The genus Candida includes approximately 154 species. Among these, eight are most frequently isolated in human infections. While *Candida albicans* is the most abundant and significant species, *Candida tropicalis*, *Candida glabrata*, *Candida parapsilosis*, *Candida kefyr*, *Candida krusei*, *Candida dubliniensis* and *Candida lusitaniae* are also isolated as causative agents of candidiasis infections (Table 1).

Candida species other than *C. albicans* have emerged as causes of human candidiasis. The variety of non-albicans Candida species involved in human pathology, their rising contribution to invasive infections and the unusual antifungal susceptibility profiles of some of these species makes their identification at the species level essential for epidemiological investigations and for optimizing therapy and patient management. The causes of this change in epidemiology are not entirely clear (1). The use of fluconazole in prophylactic regimens for severely immunosuppressed patients has been strongly associated with changes in the etiology of candidemia in this population (2, 3, 4) (Table 2). However, the same phenomenon has occurred in populations not exposed to this agent (5).

### Candida dubliniensis

*Candida dubliniensis* was first described as a novel species in 1995. This organism is very closely related to the important human yeast pathogen, *Candida albicans*. However, despite the very close phylogenetic relationship between *C. albicans* and *C. dubliniensis* and the fact that they share a large number of phenotypic traits, epidemiological and virulence model data indicate that they differ in pathogenicity and pharmacology. *C. dubliniensis* has been implicated as an agent of oral candidiasis in HIV-positive persons but has also been recovered from HIV-negative persons with clinical signs of oral candidiasis and from the genital tract of some women with vaginitis (6, 7, 8). First isolated from AIDS patients in Dublin, Ireland, *C. dubliniensis* has a worldwide distribution (9, 10). In a study of Irish subjects, *C. dubliniensis* was recovered from the oral cavities of 27% of HIV-infected individuals and 32% of AIDS patients presenting with symptoms of oral candidiasis (7). The majority of *C. dubliniensis* clinical isolates tested to date are susceptible to fluconazole (MIC range, 0.125 to 1.0 g/ml) and to other commonly used antifungal drugs including ketoconazole, itraconazole and amphotericin B (11). A study by Moran et al., reported an occurrence of fluconazole resistance in 20% of oral isolates of *C. dubliniensis* recovered from AIDS patients who had been treated previously with fluconazole. Furthermore, sequential exposure of fluconazole-susceptible clinical isolates of *C. dubliniensis* to increasing concentrations of fluconazole in agar medium resulted in the recovery of derivatives that expressed a stable fluconazole-resistant phenotype (12). It has been suggested that the ability of *C. dubliniensis* to rapidly develop resistance to fluconazole may contribute to its ability to successfully colonize the oral cavities of HIV-infected individuals who are receiving long-term therapy with this compound (12). Furthermore, this may, at least in part, explain the apparent recent emergence of this organism.

Molecular mechanisms of azole resistance in *C. dubliniensis* include increased drug efflux, modifications of the target enzyme and alterations in the ergosterol biosynthetic pathway (13). Its potential to cause deep or disseminated candidiasis is not known, largely because *C. dubliniensis* has rarely been isolated from sterile body sites (14); however, the phenotypic characteristics the organism shares with *C. albicans* (producing germ tubes and chlamydospores) suggest that some *C. dubliniensis* isolates may have been misidentified as *C. albicans*.

### Table 1. Candida species commonly causing Candidiasis.

<table>
<thead>
<tr>
<th>Species</th>
<th>Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Candida albicans</em></td>
<td>50</td>
</tr>
<tr>
<td><em>Candida tropicalis</em></td>
<td>15-30</td>
</tr>
<tr>
<td><em>Candida glabrata</em></td>
<td>15-30</td>
</tr>
<tr>
<td><em>Candida parapsilosis</em></td>
<td>15-30</td>
</tr>
<tr>
<td><em>Candida krusei</em></td>
<td>~2</td>
</tr>
<tr>
<td><em>Candida lusitaniae</em></td>
<td>~1</td>
</tr>
<tr>
<td><em>Candida dubliniensis</em></td>
<td>~1</td>
</tr>
<tr>
<td><em>Candida kefyr</em></td>
<td>~1</td>
</tr>
</tbody>
</table>

### Table 2. Susceptibility of Candida species to antifungal drugs.

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Fluconazole</th>
<th>Itraconazole</th>
<th>Voriconazole (not standardized)</th>
<th>Amphotericin B (not standardized)</th>
<th>Caspofungin (not standardized)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>S-DD to R</td>
<td>S-DD to R</td>
<td>S to I</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>R</td>
<td>S-DD to R</td>
<td>S to I</td>
<td>S to I</td>
<td>S</td>
</tr>
<tr>
<td><em>C. lusitaniae</em></td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>S to R</td>
</tr>
</tbody>
</table>

S=Susceptible S-DD= Susceptible dose-dependant I=Intermediate R=Resistant
Table 3. Candida albicans and Candida krusei susceptibilities to various antifungal drugs.

<table>
<thead>
<tr>
<th>Antifungal Agent</th>
<th>C. albicans (n=20)</th>
<th>C. krusei (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC range, µg/mL</td>
<td>MIC&lt;sub&gt;90&lt;/sub&gt;</td>
</tr>
<tr>
<td>Clothinazole</td>
<td>0.006 – 0.50</td>
<td>0.010</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>0.050 – 1.00</td>
<td>0.250</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>0.130 – 8.00</td>
<td>0.130</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.0160 – 0.25</td>
<td>0.016</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>0.006 – 0.13</td>
<td>0.030</td>
</tr>
<tr>
<td>Miconazole</td>
<td>0.010 – 0.13</td>
<td>0.013</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>0.030 – 0.50</td>
<td>0.120</td>
</tr>
</tbody>
</table>

**Note:** C. albicans isolates were recovered from women who experienced recurrent vaginal candidiasis. (Adopted with modification Singh et al., 2002.)

**Candida krusei**

Although *C. albicans* is the predominant etiologic agent of candidiasis, other Candida species that tend to be less susceptible to the commonly used antifungal drugs, such as *C. krusei*, *C. glabrata*, *C. lusitaniae*, and the newest Candida species, *C. dubliensis*, have emerged as substantial opportunistic pathogens.

*Candida krusei* is an opportunistic pathogen commonly implicated in urinary tract infections in immunocompromised patients and has emerged as a true, albeit uncommon, cause of fungal vaginitis (15, 16). Infections with *Candida krusei* have increased in recent years as a consequence of its intrinsic resistance to fluconazole, an antifungal azole widely used in immunocompromised individuals to suppress infections due to azole-susceptible *C. albicans*.

Since cultures are rarely performed, there is limited data regarding the antifungal susceptibility of yeast causing vulvovaginal candidiasis. In a study by Singh et al., susceptibility testing was performed on vaginal yeast isolates from 593 patients with suspected vulvovaginal candidiasis. The results demonstrated the following infectious hierarchy: *Candida albicans* (n = 420), *Candida glabrata* (n = 112), *Candida parapsilosis* (n = 30), *Candida krusei* (n = 12), *Saccharomyces cerevisiae* (n = 9), *Candida tropicalis* (n = 8), *Candida lusitaniae* (n = 1) and *Trichosporon sp.* (n = 1). Among the different species, elevated fluconazole MICs (> or = 16 microg/ml) were only observed in *C. glabrata* (15.2% resistant [R], 51.8% susceptible-dose dependent [S-DD]), *C. parapsilosis* (3.3% S-DD), *S. cerevisiae* (11.1% S-DD) and *C. krusei* (50% S-DD, 41.7% R, considered intrinsically fluconazole resistant). Resistance to itraconazole was observed among *C. glabrata* (74.1%), *C. krusei* (58.3%), *S. cerevisiae* (55.6%) and *C. parapsilosis* (3.4%). Among 84 patients with recurrent episodes, non-albicans species were detected more frequently (42% versus 20%) and treatment is further complicated by the fact that azole agents are less effective against these species (17).

*C. krusei* is predominately seen as a cause of vaginitis in comparatively older women. A possible pathophysiological explanation for the selection of *C. krusei* is that the older population may have been exposed to repeated episodes of vulvovaginal candidiasis and thus had been exposed to many courses of a wide array of antifungal therapy. The repeated exposure toazole-based antifungals, including topical agents, may cause a shift in the vaginal mycoflora from the more drug-susceptible *C. albicans* to the less drug-susceptible Candida species, such as *C. krusei* (18, 2).

In patients with chronic and recurrent fungal vaginitis, it should never be assumed that the yeast species responsible is invariably *C. albicans*. Signs and symptoms of vaginitis due to *C. krusei* appear to be indistinguishable from those of vaginitis due to other Candida species, an observation that emphasizes the need to obtain subspeciation of Candida prior to the initiation of antifungal therapy.

Prolonged, not abbreviated, therapy with either topical boric acid or topical clotrimazole or oral therapy with either ketoconazole or itraconazole should be considered as the first line therapy for patients with *C. krusei* vaginitis. Therapy with all active antifungal agents should also be prolonged (duration, usually 2 to 6 weeks), regardless of the agent used (16) (Table 3).

**Candida lusitaniae**

Among the non-*C. albicans* species, *Candida lusitaniae* is of special interest owing to its uncommon susceptibility pattern (19, 20, 21). Rapidly acquired resistance to amphotericin B has been described or suspected, and some strains of *C. lusitaniae* may be intrinsically resistant (22, 23); therefore, the detection of amphotericin B resistance is essential for treatment of *C. lusitaniae*-associated infections (24).

The yeast *Candida lusitaniae* was first described by van Uden and by Carmo-Sousa as a common organism in the gastrointestinal tracts of warm-blooded animals (25). *C. lusitaniae* was found as a part of the mycoflora of the upper-respiratory, gastrointestinal and urinary tracts of hospitalized patients. This yeast species was recovered from both the skin and vagina of only one patient. Although an infrequent isolate overall (0.64% of 9,105 yeast isolates) (26), lately it has been recovered from a variety of clinical specimens including urinary tract infection and from vaginal candidiasis patients (27, 28).

In a study by Favel et al., the antifungal susceptibility of thirty-five *Candida lusitaniae* isolates was determined in vitro by the National Committee for Clinical Laboratory Standards (NCCLS) M27-P macrodilution methodology. All the isolates were susceptible to ketoconazole, itraconazole and fluconazole. Of the thirty-five isolates, eight (23%) were resistant to flucytosine. For amphotericin B, M27-P yielded a narrow range of MICs (0.06-0.5 mg/L) (Table 4) (30).
Table 4. Antifungal susceptibility of C. lusitaniae (Adopted with modification from Favel et al., 1997 [29])

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>MIC&lt;sub:min&lt;/sub&gt; (µg/L)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B</td>
<td>0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>0.06</td>
<td>&gt;=64</td>
</tr>
<tr>
<td>Econazole</td>
<td>0.12</td>
<td>0.12</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>0.03</td>
<td>0.06</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>0.12</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Amphotericin B is the drug of choice for many systemic fungal infections (30). Amphotericin B susceptibility testing was recently performed and reported on 4,936 isolates of Candida spp. by the Etest methodology (31) (Table 5).

Table 5. Comparative amphotericin B susceptibility testing results for 4,935 isolates of Candida spp. (Adopted and modified from Pfaller MA, et al., 2004).

<table>
<thead>
<tr>
<th>Species (no. of isolates)</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/L)</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans (2,728)</td>
<td>0.5</td>
<td>0.5</td>
</tr>
<tr>
<td>C. glabrata (722)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C. parapsilosis (666)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C. tropicalis (528)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>C. krusei (143)</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>C. lusitaniae (54)</td>
<td>0.25</td>
<td>1</td>
</tr>
<tr>
<td>Candida spp. (95)</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>All Candida (4,936)</td>
<td>0.5</td>
<td>2</td>
</tr>
</tbody>
</table>

<sup>a</sup> 50% and 90%, MICs at which 50 and 90% of isolates tested, respectively, are inhibited.

<sup>b</sup> Includes C. guilliermondii (39 isolates), C. pelliculosa (17 isolates), C. kefyr (15 isolates), C. rugosa (11 isolates), C. dubliniensis (5 isolates), C. zeylanoides (4 isolates), C. lipolytica (3 isolates), and C. famata (1 isolate).

Table 6. Geographical distribution of infectious Candida species. Adapted with modification from Pfaller, MA et al., 2006 [39]

<table>
<thead>
<tr>
<th>Candida species</th>
<th>Asia (518)</th>
<th>Latin Amer. (548)</th>
<th>Europe (847)</th>
<th>Canada (156)</th>
<th>U.S. (587)</th>
<th>Total (2655)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>60.2</td>
<td>48.9</td>
<td>63.5</td>
<td>64.1</td>
<td>44</td>
<td>55.6</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>7.3</td>
<td>4.2</td>
<td>11.8</td>
<td>21.8</td>
<td>27.4</td>
<td>13.4</td>
</tr>
<tr>
<td>C. kefyr</td>
<td>0.2</td>
<td>0.4</td>
<td>1.3</td>
<td>0</td>
<td>0.5</td>
<td>0.6</td>
</tr>
<tr>
<td>C. krusei</td>
<td>0.8</td>
<td>1.8</td>
<td>4.1</td>
<td>1.3</td>
<td>2.0</td>
<td>2.4</td>
</tr>
<tr>
<td>C. lusitaniae</td>
<td>1.0</td>
<td>0.5</td>
<td>0.4</td>
<td>0.6</td>
<td>2.0</td>
<td>0.9</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>16.2</td>
<td>19.7</td>
<td>10.6</td>
<td>9.0</td>
<td>14.8</td>
<td>14.4</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>12.5</td>
<td>16.4</td>
<td>7.6</td>
<td>2.6</td>
<td>7.8</td>
<td>10.1</td>
</tr>
</tbody>
</table>

Table 7. Susceptibility of Candida kefyr to common antifungal agents. Compiled with modification from Pfaller, MA et al., 2006 and Pfaller, MA et al., 2004.

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>No. of isolates</th>
<th>Cumulative % susceptible at MIC (µg / mL) values of:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.007</td>
<td>0.015</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>29</td>
<td>0</td>
</tr>
<tr>
<td>Ravuconazole</td>
<td>&quot;</td>
<td>100</td>
</tr>
<tr>
<td>Flucytosine</td>
<td>&quot;</td>
<td>31</td>
</tr>
<tr>
<td>Micafungin</td>
<td>17</td>
<td>0</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>&quot;</td>
<td>12</td>
</tr>
</tbody>
</table>

Candida utilis

This organism adds to the growing list of Candida species associated with human disease. *Candida utilis* was cultered from the blood of a patient with acquired immunodeficiency syndrome. The candidemia was apparently associated with catheter implantation. A report by Hazen KC, et al. describes the first demonstration and isolation of the industrially important yeast *C. utilis* from a urinary tract infection. In this present case, the organism was associated with chronic, symptomatic disease (32). In addition, *C. utilis* was also associated with fungal keratitis. The clinical features exhibited typical feather-like infiltration at the ulceration margin in this case. After treatment with topical fluconazole and amphotericin-B, the ulceration healed within 3 weeks (33).

Candida kefyr

Identified in 1931 and originally classified as *Endomyces pseudotropicalis*, *Candida kefyr* was considered a rarely isolated species that occasionally caused disease within immunocompromised individuals (34). Since then the organism has been reclassified several times and, most recently, has been deemed an emerging pathogen (35). Despite the limited literature documentation on *C. kefyr*, eight clinical studies and two case reports have established this organism’s ability to cause disease in humans (35). Though still a relatively rare cause of Candidiasis and fungemia, *Candida kefyr* has been isolated from a variety of body regions, including blood, urine, the esophagus and the cervical-vaginal tract in populations other than the immunocompromised (36,37). Geographical distribution studies of clinically relevant Candida strains demonstrates a relatively low prevalence rate within the United States (~0.5%) with higher rates reported within Europe (Table 6). Resistance of *C. kefyr* isolates has been observed in conjunction with amphotericin B therapy (38) and building resistance to common antifungal agents (38,39) (Table 7).
REFERENCES:


