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Candida Infections of Medical Devices

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INTRODUCTION

Ever since Elek and Conen demonstrated in 1957 that the presence of a foreign body significantly reduces the number of bacteria required to produce infection (31), the inherent susceptibility of medical devices to infection has been increasingly appreciated. Modern technology has allowed the use of a wider and newer variety of medical devices. The combination of an increasingly aging population and consistently growing number of inserted devices is likely to escalate the occurrence of infectious complications related to medical devices.

At least half of all cases of nosocomial infections are associated with medical devices (97). The medical consequences of device-related infections can be disastrous; they include potentially life-threatening systemic infections and device malfunction that may require device removal, often complicated by tissue destruction. Management of device-related infections can be difficult and is costly. An increasing proportion of device-related infections, particularly those involving the bloodstream and urinary tract, are being caused by *Candida* spp. (48, 97). A number of published reviews have focused on infections associated with a specific device or a particular bacterial organism. Here, we review *Candida* infections of commonly used medical devices.

The objectives of this comprehensive review are to (i) discuss the formation of *Candida* biofilms around medical devices and compare them to bacterial biofilms and (ii) review, in a systematic fashion, the impact of *Candida* infections on commonly used medical devices.

CANDIDA BIOFILMS

A significant proportion of human infections involve biofilms (88). Microbial biofilms develop when organisms adhere to a surface and produce extracellular polymers that provide a structural matrix and facilitate further adhesion (28). Organisms in biofilms behave differently from freely suspended microbes and have been shown to be relatively refractory to medical therapy (28, 29, 90). Therefore, biofilm-associated infections of retained devices may recur after cessation of antibiotic therapy and hence may necessitate device removal. The formation of bacterial biofilms around devices has been comprehensively investigated (97), but until recently, less focus has been placed on the formation of fungal biofilms. *Candida* species are emerging as important nosocomial pathogens, and an implanted device with a detectable biofilm is frequently associated with these infections (30). The evidence linking *Candida* biofilms to device-related infections is growing as more standardized methods for evaluating *Candida* biofilms in vitro emerge. Here, we review the role of biofilm production in the pathogenicity of *Candida*-related device infection and the antifungal drug susceptibility of *Candida* biofilms.

Formation and Structure

Fungal biofilm formation is a complex and diverse phenomenon. *Candida albicans* biofilm formation has been studied

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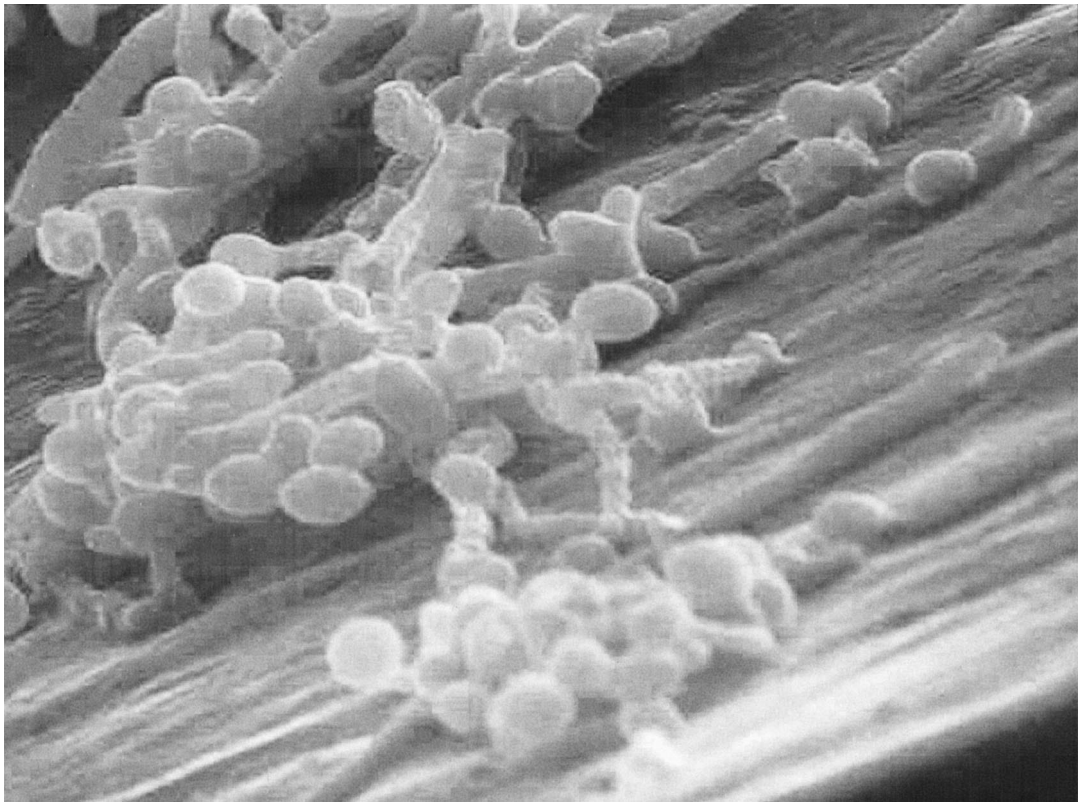

FIG. 1. Scanning electron micrograph of a *C. albicans* biofilm that has formed in vitro on the surface of a vascular catheter. Reprinted from reference 61a.

more extensively than biofilms of other *Candida* species. *C. albicans* biofilm formation has three developmental phases: adherence of yeast cells to the device surface (early phase), formation of a matrix with dimorphic switching from yeast to hyphal forms (intermediate phase), and increase in the matrix material taking on a three-dimensional architecture (maturation phase) (19, 43). Fully mature *Candida* biofilms have a mixture of morphological forms and consist of a dense network of yeasts, hyphae, and pseudohyphae in a matrix of polysaccharides (19), carbohydrate, protein, and unknown components (Fig. 1). The formation and structure of *Candida* biofilms is influenced by the nature of the contact surface, environmental factors, *Candida* morphogenesis, and the *Candida* species involved. These factors are discussed in detail the following paragraphs.

(i) The chemical nature of the contact surface has been shown to influence the magnitude of biofilm formation (43), which is increased on latex compared with polyvinyl chloride but substantially decreased on polyurethane and 100% silicone (43). The architecture of *C. albicans* biofilm is different when it is formed on cellulose filters from when it is formed on catheter disks (7), indicating that it may depend on highly specific contact-induced gene expression (30).

(ii) High-glucose medium promotes the formation of biofilms (43), particularly of *C. parapsilosis*, reflecting its potential to cause device-related infections in patients receiving parenteral nutrition (103). Cell surface hydrophobicity correlates positively with *Candida* biofilm formation (62), and gentle shaking (42) also enhances biofilm formation. These conditions are also encountered in vivo (like in the circulation and urinary system), favoring biofilm formation when devices are inserted.

(iii) The different morphological forms are important in biofilm formation, as evidenced by a study that compared biofilms formed by wild-type strains of *C. albicans* and two mutants incapable of yeast and hyphal growth, respectively. The wild-type mutant produced a distinct two-layer biofilm as described above, the hypha-negative mutant produced only the basal layer, and the yeast-negative mutant produced only the outer layer, which was more easily detached from the catheter disks. This suggests that dimorphism might be necessary for biofilm architecture and structure (7) and is a pivotal factor for the pathogenic potential of *C. albicans*.

(iv) Most *Candida* spp. have been shown to produce biofilm in vitro to various degrees. An in vitro study showed that *C. parapsilosis*, *C. pseudotropicalis*, and *C. glabrata* produced significantly less biofilm on polyvinyl chloride disks than did the more pathogenic *C. albicans*, as determined by dry-weight, colorimetric, or radioisotope assays (43). Another study confirmed this finding (56) when measured by dry weight and also found that, on microscopy, *C. albicans* biofilms had a more complex morphology than *C. parapsilosis* biofilms, which were composed only of clumped blastospores. The interstrain variability in biofilm production differs between *Candida* spp., but studies have been inconsistent. Some studies have shown little variability in biofilm production in vitro between *C. albicans*

isolates from active infections (invasive isolates) and carrier sites (noninvasive isolates) (43, 62, 103), whereas others have found that invasive *C. albicans* isolates have an increased ability to form biofilms compared with noninvasive isolates when measured by dry weight but not by biochemical assay (56). Additionally, a study that examined the variation of biofilm formation in 115 *C. albicans* strains from three different sources (the oral cavity, the vagina, and the environment) found significant differences in biofilm formation within clones and clonal lineages of *C. albicans* from each source but not between the three different sources by biochemical assay and absorbance following staining (62). This underscores the importance of methodology in evaluating biofilms as well as the importance of fact that *Candida* exhibits wide phenotypic diversity, which may correlate with pathogenicity.

Antifungal Drug Susceptibility

Organisms in biofilms behave differently from freely suspended cells with respect to antimicrobial resistance (29). Both bacteria and *Candida* cells within biofilms are markedly resistant to antimicrobial agents. *C. albicans* in biofilms on polyvinyl chloride disks has been reported to be 30 to 2,000 times more resistant to fluconazole, amphotericin B, flucytosine, itraconazole, and ketoconazole than planktonic cells (44), and the biofilm structure remained intact at an amphotericin B concentration of 11 times the MIC. Non-*albicans Candida* species were also resistant. In vitro, the newer triazoles were also found to be ineffective against *C. albicans* and *C. parapsilosis* biofilms (57); however, caspofungin has been shown to be effective against *C. albicans* biofilms (91). Glucan synthesis may thus prove to be an effective target for biofilms. Suggested mechanisms of biofilm resistance include restricted penetration of drugs through the matrix, slow growth of organisms in biofilms accompanied by changes in cell surface composition affecting their susceptibility to drugs, and unique biofilm-associated patterns of gene expression (30, 58).

In summary, *Candida* spp. produce biofilms on medical devices to various degrees and the difference in biofilm production and architecture by *Candida* spp. on different device materials is reflected in the different epidemiological trends in *Candida* device-related infections. In vitro, *Candida* biofilms are highly resistant to most antifungal agents except caspofungin, thereby posing a therapeutic challenge in managing device-associated *Candida* infections.

CLINICAL FACTORS RELATED TO THE PATHOGENESIS OF *CANDIDA* INFECTIONS

Candida organisms are commensals, and to act as pathogens, interruption of normal host defenses is necessary. Therefore, general risk factors for *Candida* infections include immunocompromised states, diabetes mellitus, and iatrogenic factors like antibiotic use, indwelling devices, intravenous drug use, and hyperalimentation fluids. There are several specific risk factors for particular non-*albicans* species: *C. parapsilosis* is related to foreign-body insertion, neonates, and hyperalimentation; *C. krusei* is related to azole prophylaxis and, along with *C. tropicalis*, to neutropenia and bone marrow transplantation; *C. glabrata* is related to azole prophylaxis, surgery, and urinary or vascular catheters; and *C. lusitaniae* is related to previous polyene use (55).

The source of *Candida* infections has been the subject of considerable debate. An endogenous source has been shown by using DNA typing of paired *Candida* samples from colonized sites and subsequent bloodstream infection in patients with hematological abnormalities (93) and in nonneutropenic patients (116). A recent review of published studies on potential sources of candidemia found support for a gastrointestinal origin of candidemia based on experimental, clinical, and molecular similarity studies (84). However, a cutaneous origin is suggested for *C. parapsilosis* since it is frequently recovered from skin samples and since it occurs more frequently in patients with venous catheters in place. Furthermore, the skin may be the origin of candidemia in patients with burns. The authors note that the data used to support skin as the source of candidemia are rather incomplete. The gastrointestinal tract is the primary source of candidemia in neutropenic patients, probably due to the gastrointestinal mucositis and subsequent gut invasion by *Candida* in this patient population.

IMPACT OF *CANDIDA* INFECTIONS OF MEDICAL DEVICES

Table 1 summarizes the annual use of commonly used medical devices, the overall rate of infection, the proportion and mortality of infections due to *Candida*, and the device-specific risk factors predisposing to *Candida* infections. Additionally, it lists the most common *Candida* species and whether removal of the device is generally needed for cure. Additional risk factors that have been associated with specific devices are also summarized.

CENTRAL VENOUS CATHETERS

Over 5 million central venous catheters (CVC) are inserted annually in the United States, accounting for 0.28 to 0.8 central-line days/patient-day (24, 79a). It is estimated that 2 to 12% of CVCs result in sepsis (109). Analysis of the National Nosocomial Infections Surveillance (NNIS) data shows that 87% of primary bloodstream infections occurred in patients with a central line. In U.S. intensive care units (ICUs), approximately 80,000 catheter-related bloodstream infections occur each year and result in up to 20,000 deaths (68). The impact and cost of such infections is thus enormous. Before 1992, there was a steady increase in the incidence of candidemia in combined medical-surgical ICUs (79a), but the contribution of *Candida* to bloodstream infections stabilized between 1992 and 1998 at about 11.5% (96). A total of 72 to 87% of bloodstream infections, including candidemia, are considered to be catheter related in ICU patients (94, 96). The role of catheters in neutropenic patients is less clear than that in ICU patients because gastrointestinal mucositis is a probable source of candidemia in these patients. Candidemia is an independent risk determinant for predicting death in patients with nosocomial bloodstream infections (70).

The crude mortality due to candidemia has been estimated to be as high as 57%, but the attributable mortality is reported to be 38% (118). The attributable mortality of candidemia was correlated, in a multivariate logistic analysis, with the

TABLE 1. Impact of *Candida* infections of medical devices

Device	Annual use in the United States	Overall rate of infection (%)	Proportion of infections due to *Candida* (%)	Mortality due to *Candida* infections (%)	Risk factors for infection in general	Risk factors for *Candida* infections	Most common *Candida* species	Removal needed to achieve cure
Vascular catheters	5×10^6 (24)	3–8 (24)	10 (94, 96)	26–38 (118)	Neutropenia for >8 days; Hematologic malignancy; total parenteral nutrition; duration of site use; frequent manipulation of catheter; improper insertion and maintenance of catheter; high APACHE II score (89, 109)	*C. parapsilosis* in blood; positive quantitative or differential time to positivity of cultures; candidemia without other source; Hyperalimentation; persistent candidemia on antifungal drugs	*C. albicans*, *C. glabrata* (32, 96)	Yes, in most cases[b]
Joint prostheses	6×10^5 (24)	1–3 (108)	<1	NK[a]	Prior surgery; rheumatoid arthritis; immunocompromise; diabetes mellitus; poor nutrition; obesity; psoriasis; advanced age (13)	NK	*C. albicans*, *C. parapsilosis* (25)	Yes
Dialysis access								
Hemodialysis fistulas	2.4×10^5 (patients treated) (24)	1–4 (20, 61)	≪1	25–50 (83)	PTFE grafts; number of graft revisions; nursing home residents; poor hygiene; bacterial infection at a distant site; hospitalization; duration of graft use; femoral site; diabetes mellitus; *S. aureus* nasal carriage (5, 61, 71)	NK	*C. albicans*	Yes (83)
Hemodialysis grafts		10–35 (5, 20, 61)	≪1 (5)	25–50 (83)		NK	*C. albicans*	Yes
Peritoneal dialysis catheters		23 (61)	2.4–7 (39, 61, 69, 114, 117)	5–25 (69, 117)		Prior hospitalization; recent bacterial peritonitis; gastrointestinal diseases; prior antibiotics; lupus (39, 71)	*C. albicans*, *C. parapsilosis* (69)	Yes (39, 54)
Cardiac devices								
Prosthetic valves	8.5×10^4 (24)	2.9 (66)	2–10 (45, 66)	33[g] (112)	Native valve endocarditis; black race; mechanic prosthesis (versus bioprosthesis); male sex; longer cardiopulmonary bypass time; receipt of multiple valves (16, 45)	Intravenous catheters; intravenous drug use; prosthetic valve recipients; fungemia; immunosuppression; total parenteral nutrition; prior bacterial endocarditis; prolonged antibiotic use (8, 66, 78)	*C. albicans*, *C. glabrata* plus *C. parapsilosis* (66)	Yes (80, 122)

Pacemakers	4×10^5 (24)[f]	0.5–7.0 (36, 50, 120)	4.5 (6, 50, 120)	NK	Malnutrition; malignancy; diabetes mellitus; skin disorders; steroid or anticoagulant use (50)	NK	*C. glabrata*, *C. albicans*	Yes[c] (11, 52)
ICDs		2.2–7.2 (60)	<1	NK	Median sternotomy; longer duration of surgery; generator replacement; depressed immunity; diabetes mellitus; advanced age; another nidus of infection (107)	NK	*C. albicans*	Yes[c] (60)
VADs	700 (24)	28–66 (77)	25–39 (38)	100 (patients with other complications affecting mortality)	Postoperative bleeding necessitating reoperation; chronic underlying disease; receipt of broad-spectrum antibiotics; presence of indwelling tubes (77)	NK, but possibly same as for fungal infections in ICUs (38)	*C. albicans*, *C. tropicalis* (40)	Yes[d] (38)
Central nervous system devices								
VPSs	4×10^4 (24)	6–15 (73, 99)	1 (99)	9–30 (99)	Yong age; other risk factors not well documented (74)	Broad-spectrum antibiotics; prior or concurrent bacterial meningitis; cerebrospinal fluid leakage; bowel perforation; abdominal surgery; steroids; indwelling catheters (35, 73, 82, 99)	*albicans tropicalis* (35)	Yes[e] (76, 99, 104)
Urinary catheters	3×10^7 (24)	10–30 (24)	21 (97)	19.8–39 (46, 53, 105)	Duration of catheterization; lack of drainage; microbial colonization of the drainage bag; diabetes mellitus; absence of antibiotic use; female sex; abnormal serum creatinine level; errors in catheter care (87)	Diabetes mellitus; urinary tract infection; malignancy; antibiotic use; female sex; ICU patient (41, 53)	*C. albicans*, *C. glabrata* (97, 105)	Yes[f]
Penile implants	1.5×10^4–2×10^4 (24)	1–9 (17, 47)	5–9.2 (75)	NK	Urinary tract infection; Spinal cord injury; Insertion of an inflatable device; Neurogenic bladder; Diabetes mellitus; reimplantation; revisions (18, 47)	NK	*C. albicans*	Yes[c]

[a] NK, not known.
[b] Catheter removal may not be necessary in neutropenic patients in whom the infecting fungal organisms originate primarily from the gastrointestinal tract (see the text).
[c] Based on case reports.
[d] Little evidence in the literature to guid treatment.
[e] Not well documented in the literature.
[f] If symptomatic.
[g] Mortality with combined antifungal and surgical therapy.
[f] Includes both pacemakers and ICDs.

APACHE II score, the duration of candidemia, and rapidly fatal underlying illnesses (29% of study patients were neutropenic) (32). Other predictors of adverse outcome included evidence of neutropenia and visceral dissemination (4). In general, the likelihood of developing CVC-related infections depends on the type of catheter, the hospital service, the site of insertion, and the duration of catheter placement (68). Risk factors for CVC-related-infections include neutropenia for >8 days, hematologic malignancy, total parenteral nutrition, duration of site use, frequent manipulation of the catheter, improper insertion and maintenance of the catheter, and high APACHE II score (89, 109).

Candidemia most frequently occurs in immunocompromised patients with underlying malignancy, hematologic disorder, gastrointestinal disease, burns, or critical illness (119). Independent risk factors for candidemia include *Candida* isolated from other sites than blood, hemodialysis, prior insertion of a Hickman catheter, and previous exposure to antibiotics (118, 119). One study, however, found that neutrophil count rather than underlying disease was the most important risk factor (3). Catheter-related infection should be suspected in the presence of the following findings: growth of *C. parapsilosis* from blood cultures, positive quantitative or differential time to positivity of central versus peripheral blood cultures, receipt of hyperalimentation through the catheter, lack of other potential sources of *Candida* infection, and persistent candidemia despite appropriate systemic antifungal therapy.

Diagnosis of CVC-related infections can be difficult because the clinical findings for both fungal and bacterial infections are often unreliable. Laboratory methods include semiquantitative (roll plate, the most widely used method) and quantitative (vortex or sonication method) methods for culturing the catheter. The quantitative culturing method retrieves organisms from both the external and internal surfaces of the catheter, whereas the semiquantitative method retrieves organisms from only the external surface. Although the quantitative culturing method can be 20% more sensitive than the semiquantitative method, it is more time-consuming. Other diagnostic approaches include paired blood cultures, with one drawn from the CVC and the other obtained percutaneously. When using quantitative blood cultures, the growth of 5- to 10-fold-greater colony counts from blood samples obtained via the CVC than from peripherally drawn blood samples can accurately relate the episode of bloodstream infection to the indwelling catheter (68), particularly a tunneled catheter. The differential time to positivity constitutes another potentially helpful method for associating a bout of bloodstream infection with an indwelling catheter, if cultures of blood obtained through a CVC become positive at least 2 h earlier than cultures of peripherally obtained blood, the infection is concluded to be associated with the catheter.

C. albicans accounts for up to 63% of all cases of candidemias (32, 96), followed by *C. glabrata* or, in some hospitals, *C. tropicalis* (32). However, in recent years, non-*albicans* species have been isolated more frequently (23, 81). For instance, one prospective study of 427 patients with candidemia (81) found that non-*albicans* species accounted for 48% of all cases of candidemia, a disturbing fact since the non-*albicans* spp. can be associated with higher mortality and complication rates than *C. albicans*, including breakthrough candidemia during antifungal therapy (32, 81). A similar shift in *Candida* epidemiology was also reported in a study of 474 patients with malignancies (3), presumably due to antifungal prophylaxis use.

Whereas the prevention of CVC-related infections by using an antimicrobial coating has been shown to be beneficial in preventing bacterial infections (26, 67), this approach has not been specifically studied for preventing fungal infections of CVCs. Optimal treatment of CVC-related infections depends on the kind of catheter used (tunneled versus nontunneled), the severity of illness, and the type of causative organism. For instance, coagulase-negative staphylococcal infections of nontunneled catheters may be cured without catheter removal. Such patients are usually treated with intravenous antibiotics, often in combination with antibiotic lock therapy, which involves exposing the catheter lumen to pharmacological concentrations of antibiotics for hours or even days. The potential ability of this therapeutic approach to increase the likelihood of catheter salvage has been reported only in a noncomparative fashion. This antibiotic lock technique, however, has not been studied for the treatment of documented CVC-related candidemia. Recently published guidelines by the Infectious Disease Society of America recommended treatment of both complicated and uncomplicated *Candida* infections of tunneled and nontunneled CVCs by catheter removal in addition to systemic antifungal therapy, generally for 14 days after the last positive blood culture (95). However, catheter removal may not be necessary for cure of candidemia in neutropenic patients in whom the infecting fungal organisms originate primarily from the gastrointestinal tract (85). A review of published data on the effect of CVC removal on the outcome of patients with candidemia found that studies were somewhat conflicting, and the authors of that review suggested that removal of infected CVCs may not have an impact on the outcome in neutropenic patients (85).

JOINT PROSTHESES

In modern medicine, the most commonly implanted joint prostheses are hip and knee prostheses. The incidence of infection is low, 1% in primary cases and up to 3% in secondary procedures (108). *Candida* accounts for less than 1% of all cases of infections of joint prostheses. Nevertheless, the magnitude of this infectious complication is quite remarkable, considering that in 1995 about 216,000 total knee replacements were performed, and this number is expected to more than double by the year 2030 (108). This increase in the number of implanted joint prostheses is stimulated by the growing size of the patient population, particularly of older persons, who are most likely to require the implantation and revision of joint prostheses (108). *Candida* infections of prosthetic joints mostly involves hip and knee prostheses, with only a case report involving other joint prostheses (63). Implantation of knee and hip prostheses carries a higher risk for infection than smaller joint prostheses due to the longer duration of these operations, the inherently low blood flow to cortical bone, and the formation of a hematoma in a larger dead space around such larger devices. These hematomas can devascularize the surrounding tissue and prevent the entry of antibiotics (108). In general, the mean cost of management of an episode of joint infection is

estimated to exceed $50,000. The cost is probably even higher for *Candida* infection because of frequent delays in diagnosis and more prolonged treatment of this fungal infection compared with bacterial infection. The mortality due to prosthetic joint infections is low (24); mortality due to *Candida* infections is not known in this setting.

Risk factors for infection of prosthetic joints include prior surgery at the site of the prosthesis, rheumatoid arthritis, immunocompromised state, diabetes mellitus, poor nutritional status, obesity, psoriasis, and advanced age (13). A large case-control study of patients at high risk for prosthetic joint infection identified four independent risk factors: surgical site infection, NNIS System surgical patient risk index score of ≥1, history of malignancy, and history of prior total joint arthroplasty (9). In that study (9), rheumatoid arthritis was not found to be an independent risk factor after adjustment for other potentially confounding variables associated with that condition such as steroid therapy, immunologic abnormalities, higher prevalence of revisions, and skin ulcers. Because there are no comprehensive reviews of *Candida* infections of prosthetic joint infections, it is unclear if the above-mentioned risk factors apply. A review of 10 cases of *Candida* prosthetic joint infections concluded that such patients, unlike those with *Candida* infections of natural bone and joints, are not inherently predisposed to *Candida* infections and are less likely to have evidence of extra-articular candidiasis (25).

The clinical presentation of prosthetic joint infections depends on early (<3 months after surgery) versus late (3 months to 2 years after surgery) manifestations (123). Early infections manifest with pain, erythema, edema, wound healing disturbances, and fever, whereas late manifestations include persistent pain and early loosening with or without fever (123). In the review of *Candida* prosthetic joint infections, 2 of 10 patients presented late (25). Although hematogenously disseminated fungi other than *Candida* most often cause fungal infections of natural joints, fungal prosthetic joint infections are usually caused by *Candida* spp., including *C. albicans*, *C. parapsilosis*, and *C. glabrata* (25). *Candida* prosthetic infections can occur up to 4 years after surgery (25, 92).

Because joint infections constitute a relatively rare complication and because confirmation of successful treatment requires a long follow-up (up to 2 years), treatment strategies have not been standardized (37, 108). This is particularly true for *Candida* prosthetic infections, where the relevant medical literature contains only case reports. In general, treatment of *Candida* prosthetic infection consists of both prosthesis removal and systemic antifungal therapy. Few reports (33) have described cure of *Candida* infection without removal of the infected prosthesis. Removal of the implant is associated with large skeletal defects, shortening of the extremity, and severe functional impairment. The impact of the type of causative organism on salvage rates is not clear (51). For bacterial infections, it has been suggested that in a selected group of patients, prosthesis salvage may be achieved with prolonged suppressive treatment (101). So far, this strategy has not been successfully applied to *Candida* infections. Factors that reportedly contribute to failure of therapy for infection of hip prostheses include previous operations, immunocompromised status, early postoperative infection, and retention of bone cement (111).

DIALYSIS ACCESS

The number of persons with a dialysis access continues to rise. In the 1999 United States Renal Data System report (http://www.usrds.org), about 243,000 persons required either hemodialysis or peritoneal dialysis, as compared with 128,000 persons in 1990. Infection is the second most common cause of death in patients with end-stage renal disease. It is the most frequent cause of hospitalizations and is a leading cause of morbidity and mortality in patients requiring dialysis (5, 20). Hemodialysis access can be an arteriovenous prosthetic graft, an arteriovenous fistula, or a catheter. Associated infection rates per patient-day are the lowest with arteriovenous fistulae, followed by grafts, tunneled or cuffed catheters, and nontunneled or noncuffed catheters (39, 61). Bacteria account for the majority of cases of hemodialysis-related infections. Fungal infections of hemodialysis access sites are rare; *Candida* accounts for 2.6 to 7% of peritoneal dialysis-related infections (39, 61, 69, 114). Dialysis patients are more prone to infection than are the general population, both because of the uremia and because of the dialysis itself. This predisposition is multifactorial and is attributed to impairments in lymphocyte and granulocyte function, circulating inhibitors to chemotactic factors, frequent violation of skin and mucosal barriers, baseline hypothermia and iron overload, underlying disorders, low albumin levels, and metabolic acidosis (20, 71). In addition, in patients undergoing peritoneal dialysis the high glucose concentration, the low pH, and the osmolarity of the dialysis solution further affect the ability of the immune system to handle microbes. Risk factors for all infections in patients receiving dialysis include polytetrafluoroethylene (PTFE) grafts, number of graft revisions, residence in a nursing home, poor hygiene, bacterial infection at a distant site, hospitalization, duration of graft use, femoral site, diabetis mellitus, and *S. aureus* nasal carriage (5, 10, 61, 71).

Permanent Hemodialysis

Permanent hemodialysis access is preferable secured with an arteriovenous fistula or, if not feasible, with arteriovenous grafts that are made mostly of PTFE (5). Whereas the overall infection rate of these grafts can be as high as 35%, fungal etiology is extremely rare, with only case reports published in the literature (5). Use of PTFE grafts and a larger number of graft revisions are independently associated with hemoaccess site infections (10). Most patients with *Candida* infection of PTFE grafts received antecedent antibacterial agents (83). The onset of *Candida* infection can be acute or subacute and most commonly manifests with drainage at the fistula site (20, 83). Whereas graft salvage may be successfully accomplished in selected patients with bacterial infections (5), treatment of *Candida* infections usually requires graft removal to achieve long-term cure (83).

Peritoneal dialysis

In 1999, a total of 22,797 persons received peritoneal dialysis. In general, peritoneal dialysis is associated with higher rates of infection than hemodialysis (61) because the hyperosmolar peritoneal dialysis fluid with high glucose and low pH

can act as an irritant, provide a good growth medium for pathogens, and suppress the host response (61). Infection can affect the exit site, the catheter tunnel, and the peritoneal space. We focus our discussion in this section on peritonitis related to the dialysis catheter. The currently used permanent catheters are made of silicone rubber and are affixed with one or two Dacron cuffs to stabilize the catheter (114). In general, infection can be transluminal, periluminal, transmural, hematogenous, or ascending. The diagnosis is made on the basis of the presence of two of the following criteria: symptoms of peritoneal inflammation, cloudy fluid (>100 white blood cells/mm^3), and/or organisms on Gram stain or in culture of the peritoneal dialysis fluid (114).

As many as 23% of peritoneal dialysis catheters become infected. Fungi reportedly cause up to 15% of peritonitis cases, and *Candida* spp. are the most common fungal isolates (54). The incidence of fungal peritonitis over the past decade appears to have stabilized, whereas the incidence of bacterial peritonitis seems to be decreasing (39). This finding is quite interesting given that fungal peritonitis is most often preceded by bacterial peritonitis (54). Recent reports indicate that about 2.6 to 7% of patients undergoing peritoneal dialysis develop *Candida* peritonitis. Non-*albicans Candida* spp. account for up to two-thirds of *Candida* isolates (39, 69, 117). In these reports, *C. parapsillosis* seems to be the most prevalent non-*albicans* sp. This infectious complication is associated with a high mortality (5 to 25 %) and morbidity, including prolonged hospital stay and recourse to hemodialysis (69, 117).

Risk factors for fungal peritonitis include prior hospitalization, recent episodes of bacterial peritonitis, gastrointestinal disease, and treatment with antibiotics (39, 69, 114). There is often a diagnostic delay in diagnosing fungal peritonitis, and failure to respond to treatment with antibacterial agents can be a helpful clue. Treatment of fungal peritonitis can be difficult due to poor penetration of older antifungal agents into the peritoneal cavity and their irritant nature (54). The role of newer antifungal agents for treatment of fungal peritonitis has not been thoroughly investigated. Although there is no real consensus on the choice and duration of systemic antifungal therapy for fungal peritonitis, most authors agree that catheter removal is usually needed to achieve cure (39, 54, 69).

CARDIOVASCULAR DEVICES

Heart Valves

Prosthetic valve endocarditis (PVE) is an infrequent but serious complication of cardiac valvular replacement, with a reported rate of 2.9 to 4.4% (15, 66). The incidence changes over time, and the actuarial risk has been estimated at 3.1% at 1 year and increases to 5.7% at 5 years (16). Fungi are responsible for 2 to 10% of all cases of PVE, and *Candida* accounts for up to 90% of these fungal infections (45, 66). Patients with prosthetic heart valves who develop nosocomial candidemia have a notable risk of developing *Candida* PVE, often months or years later (up to 690 days later). In a review of 44 cases of candidemia in patients with prosthetic heart valves, *Candida* PVE developed in 25% of such patients (78).

Fungal PVE is associated with a higher mortality rate than bacterial PVE. A review (112) of fungal endocarditis concluded that untreated fungal PVE was uniformly fatal, antifungal agents alone or surgery alone reduced the mortality rate to 82%, whereas combined surgery and antifungal therapy decreased the mortality rate to 33%. Others (66) found a 33% overall mortality rate due to fungal PVE with a mean follow-up of 4.5 years. Patients with complicated PVE (congestive heart failure or persistent fungemia) had higher mortality rates regardless of the mode of therapy (80). Surprisingly, one study reported that patients with *Candida* PVE had a better survival than those with candidemia alone (mortality rates of 25 and 83%, respectively, at 1 year) (78).

Risk factors for PVE generally include receipt of multiple heart valves (16), male gender, prolonged cardiopulmonary bypass time, antecedent native valve endocarditis, mechanic prosthetic valve (as opposed to bioprosthetic valve), and black race (45). Mechanical prostheses seem to be associated with a higher risk of early PVE; however, one study found that porcine valve recipients have a higher risk of late PVE (16). There seems to be a discrepancy between studies regarding the difference in incidence of infection of aortic versus mitral prostheses. Specific risk factors for fungal PVE include the presence of intravascular catheters, prior bacterial endocarditis, prolonged (more than 4 weeks) antibiotic treatment, total parenteral nutrition, intravenous drug use, disseminated fungal infection, prosthetic valve recipient, and immunosuppression (8, 66).

Diagnosis of fungal PVE can be challenging because up to one-third of patients may not have any of the classic signs of endocarditis (100). Making a correct diagnosis carries therapeutic implications because fungal PVE usually requires surgical intervention whereas fungemia without PVE may be treated with antifungal agents alone (78). Fungal PVE should be suspected in the presence of negative bacterial blood cultures, bulky vegetations, metastatic infection, perivalvular invasion, embolization to large blood vessels, and disseminated fungal infection (66, 80, 100). *C. albicans* is the most common pathogen, accounting for 56 to 66% of all cases of *Candida* PVE. Less common causes include *C. glabrata* and *C. parapsilosis* (66, 78).

Combined medical-surgical therapy is the current standard of therapy of fungal PVE (80, 122). Although one study reported that the mortality in patients with uncomplicated PVE was rather similar in those who received medical therapy alone and in those who underwent combined medical-surgical therapy (40 and 33%, respectively) (80), the authors of that study concluded that medical therapy alone should be considered only for patients for whom surgery is regarded as unduly hazardous.

Pacemakers

It has been estimated that about 400,000 implantable electrophysiologic cardiac devices are placed annually in the United States (24). Infectious complications involving pacemakers have decreased in frequency as a result of improvements in surgical techniques and device technology, but they remain in the range of 0.5 to 7% (36, 50, 120). *Candida* spp. account for up to 4.5% of these infections (6, 49, 120). One study of more than 8,000 procedures noted pacemaker infections in 5.6% and endocarditis in 0.5% of patients, using care-

ful definitions (6). *Candida* pacemaker infections have been described mostly in case reports or as single cases in series (14, 49, 59, 98, 115, 120), and so the mortality due to these infections is not well assessed. Risk factors for pacemaker infections include malnutrition, malignancy, diabetes mellitus, skin disorders, and steroid or anticoagulant use (52). Specific risk factors for *Candida* pacemaker infections have not been identified. The reported cases have been caused by *C. glabrata*, *C. albicans*, and, less frequently, *C. tropicalis*.

Pacemaker infections can be categorized into two groups: (i) Infections of the pulse generator pocket and/or the subcutaneous portion of the lead (pocket infections), and (ii) infections of the transvenous intravascular electrode component (pacemaker-related endocarditis). Pacemaker pocket infections occur either within a month of the pacemaker placement or later as a consequence of the device eroding through the skin (36, 52). These infections are mostly caused by skin organisms; *C. albicans* has been implicated in a single case report (22). Early infections usually present with local erythema, pain, wound breakdown, and drainage (21, 52). Fever is often absent. In one series of 87 pacemaker pocket infections, fever was documented in only 19% of the patients (21). The optimal management is under debate in the literature. In general, complete device removal and antimicrobial therapy has been most successful (11, 21), although lead-preserving procedures have been shown to be successful in certain cases (121). Conservative treatment should be limited to patients presenting with skin erosions or low-grade pocket infection (11). In the single report of *C. albicans* pacemaker pocket infection, cure required both device removal and antifungal therapy (22).

Pacemaker-related endocarditis represents about 10% of pacemaker infections (49) and most commonly arises from infection of the subcutaneous portion that has tracked intravascularly, seeding the intracardiac electrode. Therefore, pacemaker endocarditis and early PVE have similar microbiological profiles (49). Most infections are caused by *Staphylococcus* spp. By 1997, only six cases of pacemaker endocarditis due to *Candida* had been reported (49). Since then, we have found five additional cases: one due to *C. albicans* in a polymicrobial infection (14), one due to *C. glabrata* and *C. albicans* (98), two caused by *C. glabrata* (one of these patients had polymicrobial infection) (115, 120), and one caused by *C. tropicalis* (59). A review of published cases of *Candida* pacemaker endocarditis revealed a delay between pacemaker placement and diagnosis from <2 months to 8 years (49). Most patients with *Candida* pacemaker-related endocarditis presented with fever; other symptoms included lethargy, chills, and dyspnea. As with pocket infection, there generally appears to be an advantage for combining surgical and medical treatment of pacemaker-related endocarditis over using medical treatment alone (11, 52). Total removal of the pacemaker system is the most reliable way of eradicating pacemaker-related infection (11). Reports of success with conservative management alone have been based on small numbers of patients (52). The literature does not specify whether the nature of the pathogen affects the need for surgery, and so it is likely that the same surgical recommendations apply to bacterial and candidal pacemaker infections.

Implantable Cardioverter Defibrillators

The use of implantable cardioverter defibrillators (ICD) constitutes an important modality in the management of cardiac arrhythmias. These devices can be implanted either through thoracotomies or via the more recently utilized transvenous approach. One of the most serious complications of the use of ICDs is infection, with an incidence rate as high as 7.2% (60). Risk factors for infection of ICDs placed through thoracotomy include median sternotomy, long duration of surgery, generator replacement, depressed immunity, diabetes mellitus, advanced age, and the presence of another nidus of infection. A retrospective study of 202 ICDs implanted using the thoracotomy approach found that diabetes mellitus was the only variable associated with the development of infection (107). Of the 171 implants analyzed, 9 (4.5%) became infected, and most infections occurred in the first 3 months after implantation. The clinical presentation included pain, fever, and fluid collection around the generator. All nine cases of infection were bacterial, and all required device removal in addition to antimicrobial therapy. Transvenously placed ICDs are associated with a significantly lower incidence of infection than are those implanted through thoracotomy (110). A study of ICD infections from 1992 to 1995 related the escalating use of the transvenous approach to the decrease in the overall incidence of infection from 16.7 to 6.9% (60). Of the seven infected patients, only one had *Candida* infection, and that occurred in conjunction with bacterial infection. In conclusion, fungal ICD infections are extremely rare and usually co-occur with bacterial infections.

Ventricular Assist Devices

Ventricular assist devices (VADs) are either implantable or extracorporeal. Implantable VADs are usually used to provide temporary support, sometimes for up to 1 year, until patients receive a heart transplant (113). Such implantable VADs are currently being evaluated as a permanent therapy for end-stage heart failure, and so their use is expected to rise in the near future. Extracorporeal VADs are usually used to support patients with severe heart failure when cardiac function is expected to improve within days to weeks. Infectious complications affect both types of devices, affecting about 50% of all VAD recipients (77). However, due to different definitions and duration of VAD support, the reported incidence rates vary greatly, being anywhere from 28 to 66% (77). Fungal colonization or infection has been detected in 35 to 39% of patients with VADs (38). A recent study found that 49% patients with VADs develop bloodstream infections and that 38% of such infections were associated with the device. *Candida* spp. were found in 19 of these patients and had the highest hazard ratio of 10.9 (40).

Mortality rates are hard to assess in the literature because patients needing VADs most often have other serious complications affecting both mortality and morbidity. Nevertheless, the impact of infection of VADs is enormous because persistent infection may require VAD removal, which can be done only if a heart donor is available or if heart function significantly improves (77).

Risk factors for VAD infections include postoperative

bleeding necessitating reoperation, chronic underlying diseases, receipt of broad-spectrum antibiotics, and presence of indwelling tubes (77). Additionally, the VAD itself affects the immune system. The interaction of the VAD with blood seems to activate T cells, causing their death, and causes B-cell hyperreactivity with dysregulated immunoglobulin synthesis. This progressive defect in cellular immunity increases the risk of fungal infections (38). Specific risk factors for fungal VAD infections have not been defined. It has been suggested that the same risks apply for fungal infections of VAD recipients and for patients in ICUs: fungal colonization, prior antibiotics, total parenteral nutrition, prior hemodialysis, indwelling catheters, abdominal surgery, and prolonged ICU stay (38).

Treatment of fungal infections of VADs usually consists of systemic antifungal therapy and device removal. So far, there have been no reports in the literature of long-term survival after a fungal VAD infection (38).

CENTRAL NERVOUS SYSTEM DEVICES

Ventriculoperitoneal Shunts

Most currently used ventriculoperitoneal shunts (VPS) are made of silicone polymers. Obstruction and infections are the two most common complications, with infection occurring in 6 to 15% patients with these devices (73, 99). *Candida* is the causative agent in 1% of these infections (99). However, this reported incidence may be underestimated, considering that some of the culture-negative shunt infections may be fungal in etiology (65). The mortality of *Candida* VPS infections is estimated to be 9% (99).

Risk factors for *Candida* shunt infections and meningitis include the use of broad-spectrum antibiotics, prior or concurrent bacterial meningitis, cerebrospinal fluid leakage (35, 82, 99), bowel perforation and/or abdominal surgery (99), steroids, and indwelling catheters (73).

In one review (99), 77% of *Candida* infections developed within 3 months of shunt manipulation, suggesting inoculation of the organism during the surgery. Transient candidemia and secondary colonization of the VPS have been suggested by other investigators as possible sources of the infecting *Candida* organisms (102). The most common species are *C. albicans* and *C. tropicalis*. The clinical presentation of *Candida* shunt infection depends on the location of the infection. Distal shunt infection refers to an infection at the site of shunt drainage, which is either a vascular site or the peritoneum. If the shunt drains into a vascular site like the right atrium, the symptoms are usually nonspecific and include fever and malaise. An infected shunt draining into the peritoneum causes mesothelial inflammation and subsequently decreases drainage. A "shuntoma" can develop when the peritoneum encysts the fluid. Proximal *Candida* shunt infections are manifested by symptoms of shunt malfunction associated with high intracranial pressure, including headaches, nausea, vomiting, and altered mental status. The most common symptoms of VPS infections include fever (31%), hydrocephalus (36%), and meningoencephalitis (21%) (99). Compared to patients with *Candida* meningitis without shunt infection, patients with *Candida* infection of VPSs had a lower frequency of hypoglycorrhagia and lower white blood cell count (73 cells/mm^3) in the cerebrospinal fluid. Other rarer clinical manifestations of *Candida* shunt infections include basal ganglion granuloma surrounding a nonfunctional shunt in a previously healthy person (106).

Candida shunt infections present some therapeutic dilemmas, which are far from being universally approached (76). Most authors agree that removal of the device is necessary to clear the infection (99). So far, the most commonly used antifungal agent is intravenous amphotericin B with or without flucytosine (76, 104). Several factors limit the use of amphotericin B in central nervous system fungal infections. This drug crosses the blood-brain barrier poorly, adverse events limit the amounts that can be given systemically, and its intrathecal use is associated with significant toxicity such as arachnoiditis (27). Delayed sterilization does not seem to worsen the prognosis of *Candida* meningitis (104), and so most authors recommend shunt removal and only intravenous amphotericin B. Some authors (99) recommend intrathecal use of antifungal therapy only if the patient's clinical condition is poor. The role of the newer antifungal agents has not been established yet. Although the lipid formulations do not cross the blood-brain barrier significantly better than native amphotericin B, several of the new azole agents do.

URINARY CATHETERS

Over 30 million bladder catheters are inserted annually in the United States, with a 10 to 30% overall rate of infection (24). In a NNIS report of nosocomial infections between 1992 and 1997, the urinary tract was the most common site of infection in medical ICUs (31%) and most cases of urinary tract infections were catheter related. *Candida* species accounted for 31% of urinary isolates in the same study, compared to 22.1% reported between 1986 and 1989 (97).

Candida infections of the urinary tract are strongly associated with the presence of a urinary catheter. The NNIS data indicated that *C. albicans* caused 21% of catheter-associated urinary tract infections, in contrast to 13% of non-catheter-associated infections (97). In a multicenter surveillance study of 861 patients with funguria, 83% of patients had some form of urinary tract drainage systems, the majority of which were urethral catheters (53). Although the overall mortality among patients with candiduria is reported to be as high as 39% (46, 53, 105), this high mortality rate is mostly attributed to the multiple serious underlying illnesses found in patients with funguria.

Candida growth in urine represents a spectrum of states, ranging from external perineal colonization, catheter infection, cystitis, or even secondary seeding from undetected bloodstream infection. Risk factors for funguria include diabetes mellitus, urinary tract abnormalities, malignancy, and antibiotic use (53). In one study (41), female gender and ICU stay were most strongly associated with funguria due to *C albicans* and *C. glabrata* whereas fluconazole and quinolone exposure were specific risk factors for funguria due to *C. glabrata*.

C. albicans is the fungal species isolated most frequently from urine specimens. According to the NNIS findings, *C. albicans* accounts for 21% of all urinary isolates and other *Candida* spp. account for only 10% of isolates (97, 105). In another study (53), *C. albicans* was found in 51.8% of patients with candiduria, followed by *C. glabrata* (15.6%).

There are no universally established criteria for assessing the clinical significance and therefore guiding the management of asymptomatic candiduria. Some authors think that asymptomatic candiduria is an early marker of disseminated infection in critically ill patients and may require treatment (79), whereas others have not found asymptomatic candiduria to be a predictor for candidemia or dissemination but, rather, a benign and self-limiting condition (53, 105).

Controversy also exists about whether to treat asymptomatic candiduria. In a surveillance of 861 patients, funguria cleared in 75% of patients without any therapy (53), in 35.5% of patients who had the catheter removed as the only intervention, and in 50.2% of patients given antifungal therapy. Treatment regimens vary. Bladder irrigation with amphotericin B and with oral fluconazole were equally efficient in eliminating candiduria, but recurrences were common with both approaches (46). A prospective study that compared fluconazole with placebo in eradicating candiduria in asymptomatic or minimally symptomatic patients found that fluconazole initially cleared candiduria in 50% of patients, in contrast to 29% in the placebo group. However, cultures at 2 weeks revealed similar rates of candiduria among treated and untreated groups (105). Debate also exists about the threshold of organism concentration (10^4 versus 10^5 CFU/ml) in urine that may potentially be used as a criterion for treating candiduria (46, 53). Symptomatic *Candida* infection of the catheterized urinary tract is treated with antifungal therapy, usually for at least 5 to 7 days in patients with cystitis and 14 days in those with pyelonephritis.

PENILE IMPLANTS

About 15,000 to 20,000 silicone penile prostheses are inserted each year in the United States (24). A pseudocapsule forms around the device, and infections usually occur in the periprosthetic space between the pseudocapsule and the device surface (72). The reported overall rate of infection ranges from 1 to 9% and is higher (18%) in patients with reconstructive procedures or surgical revisions (17, 47). Bacteria account for the vast majority of cases of penile implant-related infections, whereas yeast infections are relatively rare. *C. albicans* has been reported to cause 5 to 9.2% of infections of penile implants (75).

The mortality specifically related to *Candida* infections of penile implants remains unknown. However, these infections result in major morbidity with potentially disastrous complications. Cure of infection usually requires removal of the infected device, which can be complicated by subsequent fibrosis formation and loss of tissue. This can make later reimplantation of another penile prosthesis rather difficult or even impossible.

Known risk factors for infections of penile prostheses include urinary tract infection, spinal cord injury, insertion of an inflatable device, neurogenic bladder, diabetes mellitus, reimplantation, and revisions (18, 47). Whether the rate of penile prosthesis-related infection is higher in diabetic and spinal cord-injured patients than in the general population remains controversial (47). Some authors found a statistically insignificantly higher rate of infection in diabetics than nondiabetics, with reported rates of 2.8 and 0.9% (34) and 22 and 6.7% (64), respectively. However, in other reports, diabetics did not appear to be at a greater risk for infection than nondiabetics (47, 72).

In one study (47), the majority of bacterial infections occurred within 3 months after surgery, whereas others observed more than half of the cases manifesting more than 7 months after either implantation or revision. Hematogenous infections occurred anywhere from 8 to 54 months after implantation. Due to the paucity of reported cases of *Candida* infections of penile prostheses, it is unclear whether the clinical profiles in such cases are similar to those of bacterial infections. *C. albicans* abscess following penile prosthesis placement reportedly formed 3 months postoperatively (86). The type of infecting *Candida* species is often not specified in the case reports. One small study of 11 patients undergoing salvage operation reported two *Candida* infections, one *C. albicans* infection, and one *C. glabrata* infection (12).

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