Candida infection and colonization among trauma patients

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Background: Data on Candida infection among critically ill trauma patients are limited and not recently updated. Here we study the epidemiology and economic impact of Candida and examine potential risk factors for Candida infection in this population.

Results: 374 patients were included. Upon comparisons between groups, candidiasis patients received significantly more blood transfusions (p = 0.013), antibiotics (p = 0.005) and total parenteral nutrition (TPN) (p = 0.004), had a longer duration of mechanical ventilation (MV) (p = 0.008) and underwent more laparotomy procedures than Candida free patients (56.5% versus 16.4%; p < 0.001). Surgical complications (13% versus 1.4%; p = 0.013), injury of the upper (13% versus 0.9%; p = 0.007) and lower gastrointestinal tract (8.7% versus 0.9%; p = 0.048) and bacterial wound or intra-abdominal infections (17.4% versus 1.9%; p = 0.004) were also more common in candidiasis patients. Upon multivariate analysis, patients receiving TPN had 7-fold higher odds for developing candidiasis [Odds ratio (OR): 7.2; 95% Confidence Interval (CI): 2.6–19.4; p = 0.0001]. Other predisposing factors included laparotomy (OR: 3.8, 95% CI: 1.5–9.9; p = 0.0057) and female gender (OR: 5.7; 95% CI: 2.1–15.6; p = 0.0007). Average total hospital charges were higher for patients with Candida infection compared to patients with Candida colonization or without a positive Candida culture.

Methods: In this 5-year retrospective study, all severely injured patients with ≥4 days of intensive care unit stay were included, with the primary outcome being Candida infection. We identified 3 distinct patient groups: (1) The Candida infection, (2) The Candida colonization and (3) the Candida-free group. All comparisons between groups with p values ≤0.2 from the univariate analysis were entered into stepwise logistic regression to identify independent risk factors for candidiasis.

Conclusions: TPN, laparotomy and female gender independently predict the development of candidiasis among trauma patients. Severely injured women requiring laparotomy and TPN therapy should be carefully managed for the possibility of increased risk for candidiasis.

Introduction

Candida is a commensal human colonizer of almost all mucosal surfaces and especially the gastrointestinal tract as well as the skin.1 Trauma patients often face an abrupt disruption of epithelial barriers allowing deep-seated contamination from various pathogens either from the environment or from their own flora, such as Candida spp. Also, established risk factors for the development of candidiasis such as central venous catheters (CVC), total parenteral nutrition (TPN) and antibiotic therapy are inevitable in this particular population. Candida remains a significant cause of morbidity and mortality among trauma patients, even when fluconazole prophylaxis is intensely administered in trauma centers.2

Unfortunately, data for Candida infection focusing on trauma patients are limited and not recently updated, thus, new studies are needed reflecting the change of recent medical practices.3-5

In this study we aim to investigate the epidemiology as well as the clinical and economic impact of Candida infection and colonization. We also identify potential risk factors for candidiasis among trauma patients and examine the effect of Candida infection and colonization on total hospital costs.

Results

Overall, 374 critically ill trauma patients with a minimal ICU stay of 4 days were identified from May 1st 2002 to June 1st 2007. The mean (SD) age was 47 ± 20 years and the majority of patients (75.4%) were male. Mean (SD) injury severity score (ISS) was 27 ± 12. Overall, blunt trauma involved 344 patients (92%) and penetrating trauma 30 (8%). Interestingly, blunt trauma complicated the majority of cases with Candida infection (n = 19, 82.6%) whereas all other cases were complicated from penetrating trauma (n = 4, 17.4%). Different
types of operations were performed including 166 orthopaedic procedures, 80 laparotomies, 19 thoracotomies and 20 craniotomies. Gastrostomies, tracheotomies, wound debridements and fasciotomies were performed less frequently.

Candida was isolated from the cultures of 160 patients (42.8%). Among all 374 patients 137 (36.6%) developed Candida colonization and 23 (6.1%) Candida infection. Surprisingly, only 3 patients (0.8%) developed candidemia and all of them had complicated post-traumatic courses. One patient was an 80-year-old male suffering from multiple penetrating wounds, while the other 2 patients had multiple surgical interventions and an open abdomen. Two of the patients died (66.7%) but causation between candidemia and death could not be established.

In Candida infection patients the average time interval (SD) between admission and the first positive fungal culture was 6.6 ± 5.6 days whereas in patients with Candida colonization it was 6.5 ± 6.1 days. 21 out of 23 patients with Candida infection received antifungal treatment: 11 received fluconazole, 3 caspofungin, 2 liposomal amphotericin B and 5 received two or more antifungal agents. In the last 2 patients without antifungal treatment, the one died before receiving therapy, and the second one received antifungal prophylaxis prior to the development of candidiasis. Of note is that antifungal prophylaxis was administrated in 19 patients. 16 of them did not develop any positive Candida culture, 2 of them developed Candida colonization and 1 later on developed Candida infection.

Comparisons between patients with Candida infection and patients with negative Candida cultures are presented on Table 1. Evenly distributed variables between the two groups included basic demographics (except sex), hematocrit on admission, WBC and peak blood glucose on admission as well as all peak blood glucose values of the first 5 days of admission. Also, no difference was found on basic liver function tests on admission (SGOT, SGPT, ALP). The number of days with CVC placement was higher for the infection group but the p value was borderline (p = 0.05). Charlson comorbidity score, comorbidity sum and AIS had no difference between the two groups. Regarding statistically significant differences, patients with Candida infection had increased numbers of blood transfusions (p = 0.013), received an increased number of antibiotics (p = 0.005) and total parenteral nutrition (TPN) (p = 0.004) and had a longer duration of MV (p = 0.008). Also, laparotomy was the predominant procedure among patients with Candida infection (56.5% versus 16.4%, p < 0.001) whilst all other types of procedures were evenly distributed. Injury severity score was also significantly higher (p = 0.003). Focusing on surgical complications (bleeding, wound infection, intra-abdominal fluid collection) the comparison was again significant (13% versus 1.4%, p = 0.013). Injury of the upper as well as the lower gastrointestinal tract was more common among patients with Candida infection (esophageal-stomach injury 13% versus 0.9%, p = 0.007; colon injury 8.7% versus 0.9%, p = 0.048).

Of note is that infections with bacteria (pneumonia, bacteremia, sepsis and urinary tract infections) were also evenly distributed with the exception of wound and intra-abdominal infection that were more common in the Candida infection group (17.4% versus 1.9%, p = 0.004). Bacterial infection may be an indication of wound or intra-abdominal collection and/or might aid fungal virulence through cross-kingdom pathogen-pathogen interactions (reviewed in ref. 10). Mortality was essentially identical between the two groups and reached a p value of 1 (n = 3, 13% versus n = 28, 13.2%), probably a result of low patient numbers or low incidence of candidemia, complication rates in our population and the relatively young age of the patients.

As noted above, Candida colonization was a secondary endpoint in our study. Colonization with Candida is probably the most critical step for the development of Candida infection. Once a surface is colonized, the fungus transforms into virulent forms allowing its passing through the thick mucosal layers. The comparison of patients with Candida colonization with those without a positive Candida culture is presented on Table 2 and the findings were similar to the previous comparisons. Patients with Candida colonization received an increased number of blood transfusions (p = 0.01) and antibiotics (p < 0.001). The duration of MV, CVC and TPN was significantly longer among these patients (p < 0.001, <0.001 and 0.017 respectively). These patients had also higher rates of all post-operative bacterial infections, including pneumonia, wound infection and intra-abdominal infection.

Finally, the comparison between infected and colonized patients with Candida spp. is presented on Table 3. Both groups of patients had similar age distributions but colonized patients were more likely to be male (p = 0.01). No hematologic test was unevenly distributed between the colonization and infection groups including peak glucose levels and liver function tests. Comorbidity scores and AIS showed no difference except of ISS (p = 0.019). Patients in both groups received blood transfusions equally and they also received similar numbers of antibiotics, similar duration of MV and CVC. TPN was more pronounced in the Candida infection group (p = 0.01). Focusing on types of operations the Candida infection group underwent significantly more laparotomies (56.5% versus 23.4%, p = 0.002). Taken in their entirety, gastrointestinal tract injuries were higher in the infection group (17.4% versus 3.6%, p = 0.025). Intra-abdominal fluid collections were also higher in Candida infected patients (p = 0.02). Interestingly, post-operative infections (other than candidiasis) were evenly distributed between the two groups.

We also performed a pilot analysis of the correlations of Candida colonization and infection with total hospital costs as well as ICU and total hospital stays. Focusing on the comparisons between infected and colonized patients with Candida, as expected, patients with Candida infection had longer ICU (p = 0.013) and total hospital stays (p = 0.001) as well as hospital charges ($176,607 ± 90,499 versus 116,298 ± 60,833, p = 0.005) comparing with simply colonized patients. Similarly, patients with Candida infection had a dramatically higher cost compared to patients without a positive Candida culture ($176,607 ± 90,499 versus 73,073 ± 49,100) (p < 0.001 for all comparisons). This dramatic difference in cost may reflect not only the cost associated with Candida therapy but also the increased rate of post-surgical complications in the Candida infection group. It is particularly interesting to note that Candida colonization correlated with statistically significant rises in ICU.
Table 1. Comparisons between patients with Candida infection and patients with negative Candida cultures

| Variables               | Patients with Candida infection (±SD) (%), (n = 23) | Patients without positive Candida culture (±SD) (%), (n = 214) | p value |
|-------------------------|-----------------------------------------------------|-------------------------------------------------------------|---------|
| Age (years)             | 42.7 ± 20.3                                         | 45.4 ± 19.7                                                 | 0.542   |
| Male gender             | 12 (52.2%)                                          | 161 (75.6%)                                                 | **0.024** |
| Hematologic Tests       |                                                     |                                                             |         |
| Hematocrit on admission | 34.5 ± 7.7                                          | 36.3 ± 6.3                                                  | 0.306   |
| White blood cell count on admission | 17.7 ± 12.1                                       | 15.9 ± 7.5                                                  | 0.501   |
| HBGL on admission       | 195.6 ± 107.5                                       | 166.5 ± 55.9                                                | 0.214   |
| SGOT on admission       | 337.6 ± 445.9                                       | 163.7 ± 240.3                                               | 0.078   |
| SGPT on admission       | 263.3 ± 453.4                                       | 128.8 ± 235.4                                               | 0.174   |
| Alkaline phosphatase on admission | 65.6 ± 28.9                                      | 74.4 ± 35.9                                                 | 0.188   |
| Charlson Comorbidity    |                                                     |                                                             |         |
| Comorbidity score       | 0.3 ± 0.6                                           | 0.35 ± 0.9                                                  | 0.736   |
| Comorbidity sum         | 0.3 ± 0.5                                           | 0.3 ± 0.6                                                   | 0.891   |
| Injury Scores           |                                                     |                                                             |         |
| AIS abdomen             | 3.1 ± 0.9                                           | 2.6 ± 0.8                                                   | 0.066   |
| AIS chest               | 3.9 ± 0.8                                           | 3.5 ± 0.9                                                   | 0.067   |
| AIS extremity           | 2.8 ± 0.6                                           | 2.6 ± 0.6                                                   | 0.451   |
| AIS face                | 2 ± 0.8                                             | 2.1 ± 0.6                                                   | 0.888   |
| AIS head neck           | 3.9 ± 0.9                                           | 3.7 ± 1                                                     | 0.489   |
| AIS skin                | 1.1 ± 0.4                                           | 1 ± 0.2                                                     | 0.498   |
| ISS                     | 34 ± 10.5                                           | 26.5 ± 11.9                                                 | **0.003** |
| Interventions           |                                                     |                                                             |         |
| No. of RBC transfused 24-hours on admission* | 11.6 ± 15.1                                         | 3.1 ± 5                                                     | **0.013** |
| No. of antibiotics until positive culture for fungus* | 3.9 ± 2.5                                           | 2.3 ± 1.3                                                   | **0.005** |
| Days of MV until positive culture for fungus* | 5.4 ± 3.6                                           | 3.3 ± 1.8                                                   | **0.008** |
| Days of CVC until positive culture for fungus* | 6.1 ± 8.3                                           | 2.5 ± 2.1                                                   | 0.050   |
| Days of total parenteral nutrition | 12.2 ± 16.7                                        | 1 ± 4.1                                                     | **0.004** |
| Days of Total parenteral nutrition until positive culture for fungus* | 2.1 ± 6.4                                           | 0.1 ± 6                                                     | 0.148   |
| IVC filter              | 11 (47.8%)                                          | 51 (23.9%)                                                  | **0.022** |
| Operation               | **22 (95.7%)**                                      | **172 (80.8%)**                                             | **0.088** |
| Laparotomy              | 13 (56.5%)                                          | 35 (16.4%)                                                  | <0.001  |
| Thoracotomy             | 3 (13%)                                             | 8 (3.8%)                                                    | 0.080   |
| Orthopedic              | 9 (39%)                                             | 89 (41.8%)                                                  | 1.000   |
| Craniotomy              | 2 (8.7%)                                            | 11 (5.2%)                                                   | 0.368   |
| Other                   | 10 (43.5%)                                          | 88 (41.3%)                                                  | 0.828   |
| Surgical complications  | **3 (13%)**                                         | **3 (1.4%)**                                                | **0.013** |
| Bleeding                | 1 (0.5%)                                            | 1 (0.5%)                                                    | 1.000   |
| Wound infection         | 1 (4.3%)                                            | 2 (0.9%)                                                    | 0.266   |
| Intra-abdominal fluid collection | 2 (8.7%)                                           | 0                                                           | **0.009** |
| Pertinent Findings      | **4 (17.4%)**                                       | **4 (1.9%)**                                                | **0.004** |
| Esophagus-Stomach injury| 3 (13%)                                             | 2 (0.9%)                                                    | **0.007** |
| Colon injury            | 2 (8.7%)                                            | 2 (0.9%)                                                    | **0.048** |
| Infection after operation | **22 (95.7%)**                                     | **106 (49.8%)**                                             | <0.001  |

*As discussed in Methods, the days of each intervention (transfusion, antibiotics, mechanical ventilation, central venous catheterization, total parenteral nutrition) in the group without FI were calculated within the 5 first days of ICU stay. **HBGL, Highest Blood Glucose Level; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; RBC, Red blood cells; MV, Mechanical ventilation; CVC, Central venous catheter; AIS, Abbreviated injury score; ISS, Injury Severity Score; IVC, Intravenous catheter.
Table 1. Comparisons between patients with Candida infection and patients with negative Candida cultures

|                  | Patients with Candida infection | Patients without positive Candida culture | p value |
|------------------|---------------------------------|------------------------------------------|---------|
| Pneumonia        | 12 (52.2%)                      | 91 (42.7%)                               | 0.388   |
| Bacteremia       | 3 (13%)                         | 7 (3.3%)                                 | 0.062   |
| Sepsis           | 1 (4.3%)                        | 0 (0%)                                   | 0.097   |
| Urinary tract infection | 3 (13%)                      | 7 (3.3%)                                 | 0.062   |
| Other (Wound-Intrabdominal infection) | 4 (17.4%)                  | 4 (1.9%)                                 | 0.004   |

Outcomes

|                                      | Intensive Care Unit stay (days) | Hospital stay (days) | p value |
|--------------------------------------|---------------------------------|----------------------|---------|
|                                      | 23.6 ± 14.8                     | 8.8 ± 6.2            | <0.001  |
|                                      | 41.7 ± 18.8                     | 17.6 ± 12.8          | <0.001  |
|                                      | 3 (13%)                         | 28 (13.2%)           | 1.000   |
| Hospital charges ($)                 | 176,607 ± 90,499                | 73,073.4 ± 49,100.2  | <0.001  |

Variables as discussed in Methods, the days of each intervention (transfusion, antibiotics, mechanical ventilation, central venous catheterization, total parenteral nutrition) in the group without FI were calculated within the 5 first days of ICU stay. ¶HBGL, Highest Blood Glucose Level; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; RBC, Red blood cells; MV, Mechanical ventilation; CVC, Central venous catheter; AIS, Abbreviated injury score; ISS, Injury Severity Score; IVC, Intravenous catheter.

Table 2. Comparison between patients with Candida colonization and patients without any positive Candida culture

| Variables†             | Patients with Candida colonization (n = 137) | Patients without positive Candida culture (n = 214) | p value |
|------------------------|---------------------------------------------|------------------------------------------------------|---------|
| Age (years)            | 49.2 ± 19.6                                 | 45.4 ± 19.7                                          | 0.081   |
| Male gender            | 108 (78.8%)                                 | 161 (75.6%)                                          | 0.518   |

Hematologic Tests

| Hematocrit on admission | 35.7 ± 5.9                                  | 36.3 ± 6.3                                          | 0.426   |
| White blood cell count on admission | 16.1 ± 8.4                               | 15.9 ± 7.5                                          | 0.916   |
| HBGL on admission (higher blood glucose on admission) | 176.9 ± 82.4                                | 166.5 ± 55.9                                       | 0.193   |
| SGOT on admission       | 166.2 ± 214.9                               | 163.7 ± 240.3                                       | 0.921   |
| SGPT on admission       | 107.3 ± 140.4                               | 128.8 ± 235.4                                       | 0.285   |
| Alkaline phosphatase on admission | 76.1 ± 37.8                               | 74.4 ± 35.9                                        | 0.680   |

Charlson Comorbidity

| Comorbidity score       | 0.3 ± 0.8                                   | 0.3 ± 0.9                                            | 0.925   |
| Comorbidity sum         | 0.3 ± 0.6                                   | 0.3 ± 0.6                                            | 0.887   |

Injury Scores

| AIS abdomen             | 2.8 ± 0.9                                   | 2.6 ± 0.8                                            | 0.082   |
| AIS chest               | 3.6 ± 0.9                                   | 3.5 ± 0.9                                            | 0.390   |
| AIS extremity           | 2.8 ± 0.5                                   | 2.6 ± 0.6                                            | 0.049   |
| AIS face                | 2.1 ± 0.5                                   | 2.1 ± 0.6                                            | 0.404   |
| AIS head neck           | 3.9 ± 0.9                                   | 3.7 ± 1.1                                            | 0.076   |
| AIS skin                | 1.1 ± 0.3                                   | 1 ± 0.2                                              | 0.581   |
| ISS                     | 28 ± 12.1                                   | 26.5 ± 11.9                                          | 0.234   |

Interventions

| No. of RBC transfused 24-hours on admission† | 5.4 ± 9.6                                    | 3.1 ± 5                                              | 0.010   |
| No. of antibiotics until positive culture for fungus† | 3.2 ± 1.8                                   | 2.3 ± 1.3                                            | <0.001  |
| Days of MV until positive culture for fungus† | 4.9 ± 4.6                                   | 3.3 ± 1.8                                            | <0.001  |
| Days of CVC until positive culture for fungus† | 4.4 ± 5.2                                   | 2.5 ± 2.1                                            | <0.001  |
| Total parenteral nutrition | 2.3 ± 5.2                                   | 1 ± 4.1                                              | 0.017   |

*As discussed in Methods, the days of each intervention (transfusion, antibiotics, mechanical ventilation, central venous catheterization, total parenteral nutrition) in the group without FI were calculated within the 5 first days of ICU stay. ¶HBGL, Highest Blood Glucose Level; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; RBC, Red blood cells; MV, Mechanical ventilation; CVC, Central venous catheter; AIS, Abbreviated injury score; ISS, Injury Severity Score; IVC, Intravenous catheter.
Costs were significantly correlated with Candida infection and this group had an average cost that was approximately $60,000 higher than the Candida colonization group and approximately $103,000 higher than the patients without a positive Candida culture.

For comparison, we simultaneously reviewed the incidence of candidiasis among non-trauma emergency surgery patients in our institution and found that the incidence was almost 6 times higher.11 Of note is that the criteria for Candida infection and the time period were similar to those in our study presented here. Nearly half of all fungal infections are manifested among surgical ICU patients 12 however when trauma is the primary etiology then these rates fall substantially. Other studies involving trauma patients reported a rate of candidemia <10%.3,5,13 For example, the incidence of Candida infection in our population was similar to that reported by Borzotta et al.5 In this study, among 459 trauma patients Candida infections were reported to only 20 patients (4.4%) and 7 of them had candidemia (1.5%). This difference between the rate of Candida infection in trauma patients and the rate among other non-trauma critically ill surgical patients might indicate the relatively low initial inoculum of Candida, prompt surgical attention and the relatively younger

Discussion

This study shows that positive Candida cultures were detected in 42.8% of critically injured patients remaining in the SICU for 4 days or longer. Candida infection developed in 6.1% and only 3 patients (0.8%) developed candidemia. Three independent predictors of Candida infection were identified: TPN, laparotomy and female gender. All-cause mortality did not seem to correlate with either Candida colonization or infection but total hospital costs were significantly correlated with Candida infection and this group had an average cost that was approximately $60,000 higher than the Candida colonization group and approximately $103,000 higher than the patients without a positive Candida culture.

For comparison, we simultaneously reviewed the incidence of candidiasis among non-trauma emergency surgery patients in our institution and found that the incidence was almost 6 times higher.11 Of note is that the criteria for Candida infection and the time period were similar to those in our study presented here. Nearly half of all fungal infections are manifested among surgical ICU patients12 however when trauma is the primary etiology then these rates fall substantially. Other studies involving trauma patients reported a rate of candidemia <10%.3,5,13 For example, the incidence of Candida infection in our population was similar to that reported by Borzotta et al.5 In this study, among 459 trauma patients Candida infections were reported to only 20 patients (4.4%) and 7 of them had candidemia (1.5%). This difference between the rate of Candida infection in trauma patients and the rate among other non-trauma critically ill surgical patients might indicate the relatively low initial inoculum of Candida, prompt surgical attention and the relatively younger

Table 2. Comparison between patients with Candida colonization and patients without any positive Candida culture

| Days of Total parenteral nutrition until positive culture for fungus* | 0.4 ± 1.7 | 0.1 ± 0.6 | 0.061 |
|---------------------|------------|------------|-------|
| IVC filter          | 48 (35%)   | 51 (23.9%) | 0.029 |
| Operation           | 128 (93.4%) | 172 (80.8%)| 0.001 |
| Laparotomy          | 32 (23.4%) | 35 (16.4%) | 0.126 |
| Thoracotomy         | 8 (5.8%)   | 8 (3.8%)   | 0.434 |
| Orthopedic          | 68 (49.6%) | 89 (41.8%) | 0.154 |
| Craniotomy          | 7 (5.1%)   | 11 (5.2%)  | 1.000 |
| Other               | 80 (58.4%) | 88 (41.3%) | 0.002 |
| Surgical complications | 4 (2.9%)  | 3 (1.4%)   | 0.439 |
| Bleeding            | 1 (0.7%)   | 1 (0.5%)   | 1.000 |
| Wound infection     | 3 (2.2%)   | 2 (0.9%)   | 0.384 |
| Pertinent Findings  | 5 (3.6%)   | 4 (1.9%)   | 0.321 |
| Esophagus-Stomach injury | 4 (2.9%) | 2 (0.9%) | 0.215 |
| Colon injury        | 1 (0.7%)   | 2 (0.9%)   | 1.000 |
| Infection after operation | 109 (79.6%) | 106 (49.8%) | <0.001 |
| Pneumonia           | 89 (65%)   | 91 (42.7%) | <0.001 |
| Bacteremia          | 5 (3.6%)   | 7 (3.3%)   | 1.000 |
| Urinary tract infection | 6 (4.4%) | 7 (3.3%) | 0.579 |
| Other (Wound-Intrabdominal infection) | 15 (10.9%) | 4 (1.9%) | <0.001 |

*As discussed in Methods, the days of each intervention (transfusion, antibiotics, mechanical ventilation, central venous catheterization, total parenteral nutrition) in the group without FI were calculated within the 5 first days of ICU stay. HBGL, Highest Blood Glucose Level; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; RBC, Red blood cells; MV, Mechanical ventilation; CVC, Central venous catheter; AIS, Abbreviated Injury score; ISS, Injury Severity Score; IVC, Intravenous catheter.
| Variables                       | Patients with Candida infection (n = 23) | Patients with Candida colonization (n = 137) | p value |
|--------------------------------|----------------------------------------|---------------------------------------------|---------|
| Age (years)                    | 42.7 ± 20.3                             | 49.2 ± 19.6                                 | 0.163   |
| Male gender                    | 12 (52.2%)                              | 108 (78.8%)                                 | **0.010**|
| Hematologic Tests              |                                        |                                             |         |
| Hematocrit on admission        | 34.5 ± 7.7                              | 35.7 ± 5.9                                  | 0.482   |
| White blood cell count on admission | 17.7 ± 12.1                           | 16.1 ± 8.4                                  | 0.531   |
| HBGL on admission (higher blood glucose on admission) | 195.6 ± 107.5                           | 176.9 ± 82.4                                | 0.435   |
| SGOT on admission              | 337.6 ± 445.9                           | 166.2 ± 214.9                               | 0.083   |
| SGPT on admission              | 263.3 ± 453.4                           | 1073 ± 140.4                                | 0.115   |
| Alkaline phosphatase on admission | 65.6 ± 28.9                            | 76.1 ± 37.8                                 | 0.135   |
| Charlson comorbidity           |                                        |                                             |         |
| Comorbidity score              | 0.3 ± 0.6                               | 0.3 ± 0.8                                   | 0.782   |
| Comorbidity sum                | 0.3 ± 0.5                               | 0.3 ± 0.6                                   | 0.835   |
| Injury Scores                  |                                        |                                             |         |
| AIS abdomen                     | 3.1 ± 0.9                               | 2.8 ± 0.9                                   | 0.386   |
| AIS chest                       | 3.9 ± 0.8                               | 3.6 ± 0.9                                   | 0.187   |
| AIS extremity                   | 2.8 ± 0.6                               | 2.8 ± 0.5                                   | 0.973   |
| AIS face                        | 2 ± 0.8                                 | 2.1 ± 0.5                                   | 0.742   |
| AIS head neck                  | 3.9 ± 0.9                               | 3.9 ± 0.9                                   | 0.839   |
| AIS skin                        | 1.1 ± 0.4                               | 1.1 ± 0.3                                   | 0.638   |
| ISS                             | 34 ± 10.5                               | 28 ± 12.1                                   | **0.019**|
| Interventions                  |                                        |                                             |         |
| No. of RB transfused 24-hours on admission | 11.6 ± 15.1                             | 5.4 ± 9.6                                   | 0.067   |
| No. of antibiotics until positive culture for fungus | 3.9 ± 2.5                               | 3.2 ± 1.8                                   | 0.184   |
| Days of MV until positive culture for fungus | 5.4 ± 3.6                               | 4.9 ± 4.6                                   | 0.579   |
| Days of CVC until positive culture for fungus | 6.1 ± 8.3                               | 4.4 ± 5.2                                   | 0.355   |
| Total parenteral nutrition     | 12.2 ± 16.7                             | 2.3 ± 5.2                                   | **0.010**|
| Days of Total parenteral nutrition until positive culture for fungus | 2.1 ± 6.4                               | 0.4 ± 1.7                                   | 0.214   |
| IVC filter                     | 11 (47.8%)                              | 48 (35%)                                    | 0.252   |
| Type of Operation              |                                        |                                             |         |
| Laparotomy                     | 22 (95.7%)                              | 128 (93.4%)                                 | 1.000   |
| Thoracotomy                    | 13 (56.5%)                              | 32 (23.4%)                                  | **0.002**|
| Orthopedic                     | 3 (13%)                                 | 8 (5.8%)                                    | 0.197   |
| Craniotomy                     | 9 (39.1%)                               | 68 (49.6%)                                  | 0.377   |
| Other                          | 2 (8.7%)                                | 7 (5.1%)                                    | 0.618   |
| Pertinent Findings             |                                        |                                             |         |
| Esophagus-Stomach injury       | 4 (17.4%)                               | 5 (3.6%)                                    | **0.025**|
| Colon injury                   | 3 (13%)                                 | 4 (2.9%)                                    | 0.062   |
| Surgical complications         | 2 (8.7%)                                | 1 (0.7%)                                    | 0.054   |
| Bleeding                       | 0                                       | 1 (0.7%)                                    | 1.000   |
| Wound infection                | 1 (4.3%)                                | 3 (2.2%)                                    | 0.466   |
| Intra-abdominal fluid collection | 2 (8.7%)                                | 0                                           | **0.020**|
| Infected after operation       | 22 (95.7%)                              | 109 (79.6%)                                 | 0.080   |

*As discussed in Methods, the days of each intervention (transfusion, antibiotics, mechanical ventilation, central venous catheterization, total parenteral nutrition) in the group without FI were calculated within the 5 first days of ICU stay. *HBGL, Highest Blood Glucose Level; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; RBC, Red blood cells; MV, Mechanical ventilation; CVC, Central venous catheter; AIS, Abbreviated injury score; ISS, Injury Severity Score; IVC, Intravenous catheter.
age of trauma patients. We should also note that Charlson score, which is a widely used index of co-morbidities was particularly low among our study subjects and that in this single center study surgical complications were also low (only 10 patients had surgical complications).

Another explanation of the low number of infections would be the relatively low rate of TPN among our trauma patients. Parenteral nutrition is an established major risk factor for the development of fungal infection however, only 75 patients (20%) out of 374 received TPN. Parenteral nutrition results in atrophy of the intestinal villi and allow Candida, which colonizes nearly the 100% of human intestines, to invade local structures.14 Moreover, hyperglycemia, which is often induced by TPN, may play important roles for the invasion of Candida.15 As suggested by Hostetter et al. hyperglycemia (induced by either diabetes, corticosteroids or TPN) may cause the expression of several glucose-induced proteins from Candida, that promote adhesion of the microorganism and inhibit phagocytosis.16 Taken in their totality, our findings on the role of TPN in Candida infection in this population indicate that the few patients on TPN have a substantial risk for Candida infection.

Importantly, we found that critically ill trauma patients have several important risk factors that can identify those at high risk for candidiasis (Table 4). As described above the first correlation involved the use of TPN. The second correlation had to do with the increased risk of patients undergoing laparotomy. Laparotomies most often include manipulations of the gastrointestinal tract; the main human reservoir of C. albicans and often indicate gastrointestinal trauma. Finally, Candida infection was correlated with female gender. Women accounted approximately for the one-third of the subjects, however they had a greater risk for Candida infection, a finding that is also reported to recent and past studies.17,18 The high rate of vaginal colonization and the short length of the female urethra may predispose women to Candida infection. Notably, 20 to 50% of healthy and asymptomatic women harbor Candida in the lower genital tract19 and the receipt of antibiotics increases this rate.20 These correlations are particularly important for the clinician because it is possible to select high-risk trauma patients and through targeted antifungal prophylaxis reduce the clinical burden of Candida infection and the substantially high costs correlated with such an infection.

It is noteworthy that Candida infection was correlated with very high ICU and total hospital stays and also total healthcare associated costs. Most studies correlate candidemia with excess healthcare costs however, in our study only three incidences of candidemia occurred.21 Our findings indicate that among trauma patients with Candida infection, the cost could also be associated with other Candida infections and not necessarily only with candidemia. Since this was a pilot economic study, we were not able to assess costs directly attributed to Candida infection. However, our data strongly suggest that Candida infection significantly contributes to higher cost among trauma patients. Nevertheless, simple colonization was also significantly correlated with increased total hospital costs a finding that probably indicates Candida colonization as a potential marker of complicated hospital stay.

An interesting finding was that mortality was not higher for patients with Candida infection compared with those without a positive Candida culture. As stated above, trauma patients seek medical attention and undergo surgical procedures immediately; thus, they are probably exposed to a low initial fungal inoculum. Candidemia, which is linked to high mortality rates, was rare in our study and also the mean age of our subjects with invasive candidiasis, was 47 years, a fact that could partially explain our low mortality rates. Due to the ambiguity that resides among non-blood Candida infections, most studies involving critically ill trauma patients focus mainly on the mortality of candidemia,

| Table 3. Comparisons between patients with Candida infection and patients with Candida colonization |
|--------------------------------------------------|---------------|---------------|----------------|
| Pneumonia                                      | 12 (52.2%)    | 89 (65%)      | 0.252          |
| Bacteremia                                     | 3 (13%)       | 5 (3.6%)      | 0.090          |
| Sepsis                                         | 1 (4.3%)      |               | 0.144          |
| Urinary tract infection                        | 3 (13%)       | 6 (4.4%)      | 0.122          |
| Other (Wound-Intrabdominal) infection          | 4 (17.4%)     | 15 (10.9%)    | 0.482          |

| Outcomes                                      |               |               |               |
|------------------------------------------------|---------------|---------------|---------------|
| Intensive Care Unit stay (days)               | 23.6 ± 14.8   | 15.2 ± 9.6    | 0.013         |
| Hospital stay (days)                          | 41.7 ± 18.8   | 26.9 ± 13.2   | 0.001         |
| Mortality                                     | 3 (13%)       | 17 (12.4%)    | 1.000         |
| Hospital charges ($)                          | 176,607.1 ± 90,499.1 | 116,298.9 ± 60,833 | 0.005 |

As discussed in Methods, the days of each intervention (transfusion, antibiotics, mechanical ventilation, central venous catheterization, total parenteral nutrition) in the group without FI were calculated within the 5 first days of ICU stay. HBGGL Highest Blood Glucose Level; SGOT, Serum glutamic oxaloacetic transaminase; SGPT, Serum glutamic pyruvic transaminase; RBC, Red blood cells; MV, Mechanical ventilation; CVC, Central venous catheter; AIS, Abbreviated injury score; ISS, Injury Severity Score; IVC, Intravenous catheter.

| Clinical condition | Odds ratio | 95% Confidence interval |
|--------------------|------------|-------------------------|
| TPN                | 7.2        | 2.6–19.4                |
| Laparotomy         | 3.8        | 1.5–9.9                 |
| Female gender      | 5.7        | 2.1–15.6                |

Table 4. Independent risk factors for the development of Candida infection through the multivariable logistic regression analysis.
ignoring any possible implications of other forms of candidiasis.\textsuperscript{22} Taken in their totality, our findings on mortality suggest that among trauma patients, mortality due to Candida can be controlled, as long as the rate of candidemia remains low.

In conclusion, use of TPN, laparotomy procedures and female gender are all highly correlated with the development of fungal infection among severely injured trauma patients. Based on our study, women that require laparotomy and TPN therapy or all patients with TPN and laparotomy alone, have approximately a 1 in 3 probability to develop Candida infection. Identifying specific risk factors for the development of fungal infections in this population could lead to the initiation of proper antifungal prophylaxis lowering the significant burden of candidiasis and improving hospital costs.

**Methods**

**Study design and patient population.** This is a retrospective chart-based evaluation of all trauma emergency surgery patients that were admitted in the Massachusetts General Hospital from May 1\textsuperscript{st} 2002 to June 1\textsuperscript{st} 2007, and remained in the surgical intensive care unit (ICU) for at least 4 days. The 4-day cutoff was used to define severely injured patients and exclude brief post-operative stays, which are unlikely to be complicated by fungal infections. Each patient was identified through the records of Hospital Administrative Database, hosted by Partners Healthcare. Concentrating only on trauma patients, we excluded all patients with neutropenia (defined as absolute neutrophil count <500 cell/m\textsuperscript{3}) or with an admission diagnosis of burns. The study protocol was approved by the Massachusetts General Hospital Institutional Review Board (IRB).

The following variables were collected: basic demographics (age, sex), type of trauma (penetrating, blunt), type of operation (laparotomy, thoracotomy, orthopaedic, craniotomy, other), hollow visceral organ involvement, type of surgical complications, abbreviated injury score (AIS), injury severity score (ISS), major comorbidities as expressed by the Charlson comorbidity score and comorbidity sum, results of basic laboratory blood tests [hematocrit, white blood cell count (WBC), peak blood glucose levels] on admission and during the next five days, amount of units of blood transfused within 24-hours of admission, and the type and time interval of bacterial infections from admission to occurrence, focusing on pneumonia, bacteremia and central line sepsis. All cultures were obtained upon the clinicians' request.

Additionally, we examined a number of previously examined risk factors associated with Candida infection such as the number of different types of antibiotics administered from the day of admission till the day of the positive culture and the duration (in days) of mechanical ventilation (MV), central venous catheter (CVC) placement and total parenteral nutrition (TPN). For patients with Candida infection or colonization, these potential predisposing factors were studied up to the first positive culture for Candida. The median number of days to the first culture was 5 days and in Candida-free patients, we examined the same factors within the first 5 days of admission. Detailed data were also recorded on Candida infection and colonization including the date of positive culture and type of specimen.

**Outcomes.** Our primary outcome was the occurrence of Candida infection. As secondary outcomes we considered any positive Candida culture without infection (which we defined as Candida colonization). Candida commonly colonizes mucosal surfaces, the skin and the gastrointestinal epithelium. An abrupt discontinuation of the epithelial basic membranes however, aids to evasion of this microorganism, which then can metastasize and be spread via the bloodstream.\textsuperscript{1} Candida colonization has been proven as an important risk factor for the development of invasive candidiasis and therefore it was studied in detail.\textsuperscript{5,6} We considered length of ICU stay, mortality and total hospital costs as tertiary outcomes.

**Definition of variables.** Candidemia was defined as the isolation of Candida from at least one blood culture. However, even though a consensus is reached on the definition of candidemia, ambiguity resides on all other definitions of Candida infections involving non-sterile sites (sites other than blood and the cerebrospinal fluid).\textsuperscript{7} Thus, in order to document other infections we evaluated clinical criteria and reviewed each case to exclude any other infectious processes. More specifically, Candida urinary tract infection was defined the isolation of Candida in the urine >10\textsuperscript{4} cfu/ml (in catheterized patients) or ≥10\textsuperscript{4} cfu/ml (in patients without a Foley catheter) without co-isolation of bacterial pathogens at the same site exhibiting at least 2 systemic inflammatory response (SIRS) criteria (temperature >38\textdegree C or < 36\textdegree C, heart rate >90 beats/minute, respiratory rate >20 breaths/minute, white blood cell count >12,000/mm\textsuperscript{3} and acute organ failure).\textsuperscript{8} Candida peritonitis and Candida wound infection were defined as Candida isolated from the peritoneal fluid or tissue, drain and wound respectively from a patient with at least two SIRS criteria.\textsuperscript{9} Since, not all the SIRS criteria are indicative for an underlying infectious process, we correlated each case with the initiation of proper systemic antifungal treatment. As detailed below, 23 out of 21 candidiasis patients received antifungal treatment. In the other two cases, candidiasis was diagnosed upon individual consideration. Finally, we considered a patient colonized with Candida by having a positive culture however without fulfilling our criteria for infection.

**Statistical analysis.** We performed comparisons between patients of the three groups (Candida infection, Candida colonization and Candida—free patients) using the 2-sample Student t-test for continuous variables and the $\chi^2$ or Fisher’s exact test for categorical variables. Variables with p values of 0.2 or lower were entered into stepwise logistic regression to identify independent risk factors for Candida infection. Based on the combination of the identified independent risk factors we also tried to predict the occurrence of Candida infection. A p < 0.05 was considered as statistically significant. Stata V8 was used for the statistical analysis.

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References

1. Toya SP, Schraufnagel DE, Tielepis GE. Candiduria in intensive care units: association with heavy colonization and candidaemia. J Hosp Infect 2007; 66:201-6.
2. Safran DB, Dawson E. The effect of empiric and prophylactic treatment with fluconazole on yeast isolates in a surgical trauma intensive care unit. Arch Surg 1997; 132:1184-8.
3. Beck-Sague C, Jarvis WR. Secular trends in the epidemiology of nosocomial fungal infections in the United States, 1980–1990. National Nosocomial Infections Surveillance System. J Infect Dis 1993; 167:1247-51.
4. Pitter D, Monod M, Suter PM, Freik E, Ackenhäuser R. Candida colonization and subsequent infections in critically ill surgical patients. Ann Surg 1994; 220:751-8.
5. Borza AM, Beardsley K. Candida infections in critically ill trauma patients: a retrospective case-control study. Arch Surg 1999; 134:657-64.
6. Wey SB, Morii M, Pfaffer MA, Woolson RF, Wenzel RP. Risk factors for hospital-acquired candidemia. A matched case-control study. Arch Intern Med 1989; 149:2439-53.
7. Pappas PG, Kauffman CA, Andes D, Benjamin DK Jr, Calandra TF, Edwards JE Jr, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. Clin Infect Dis 2009; 48:503-35.
8. Calandra T, Cohen J. The international sepsis forum consensus conference on definitions of infection in the intensive care unit. Crit Care Med 2005; 33:1538-48.
9. Montoars P, Dupont H, Gauzit R, Veber B, Auboyer C, Blin P, et al. Candida as a risk factor for mortality in peritonitis. Crit Care Med 2006; 34:646-52.
10. Peleg AV, Huggan D, Mylonakis E. Medically important bacterial-fungal interaction. Nature Reviews Microbiology 2009; In press.
11. Kourkoumpetis T, Manolakaki D, Velmados G, Chang Y, Alam H, De Moya M, et al. Candida infection and colonization among non-trauma emergency surgery patients. Virulence 2010; 1:562-9.
12. Blumberg HM, Jarvis WR, Soucie JM, Edwards JE, Parterson JE, Pfaffer MA, et al. Risk factors for candidal bloodstream infections in surgical intensive care patients: the NEMIS prospective multicenter study. The National Epidemiology of Mycosis Surveillance study. Clin Infect Dis 2001; 33:177-86.
13. Pitter D, Wenzel RP. Nosocomial bloodstream infections. Secular trends in rates, mortality and contribution to total hospital deaths. Arch Intern Med 1995; 155:1177-84.
14. Eggermann P, Garbino J, Pitter D. Epidemiology of Candida species infections in critically ill non-immunosuppressed patients. Lancet Infect Dis 2003; 3:685-702.
15. Ziegler TR. Parenteral nutrition in the critically ill patient. N Engl J Med 2009; 361:1088-97.
16. Hostetter MK. Handicaps to host defense. Effects of hyperglycemia on C3 and Candida albicans. Diabetes 1990; 39:271-5.
17. Holley A, Dulhunty J, Blot S, Lipman J, Lobo S, Dancer C, et al. Temporal trends, risk factors and outcomes in albicans and non-albicans candidaemia: an international epidemiological study in four multidisciplinary intensive care units. Int J Antimicrob Agents 2009; 33:5541-7.
18. Harris AD, Castro J, Sheppard DC, Carmeli Y, Samore MH. Risk factors for nosocomial candiduria due to Candida glabrata and Candida albicans. Clin Infect Dis 1999; 29:926-8.
19. Goldacre MJ, Warr B, Loudon N, Milne LJ, Loudon JD, Vessey MP. Vaginal microbial flora in normal young women. Br Med J 1979; 1:1450-3.
20. Oriel JD, Waterworth PM. Effects of minocycline and tetracycline on the vaginal yeast flora. J Clin Pathol 1975; 28:403-6.
21. Miller LG, Hajjeh RA, Edwards JE Jr. Estimating the cost of nosocomial candidemia in the united states. Clin Infect Dis 2001; 32:1110.
22. Cruciati M, de Lalla F, Mengoli C. Prophylaxis of Candida infections in adult trauma and surgical intensive care patients: a systematic review and meta-analysis. Intensive Care Med 2005; 31:1479-87.