**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 $\chi^2$ 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.

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.10 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.2,3 Length of stay in the ICU and final Injury Severity Score20 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 were further categorized as none to 2 or 3 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.23 Catheter-related candidemia occurred when the same species of Candida was isolated in the blood and if more than 1 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 105 colonies or more per milliliter; if all of these criteria were not met, the bladder was considered colonized.22 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 × 109/L,

Candida species, and resistant forms of Candida.18,12 We hypothesize that the commonly stated risk factors for fungal infections also apply to trauma patients, and that the presence of multiple risk factors requires routine antifungal prophylaxis in this population.

RESULTS

Age, sex, and mortality rates were not significantly different among the entire ICU cohort and the infected and control patient groups (Table 1). Significantly more infected patients incurred penetrating injuries than the entire population (there is a 12.88 ratio of penetrating to blunt injuries at this center). Length of stay in the ICU and hospital were significantly longer for the infected patients, but not between controls and the total population. In 9 patients, the isolation of yeast was within 8 days of injury (4 in the pleura and 3 in the peritoneum, and 1 each in the bloodstream or wound), which is typically associated with penetrating trauma. Eleven patients developed 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, Mo) 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 speculate 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.

by species in Table 2. Candida albicans was the most commonly identified pathogen in this series (73%), with an almost equal distribution of other species, including Candida glabrata. There are insufficient numbers of non-albicans species to draw any conclusions concerning characteristic sites of infection.

Seven cases of candidemia occurred (36.8% in the infected group, or 1.5% in the entire study population) and the mortality rate was 28%. Five catheters had 15 or more colony-forming units of Candida species, and none of the 7 catheters were infected or colonized with bacteria. There were 3 concurrent bacteremias (15%) in the infected group (of 59 paired sets of blood cultures in 17 patients, with 3 contaminated sets). One control patient (2%) had persistent Staphylococcus aureus bacteremia for 6 days (of 109 sets in 21 patients, with 4 contaminated sets).

In addition to the risk factors listed in Table 3, all patients had indwelling urinary bladder catheters, only 1 patient was burned, and no patients had malignant neoplasms, neutropenia, human immunodeficiency virus infection, or were receiving chemotherapy. Steroid use, colonization with candida, the presence of a CVC, the initial 24-hour APACHE II score, and mechanical ventilation for 3 or more days were not significantly different between the 2 groups. Risk factors significantly greater among infected patients than controls by univariate analysis include the number of units of blood transfused in the first 24 hours after injury, gastrointestinal perforation at any time during the ICU course, hemodialysis, and the use of central parenteral nutrition.

The infected patients required more invasive support for longer periods than the controls, as presented in Table 4. Significant differences occurred in total hospital days of CVC use (infected patients, 23.6±2.9 vs controls, 10.5±1.2), of TPN administration (infected patients, 16.0±3.0 vs controls, 10.0±5.6), and mechanical ventilation (infected patients, 21.3±3.4 vs controls, 9.6±1.7). However, when these last 3 variables are mean-
### Table 1. Patient Characteristics

<table>
<thead>
<tr>
<th>Variable and Group</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 ± 1.0</td>
<td>39.2 ± 2.5</td>
<td>38.6 ± 3.4</td>
</tr>
<tr>
<td>Mechanism of injury, %</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</td>
<td>29.2 ± 0.6</td>
<td>32.4 ± 1.8</td>
<td>29.1 ± 2.5</td>
</tr>
<tr>
<td>Severity Score</td>
<td>21.5 ± 1.9</td>
<td>20.0 ± 1.7</td>
<td>39.8 ± 4.0</td>
</tr>
<tr>
<td>Mortality, %</td>
<td>10.8</td>
<td>6.7</td>
<td>25</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>Candida albicans</th>
<th>Candida parapsilosis</th>
<th>Candida krusei</th>
<th>Candida lusitania</th>
<th>Candida glabrata</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td>6</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Central venous catheter</td>
<td>4</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Peritoneum</td>
<td>6</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Respiratory†</td>
<td>2</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Urine</td>
<td>2</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Pleura</td>
<td>1</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Sinus</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Wound</td>
<td>1</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Abscess</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td>1</td>
<td>...</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

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

### Table 3. Case-Control Statistical Analysis of Risk Factors for Candida Infections in Trauma Patients

<table>
<thead>
<tr>
<th>Variable and Group</th>
<th>Result</th>
<th>f Test</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics, d</td>
<td>Infected</td>
<td>8.9 ± 1.5</td>
<td>.44</td>
</tr>
<tr>
<td>Control</td>
<td>10.4 ± 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotics, No.</td>
<td>Infected</td>
<td>2.3 ± 0.3</td>
<td>.77</td>
</tr>
<tr>
<td>Control</td>
<td>2.4 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GI perforation, %</td>
<td>Infected</td>
<td>100.31</td>
<td>−0.254 to 0.032</td>
</tr>
<tr>
<td>Control</td>
<td>89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dialysis, %</td>
<td>Infected</td>
<td>20.03</td>
<td>−0.316 to 0.040</td>
</tr>
<tr>
<td>Control</td>
<td>2.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enteral nutrition, %</td>
<td>Infected</td>
<td>85</td>
<td>0.367 to 0.118</td>
</tr>
<tr>
<td>Control</td>
<td>70.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gl perforation, %</td>
<td>Infected</td>
<td>55.02</td>
<td>−0.376 to 0.118</td>
</tr>
<tr>
<td>Control</td>
<td>15.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRBC, No.</td>
<td>Infected</td>
<td>15.2 ± 3.4</td>
<td>0.02</td>
</tr>
<tr>
<td>Control</td>
<td>7.9 ± 1.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steroids, %</td>
<td>Infected</td>
<td>20.017</td>
<td>−0.299 to 0.032</td>
</tr>
<tr>
<td>Control</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose &gt; 9.99 mmol/L (≥180 mg/dL), %</td>
<td>Infected</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td>22.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPN, d</td>
<td>Infected</td>
<td>17 ± 2.5</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control</td>
<td>10 ± 1.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TPN, %</td>
<td>Infected</td>
<td>85</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Control</td>
<td>15.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>≥3 d, %</td>
<td>85</td>
<td>1.00</td>
</tr>
<tr>
<td>Control</td>
<td>82.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Data are reported as mean ± SEM unless otherwise indicated. Colony indicates number of body sites colonized; APACHE II, Acute Physiology and Chronic Health Evaluation II; CVC, central venous catheter; dialysis, use of hemodialysis; GI perforation, gastrointestinal perforation at any time during the hospital stay; PRBC, number of packed red blood cell transfusions given in the first 24 hours; steroids, any mineralocorticoid; TPN, total parenteral nutrition; and ellipses, data not available.

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.

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.11-13 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 some1,3,6,7,25 but not all,24 previous studies. For Marsh et al,23 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 candidemia2,4,7,24; however, when use is controlled for by multivariate analysis, CVCs are not independent risk factors.6 Further, in a prospective cohort study of routine surveillance cultures in a surgical ICU, CVCs were not a risk factor for fungal infections.24

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.26 Safety increases with the use of antiseptic-impregnated catheters27 (such as the ones used in our center), subdermally inserted cuffs impregnated with slowly released silver compounds,28 or catheters manufactured with antibiotics.29 Pulmonary artery catheters can be used safely to deliver TPN in the critical-care unit,30 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.31 Removal of any intravascular device associated with candidemia is generally recommended.4

Total parenteral nutrition was significantly and independently associated with fungal infections here and in other studies,1,3,7,21 and remained an independently associated variable using logistic regression analysis. Four possible mechanisms are described.32 One is that hyperalimentation fluid is an excellent medium, with in vitro growth curves showing a selective advantage of Candida species over bacteria.33 Another is that frequent entry into a TPN delivery sys-

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

<table>
<thead>
<tr>
<th>Site</th>
<th>Infected</th>
<th>Concomitant</th>
<th>Total Episodes</th>
<th>Control</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteremia</td>
<td>4</td>
<td>6</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Central catheter</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;15 CFU/TIP</td>
<td>1</td>
<td>2</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No growth</td>
<td>6</td>
<td>24</td>
<td>17</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>9</td>
<td>17</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pleura</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sinuses</td>
<td>0</td>
<td>3</td>
<td>6 (23 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urine</td>
<td>0</td>
<td>3</td>
<td>1 (2 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peritonaeum</td>
<td>6</td>
<td>7</td>
<td>1 (2 patients)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound/draines</td>
<td>...</td>
<td>4</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>...</td>
<td>1</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Orthopedic</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biliary</td>
<td>...</td>
<td>...</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Otitis</td>
<td>...</td>
<td>...</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-positive bacteria</td>
<td>...</td>
<td>46</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gram-negative bacteria</td>
<td>...</td>
<td>69</td>
<td>34</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anaerobes</td>
<td>...</td>
<td>11</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No bacterial isolates</td>
<td>...</td>
<td>0</td>
<td>16</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CFU indicates colony-forming units; TIP, tip of catheter; ellipses, data not available.
tem increases the likelihood of contamination. 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. When trauma patients were randomized to receive intravenous glucose plus fat emulsions or glucose only during TPN, the lipid group had more infections. Nevertheless, there is conflicting evidence that lipids impair polymorphonuclear cells, macrophage or reticuloendothelial system function, or have a clearly adverse clinical effect.

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, Hostetter 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 al 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 peri toneal macrophage superoxide production and Candida phagocytosis and similar impairments in alveolar macrophages. In small-animal models, infusion of lipids shifts the distribution of injected bacteria from splenic sequestration to accumulation in the lungs. 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.

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. At high concentrations, yeast will pass across even the intact, healthy gut, 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. 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, and was an independent risk factor for candidemia in a university hospital population. Positive surveillance cultures were predictive of systemic infection, 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 Solomkin and Anaisse recommend prophylactic fluconazole in ICU patients with Candida colonization, this practice does not lower the yeast sepsis rate and is associated with a significant frequency of secondary mycoses, which have a 38% suspected infectious mortality rate. 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. 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. 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 bySolomkin et al 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 al 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.

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 al2 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 immunosuppres-
sion due to increased prostaglandin E2 production, sup-
pressor-soluble serum factors, suppressor cell appear-
ance, decreased cellular adenosine triphosphate level, and
altered calcium homeostasis.53 Thus, the severity of hem-
orrhage and/or the magnitude of red blood cell transfu-
sions may be risk factors for candidiasis particular to
trauma patients.

The role of corticosteroid therapy as a risk factor is re-
peatedly found in studies involving preterm infants,55 leu-
kemic children,26 surgical patients,2 and in a case-control study of a
general hospital population.6 But Karabinis et al9 did not
identify steroids as a risk factor using multivariate analy-
sis in a case-control study of patients with cancer, nor
was their use a prognostic indicator of mortality in fun-
genic 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,15 and
independently predicted Candida infections in a multi-
variate analysis by Pittet et al.24 When coupled with can-
diduria, an elevated APACHE II score predicted dissemi-
nated disease, and was considered an indicator for early
empiric antifungal therapy.10 The APACHE II scores were
different in control and infected cases in the present
study, whether considered as continuous variables or as
categorical variable (score > 10). Most likely, it is the
excessive weight of the Glasgow Coma Scale compo-
ent of APACHE II in trauma patients, as opposed to gen-
eral surgical or medical patients, that may account for
this disparity with earlier reports.

This population of critically ill ICU patients with Can-
dida infections is characterized by a high incidence of gut
perforations and a sustained need for TPN, implying pro-
longed 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 nei-
ther number of antibiotics nor duration of antibiotic use
were significant risk factors for candidiasis is of particu-
lar interest. Although many studies have associated an-
timicrobials with increased risk, most of the studied pa-
tients also had severe deficiencies in host defenses.58 In
immunosuppressed patients with leukemia, candidiasis
was more closely associated with the duration of leuko-
penia and steroid therapy than with antimicrobial
therapy.59 It may be that restrictive antibiotic ordering
practices and a policy of early enteral nutritional sup-
port combine to minimize multiplication of a common
enteric commensal organism into numbers sufficient to
overcome local host defenses. As a result, we cannot sup-
port recommendations favoring routine systemic anti-
fungal 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 inves-
tigation into the roles of antibiotic ordering policies, use
of surveillance cultures, alternatives to enteral nutri-
tional support, and control of local immune systems
needs to be done before such recommendations are
generally put into effect.

The study was supported by a grant from Pfizer Roerig Inc,
New York, NY.

Presented at the 106th Scientific Session of the West-
ern Surgical Association, Indianapolis, Ind, November 17,
1998.

We thank George Burnstein, RN, for help in gather-
ing data, Andrew Michaels, MD, for review and statistical
assistance, and John Woon, PharmD, for support and en-
couragement.

Corresponding author: Anthony P. Borzotta, MD, 501
N Graham St, Suite 125, Portland, OR 97227.

REFERENCES

1. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fun-

171:374-382.

3. Harvey RL, Myers JP. Nosocomial fungemia in a large community teaching hos-

4. Komshian SV, Uvaydak AK, Sobel JD, Crane LR. Fungemia caused by Candida
species and Torulopsis glabrata in the hospitalized patient: frequency, charac-
teristics, and evaluation of factors influencing outcome. Rev Infect Dis. 1989;
11:379-390.

5. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Hospital-acquired can-
didemia: the attributable mortality and excess length of stay. Arch Intern Med.

6. Wey SB, Mori M, Pfaller MA, Woolson RF, Wenzel RP. Risk factors for hospital-

7. Fraser VJ, Jones M, Dunkel J, Storter S, Medoff G, Dunagan WC. Candidemia in

8. Smith DJ, Thomson PD. Changing flora in burn and trauma units: historical per-
spective experience in the United States. J Burn Care Rehabil. 1992;13:276-
280.

26:429-432.

10. Anaisis E, Bodey GP. Nosocomial fungal infections: old problems and new chal-

11. Mahr CC, Fildes JJ, Becker EJ, et al. The alarming rate of fungal recovery in criti-
cally ill trauma patients with unresolved sepsis. In press.

12. Safran DB, Dawson E. The effect of empiric and prophylactic treatment with flu-

13. Cornwell EE, Belzberg H, Berne TV, et al. The pattern of fungal infections in criti-


15. Savino JA, Agarwal N, Wry P, Policastro AI, Cerabona T, Austria L. Routine pro-
phylactic antifungal agents (clotrimazole, ketoconazole and nystatin) in non-
transplant/nonburned critically ill surgical and trauma patients. J Trauma. 1994;

marker of disseminated infection in critically ill surgical patients: the role of flu-

systemic Candida infection in surgical patients under intensive care. Intensive
Care Med. 1998;24:206-216.

18. Abi-Said D, Anaisis E, Uzun O, Raad I, Pizzilowsky H, Vartivarian S. The epidemi-
ology of hematogenous candidiasis caused by different Candida species. Clin


at best in defining whether infection exists. So I am really curious as to whether you have reexamined the data in just looking 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 convinced that our continued practice of obliterating anaerobic colonization of the patient when they are in the ICU and experiencing 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 setting of the ICU patient may selectively be a negative issue. I would be interested in whether he has examined the presence or absence of anaerobic bacterial activity in the antibiotics as a variable 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 later in their course, and that patients receiving enteral feeding did so earlier in their course. The question then is whether Candida can be prevented by going to fewer antianaerobic antibiotics 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 antibiotics 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 antibiotic. 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 generalize 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 population 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 candidemia patients or candidiasis patients, how could you control for antibiotics? In most critically ill populations, candidiasis is a perversive index of management success. In burn patients, candidemia, on the average, occurs 33 to 41 days after injury and candidal infections correlate with repetitive or prolonged antibiotic 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 during the course and later in the study patients. My question is whether there was any difference in nutritional status between the 2 groups, and when the study group was initiated later, could this lack of nutritional support actually have contributed to the fungal infection? Also, as you all know, the protocol for care for the parenteral nutritional support, the types of catheters, and many other factors involved influence the infection rate in patients receiving the parenteral nutrition. I wondered 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 evolution 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 leukemics there is a nice article showing that low-dose amphotericin at half the usual dose is an excellent 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 being for potential overgrowth.

At this time we are not 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 candiduria 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 concurrent bacteremias. There was only 1 preceding bacteremia, which has been considered a risk factor. The date of onset of candidemia 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 actually 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 venous 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 feeding 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 catheters, 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.