Hypothesis: We sought to determine whether the usual risk factors for fungal infections are applied to trauma patients.

Design: Case-control study.

Setting: American College of Surgeons Committee on Trauma–certified Level I trauma center in a tertiary care community hospital.

Patients: Screening of medical records of a consecutive sample of 459 patients aged 16 years or older admitted to an intensive care unit for 4 days or more from 1993 through 1996 identified 20 patients infected with Candida species. Two case controls for each were selected from the remaining patients using sex, age within 5 years, mechanism of injury, and best fit of first 4 Abbreviated Injury Scale scores; the Injury Severity Score and intensive care unit length of stay were also used if needed.

Interventions: None.

Results: Univariate analyses by t and χ² tests showed significance (P<.05) for number of units of blood transfused in the first 24 hours after injury, gastrointestinal perforation, hemodialysis, and total parenteral nutrition. Steroids, fungal colonization, use of central venous catheters, Acute Physiology and Chronic Health Evaluation II score, mechanical ventilation for 3 days or more, and the number and duration of antibiotics were not significantly different. Logistic regression analysis showed that only total parenteral nutrition was an independent risk factor in this trauma population.

Conclusion: Many of the classic risk factors for fungal infection in other populations are actually concomitants of injury severity and its requisite level of care in trauma patients. Hyperalimentation in persistently critically ill trauma patients significantly increases the risk of Candida infection.


The critically ill injured patient is immunosuppressed, invasively monitored, and exposed to microbial pathogens at the time of injury and while residing in the intensive care unit (ICU). The incidence of nosocomial infections by Candida species has surged over the past decade, from the eighth to the fourth most common cause of nosocomial bloodstream infection in the general hospital population. In surgical patients, the incidence of Candida infections has increased from 2.5 to 5.6 per 1000 discharges, with mortality rates of 30% to 75%. The mortality rate due to candidemia is 38%, with almost half of the deaths occurring in the first week after diagnosis.

Most reports are drawn from general hospital populations, or general surgery, burn, and oncology services. In these reports, the predisposing factors include hematological malignancy and myelosuppression, solid organ tumors, neutropenia, intravascular devices and hyperalimentation, skin damage, gastrointestinal surgery, infancy, antimicrobial therapy, and adrenal corticosteroid therapy. Few reports specifically concern the trauma patient population. Isolates of Candida species were recovered in up to 22% of trauma patients who did not respond to antibiotics while in the critical care unit and more than 18% of patients who stayed in a surgical ICU for more than 3 days. Reports of increasing infection rates combined with the frequent presence of such risk factors in critically ill trauma patients has led to recommendations for both prophylactic and early presumptive use of antifungal therapy. However, one result of widespread use of powerful antifungal drugs administered for increasingly broader indications has been a dramatic increase in the isolation of nonalbicans.
MATERIALS AND METHODS

CASE FINDING

This investigation was carried out as a retrospective, case-control study. The trauma registry at the Legacy Emanuel Hospital Level I trauma center, Portland, Ore, was used to search all admissions from January 1, 1993, through December 31, 1996. There were 4631 admissions of patients aged 16 years or older, and 1746 spent at least 1 day in the ICU. All patients admitted to the ICU for 4 or more days were eligible for the study. Of 464 such patients, 460 medical records were found and screened by trained reviewers for any evidence of fungal infection or treatment. All positive records were also reviewed by us. Using predetermined definitions, infected patients were identified and their medical records were abstracted in detail.

Case controls were selected at a 2:1 ratio from the remaining sample population using the following characteristics in a stepwise fashion: sex, mechanism (blunt or penetrating), age within 5 years, and best fit of the first 4 Abbreviated Injury Scale scores. The latter is a unique approach that accounts not only for specific areas of injury, but also for multiple injuries in a given body area, patterns obscured when using only the final Injury Severity Score. Body area of injury was believed to be an important potential confounding variable for risk for fungal infection and it was thought that using the Abbreviated Injury Scale score would best control for this variable. For example, abdominal surgery has been cited as a specific risk factor for yeast infections. Length of stay in the ICU and final Injury Severity Score were secondary considerations for matching. Third controls were sometimes chosen to balance injury patterns or length of stay. The control patients were selected without knowledge of their outcome.

RISK FACTORS

Previously defined risk factors were abstracted from medical records. Risk factors recorded as yes (factor present or treatment delivered) or no (not present) included steroids, dialysis, burns, gastrointestinal tract perforation, and hyperglycemia (a blood glucose level >9.99 mmol/L, [>180 mg/dL] for 48 hours or longer). Continuous variables included colonization with yeast (as the number of sites), the Acute Physiology and Chronic Health Evaluation (APACHE) II score on the first injury day, and the number of units of packed red blood cells transfused in the first 24 hours after injury. The number of days of exposure was obtained for the following: total parenteral nutrition (TPN), central venous devices, and mechanical ventilation, all of which were also analyzed as yes/no variables.

Antibiotic therapy was counted in terms of days of exposure to treatment and number of antibiotics given for 24 hours or longer, including those given prophylactically. The number of antibiotics was further categorized as none to 2 or 3 or more. A broad-spectrum drug was defined as second- or third-generation cephalosporins, lactamase-resistant forms of drugs, or combinations of narrower-spectrum drugs used simultaneously. All specimens obtained for culture were recorded by site and microbe, if any.

DEFINITIONS

Candidemia was defined by the isolation of yeast in at least 1 blood culture. Catheter-related candidemia occurred when the same species of Candida was isolated in the blood and if more than 15 colony-forming units were found in semi-quantitative culture of an intravascular device. Yeast isolated from any sterile area such as the pleura, peritoneum, or other site was considered a pathogen, including specimens with concurrent bacterial isolates. Funguria was considered evidence of systemic infection regardless of whether a bladder catheter was in place if the patient had signs of sepsis and no bacterial pathogen at the same or a remote site and if there were 10^5 colonies or more per milliliter; if all of these criteria were not met, the bladder was considered colonized. Patients with any amount of Candida growth from 2 or more sites who had a fever (temperature >38.5°C), a white blood cell count greater than 12 × 10^9/L, opened infections between 11 and 55 days following injury, mainly in the bloodstream and at pulmonary sites.

Three (15%) of 20 infected patients died: one 79-year-old woman owing to candidemia, Pseudomonas pneumonia, and Enterococcus bacteremia infection; a 27-year-old man owing to multiple organ failure due to progressive peritonitis; and a 55-year-old man from whom support was withdrawn when renal failure added to respiratory failure, thereby complicating steroid-dependent chronic obstructive pulmonary disease. Three patients (6.7%) died in the control group: a 73-year-old woman owing to multiple organ failure; a 38-year-old man owing to anoxic brain injury, renal failure, and pneumonia; and a 54-year-old man owing to pulmonary embolus. All 20 infected patients received fluconazole in doses ranging from 100 to 400 mg/d for 4 to 35 days. Five received amphotericin B for 2 to 21 days.

Mucosal and skin colonization occurred in 152 patients (32.8%): 108 at a single site, 35 at 2 sites, and 9 at 3 sites. The sites from which yeasts were cultured are listed.
and no coexisting bacterial isolates from clinical specimens within 48 hours of the fungal isolate were considered to have yeast sepsis.22

For the purpose of the initial screening of the medical records, colonization was broadly defined as cultures growing yeast, a clinical narrative report of typical yeast colonization (thrush, vulvovaginal, intertrigenous skin), and/or the use of topical antifungal drugs. An empiric course of intravenous antifungal therapy with no demonstrated yeast isolates in any specimen was not considered to represent a *Candida* infection. No patient demonstrated disseminated candidiasis marked by embolic cutaneous, ocular, or deep tissue invasion with or without candidemia.

**MICROBIOLOGIC STUDIES**

Blood cultures were drawn by the nursing staff using the standard broth blood culture system (Bectec; Johnston Laboratories, Towson, Md). Blood cultures are reported in this article as growth in a set; that is, as growth in either or both of 1 aerobic and 1 anaerobic bottle. Body fluids were plated onto Sabouraud agar and colonies were identified using the Vitek method (Vitek Systems, Hazelwood, Miss) and assimilation of carbohydrate and nitrogen and fermentation of carbohydrates. This system was in use throughout the review.

**CLINICAL PRACTICES**

The ICU in which these patients resided is a mixed surgical specialty ICU with an open staffing pattern, although trauma patients are cared for by the trauma surgery service. Sucralfate is preferred for gastritis prophylaxis over histamine2 blockers. Routine surveillance cultures of patients in the ICU are not done. All cultures are obtained for the usual clinical reasons: to speciate the cause of purulence or to search for a cause of fever and leukocytosis. Indwelling, thermistor-equipped urinary bladder catheters are routinely used in all patients. Only urine specimens suggestive of infection by urinalysis are fully cultured.
Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>All*</th>
<th>Control</th>
<th>Infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>459</td>
<td>45</td>
<td>20</td>
</tr>
<tr>
<td>Sex, % men</td>
<td>70.2</td>
<td>56.8</td>
<td>60</td>
</tr>
<tr>
<td>Mean ± SEM age, y</td>
<td>42.9</td>
<td>39.2</td>
<td>38.6</td>
</tr>
<tr>
<td>Mechanism of injury, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunt</td>
<td>91.6</td>
<td>84.1</td>
<td>75</td>
</tr>
<tr>
<td>Penetrating</td>
<td>8.4</td>
<td>15.9</td>
<td>25</td>
</tr>
<tr>
<td>Mean ± SEM Injury Severity Score</td>
<td>29.2</td>
<td>32.4</td>
<td>29.1</td>
</tr>
<tr>
<td>Mean ± SEM length of stay, d</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospital</td>
<td>21.5</td>
<td>20.0</td>
<td>39.8</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>9.7</td>
<td>9.9</td>
<td>20.4</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>10.8</td>
<td>6.7</td>
<td></td>
</tr>
</tbody>
</table>

* All indicates entire sample of patients in the intensive care unit for 4 days or more.
†P < .001 compared with infected cases.

Table 2. Candida Species in Both Infected and Colonized Sites in Infected Patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Species</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Candida albicans</td>
</tr>
<tr>
<td>Blood</td>
<td>6</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>4</td>
</tr>
<tr>
<td>Peritonitis</td>
<td>6</td>
</tr>
<tr>
<td>Respiratory†</td>
<td>2</td>
</tr>
<tr>
<td>Urine</td>
<td>2</td>
</tr>
<tr>
<td>Pleura</td>
<td>1</td>
</tr>
<tr>
<td>Sinus</td>
<td>1</td>
</tr>
<tr>
<td>Wound</td>
<td>1</td>
</tr>
<tr>
<td>Abscess</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
</tr>
</tbody>
</table>

* Ellipses indicate data not available.
† Respiratory indicates tracheal or bronchoscopic aspirates, not tissue culture.

The number and duration of antibiotics used prior to fungal isolation are not significantly different compared with control patients (Table 3). No difference was found when the number of antibiotics was dichotomized into categories of 2 or less or 3 or more drugs. Throughout their hospital course, infected patients received significantly more antibiotics (exclusive of antifungal agents) (5.2 ± 0.5) given for significantly longer (22.8 ± 2.0 days) than control patients (2.4 ± 0.3 and 10.5 ± 1.3 days, respectively).

Microbiological findings of the infected and control cases are presented in Table 5. Concomitant bacterial infections were considered clinically relevant isolates from any site within 48 hours of a candidal isolate.

Three patients with sustained fever and leukocytosis and signs of sepsis had Candida alone isolated as a pathogen: 1 with budding, mycelial forms in the upper respiratory tract; a quadriplegic patient with candiduria who had an indwelling bladder catheter; and 1 with CVC-related candidemia. Six patients had candidal isolates with simultaneous bacterial pathogens at anatomically remote sites. Eleven patients had mixed yeast and bacterial infections, including peritonitis (6 patients), pneumonia/
tracheobronchitis (4 patients), empyema (1 patient), bacteremia (1 patient), sinusitis (1 patient), and deep-wound infection (1 patient). If more restrictive definitions are applied to the same population (that is, *Candida* infection defined as fungemia or exclusive isolation of yeast from a usually sterile site in a septic host), only 8 cases occurred in 459 patients housed in the ICU for longer than 3 days, an incidence of 1.7%.

A forward conditional logistic regression was performed using categorical (yes/no) variables of TPN, CVC, steroids, hemodialysis, gastrointestinal tract perforation, and the number of antibiotics used as a single continuous variable (throughout the hospital course in the control group but only prior to yeast isolation in the infected group). Only TPN (*P* < .001) was independently associated with fungal infections.

### Table 4. Days of Exposure to Risk Factors in the Hospital

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control Cases, Total Days</th>
<th>Index Cases, Total Days</th>
<th>Prefungal Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>10.5 ± 1.3 (45)</td>
<td>22.8 ± 2.8† (20)</td>
<td>8.8 ± 1.6 (20)</td>
</tr>
<tr>
<td>Central venous catheters</td>
<td>10.5 ± 1.2 (37)</td>
<td>23.6 ± 2.9† (20)</td>
<td>10.2 ± 2.0 (18)</td>
</tr>
<tr>
<td>Enteral feeding</td>
<td>11.4 ± 1.6 (40)</td>
<td>18.7 ± 3.8 (15)</td>
<td>4.9 ± 1.7† (12)</td>
</tr>
<tr>
<td>Total parenteral nutrition</td>
<td>10.0 ± 5.6 (5)</td>
<td>17.0 ± 2.5 (17)</td>
<td>5.4 ± 1.6 (15)</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>9.6 ± 1.7 (43)</td>
<td>21.5 ± 5.4† (20)</td>
<td>10.6 ± 2.8 (19)</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± SEM (number of patients).
†*P* < .05, t test.

### Table 5. Microbiological Findings in Patients Infected With *Candida* and in Control Patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Infected Site</th>
<th>Control, Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Central catheter</td>
<td>&gt;15 CFU/TIP</td>
<td>1</td>
</tr>
<tr>
<td>No growth</td>
<td>6</td>
<td>24</td>
</tr>
<tr>
<td>Respiratory</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>Sinuses</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Urine</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound/drains</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedic</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bacterial isolates</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CFU indicates colony-forming units; TIP, tip of catheter; ellipses, data not available.

A powerful finding in this study is the low rate of fungal infections in a large group of badly injured, critically ill trauma patients who do not receive antifungal prophylaxis. The infection rate is 4.4%, compared with 18% to 22% in other centers. This rate may be elevated by the definitions of infection used in the study design. A few of the usual risk factors for *Candida* infection were found to pertain to trauma patients in the ICU, and only the use of TPN is independently correlated. A complex set of interactions is necessary for these ubiquitous commensal organisms to become pathogenic. Failures of local or systemic immunity are implicit in fungal infections. In this sense, risk factors can be considered predisposing conditions that alter host defenses (chemotherapy, immunosuppressive drugs, corticosteroids, or acquired immunodeficiency syndrome) or actions that breach them (open wounds, gut perforations, intravascular devices, or hemodialysis). Prior treatment with broad-spectrum antibiotics may be an important factor in altering colonization and permitting yeast numbers to increase to a concentration at which they become pathogenic.

The presence of a CVC was not significant as a risk factor, although the duration of use was significantly greater in the index than the control group. Central venous catheter use is a risk factor for candidemia in some previous studies. For Marsh et al, catheters, TPN, and antibiotics increased risk, but only conjointly and not as independent variables. The administration of fluids and medications in very ill patients for long periods often requires CVCs, reflected by the presence of CVCs in 85% to 100% of patients in many studies of candidemia; however, when use is controlled for by multivariate analysis, CVCs are not independent risk factors. Further, in a prospective cohort study of routine surveillance cultures in a surgical ICU, CVCs were not a risk factor for fungal infections.

Central venous catheter infections are associated with the site of placement, local site care, and the composition of the devices themselves. Careful attention to the mechanics of skin preparation and routine site care are beneficial, and risk increases with the degree of difficulty at the time of insertion. Safety increases with the use of antiseptic-impregnated catheters (such as the ones used in our center), subdermally inserted cuffs impregnated with slowly released silver compounds, or catheters manufactured with antibiotics. Pulmonary artery catheters can be used safely to deliver TPN in the critical-care unit, at least for brief periods, but multilumen CVCs create an increased risk for infection compared with single-lumen devices, particularly when used to deliver TPN. Removal of any intravascular device associated with candidemia is generally recommended.

Total parenteral nutrition was significantly and independently associated with fungal infections here and in other studies, and remained an independently associated variable using logistic regression analysis. Four possible mechanisms are described. One is that hyperalimentation fluid is an excellent medium, with in vitro growth curves showing a selective advantage of *Candida* species over bacteria. Another is that frequent entry into a TPN delivery sys-
tem increases the likelihood of contamination.35 Although our hospital’s policy is not to invade TPN delivery systems, it is quite likely that this happens in the ICU.

A third mechanism is the immunosuppressive effect of long-chain unsaturated fatty acids used in intravenous lipid emulsions. Linoleic and linolenic acids inhibit several immune responses in human and murine cells.34 When trauma patients were randomized to receive intravenous glucose plus fat emulsions or glucose only during TPN, the lipid group had more infections.35 Nevertheless, there is conflicting evidence that lipids impair polymorphonuclear cells, macrophage or reticuloendothelial system function, or have a clearly adverse clinical effect.36,37

A fourth mechanism may be TPN-induced hyperglycemia, which in turn alters host defenses. Although no significant difference in the frequency of hyperglycemia existed between the index group (20%) and controls (26.7%) in the current study, Hostetter38 showed that a blood glucose level higher than 11.1 mmol/L [≥200 mg/dL] within 3 days of isolation of Candida was the most common risk factor for hospitalized patients. Overett et al39 found that CVC infections were 5 times more frequent in diabetic patients compared with nondiabetic patients given the same TPN solution.

This article suggests another mechanism by which TPN may be linked to candidiasis: via its opposite relationship to enteral nutrition. Three quarters of the index cases received TPN for at least 5 days prior to fungal isolation, compared with only 11% of control patients. The difference was not owing to surgeon preference for the parenteral route, but was related to gut dysfunction, even with jejunal feeding. The gut was not so much rested as it was unusable for nutritional support, and TPN was the only alternative. Total parenteral nutrition is associated with increased bacterial translocation in animal models, with decreased peritoneal macrophage superoxide production and Candida phagocytosis40 and similar impairments in alveolar macrophages.41 In small-animal models, infusion of lipids shifts the distribution of injected bacteria from splenic sequestration to accumulation in the lungs.37 That this phenomenon may occur in humans is suggested by trials comparing enteral to TPN support in trauma patients. Enteral nutrition reduces infection rates, particularly due to pneumonia, but also from intra-abdominal abscesses.42-43

Several factors enhance translocation of microbes across the intestinal barrier. Candida species are commonly found in the oropharynx, esophagus, and rectum of humans, and will increase in density owing to antibiotic suppression of competing bacteria.44 At high concentrations, yeast will pass across even the intact, healthy gut,45 which occurs more easily when the intestinal barrier is disrupted by operation, trauma, or disuse atrophy associated with TPN. Some Candida species, such as Candida tropicalis, are more invasive of the gastrointestinal tract than C. albicans.46 Once the mucosal barrier is breached, immune defects associated with the host response to severe injury and to blood transfusions may predispose patients to disseminated infection.

Colonization is associated with increased rates of hematogenous candidiasis in patients with cancer and neutropenia,47 and was an independent risk factor for candidemia in a university hospital population.48 Positive surveillance cultures were predictive of systemic infection,49 and severity of illness and the intensity of colonization independently increased risk for later candidal infection in a surgical ICU population. However, we could identify no increased risk for candidemia, disseminated disease, or mortality associated with colonization in our study. Colonization occurred in 152 trauma patients (33.1%), 12 of whom died (7.9%), compared with 35 deaths (11.4%) in 307 noncolonized patients (χ² test, P>.10). It is possible that a microbiological laboratory-based definition of colonization, rather than the less precise one used here, may have led to findings similar to previous reports. However, the low intensity of growth in the clinical specimens (usually described as “scant” or “light”) suggests that a lower burden of candidal growth may account for the failure to identify colonization as a risk factor. Although Solomon and Anaissie50 recommend prophylactic fluconazole in ICU patients with Candida colonization, this practice does not lower the yeast sepsis rate51 and is associated with a significant frequency of secondary mycoses, which have a 38% suspected infectious mortality rate.12 This phenomenon occurred in 2 patients in this series. One patient was treated for 35 days with fluconazole for persistent C albicans as indicated by peritoneal and wound drain cultures, which evolved to Candida krusei on day 29. A second patient began with Candida albicans in the peritoneum, and after a course of fluconazole had Torulopsis glabrata in the pleura.

Candida species are frequently cultured from intra-abdominal abscess or peritoneal fluid, but rarely result in disseminated candidiasis except in immunocompromised patients.52 Their isolation requires only routine drainage and treatment of the bacterial infection. The presence of yeast may put a debilitated patient at risk of serious infection rather than act as a commensal organism.53 Patients who go on to develop systemic Candida infections have recurrent intra-abdominal infections and/or extensive communication with the external environment through drains or fistulas. The study by Solomon et al51 dealing with purulent peritonitis in 55 patients lowered a 70% mortality rate to 33% if amphotericin B was administered prior to candidemia, but it excluded patients with acute peritoneal contamination by yeast-containing enteric contents, as in this study.

Rutledge et al49 found no localized intraperitoneal or systemic complications in the peritoneal fluid or in 24 intra-abdominal abscesses in 39 patients with Candida who were not given antifungal therapy. All 6 patients with peritoneal Candida isolates in this study had polymicrobial infections, and all underwent drainage and received antibacterial and antifungal therapy. Three also had Candida in the urine, pleura, mouth, or skin. Two had persistent fungal isolates from abscesses, drains, or wounds, and 1 died of multiple organ failure despite amphotericin B therapy. Patients with repeated isolation of Candida species from peritoneum or drains or with multiple risk factors can be treated with antifungal agents.19

To our knowledge, this is the first report of an association between candidiasis and red blood cell trans-
fusions. During the first 24 hours of hospitalization, 7 index cases (35%) had fewer than 5 blood transfusions and 65% received 23.1 ± 3.6 U, compared with 26 (58%) of control patients with fewer than 5 and the remainder given 13.9 ± 1.6 U (P < .05). Rosemurgy et al52 reported an average of 18 ± 3 U of blood transfused per person in a review of 33 trauma patients with candidiasis, but had no control group for comparison. Blood transfusions have immunomodulatory effects that may lead to an increased frequency of postoperative infections.53 Aside from any immunologic influences of blood transfusion itself, hemorrhage and resuscitation produce immunosuppression due to increased prostaglandin E2 production, suppressor-soluble serum factors, suppressor cell appearance, decreased cellular adenosine triphosphate level, and altered calcium homeostasis.54 Thus, the severity of hemorrhage and/or the magnitude of red blood cell transfusions may be risk factors for candidiasis particular to trauma patients.

The role of corticosteroid therapy as a risk factor is repeatedly found in studies involving preterm infants,55 leukemic children,56 surgical patients,2 and in a case-control study of a general hospital population. But Karabinis et al58 did not identify steroids as a risk factor using multivariate analysis in a case-control study of patients with cancer, nor was their use a prognostic indicator of mortality in fungemic surgical patients.57 Steroids were not statistically important in our population, most likely owing to too few examples for reliable statistical analysis.

Severity of illness defined by an APACHE II score greater than 10 has been reported as a risk factor,13 and independently predicted Candida infections in a multivariate analysis by Pittet et al.24 When coupled with candiduria, an elevated APACHE II score predicted disseminated disease, and was considered an indicator for early empiric antifungal therapy.10 The APACHE II scores were no different in control and infected cases in the present study, whether considered as continuous variables or as a categorical variable (score >10). Most likely, it is the excessive weight of the Glasgow Coma Scale component of APACHE II in trauma patients, as opposed to general surgical or medical patients, that may account for this disparity with earlier reports.

This population of critically ill ICU patients with Candida infections is characterized by a high incidence of gut perforations and a sustained need for TPN, implying prolonged dysfunction of the gastrointestinal tract. The use of corticosteroids or hemodialysis is simultaneously a sign of progressively deteriorating physiology and indicates an abrogation of immune defenses. Our finding that neither number of antibiotics nor duration of antibiotic use were significant risk factors for candidiasis is of particular interest. Although many studies have associated antimicrobials with increased risk, most of the studied patients also had severe deficiencies in host defenses.56 In immunosuppressed patients with leukemia, candidiasis was more closely associated with the duration of leukopenia and steroid therapy than with antimicrobial therapy.59 It may be that restrictive antibiotic ordering practices and a policy of early enteral nutritional support combine to minimize multiplication of a common enteric commensal organism into numbers sufficient to overcome local host defenses. As a result, we cannot support recommendations favoring routine systemic antifungal therapy for most critically ill trauma patients. Such policies have led to a progressive shift toward resistant species of Candida in less than a decade. Further investigation into the roles of antibiotic ordering policies, use of surveillance cultures, alternatives to enteral nutritional support, and control of local immune systems needs to be done before such recommendations are generally put into effect.

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at best in defining whether infection exists. So I am really cur-
rious as to whether you have reexamined the data in just look-
ing at blood-borne infections. Obviously that is problematic for
you because there are only 7 in the entire series.

Dr Borzotta has identified that the duration of antibiotics did
not seem to be predictive of Candida infection. However, he hasn't
really tried to detail the types of antibiotics. I am absolutely con-
vinced that our continued practice of obliterating anaerobic colo-
nization of the patient when they are in the ICU and experienc-
ing nosocomial infections, which are never anaerobic, proves to
be a liability for the host. Anaerobes are in fact man's best friend
when they are colonizing the colon. They are not our best friend
when they are in our soft tissues and in our peritoneal cavity. So
one of the questions that arises is whether anaerobic antibiotic
administration on an aggressive and long-term basis in the set-
ting of the ICU patient may selectively be a negative issue. I would
be interested in whether he has examined the presence or ab-
sence of anaerobic bacterial activity in the antibiotics as a vari-
able in predicting Candida infection in his situation.

Everybody likes to bash on total parenteral nutrition (TPN).
I am now old enough to remember when it was considered the
saving grace of surgical science. I am curious as to whether we
might take the flip side in this argument and say, not that TPN
is bad, but rather that enteral feeding is good. Dr Borzotta noted
in his comments that the TPN patients receiving TPN did so late
in their course, and that patients receiving enteral feeding did
so earlier in their course. The question then is whether Can-
dida can be prevented by going to fewer antianaerobic antibi-
otics in our ICU and earlier applications of enteral feeding.

Michael A. West, MD, Minneapolis, Minn: I would also
like to compliment Dr Borzotta on a very nice presentation and
particularly compliment him on the relatively low use of an-
tibiotics in the ICU where only a couple of patients in the ICU
for the greater than 3 or 4 days were on more than one antibi-
otic. Several of the patients were not on any antibiotics at all.

My question relates to the very marked difference seen in
the infected patients vs the control patients in the duration of
time in the ICU. Is this because they developed infection, or
did they develop infection with Candida because they were in
the ICU for a long time? Was there a difference in the duration of
ICU treatment prior to the development of the infection?

Basil A. Pruitt, Jr, MD, San Antonio, Tex: I think that you
were wise to confine your conclusions to Candida and not gen-
eralize to all fungi since the true or filamentous fungi are quite
different. Candida often colonize and seldom invade so I would
ask whether you had occasion to look at other fungi in this popu-
lation of patients since true fungi often invade and can be quite
troublesome. Infections caused by true fungi have been found
to be associated with acidosis, so I ask whether acidosis was a
common risk factor in your ICU population. Since the length of
stay in the ICU was more than twice as long in the candida-
demia patients or candidiasis patients, how could you control
for antibiotics? In most critically ill populations, candidiasis
is a perversely index of management success. In burn patients, can-
didemia, on the average, occurs 33 to 41 days after injury and
candidal infections correlate with repetitive or prolonged an-
tibiotic treatment. I am quite surprised that in your patients
with candidal infections with over twice as long a stay in the
ICU that there was no correlation with antibiotic therapy.

Katherine J-M Liu, MD, Chicago, Ill: I also thoroughly
enjoyed this article regarding a very difficult problem that we
see in some of the very ill patients. My question concerns the
nutritional support of these patients. As you stated, parenteral
nutritional support in the control group was initiated early dur-
ing the course and later in the study patients. My question is
whether there was any difference in nutritional status be-
tween the 2 groups, and when the study group was initiated
later, could this lack of nutritional support actually have con-
tributed to the fungal infection? Also, as you all know, the pro-
tocol for care for the parenteral nutritional support, the types
of catheters, and many other factors involved influence the
fection rate in patients receiving the parenteral nutrition. I won-
dered if you can comment on these aspects.

Dr Borzotta: There is very little I can do about a type 2
error. I think it is apparent that we had relatively few cases, and
it is most obvious in terms of the use of steroids. If we had
a few more cases, I suspect that would have shown statistical
significance on a univariate basis.

None of the patients really had prophylaxis in the index
group. Three patients did have prophylaxis in the control group
for as long as 9 days, but there were no Candida isolates or there
was simply 1 respiratory Candida isolate in 1 of the 3 cases.

Yes, our dosing tended to be low. There has been an evo-
 tion over the last 5 years of dosing recommendations from a
minimum of 100 mg/d up to the very large 600 or 800 mg/d
doses. Interestingly, in leukemias there is a nice article show-
ing that low-dose amphotericin at half the usual dose is an ex-
cellent prophylaxis against candidiasis. I think it is not going
to be the case with fluconazole. There is going to be selective
pressure on the many Candida varieties in a given human be-
ing for potential overgrowth.

At this time we are just using any antifungal prophylaxis.
We simply treat as we see an infection arises and I think we
have backed away from putting fluconazole into patients just
because we find Candida during an acute enteric spill.

Dr Fry's comments are interesting. There was one candi-
duria case really that occurred on the ward. He had an fever of
unknown origin for 2 weeks. He had progressively increasing
numbers of colonies of Candida in the urine and finally broke
the 100,000 mark and so was put on a course of treatment which
effectively resolved his septic state.

Among the 7 candidemia patients, there were 3 concur-
rent bacteremias. There was only 1 preceding bacteremia, which
has been considered a risk factor. The date of onset of candi-
demia was 2 weeks after injury. The mean population onset was
13.5 days, but a significant number, to address one of the other
questions, occurred 3 to 4 weeks into their hospital course. Wey
and others have shown that candidemia, in particular, may not
show itself for 4 weeks after the onset of illness, admission to
the ICU, or date of injury.

The question regarding other fungi by Dr Pruitt: we ac-
tually set out to look for all fungal isolates, but all we found
were Candida. We did not find any other zygomycoses or other
kinds of nonyeast pathogens.

I don't have information about acidosis as a specific risk
factor in this group.

The use of antibiotics, TPN, and mechanical ventilation
were significantly longer throughout the entire ICU course in
the infected patients than in the control patients. It's very hard
to find a time to cut off use of central venous catheters in the
control group for comparison purposes. In the infected group,
it is obviously when the fungal isolate occurred, that being at
about 10 days. There is roughly a 2-day difference between the
infected group and the control group in terms of central ve-
 nous catheter use. I suspect this is not significant but I have to
look at that mathematically.

Dr Liu, I think TPN plays multiple roles here. It's partly a
reflection that the gut won't allow enteral nutrition to be done.
It's life-saving in that regard. It may increase risk itself, but it
may also be a marker of a patient at increased risk because of
multiple systems being dysfunctional. We use Arrowgard cath-
eters, multilumen, to deliver our TPN. We also deliver it via a
Swan-Ganz catheter, which is relatively safe early on, and then
we switch over to enteral feeding as soon as feasible.