = 2.7, 95% CI, 1.5–5.2; $P < 0.001$). Several groups of CHR residents were identified as being at increased risk for developing invasive Candida species infection (Table 1), with patients receiving chronic haemodialysis, organ transplant recipients, and patients with cancer at the highest levels of risk.

**Microbiology**

The median time from hospital admission to diagnosis of an invasive Candida species infection was 13.5 days (IQR 4, 24). Of the 209 incident invasive Candida species infections, the most common species isolated were Candida albicans, Candida glabrata and C. parapsilosis as shown in Table 2. There was no significant overall yearly variation in the proportion of cases due to C. albicans ($P > 0.1$; Figure 1). Eighty-eight percent (184/209) of isolates were available for susceptibility testing using microdilution. Only one isolate (C. albicans) demonstrated intermediate resistance to amphotericin B (MIC = 2 mg/L), all other strains tested were fully susceptible to this agent. Thirty percent (56/184; 43 susceptible-dose-dependent and 13 resistant) of isolates demonstrated reduced susceptibility to fluconazole, 41% (76/184; 26 intermediate and 50 resistant) reduced susceptibility to itraconazole, and 9% (16/184; six intermediate and 10 resistant) reduced susceptibility to flucytosine. Six (3%) isolates had MICs ≥ 1 mg/L to voriconazole (three isolates ≥ 16 mg/L, one isolate = 8 mg/L, and two isolates = 1 mg/L) and three (2%) isolates had MICs ≥ 1 mg/L to caspofungin (two isolates = 1 mg/L and one isolate = 2 mg/L). Candida species-specific susceptibility data are shown in Table 3. Among 96 C. albicans strains that were tested, none were susceptible-dose-dependent, three were resistant to fluconazole, and one was intermediate and three resistant to itraconazole.

**Discussion**

This study demonstrates that invasive Candida species infections result in a significant burden of disease in our Canadian population.

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**Figure 1.** Annual incidence of invasive Candida species infections among residents of the Calgary Health Region (July 1999–June 2004; filled bars, Candida albicans and open bars, non-albicans Candida species).

**Figure 2.** Age- and gender-specific incidence of invasive Candida species infections in residents of the Calgary Health Region (open bars, males; black bars, females; grey bars, total).
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Table 1. Risk of invasive Candida species infection, associated with selected underlying conditions

<table>
<thead>
<tr>
<th>Underlying condition</th>
<th>No. of cases/total*</th>
<th>Annual incidence/100,000</th>
<th>Relative risk (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haemodialysis</td>
<td>7/135 (5%)</td>
<td>388</td>
<td>118.8 (46.8–251.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Organ transplant</td>
<td>6/135 (4%)</td>
<td>273</td>
<td>83.1 (30.0–186)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cancer</td>
<td>47/135 (30%)</td>
<td>44</td>
<td>20.9 (14.6–29.7)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>30/135 (29%)</td>
<td>25</td>
<td>9.8 (6.5–14.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26/135 (19%)</td>
<td>14</td>
<td>4.7 (3.0–7.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Stroke</td>
<td>5/135 (4%)</td>
<td>13</td>
<td>3.8 (1.2–9.1)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lung disease</td>
<td>13/135 (10%)</td>
<td>10</td>
<td>3.2 (1.7–5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>3/135 (2%)</td>
<td>8</td>
<td>2.5 (0.5–7.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Renal dysfunction</td>
<td>13/135 (10%)</td>
<td>4.4</td>
<td>1.3 (0.7–2.3)</td>
<td>0.3</td>
</tr>
<tr>
<td>Alcoholism</td>
<td>7/135 (5%)</td>
<td>4</td>
<td>1.0 (0.4–2.2)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

*With the exception of cancer where all ages were included, analysis was restricted to patients aged 20 and older.

Table 2. Candida species causing invasive disease in the Calgary Health Region

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Number of cases (age &lt; 20)</th>
<th>Number of cases (age ≥ 20)</th>
<th>Total number of cases</th>
<th>Incidence per 100,000</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>26</td>
<td>44</td>
<td>107</td>
<td>1.5</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>4</td>
<td>4</td>
<td>8</td>
<td>0.7</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>1</td>
<td>8</td>
<td>13</td>
<td>0.2</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>1</td>
<td>10</td>
<td>12</td>
<td>0.2</td>
</tr>
<tr>
<td>C. krusei</td>
<td>2</td>
<td>8</td>
<td>10</td>
<td>0.1</td>
</tr>
<tr>
<td>Other*</td>
<td>2</td>
<td>20</td>
<td>22</td>
<td>–</td>
</tr>
</tbody>
</table>

*Other includes two Candida guilliermondii (one patient, age <20 years), one Candida lusitaniae, and 19 non-albicans Candida species (one patient, age <20 years).

Our annual rate of invasive Candida species infections of 2.9 per 100,000 population is less than American studies including reports of 10 per 100,000 in Baltimore and Connecticut during 1998 and 2000,16 8 per 100,000 during 1992–1993 in Atlanta and San Francisco,15 and 6 per 100,000 as estimated by Diekema and colleagues in 16 hospitals in Iowa during 1998 to 2001,17 but similar to reports from Finland during 1995 to 1999 of 2 per 100,000 and 4 per 100,000 population in the Lombardy region of Italy.18 It is not clear why rates of invasive Candida species infections appear higher in the United States compared with Canada and European studies but may potentially be related at least in part to different rates of sampling, different distribution of risk factors in the populations studied, different age distribution, or differences in study methodologies employed. As in studies by Kao et al.15 and Hajjeh et al.,16 we included samples submitted from both hospital and community-based laboratories in the surveillance area and performed audits to identify potentially missed cases. The lower incidence rate observed in our study was therefore not erroneously low as a result of limiting surveillance to hospital-based laboratories alone.17,18 In contrast, one American study may have overestimated the true rate of candidemia in their population by including non-residents of the surveillance area in analysis.17,18 Although moderate variability exists among the population-based studies conducted to date, it is important to note that invasive Candida species infections occur at rates comparable to many invasive bacterial diseases.21,23,36,37

Our observation of a significant increase in the incidence of invasive Candida species infections in the latter 3 years compared with the first 2 years of surveillance merits discussion (Figure 1). Given such a dramatic change in incidence, we carefully investigated our data and confirmed that this was neither an error of case identification nor database problems. We also explored the data further to see if there were potential reasons to explain the differences in rates. However, the increase in rates could not be explained by any given hospital or unit or by a different distribution in infections among certain patients with co-morbidities. Furthermore, to our knowledge, no major shifts in policies (i.e. antifungal prophylaxis) or procedures (such as laboratory culturing practices) occurred in association with the change in incidence. The differences observed therefore in all likelihood reflect true differences in the incidence of invasive Candida species infections during surveillance but the reason for this is not apparent. Future surveillance will help to define whether rates will further change over the next years.

Although this is not the first study to identify a high rate of underlying co-morbid illness among patients with invasive Candida species infection, it is novel that we quantified actual risks associated with development of invasive Candida species infection in a general population. A large body of published literature exists describing the occurrence and possible risk factors for invasive Candida infections from hospital-based studies. These studies suggest that the use of central venous catheters, parenteral nutrition, haemodialysis, immunosuppressive therapy, broad spectrum antibacterials, burns, admission to ICU with a need for prolonged admission or mechanical ventilation, and underlying conditions/diagnoses such as diabetes mellitus, haematological malignancies, and liver disease may all be risks.38–42 However, since these studies are typically based at single institutions and/or tertiary care referral centres, generalization to other centres may not be appropriate. In population-based studies, all patients resident in a defined surveillance area are included and as a result, selection bias is minimized. Further, in risk factor analysis, the actual risk for developing an infection in association with a given factor in the population may be determined. The age distribution and relative proportions of patients with underlying illnesses such as malignancies, diabetes, and immunosuppression observed in our study is comparable to other population-based studies.15,18 Unlike with previous reports, we were able to obtain or estimate denominator...
Table 3. Antifungal susceptibilities of 184 invasive Candida species isolates

<table>
<thead>
<tr>
<th></th>
<th>Amphotericin B</th>
<th>Caspofungin</th>
<th>Fluconazole</th>
<th>Flucytosine</th>
<th>Itraconazole</th>
<th>Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC</td>
<td>MIC</td>
<td>MIC</td>
<td>MIC</td>
<td>MIC</td>
<td>MIC</td>
</tr>
<tr>
<td></td>
<td>range</td>
<td>50</td>
<td>90</td>
<td>range</td>
<td>50</td>
<td>90</td>
</tr>
<tr>
<td>Candida spp.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C. albicans</td>
<td>0.06–0.25</td>
<td>0.5</td>
<td>0.25</td>
<td>0.006–0.012</td>
<td>0.06</td>
<td>0.1–0.25</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>0.1–0.25</td>
<td>0.5</td>
<td>0.25</td>
<td>0.012–0.06</td>
<td>0.06</td>
<td>0.1–0.25</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>0.25–0.5</td>
<td>0.5</td>
<td>0.25</td>
<td>0.015–0.25</td>
<td>0.06–0.25</td>
<td>0.25–0.5</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>0.5–1</td>
<td>1</td>
<td>2</td>
<td>0.006–0.06</td>
<td>0.03–0.12</td>
<td>0.5–1</td>
</tr>
<tr>
<td>C. krusei</td>
<td>1–4</td>
<td>2–4</td>
<td>4</td>
<td>0.006–0.25</td>
<td>0.06–0.25</td>
<td>2–4</td>
</tr>
<tr>
<td>Others*</td>
<td>1–16</td>
<td>2–16</td>
<td>32</td>
<td>0.006–0.25</td>
<td>0.06–0.25</td>
<td>2–16</td>
</tr>
<tr>
<td>Total</td>
<td>184</td>
<td>2</td>
<td>4</td>
<td>0.006–0.25</td>
<td>0.06–0.25</td>
<td>2</td>
</tr>
</tbody>
</table>

*aOthers refers to two Candida guilliermondii and 11 non-albicans Candida species not fully specified.

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data and therefore calculate relative risks for several factors associated with development of invasive Candida species infections (Table 1). It should be recognized that these risks do not represent independent risk factors for acquiring invasive Candida species infections. This is because multivariable analysis was not possible as linked data were not available for the approximately one million non-cases in this study.

Our study complements the few population-based studies that have reported antifungal susceptibility testing results to newer agents. The landmark population-based study conducted by Rees et al.14 did not report antifungal susceptibilities testing results and the later work conducted by this group was limited by the fact that less than one-half of the isolates were tested for susceptibility to fluconazole, itraconazole and amphotericin B.15 They observed that resistance to these agents was uncommon with the exception of Candida krusei and C. glabrata that demonstrated frequent reduced susceptibility to fluconazole. Interpretation of these data is difficult because of the lack of a widely accepted criterion for resistance in the era of that study (early 1990s). On the other hand, Hajjeh et al.16 conducted antifungal susceptibility testing of 935/1143 isolates in their study. They found that resistance (MIC ≥ 64 mg/L) to fluconazole occurred in 4% of Candida species overall (1% of C. albicans, 7% of C. glabrata, and 6% of Candida tropicalis). Although the rate of reduced susceptibility to fluconazole was much lower in their study compared with ours, the reduced susceptibility rate to amphotericin B (MIC > 1 mg/L) was similar at 2%. They did not test for susceptibility to either echinocandins or triazoles. In the 16 hospital-based study by Diekema et al.,17 they observed overall rates of resistance of 3% to fluconazole (3% of C. albicans, 10% of C. glabrata and 7% of C. tropicalis). Although this study did not explore susceptibility testing to echinocandins, they tested a number of different triazole agents and like our study, generally found that these agents were highly active against the large majority of isolates. To our knowledge, only one other study that utilized a population-based methodology tested isolates to caspofungin and found this agent to be highly active.20

In summary, we report the first population-based study of invasive Candida species infection from Canada and document that these infections result in a considerable disease burden. In addition, we report the magnitude of risks associated with development of invasive Candida species infections in association with a number of different factors in an unselected population. Although amphotericin B, caspofungin, and voriconazole demonstrated high rates of activity against a broad range of invasive Candida species isolates, reduced susceptibility to fluconazole was not uncommon. These data provide important information on the impact of invasive Candida species infections and contemporary rates of resistance to antifungal agents and support ongoing surveillance efforts.

Acknowledgements

We thank Doris Hawkins, Quality Improvement and Health Information, Calgary Health Region for providing information from the CHR Data Warehouse. The investigators had complete autonomy in study design, conduct, analysis, and presentation of results. K. B. L. has received research grants from Merck Frosst Canada Ltd, Astra Zeneca Canada Inc., and Bristol-Myers Squibb Canada. The other study authors have no potential conflicts of interest. This study was funded by an unrestricted educational grant from Merck Frosst Canada Ltd.
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