Fungal Infections in Patients with Severe Acute Pancreatitis and the Use of Prophylactic Therapy

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Data from an 8-year period for 46 patients with severe acute pancreatitis and infected pancreatic necrosis were analyzed to determine the incidence of fungal infection, to identify risk factors for the development of fungal infection, and to assess the use of early fluconazole treatment. Intraabdominal fungal infection was found in 17 (37%) of 46 patients. Candida albicans was isolated most frequently (15 patients); Candida tropicalis and Candida krusei were found in 1 patient each. Characteristics of patients with fungal infection were not different from patients without fungal infection. The difference in mortality was not statistically significant between patients with fungal infection and patients without fungal infection. Early antifungal therapy (prophylactic or preemptive antifungal therapy) was administered to 18 patients, and only 3 of them developed fungal infection. In this cohort of critically ill patients, no risk factors for fungal infection could be demonstrated, and mortality among patients who received early antifungal therapy was not different. Early treatment with fluconazole seems to prevent fungal infection in these high-risk patients.

Fungi are part of the normal flora of the intestine. The receipt of medication, such as antibiotics, and the trauma associated with surgical intervention may cause overgrowth and translocation of these organisms and may predispose patients to colonization or infection [1]. In patients with peritonitis from a nonappendical origin, the incidence of fungal infection is reported to be as high as 39% and is associated with more postoperative complications and increased mortality [2].

Also, in cases of acute necrotizing pancreatitis, the importance of fungal infection is increasing. Data from the 1980s and early 1990s are limited, but fungal involvement in pancreatic necrosis was estimated to be ~10% [3]. In hospitals where prophylactic antibiotics are routinely used, the incidence may have increased in recent years [4].

Data on the effect of fungal involvement during infection on mortality for these patients are conflicting. Whereas Hoerauf et al. [5] and Isenmann et al. [6] found increased mortality in their studies, Gloor et al. [4] did not find increased mortality among 33 patients with infected pancreatic necrosis [4].

Because of the presumed increased mortality and morbidity after surgery, antifungal prophylaxis has been advised for high-risk surgical patients. In a prospective, randomized trial of patients with recurrent gastrointestinal leakage, antifungal prophylaxis with fluconazole was associated with a lower incidence of intraabdominal fungal infection [7]. In this study, only 4 patients with severe acute pancreatitis were included. Other authors also recommended the use of antymycotic treatment on the basis of limited experience [5], but it is not clear whether the advantage of antifungal prophylaxis in patients who have undergone abdominal surgery that was complicated by anastomotic leakage or recurrent fistulization can be extrapolated to patients with severe acute pancreatitis. Also, the selection of resistant fungi in patients treated with fluconazole is cause for concern [8]. The objective of our analysis was to study the incidence of fungal infection in patients with infected...
pancreatic necrosis, to identify risk factors for the development of fungal infection, and to assess the use of early fluconazole treatment.

PATIENTS AND METHODS

From 1 January 1995 through 31 December 2002, 106 patients with severe acute pancreatitis were admitted to the intensive care unit (ICU) at Ghent University Hospital (Gent, Belgium), a teaching hospital with a total of 1059 beds. In 46 patients, at least 1 episode of infected pancreatic necrosis was documented during the ICU stay. These 46 patients are the subjects of this analysis. All patients met the criteria for severe disease proposed at the International Symposium on Acute Pancreatitis [9]. Pancreatic necrosis was diagnosed on the basis of results of a contrast-enhanced spiral CT scan of the abdomen. All patients were admitted to the ICU before and after surgical intervention. The majority of the patients (33 of 46) were treated in another hospital before admission to our unit.

We recorded the demographic characteristics, the disease etiology, the incidence of organ failure, the disease severity (assessed by the Ranson criteria), and the APACHE II score calculated at admission to the ICU (for patients transferred from other hospitals, the score was calculated using data obtained from the referring hospital). Organ failure was defined as follows: cardiovascular failure, a mean arterial pressure of <60 mm Hg or the need for vasoactive therapy; renal failure, a serum creatinine level of >2.0 mg/dL; pulmonary failure, the need for mechanical ventilation or the presence of acute lung injury or adult respiratory distress syndrome; and hepatic failure, a bilirubin level of >5.0 mg/dL.

Early antifungal therapy was defined as the administration of fluconazole ≥48 h before surgical intervention and consisted of either fluconazole prophylaxis (400 mg) or preemptive therapy, if Candida colonization was present at other sites. Colonization was defined as the presence of Candida species in ≥1 of the routine surveillance cultures (performed 3 times per week) of tracheal aspirate samples, oropharynx samples, urine samples, wound specimens, and perineum samples without signs or symptoms of infection.

Fungal infection of pancreatic necrosis was diagnosed when specimens obtained during surgical intervention yielded yeast or fungi on culture (the infection was defined as a primary infection if the specimen was procured during the first surgical intervention and as a secondary infection if the specimen was obtained during reoperation or from the abdominal drain effluent at a later period during the course of the disease) [7]. When Candida species were isolated from the abdominal drain effluent, infection was only presumed to be present when cultures of at least 2 lavage samples were positive for Candida species, together with a clinical picture of infection. These were confirmed by results of intraoperative cultures, when available. Only intraabdominal fungal infections were analyzed.

Microbiological data were retrieved from the patients’ medical files and the hospital laboratory. Microbiological studies were performed at the hospital laboratory according to standard clinical practice. Statistical analysis was performed using SPSS for Windows, version 11.0.1 (SPSS). Continuous variables were compared using Student’s t test or the Mann-Whitney U test, where appropriate. Categorical data were compared using the χ² test or Fisher’s exact test. Data are expressed as mean values (±SD), unless otherwise indicated. A 2-sided P value of <.05 was considered to be statistically significant.

RESULTS

Fungal infection of pancreatic necrosis was present in 17 (37%) of 46 patients with documented infection. Demographic characteristics were similar for patients with and without fungal infection and are summarized in table 1. Disease severity and etiology of acute pancreatitis were not different, although, among patients with fungal infection, there was a trend toward a higher APACHE II score, which was reflected by the tendency toward more cases of organ failure, but the difference between the groups did not reach statistical significance.

Outcome and duration of stay. Overall mortality among these patients was 30.4% (14 of 46 patients) and did not differ between patients with and patients without fungal infection (table 2). There was a trend toward a longer mean ICU stay after the occurrence of fungal infection, but total hospital stay was not different, as was the length of hospital stay after surgical intervention. The mean duration of postoperative continuous lavage was not different between the 2 groups.

Use of antibiotics. Antibiotics, either prophylactic or therapeutic, were administered to the majority of patients for a mean duration of 20 ± 13.5 days (table 3). The mean number of antibiotic schemes used was 2.2 ± 0.8 and did not differ between the 2 groups. For patients with primary Candida infection, the type of antibiotics administered and the mean duration of antimicrobial prophylaxis was the same as those for patients with secondary Candida infection.

Microbiological aspects. Only Candida species were isolated. Candida albicans was cultured most frequently (n = 15), whereas Candida krusei and Candida tropicalis were found in 1 patient each, both of which were cases of secondary infection. For 8 patients, Candida species were yielded on culture of intraoperative specimen obtained during the first surgical intervention (primary infection); for 9 others, Candida infection occurred later during the course of the disease (secondary infection). In the latter group, the mean interval to the onset of infection with Candida species was 10 days after the first surgical intervention.
Microorganisms recovered from patients with fungal infection are summarized in Table 4. Concomitant bacterial infection involving gram-positive bacteria was more common in patients with primary infection, whereas bacterial infection was more likely to be caused by gram-negative bacteria in patients with secondary Candida infection. No blood cultures were positive for fungi.

**Early fluconazole treatment.** Eighteen patients received early treatment with fluconazole. Nine patients received fluconazole prophylaxis, and 9 received preemptive fluconazole therapy after Candida species were cultured from other sites. The incidence of Candida infection in these patients was 16% (3 of 18 patients), compared with 58% in patients who did not receive early fluconazole treatment ($P = .13$). Two patients who received early treatment with fluconazole developed infection with C. albicans only later during the course of the disease, after treatment with fluconazole had been stopped for 3 and 4 weeks. When data for these patients are excluded, the difference between patients who did or did not receive early fluconazole treatment does reach statistical significance ($P = .023$). In 1 patient, a breakthrough infection with C. krusei occurred. At hospital admission, no significant differences were present between patients who received fluconazole prophylaxis and patients who did not (Table 1). The mean duration of hospital stay was not significantly different between both groups, but there was a trend towards a longer mean ICU stay among patients who received early antifungal treatment (Table 2). Mortality among both groups was similar.

The patient who developed a breakthrough infection with C. krusei was a 59-year-old trauma patient who developed severe acute pancreatitis shortly after admission to the hospital. Preemptive treatment with fluconazole was started 9 days after the diagnosis of severe acute pancreatitis was confirmed, because colonization with Candida species was found. She was treated surgically because of infected pancreatic necrosis and treated with necrosectomy followed by continuous postoperative lavage. Thirty-two days after the initiation of fluconazole treatment, C. krusei was cultured from the abdomen, and therapy was switched to amphotericin B. The patient eventually died of multiple-organ failure on the 92nd day after admission.

**DISCUSSION**

In patients with infected pancreatic necrosis, the overall incidence of Candida infection was 37%. If patients who received early treatment were excluded, the incidence of Candida infection was as high as 50%, the highest figure ever described for these severely ill patients.

Among patients who received early antifungal therapy, only 1 breakthrough infection with C. krusei occurred. This study suggests that early fluconazole therapy reduces the incidence of fungal infection in severe acute pancreatitis. In 2 patients, fungal infection occurred weeks after treatment with fluconazole was stopped, and these cases should not be considered treatment failures.

There are several explanations for the increased incidence of fungal infection. First of all, the severity of disease, as assessed by the APACHE II score, is higher than in all other studies on this subject [3, 4, 6]. In general, high APACHE II scores predispose for Candida infection among ICU patients [10, 11].

The role of the increased use of broad-spectrum antibiotics has been suggested by other reports [6]. Our study seems to confirm this association. The total duration of antibiotic prophylaxis was very long, and multiple types of drugs were administered to individual patients, which has been described as a risk factor for the development of Candida infection [12].
The administration of early prophylactic antifungal treatment to almost 50% of the patients makes it difficult to interpret the results of our study regarding the exact roles of both the duration of antimicrobial treatment and the number of antibiotic classes administered on the incidence of primary and secondary intraabdominal fungal infections.

An important factor explaining the long duration of antimicrobial treatment is the trend toward delaying surgery in patients with severe acute pancreatitis. Generally, early surgical intervention is often difficult, and guidelines have been issued to postpone surgery at least until 14 days after hospital admission [13]. A trial comparing early versus late surgical intervention was stopped because of the trend toward higher mortality in the group of patients who underwent early surgical intervention [14]. Apparently, the drawback here is that, when antimicrobial treatment is prolonged, the risk of subsequent fungal infection or the selection of antibiotic-resistant organisms increases.

This study was not a randomized, controlled trial of the effect of antifungal prophylaxis, but the effect of antifungal prophylaxis on the incidence of Candida infection is too important not to be considered. There are certainly other factors involved. We have no obvious explanation for the trend toward an increased ICU stay among patients who received early therapy, but the prolonged duration of continuous postoperative lavage and the trend toward an increased number of secondary infections in these patients suggest a more aggressive and protracted course of the pancreatitis that was not predicted by the initial Ranson and APACHE II scores. The initiation of antifungal therapy was left to the discretion of the treating physicians, and, possibly, some patients with more-severe disease were selected for early fluconazole therapy because of clinical deterioration during the first few days after admission.

The concept of antifungal prophylaxis for high-risk surgical patients is not new but has not been described in reports of patients with severe acute pancreatitis. In their landmark study, Eggiman et al. [7] randomized patients with recurrent gastrointestinal perforations and anastomotic leakages to receive either parenteral fluconazole prophylaxis or placebo. They found a significant decrease in the incidence of Candida infection, which prompted the widespread use of antifungal prophylaxis in patients undergoing abdominal surgery. Winston et al. [15]

### Table 2. Clinical course and outcome for patients with and patients without Candida infection.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Present (n = 17)</th>
<th>Absent (n = 29)</th>
<th>P</th>
<th>Received (n = 18)</th>
<th>Did not receive (n = 28)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of postoperative lavage</td>
<td>17 (6–28)</td>
<td>18 (9–45)</td>
<td>.64</td>
<td>30 (15–45)</td>
<td>13 (5–25)</td>
<td>.02</td>
</tr>
<tr>
<td>ICU stay</td>
<td>26 (9–33)</td>
<td>12 (5–23)</td>
<td>.10</td>
<td>20 (11–47)</td>
<td>11 (5–28)</td>
<td>.06</td>
</tr>
<tr>
<td>ICU stay after first surgical</td>
<td>13 (7–26)</td>
<td>10 (5–22)</td>
<td>.25</td>
<td>15 (8–48)</td>
<td>8 (4–22)</td>
<td>.05</td>
</tr>
<tr>
<td>intervention</td>
<td>81 (35–97)</td>
<td>55 (42–89)</td>
<td>.36</td>
<td>74 (48–95)</td>
<td>56 (31–93)</td>
<td>.26</td>
</tr>
<tr>
<td>Duration of postoperative lavage</td>
<td>56 (18–88)</td>
<td>37 (21–51)</td>
<td>.22</td>
<td>50 (35–73)</td>
<td>40 (14–73)</td>
<td>.20</td>
</tr>
<tr>
<td>ICU stay after first surgical</td>
<td>6 (35)</td>
<td>8 (28)</td>
<td>.41</td>
<td>5 (28)</td>
<td>9 (32)</td>
<td>.72</td>
</tr>
</tbody>
</table>

**NOTE.** Data are median days (interquartile range), unless otherwise indicated.

### Table 3. Data regarding antimicrobial prophylaxis and surgical intervention for 46 patients with infected pancreatic necrosis.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type of Candida infection</th>
<th>No Candida infection</th>
<th>All patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary (n = 8)</td>
<td>Secondary (n = 9)</td>
<td>(n = 29)</td>
</tr>
<tr>
<td>Therapy received, no. (%) of patients</td>
<td>Antimicrobial prophylaxis</td>
<td>7 (87)</td>
<td>8 (89)</td>
</tr>
<tr>
<td></td>
<td>Early antifungal treatment</td>
<td>0</td>
<td>3^b^</td>
</tr>
<tr>
<td>Duration of antibiotic prophylaxis, mean days ± SD</td>
<td>22 ± 7.4</td>
<td>8 ± 7.6</td>
<td>23.8 ± 14.7</td>
</tr>
<tr>
<td>Antibiotic schemes used during prophylaxis, mean number ± SD</td>
<td>2.4 ± 0.5</td>
<td>1.8 ± 0.8</td>
<td>2.2 ± 0.9</td>
</tr>
<tr>
<td>Interval between hospital admission and surgery, mean days ± SD</td>
<td>18 ± 11.8</td>
<td>14 ± 11.1</td>
<td>22 ± 15.7</td>
</tr>
</tbody>
</table>

^a^ See Patients and Methods section for definitions of primary infection and secondary infection.

^b^ Two patients developed a fungal infection after discontinuation of antifungal therapy.
studied patients who had undergone orthotopic liver transplantation and found a decreased incidence of fungal colonization and invasive infection (from 90% to 28% and from 43% to 9%, respectively), as well as lower fungal infection–associated mortality, in patients treated with prophylactic fluconazole. Recently, Garbino et al. [16] demonstrated in a cohort of non-neutropenic critically ill patients that fluconazole prophylaxis reduced the incidence of *Candida* infection (5.8% vs. 16%).

Also, the efficacy of enteral antifungal prophylaxis has been studied in high-risk surgical patients. Pelz et al. [17] randomized 260 high-risk patients to receive either fluconazole (400 mg) delivered enterally or placebo, and they found a 55% reduction in the risk of acquiring fungal infection in the treatment group. Although, in the same study, results of an orally based regimen are promising, and, although the authors presumed excellent bioavailability of the drug, oral administration actually may be problematic in patients with severe intraabdominal sepsis, rendering parenteral administration advisable to ensure systemic efficacy.

There are important risks associated with the use of antifungal prophylaxis, apart from the additional cost, such as the selection of non-*albicans* species of *Candida* with decreased susceptibility or resistance to fluconazole and the induction of resistance in previously susceptible strains of *C. albicans*. In this study, 1 patient developed an infection with *C. krusei* after prolonged therapy with fluconazole.

This problem was also addressed by Safran et al. [8]. They found a 22% incidence of secondary fungal infections that were less susceptible or resistant to antifungal prophylaxis in patients treated with fluconazole. These findings indicate potential problems if the use of antifungal prophylaxis is extended to low- or intermediate-risk patients, and, therefore, the use of antifungal prophylaxis should be carefully considered for each patient, bearing in mind the potential drawbacks of apparently harmless prophylaxis.

In our series, no apparent advantage in terms of survival was associated with antifungal prophylaxis. This raises the question whether antifungal prophylaxis should be administered to such high-risk patients. Other trials studying the prophylactic use of fluconazole in other patient groups, such as patients undergoing orthotopic liver transplantation, found a decrease in the infection rate but not a decrease in mortality [15]. In a retrospective, matched, case-control study on nosocomial candidemia, Blot et al. [18] also found no increased mortality; the overall rate of appropriate therapy was high and may have been a major factor accounting for the absence of attributable mortality. Hoerauf et al. [5] described an increased risk of mortality among patients with acute pancreatitis and fungal infections. It should be noted that, in this study, only 1 of 7 patients with fungal infections who died had received antimycotic treatment at the time of death. This may well explain that fungal infection is a risk factor for mortality.

Use of appropriate therapy for treating these severe intraabdominal infections is of paramount importance and is possibly more important than the effects of the infecting agent that is involved. Clinicians should be aware of the high incidence of *Candida* infection in patients with severe intraabdominal infection and should start empirical therapy early when severe sepsis persists, despite having seemingly achieved full antimicrobial coverage. Administration of antifungal therapy can probably be limited to these circumstances without increased mortality but with decreased costs and decreased risk of selecting organisms less susceptible to fluconazole.

In conclusion, we found a high incidence of fungal infection among patients treated for severe acute pancreatitis. The extensive use of prophylactic antibiotics and the postponement of surgery to a later time are possible explanations for this finding. Mortality is not increased when fungal infections are present. Early antifungal treatment seems to reduce the incidence of infection with *Candida* species, but the effect on the selection of resistant strains and the induction of resistance in *C. albicans* remain important drawbacks. It is unclear at this moment whether there is an advantage associated with antifungal prophylaxis, provided that empirical therapy is initiated early.

### References