NOTES

Bloodstream Infections Due to Candida Species: SENTRY Antimicrobial Surveillance Program in North America and Latin America, 1997-1998


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An international program of surveillance of bloodstream infections (BSI) in the United States, Canada, and Latin America detected 306 episodes of candidemia in 34 medical centers (22 in the United States, 6 in Canada, and 6 in Latin America) in 1997 and 328 episodes in 34 medical centers (22 in the United States, 5 in Canada, and 7 in Latin America) in 1998. Of the 634 BSI, 54.3% were due to Candida albicans, 16.4% were due to C. glabrata, 14.9% were due to C. parapsilosis, 8.2% were due to C. tropicalis, 1.6% were due to C. krusei, and 4.6% were due to other Candida spp. The percentage of BSI due to C. albicans decreased very slightly in the United States between 1997 and 1998 (56.2 to 54.4%; P = 0.68) and increased in both Canada (52.6 to 70.1%; P = 0.05) and Latin America (40.5 to 44.6%; P = 0.67). C. glabrata was the second most common species observed overall, and the percentage of BSI due to C. glabrata increased in all three geographic areas between 1997 and 1998. C. parapsilosis was the third most prevalent BSI isolate in both Canada and Latin America, accounting for 7.0 and 18.5% of BSI, respectively. Resistance to fluconazole (MIC, ≥4 μg/ml) and itraconazole (MIC, ≥1.0 μg/ml) was observed infrequently in both 1997 (2.3 and 8.5%, respectively) and 1998 (1.5 and 7.6%, respectively). Among the different species of Candida, resistance to fluconazole and itraconazole was observed in C. glabrata and C. krusei, whereas isolates of C. albicans, C. parapsilosis, and C. tropicalis were all highly susceptible to both fluconazole (98.9 to 100% susceptible) and itraconazole (96.4 to 100% susceptible). Isolates from Canada and Latin America were generally more susceptible to both triazoles than U.S. isolates were. Continued surveillance appears necessary to detect these important changes.

Surveillance programs are essential sources of information for any organized effort that is designed to identify antimicrobial resistance trends and to detect emerging pathogens (8–11, 16–22, 25, 26, 29, 35). Although a relatively large number of recent studies have addressed the issue of antimicrobial resistance and species distribution among pathogens causing bloodstream infections (BSI) (9, 10, 16, 17, 19, 27, 30, 38), most have focused on bacterial pathogens and have been limited in both longitudinal and geographic representation. Comparative and longitudinal data addressing these issues for fungal pathogens remain limited (2, 18, 20–26, 34, 36).

Among BSI due to fungi, the Candida species predominate (1, 6, 14, 20–26, 29). These agents include Candida albicans, C. glabrata, C. tropicalis, C. parapsilosis, and C. krusei, among others (15). Notable regarding these organisms are reports of emerging or increasing resistance to the triazole antifungal agents such as fluconazole and itraconazole (1, 14, 21), and the increasing prominence of species other than C. albicans (1, 7, 14, 15, 22, 28, 39, 40). Despite these concerns, very few studies have addressed these issues in a longitudinal fashion or from an international perspective (2, 3, 20, 25, 26).

The SENTRY Antimicrobial Surveillance Program is a longitudinal surveillance program designed to track antimicrobial resistance trends on a global scale using reference-quality quantitative antimicrobial susceptibility testing methods performed in a central laboratory. The SENTRY Program has been described previously (5, 19, 20, 26), and the results of the first 12 months’ surveillance of Candida BSI in the United States, Canada, Latin America, and Europe have recently been reported (20, 26). The early findings of the SENTRY Program underscore the continued importance of C. albicans as an etiologic agent of BSI in both the United States and Canada. C. parapsilosis was noted to be especially common in Latin America, and the lack of both C. glabrata and C. krusei in Canada and Latin America was in marked contrast to the frequencies of those species in the United States. The 1997 SENTRY data also documented the sustained activities of the triazole antifungal agents fluconazole and itraconazole against all BSI isolates of Candida except C. glabrata and C. krusei. In the present study, we expand upon these findings and report our results after an additional 12 months of BSI surveillance in the United States, Canada, and Latin America. The results of the 1998 surveillance year are compared with those of 1997 for BSI due to Candida species.

Study design. The SENTRY Antimicrobial Surveillance Program was established in 1997 to monitor the predominant pathogens and antimicrobial resistance patterns of nosocomial and community-acquired infections via a broad network of
sentinel hospitals categorized by geographic location and size (5, 19, 20, 26). The present report focuses on BSI due to *Candida* spp. from U.S., Canadian, and Latin American study sites. BSI due to *Candida* spp. were reported from 34 (22 in the United States, 6 in Canada, and 6 in Latin America) of 48 monitored medical centers in 1997 and from 34 (22 in the United States, 5 in Canada, and 7 in Latin America) of 40 monitored medical centers in 1998. Of the 35 medical centers reporting BSI due to *Candida* spp. in 1997 and/or 1998, 33 (94%) reported *Candida* BSI in both years.

Each participant hospital contributed results (organism identification, date of isolation, and hospital location) for consecutive blood culture isolates (1 isolate per patient) of *Candida* spp. judged to be clinically significant by local criteria, detected in each calendar month during the study period (January through December of each year). All isolates were saved on agar slants and were sent on a weekly basis to the University of Iowa College of Medicine (Iowa City) for storage and further characterization by reference identification and susceptibility testing (13, 37).

**Organism identification.** All fungal blood culture isolates were identified at the participating institutions by the routine method in use at each laboratory. Upon receipt at the University of Iowa, the isolates were subcultured onto potato dextrose agar (Remel, Lenexa, Kans.) and CHROMagar Candida medium (Hardy Laboratories, Santa Maria, Calif.) to ensure viability and purity. Confirmation of species identification was performed with Vitek and API products (bioMerieux, St. Louis, Mo.) as recommended by the manufacturer or by conventional methods, as required (37). Isolates were stored as suspensions in water or on agar slants at an ambient temperature until needed.

**Susceptibility testing.** Antifungal susceptibility testing of isolates of *Candida* spp. was performed by the reference broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS) (13). Reference powders of fluconazole and itraconazole were obtained from their respective manufacturers. Quality control was performed by testing *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258 (13).

Interpretive criteria for susceptibility to fluconazole and itraconazole were those published by Rex et al. (32) and the NCCLS (13). For the purposes of this study, isolates were classified as susceptible to fluconazole if the MIC was ≤32 μg/ml and resistant if the MIC was ≥64 μg/ml. The susceptible designation encompasses both the susceptible (MIC, ≤8 μg/ml) and susceptible-dependent-upon-dose (S-DD; MIC, 16 to 32 μg/ml) categories defined by the NCCLS (13). As discussed by Rex et al. (32), the distinction between susceptible and S-DD is moot for patients with invasive candidiasis (candidemia) because these patients are treated with high doses of fluconazole (≥400 mg/day), which provide comparable responses in patients infected with isolates classified as either susceptible or S-DD. These breakpoints apply to all *Candida* species (including *C. glabrata*) with the exception of *C. krusei*, which is considered inherently resistant to fluconazole.

The interpretive breakpoints defined by the NCCLS (13) for itraconazole are as follows: susceptible, ≤0.12 μg/ml; S-DD, 0.25 to 0.5 μg/ml; and resistant, ≥1.0 μg/ml. Isolates in this study were classified as susceptible to itraconazole if the MIC was ≤0.5 μg/ml and were classified as resistant if the MIC was ≥1.0 μg/ml.

**Statistical analysis.** Statistical analysis of the data was performed using the Z test for comparing proportions. As described previously, a total of 306 *Candida* BSI were reported by 34 SENTRY participants in 1997 (20). During the 1998 study period, a total of 328 BSI were reported from 34 participating centers, 33 of which also reported in 1997. The original identification assigned by the participating center was confirmed for 97% of the isolates in both 1997 and 1998. Among the 634 BSI, 75% were nosocomial (detected more than 48 h after admission to a hospital), and 44% occurred in patients hospitalized in an intensive care unit.

The frequencies of BSI due to the various species of *Candida* in each country and in each year are presented in Table 1. Of the 634 BSI identified over the 2-year period, 54.3% were due to *C. albicans*, 16.4% were due to *C. glabrata*, 14.9% were due to *C. parapsilosis*, 8.2% were due to *C. tropicalis*, 1.6% were due to *C. krusei*, and 4.6% were due to *Candida* spp. not otherwise specified. Whereas the percentage of BSI due to *C. albicans* decreased minimally in the United States between 1997 and 1998 (56.2 to 55.4%; P = 0.68), a substantial increase was noted in Canada (52.6 to 70.1%; P = 0.05) and a slight increase was also observed in Latin America (40.5 to 44.6%; P = 0.67). *C. glabrata* was the second most common species overall, and the percentages of BSI due to *C. glabrata* increased slightly in all three geographic areas between 1997 and 1998 (P > 0.05). The percentage of BSI due to *C. parapsilosis* decreased significantly in Canada (P = 0.016) and only slightly in Latin America (P = 0.27) between 1997 and 1998. *C. parapsilosis* was the third most common BSI isolate in both Canada and Latin America during 1998, accounting for 7.0 and 18.5% of all candidal BSI, respectively. The distribution of *C. parapsilosis* isolates was relatively even across all study sites, with no

**TABLE 1. Species distribution of *Candida* bloodstream isolates by geographic area, SENTRY Program, 1997 and 1998**

<table>
<thead>
<tr>
<th>Geographic area</th>
<th>Yr</th>
<th>No. of isolates</th>
<th>C. albicans</th>
<th>C. glabrata</th>
<th>C. parapsilosis</th>
<th>C. tropicalis</th>
<th>C. krusei</th>
<th>Unspecified Candida spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1997</td>
<td>203</td>
<td>56.2</td>
<td>18.7</td>
<td>8.9</td>
<td>6.9</td>
<td>2.5</td>
<td>6.9</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>206</td>
<td>54.4</td>
<td>21.8</td>
<td>15.0</td>
<td>5.8</td>
<td>1.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Canada</td>
<td>1997</td>
<td>61</td>
<td>52.5</td>
<td>11.5</td>
<td>22.9</td>
<td>8.2</td>
<td>1.6</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>57</td>
<td>70.1</td>
<td>12.3</td>
<td>7.0</td>
<td>5.2</td>
<td>1.8</td>
<td>3.6</td>
</tr>
<tr>
<td>Latin America</td>
<td>1997</td>
<td>42</td>
<td>40.5</td>
<td>2.4</td>
<td>38.1</td>
<td>11.9</td>
<td></td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>65</td>
<td>44.6</td>
<td>9.2</td>
<td>18.5</td>
<td>20.0</td>
<td>1.5</td>
<td>6.2</td>
</tr>
<tr>
<td>All</td>
<td>1997</td>
<td>306</td>
<td>53.3</td>
<td>15.0</td>
<td>15.7</td>
<td>7.8</td>
<td>2.0</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>328</td>
<td>55.2</td>
<td>17.7</td>
<td>14.3</td>
<td>8.5</td>
<td>1.2</td>
<td>3.1</td>
</tr>
</tbody>
</table>

* Adapted from the work of Pfaller et al. (20) and Diekema et al. (4).
single institution predominating. The frequency of *C. krusei* as a cause of BSI remained low or nil in each of the three geographic areas.

These data demonstrate the sustained importance of *C. albicans* as an etiologic agent of BSI. Similar observations have been reported recently in the United States (2, 20, 21, 23, 25), Norway (34), and Germany (33) and suggest that the role of *C. albicans* as a major BSI pathogen has not diminished and in fact may be increasing in some countries, despite the widespread use of fluconazole (2, 20, 21, 23, 25, 33, 34). Notably, none of these investigators were able to document increased resistance to antifungals among *C. albicans* isolates as a possible reason for the apparent resurgence of this species.

The only species of *Candida* whose frequency increased as a cause of BSI in all three geographic areas between 1997 and 1998 was *C. glabrata*. These data support the observation of several U.S. investigators who have noted the emergence of *C. glabrata* as an important BSI pathogen over the past decade (1, 14, 22, 24, 25, 40). We now extend these observations and document the same trend in both Canada and Latin America. As has been noted by Abi-Said et al. (1), Nguyen et al. (14), and Wingard et al. (40), the frequency of infection due to *C. glabrata* in a given institution is almost always related to the use of fluconazole; however, we are unable to confirm that association in the present study.

Of particular interest is the decline in the incidence of *C. parapsilosis* fungemia in both Canada and Latin America between 1997 and 1998. At the same time, the percentages of BSI due to this species increased slightly in the United States (P = 0.06). Because this organism is often a cause of clusters of nosocomial cases of BSI related to poor catheter care, contaminated solutions and biomedical devices, and/or poor infection control practices (1, 12, 15, 20, 24, 26), one might expect transient increases in the numbers of *C. parapsilosis* BSI due to one or more of these causes. Although we have some evidence that these factors may have influenced the high frequency of *C. parapsilosis* BSI in Latin America in 1997 (12), we do not have a ready explanation either for the increase in these infections in the United States or for their decrease in Canada and Latin America during 1998.

In vitro susceptibility testing using standardized reference methods (13) demonstrated that resistance to fluconazole (MIC, $\geq 64$ µg/ml) and itraconazole (MIC, $\geq 1.0$ µg/ml) was observed infrequently in both 1997 (2.3 and 8.3% of isolates, respectively) and 1998 (1.5 and 7.6%, respectively) (data not shown). As was seen in 1997, isolates from Canada and Latin America were more susceptible to both triazoles in 1998 than U.S. isolates were (data not shown). None of the 1998 isolates from Latin America or Canada were resistant to fluconazole, whereas 2.5% of U.S. isolates were resistant to this agent ($P > 0.05$). Likewise, 3.1 and 5.3% of Latin American and Canadian isolates, respectively, were resistant to itraconazole, compared to 9.7% of U.S. isolates ($P < 0.05$). The MICs at which 50% and 90% of the isolates tested are inhibited for both fluconazole and itraconazole were essentially unchanged between 1997 and 1998.

Among the different species of *Candida* causing BSI in the three geographic areas, resistance to fluconazole and itraconazole was almost entirely accounted for by isolates of *C. glabrata* and *C. krusei* (Table 2). Isolates of *C. albicans*, *C. parapsilosis*, and *C. tropicalis* were all susceptible to both fluconazole (98.9 to 100.0% susceptible) and itraconazole (96.4 to 100.0% susceptible). There was essentially no change in the level of susceptibility of these species to the triazoles between 1997 and 1998 (Table 2). The only geographic difference in susceptibility among the various species in 1998 was made

### TABLE 2. In vitro susceptibilities to fluconazole and itraconazole of BSI isolates of various species of *Candida* from 1997 and 1998

<table>
<thead>
<tr>
<th>Species</th>
<th>Yr</th>
<th>No. of isolates</th>
<th>Antifungal agent</th>
<th>MIC (µg/ml)</th>
<th>% R&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Range</td>
<td>50%</td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>163</td>
<td>Fluconazole</td>
<td>0.12–&gt;128</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>181</td>
<td>Fluconazole</td>
<td>0.015–&gt;8.0</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.12–&gt;128</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.008–&gt;8.0</td>
<td>0.03</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>46</td>
<td>Fluconazole</td>
<td>1.0–&gt;128</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>58</td>
<td>Fluconazole</td>
<td>0.25–&gt;128</td>
<td>8.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.06–&gt;8.0</td>
<td>0.5</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>48</td>
<td>Fluconazole</td>
<td>0.12–4.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>47</td>
<td>Fluconazole</td>
<td>0.015–0.5</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.25–4.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.015–0.5</td>
<td>0.06</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>24</td>
<td>Fluconazole</td>
<td>0.25–4.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>28</td>
<td>Fluconazole</td>
<td>0.03–1.0</td>
<td>0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.25–8.0</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.015–1.0</td>
<td>0.06</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>1997&lt;sup&gt;a&lt;/sup&gt;</td>
<td>6</td>
<td>Fluconazole</td>
<td>32–64</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>1998</td>
<td>4</td>
<td>Fluconazole</td>
<td>0.12–2.0</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>8.0–32</td>
<td>32</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Itraconazole</td>
<td>0.12–0.5</td>
<td>0.25</td>
</tr>
</tbody>
</table>

<sup>a</sup> 50% and 90%, MICs for 50 and 90% of isolates tested, respectively.

<sup>b</sup> % R, percent resistant as determined by using interpretive breakpoint criteria of the NCCLS (13): fluconazole resistance, $\geq 64$ µg/ml; itraconazole resistance, $\geq 1.0$ µg/ml.

<sup>c</sup> Adapted from the work of Pfaller et al. (20).

<sup>d</sup> Isolates of *C. krusei* are considered resistant to fluconazole, regardless of the MIC.
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REFERENCES


