

# Candida Infections in Surgical Patients

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Serious *Candida* infections were seen in 55 surgical patients from January 1977 through December 1980. Most of the patients had compromising underlying conditions and many were elderly. Broad-spectrum antibiotics and total parenteral nutrition (TPN) appeared to predispose patients to *Candida* infections. Mortality rate from *Candida* was 38%. A high percentage of patients with positive blood or bile cultures died as a result of *Candida* infection. Therapy with intravenous amphotericin B was highly effective if given in adequate dosage. No patient receiving more than 200 mg of amphotericin B died, but the mortality rate was 56% in those receiving lower doses.

CANDIDA SPECIES are constituents of the normal flora of the mouth, gastrointestinal tract, and vagina. In these locations, the organisms only become pathogenic when the normal bacterial flora is disrupted by antibiotics or other factors that produce fungal overgrowth. Clearly, it is abnormal to isolate *Candida* from blood, bile, wounds, and pleural or peritoneal spaces, but even in these settings, it is not always certain that antifungal therapy is required.

The toxicity of the major therapeutic agent, amphotericin B, makes many surgeons reluctant to use this drug without strong evidence of invasive candidiasis. Unfortunately, a conservative or "expectant" approach may result in unacceptable mortality from disseminated *Candida* infection in surgical patients. The discovery at post-mortem of unexpected cases of disseminated candidiasis in our patients prompted us to review our experience with the diagnosis and therapy of serious *Candida* infections in our Surgical Department over the past 4 years.

## Methods

Microbiology records of the Tufts-New England Medical Center were reviewed for the period of January 1, 1977, to December 31, 1980, for positive *Candida* cultures. We reviewed the clinical records of all surgical

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patients who had *Candida* isolated from blood, bile, cerebrospinal fluid (CSF), pleural fluid, peritoneal fluid, pericardial fluid, soft tissues (excluding skin and mucosal surfaces), surgical abscesses, and deep wound aspirates. In the cases of wound isolates, patients were included only if *Candida* was abundant or if the sole organism and the wound was infected clinically. Autopsy records were reviewed for the same time period and surgical patients with post-mortem evidence of deep *Candida* infection were included also. Patients with *Candida* cultured solely from the throat, sputum, urine, skin, superficial wounds, mucous membranes, or catheter tips were excluded from the study when there was no evidence of clinical infection.

*Candida albicans* was identified by growth characteristics on cornmeal agar and molybdate agar, followed by a germ tube test using standard methods. Other species of *Candida* were identified using the Yeast System (Flow Laboratories, Inc., Roslyn, NY).

Patients were characterized by age, sex, underlying conditions, surgical procedures, and risk factors that could predispose to *Candida* infection. Risk factors include broad-spectrum antibiotics, steroids, cytotoxic drugs and total parenteral nutrition, when they were given for at least 2 of the fourteen days prior to the occurrence of a significant *Candida* culture. Patients were also characterized regarding their clinical status at the time *Candida* was first isolated. Mortality was calculated for the entire group, then subdivided by site of infection. The efficacy of amphotericin B therapy was examined for the entire group by site of infection. Other aspects of therapy that might have affected the outcome were examined.

## Results

During the period from January 1977 through December 1980, 55 surgical patients with significant *Candida* infection were identified. There were seven cases

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TABLE 1. Underlying Conditions\*

	No. of Patients
Malignancy	20
Diabetes Mellitus	11
Crohn's disease	5
Chronic renal failure	3
Autoimmune diseases	3
Cirrhosis of the liver	4
Liver transplant	1
WBC defect	1
None	14

\* Total 41/55 (76%); some patients had more than one condition.

in 1977, 15 in 1978, 17 in 1979, and 16 in 1980, indicating a relatively stable incidence of disease during this period. There were 33 male and 22 female patients, ranging in age from 10 to 96 years; the median age was 64 years.

The Tufts-New England Medical Center is tertiary care facility which serves many high-risk surgical patients with serious underlying conditions. Forty-one of our 55 patients (76%) had conditions known to predispose to *Candida* infection (Table 1). Malignancies and diabetes mellitus were the most common underlying diseases. Three patients had lymphoma and one had a liver transplant. There were no patients with leukemia.

The types of surgical procedures are listed in Table 2. The majority of patients (82%) were on the general surgery service and were admitted for some type of abdominal operation. Of the 45 patients having abdominal procedures, 15 patients had upper gastrointestinal tract surgery and 17 had colonic surgery. Six patients had biliary tract surgery; three of them had transhepatic cholangiograms only (one with stent placement), two had biliary diversions, and one had a cholecystectomy. Six patients had abdominal vascular surgery. This group included one patient with a mesocaval shunt and five patients with arterial bypass grafts originating from the aorta or common iliac arteries.

Ninety-one per cent of our patients received broad-spectrum antimicrobial agents prior to *Candida* infection. Nine per cent were given antibiotics prophylactically and 82% of the patients for therapeutic reasons. Total parenteral nutrition (TPN) was administered to 56% of patients prior to isolation of *Candida*; many were receiving TPN on the day *Candida* was first cultured. Thirty-eight per cent of patients received corticosteroids prior to infection, and seven per cent of patients received cytotoxic drugs. As shown in Figure 1, TPN and steroids were significant risk factors when combined with antibiotic therapy, but not as single factors. However, antibiotics alone were an independent risk factor.

TABLE 2. Surgical Procedures

Type of Surgery	No. of Patients
Abdominal	45
Gastroduodenal	15
Colonic	17
Biliary	6
Vascular	5
Other	2
Thoracic	3
Neurosurgical	2
Gynecological	2
Urological	2
Other	1

### Site of Infection

When the patients were analyzed by site of infection, 32 patients had one or more positive blood cultures for *Candida*, 27 patients had the organism in deep wound aspirates, six in peritoneal fluid, five in bile, four in suppurative phlebitis, three in pleural fluid, and one each in CSF, pericardial fluid, and bone. In 12 patients, *Candida* was isolated from an intraabdominal abscess; in seven of these patients, it was mixed with bacteria, but in five cases, a pure *Candida* abscess was found (Table 3).

### Risk Factors for *Candida* Infection

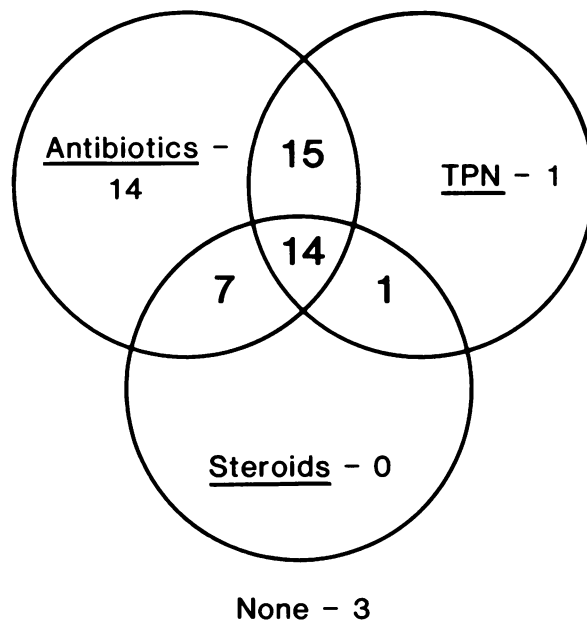


FIG. 1. Interrelationship of risk factors in surgical patients with *Candida* infections. Circles represent individual factor; overlapping of circles indicates number of patients with multiple factors.

TABLE 3. *Candida* Isolation and Mortality by Site of Infection

Site	No. of Patients	Per cent Mortality
Blood	32*	47
Wound	27	30
Peritoneal fluid	6	33
Bile	5	80
Pleural fluid	3	33
CSF	1	100
Intraabdominal abscess		
Mixed	7	14
Candida alone	5	29

\* Some patients had more than one site of infection.

*Candida albicans* was cultured in 38 cases, *Candida glabrata* in ten cases, *Candida tropicalis* in six cases, *Candida krusei* in one case, and unspiciated *Candida* in 18 cases. More than one species of *Candida* was found in 11 patients.

#### Clinical Features

In most patients, *Candida* infection was a postoperative complication; 24% of patients had yeasts prior to or at surgery, while 76% of patients developed positive cultures in the postoperative period.

Only 60% of our patients were febrile (temperature > 37.5 C) when *Candida* was cultured initially (Fig. 2). Of these patients, 71% had a leukocytosis (WBC 10,500)

### Clinical Indicators of *Candida* Infection

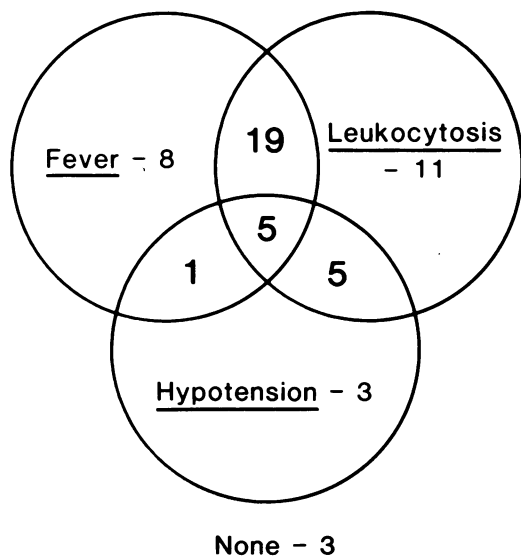


FIG. 2. Frequency of clinical signs of infection. Circles represent individual sign; overlapping of circles indicates number of patients with more than sign.

and 29% were hypotensive (systolic B.P. 100 mmHg). Of the 55 patients, all but three had one or more of these findings to suggest the presence of fungal infection. However, some patients had concurrent bacterial infections, which may have obscured the significance of the clinical findings. Many of our patients had some degree of renal insufficiency when *Candida* was first cultured: 47% of them had a serum creatinine level greater than 1.5 mg/dl.

#### Mortality

There were 32 deaths among the 55 patients, producing an overall mortality rate of 58%. Twenty-one deaths were directly related to *Candida* infection. In eight of these 21 patients, widespread *Candida* infection was found at post-mortem examination. In 13 patients, the relationship to their demise was established by clinical information and the results of cultures, since an autopsy was not performed.

Mortality was examined by site of positive culture in order to give some estimation of the significance of *Candida* in a particular location (Table 3). *Candida*-related deaths were seen in 47% of patients with positive blood cultures. The mortality rate was approximately 30% in patients with *Candida* isolated from wounds, peritoneal fluid, or pleural fluid. Four of the five patients with positive bile cultures died as a result of *Candida* infections. The one patient with *Candida* meningitis died.

The fungal-related mortality of patients with intraabdominal abscesses was lower than in other categories. In the group of seven cases with mixed *Candida* and bacterial abscesses, only one death could be related to *Candida*. Similarly, in the five patients with pure *Candida* abscesses, only one *Candida*-related death was seen. The patients with pericardial or bone involvement both survived their infection.

#### Therapy

Most clinicians are confronted with the decision of whether or not to treat *Candida* when it is isolated from a specific site. To address this issue, the effect of therapy was analyzed on the basis of outcome and the specific site of infection (Table 4). When therapy was given, intravenous amphotericin B was used in all cases (5-fluorocytosine was used with amphotericin in one patient).

The mortality statistics were analyzed in terms of total dosage of amphotericin B administered (Fig. 3). A total of 25 patients received intravenous amphotericin B. There were no *Candida*-related deaths in nine patients receiving 200 mg or more of amphotericin B.

Nine of 16 patients (56%) who received less than 200 mg of amphotericin B had a fatal outcome. Five patients

failed to receive the drug until long after positive cultures were noted. Two patients received sub-therapeutic doses of amphotericin B. One patient developed renal insufficiency and the drug was stopped; this patient later died as a result of *Candida* infection. One patient had begun therapy promptly when the infection was discovered, but he succumbed to *Candida* infection before an adequate dosage could be given. Thus, all of the *Candida*-related deaths appeared to be related to delayed and/or inadequate therapy.

We also analyzed mortality in terms of the effect of delaying therapy with amphotericin B once *Candida* was cultured. Deaths began to occur 3 days after positive cultures were obtained if no therapy was given. However, three patients survived after therapy was delayed for more than 11 days. We could draw no firm conclusions about the effect of delaying therapy in patients with serious *Candida* infections, but our data suggest that host factors may be at least as important as the timing of therapy.

Mortality was lower in patients with *Candida* isolated from intraabdominal abscesses (Table 4). In the group with mixed infections, one patient died of sepsis 1 day after three different species of *Candida* and five different bacteria were cultured from the site of cecal perforation. Another patient was treated with 200 mg amphotericin and survived when *Candida* was isolated from both a mixed abscess and blood. The other five patients received no antifungal therapy and none died as a result of *Candida* infection; one of this latter group also had a positive blood culture.

In the group of five patients with pure *Candida* abdominal abscesses, three patients received "adequate therapy" and survived. One patient had a subhepatic *Candida* abscess and died after receiving 90 mg of amphotericin B. The other patient had an ileal-urinary conduit, and she developed a peritoneal *Candida* abscess that extended into the peritoneum. This was surgically drained and the patient did well without amphotericin B therapy.

### Discussion

An increasing number of serious *Candida* infections has been noted on surgical services in recent years.<sup>1-6</sup> This increase may be related to improvements in surgical technique and perioperative care that allow high-risk patients to survive, despite serious underlying diseases. The price for increased survival is the propensity to develop unusual infections.

*Candida* has been the commonest fungal pathogen described in surgical patients in previous studies,<sup>2,3</sup> and this finding was confirmed in the surgical patients at this

TABLE 4. Effect of Amphotericin B Therapy\* on *Candida*-related Mortality

Site	More than 200 mg	Less than 200 mg	
Blood	0/9	15/23	(65%)*
Wound	0/4	8/23	(35%)
Abdominal (total)	0/14	8/19	(42%)
Peritoneal	0/2	2/4	(33%)
Bile	—	4/5	(80%)
Abscess (total)	0/4	2/8	(25%)
Mixed	0/1	1/6	(17%)
Candida alone	0/3	1/2	(50%)
Pleural	0/1	1/2	(50%)
Pericardial	0/1	—	
CSF	—	1/1	

\* Deaths/total cases (% mortality).

hospital. Many of our patients were elderly, and most had underlying conditions that would predispose them to infection. Broad-spectrum antibiotics, corticosteroids, and cytotoxic agents are commonly cited risk factors in *Candida* infections.<sup>1,2</sup> Ninety-one per cent of our patients received broad-spectrum antibiotics and 38% of them received steroids prior to *Candida* infection.

In recent years, TPN has been recognized as a risk factor for serious *Candida* infections.<sup>1,4,7</sup> The series by Curry et al.<sup>4</sup> noted that 67% of patients with fungemia had received TPN prior to infection. One reason that TPN leads to candidemia is the requirement that plastic intravenous catheters be placed for extended periods of time.<sup>4</sup> Also, *in vitro* studies have shown that *Candida* readily grows in hyperalimentation solutions containing amino acids or lipid emulsions.<sup>8,9</sup> In our study, 56% of patients with *Candida* infections received TPN prior to

### Effect of Amphotericin B Dose on Mortality

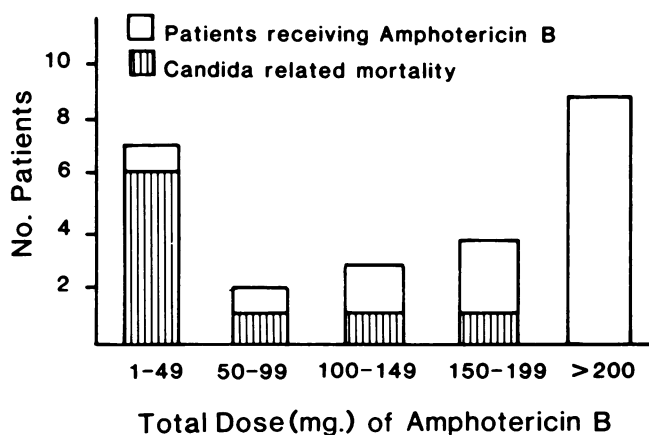


FIG. 3. Effect of amphotericin B therapy on mortality in surgical patients with *Candida* infections.

infection. When combinations of risk factors were examined, it was found that TPN and steroids become risk factors for *Candida* infection only when combined with antibiotics (Fig. 1). Antibiotics alone, however, appeared to be a significant independent risk factor.

Most patients had some clinical sign of infection when *Candida* was first isolated: 71% of patients had leukocytosis, 60% of patients were febrile, and 27% of patients were hypotensive (Fig. 2). One of these indicators was seen in all but three patients. These data indicate that when surgical patients with compromising underlying conditions develop unexplained fever, leukocytosis, or hypotension while on broad-spectrum antibiotics, a search for *Candida* infection should be made.

Several patients had unusual sites of infections. One patient had a saphenous vein bypass graft placed in his right leg at another hospital because of a diabetic foot ulcer. Several weeks later, he presented here with chest pain and fever. Diagnostic evaluation revealed purulent pericarditis and *C. glabrata* was isolated from both the foot and the pericardial sac. Surgical drainage and intravenous amphotericin B resulted in a cure. We are unaware of any reports of similar illness with this organism.

Five patients had positive bile cultures for *Candida*. Two patients had biliary diversion procedures, one had a cholecystectomy, and three had transhepatic cholangiogram (one with stent placement). Since four of these patients died, it would appear that a positive bile culture can be an ominous finding.

Suppurative phlebitis is reportedly a rare form of *Candida* infection.<sup>10</sup> Four cases were identified in our series; all were related to plastic intravenous catheters. In patients with candidemia and no clear source of infection, a careful search of catheters sites should be done to rule out this possibility.

*C. albicans* has been recovered in 57% of gastric cultures and 65% of fecal cultures from normal people.<sup>11,12</sup> Enteric colonization can be increased by hospitalization and broad-spectrum antibiotics.<sup>1</sup> *In vitro* studies have shown that *Candida* grows well in the anaerobic conditions found in abdominal abscesses.<sup>13</sup> Despite the above observations, *Candida* has rarely been noted as a significant pathogen in intraabdominal abscesses. In this study, however, 12 patients had *Candida* isolated from intraabdominal abscesses, and in five patients, it was the only organism recovered. With increasing use of antimicrobial prophylaxis and therapy employing drugs that diminish both the aerobic and anaerobic bacterial flora, *Candida* abscesses may become more common.

The overall mortality rate in this study was 60%, and two-thirds of these deaths were related directly to *Can-*

*dida* infection. This high figure is due partially to the serious underlying conditions in these patients, making them high-risk surgical candidates at the outset. When mortality was analyzed by site of infection, *Candida* in blood, bile, and CSF appeared to result in the highest death rate. Only when *Candida* was cultured from wounds or abscesses was the death rate less than one-third.

Even a single positive blood culture for *Candida* can be significant, as it was in eight of 15 patients who died of disseminated candidiasis and fungemia. The importance of a single positive blood culture for *Candida* has been noted in patients with leukemia in the medical literature,<sup>14</sup> but it has not been stressed sufficiently in terms of surgical patients.

Amphotericin B is acknowledged to be the most reliable drug in the treatment of serious *Candida* infections, although the exact dose has not been determined.<sup>15</sup> Treatment with amphotericin B resulted in considerably improved survival in our patients, since all patients receiving more than 200 mg survived (Fig. 3). Even a total dosage greater than 100 mg increased survival. For example, when patients with positive blood cultures received 100 mg or more, their mortality rate was 18%, compared to a 62% mortality rate in patients receiving no drug or lower doses.

There were few *Candida*-related deaths in the patients with this organism in an intraabdominal abscess. In the group of seven patients with mixed bacterial-fungal infection, one patient had positive blood cultures prior to surgical drainage at the abscess and was already receiving amphotericin B at the time of the procedure. Another patient developed a mixed abscess after gastric surgery and had multiple positive blood cultures for *C. glabrata*. He was treated with 756 mg of amphotericin B. When he died one month later of other causes, no fungi were seen at autopsy. Three other patients with a mixed bacterial-fungal abscess survived with surgical drainage and anti-bacterial therapy, without anti-fungal treatment. The only other death was a patient who died as a result of sepsis the day after surgery for a post-colectomy abscess; three species of *Candida* and five different bacteria were cultured from the abscess. The small number of cases make conclusions difficult, but it appears that in the absence of positive blood cultures, *Candida* in a mixed abdominal abscess may not require specific therapy.

Five patients had pure *Candida* intraabdominal abscesses. This form of *Candida* infection is reported so rarely that there are no guidelines regarding therapy. One patient had a peristomal abscess extending into the peritoneal cavity around an ileal-loop urinary conduit. She did well after undergoing surgical drainage, and she

received only 6 mg of amphotericin B. Another patient had a subhepatic abscess after surgery for a perforated gastric ulcer. The abscess was drained via a percutaneous catheter, and 211 mg of amphotericin was administered. He died 3 weeks later as a result of unrelated causes; no fungi were seen at post-mortem examination. Two patients developed Candida retroperitoneal abscesses after colonic surgery. One patient had percutaneous drainage and received 386 mg of amphotericin B, but died 1 month later as a result of unrelated causes. The other patient survived after receiving 1376 mg of amphotericin B and had adequate surgical drainage. The only Candida-related death occurred when a 68-year-old man developed a subhepatic Candida abscess after surgery to oversew a duodenal ulcer. The abscess was drained percutaneously, but only 90 mg of amphotericin B could be given before he died with persistently positive cultures from the drain site. These results suggest that drainage and amphotericin B are required for cure of a pure intra-abdominal Candida abscess.

Therapy with intravenous amphotericin B generally is begun with a 1-mg test dose, followed by 5 mg, and then gradual daily increases up to 0.7 mg/kg/day.<sup>14</sup> One large review suggested that total dosages of 1.5–2.0 gm were required for serious Candida infections, but most of their patients had leukemia.<sup>14</sup> Other authors have suggested that dosages as low as 10–350 mg can provide adequate therapy,<sup>16</sup> although many of these infections were limited to mucosal surfaces. When Solomkin et al.<sup>15</sup> reviewed the role of amphotericin B treatment in surgical patients, they found that a dosage of 6–9 mg/kg was adequate therapy to control deep-seated Candida infections. We administered amphotericin B to 25 patients. Sixteen of these patients survived or died as a result of unrelated causes and nine patients died as a result of Candida-related sepsis. When therapy was examined in terms of total dosage of amphotericin B, we found that no patient receiving more than 200 mg of amphotericin B died of Candida. Fungi were eliminated from draining sites with dosages of 200–300 mg. When lesser amounts were given, the mortality increased in a step-wise fashion with decreasing dosage. The data in this study indicate that total dosages of less than 200 mg do not reliably cure serious Candida infections in surgical patients. The exact dosage cannot be determined, but it seems reasonable to administer 200–300 mg, at which time the patient is reevaluated for the need to use

the higher dosages that are suggested by Solomkin et al.<sup>15,16</sup>

Amphotericin B is the only available drug with established efficacy in systemic Candida infections. While this drug has significant toxicity, it is often well tolerated when given by physicians who are experienced in its use. In this study, only one patient developed problems during amphotericin therapy that required discontinuation of the drug. The alternatives of not treating or using inadequate dosages can have serious consequences, resulting in dissemination and death.

### References

1. Stone HH, Kolb LD, Currie CA, Geheber CE, Cuzzell JZ. Candida sepsis: pathogenesis and principles of treatment. *Ann Surg* 1974; 179:697–710.
2. Gaines JD, Remington JS. Disseminated candidiasis in the surgical patient. *Surgery* 1972; 72:730–736.
3. Solomkin JS, Flohr AB, Quie PG, Simmons RL. The role of Candida in intraperitoneal infections. *Surgery* 1980; 88:524–530.
4. Curry CR, Quie PG. Fungal septicemia in patients receiving parenteral hyperalimentation. *N Engl J Med* 1971; 285:1221–1225.
5. Richards KE, Pierson CL, Bucciarelli L, Feller I. Monilial sepsis in the surgical patient. *Surg Clin North Am* 1972; 52:1399–1406.
6. Bayer AS, Blumerkrantz MJ, Montgomerie JZ, et al. Candida peritonitis. *Am J Med* 1976; 61:832–840.
7. Montgomerie JZ, Edwards JE. Association of infection due to *Candida albicans* with intravenous hyperalimentation. *J Infect Dis* 1978; 137:197–201.
8. Brennan MF, O'Connell RC, Rosol JA, Kundsinn R. The growth of *Candida albicans* in nutritive solutions given parenterally. *Arch Surg* 1971; 103:705–708.
9. Maki DG. Growth of microorganisms in intralipid and implications for infection control (Abstr 533). 20th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, September 1980.
10. Deitch EA, Marini JJ, Huseby JS. Suppurative Candida phlebitis of a peripheral vein. *J Trauma* 1980; 20:618–620.
11. Cohen R, Roth FJ, Delgado F, et al. Fungal flora of the normal human small and large intestine. *N Engl J Med* 1969; 280:638–641.
12. Schonebeck J. Incidence of yeast-like fungi in gastric juice under normal and pathologic conditions. *Scand J Gastroenterol* 1968; 3:351–354.
13. Szawatkowski M, Hamilton-Miller JMT. Anaerobic growth and sensitivity of *Candida albicans*. *Microbios Letters* 1978; 5:51–66.
14. Edwards JE, Kehrer RI, Stiehn ER, et al. Severe Candida infections. Clinical perspective, immune defense mechanisms, and current concepts of therapy. *Ann Intern Med* 1978; 89:91–106.
15. Solomkin JS, Flohr A, Simmons RL. Candida infections in surgical patients dose requirements and toxicity of amphotericin B. *Ann Surg* 1982; 195:177–185.
16. Medoff G, Dismukes WE, Meade RH, Moses JM. A new therapeutic approach to Candida infections. *Arch Intern Med* 1972; 130:241–245.