Invasive Candidiasis in Severe Acute Pancreatitis: Experience from a Tertiary Care Teaching Hospital

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Abstract

Background: Invasive candidiasis (IC) is associated with increased morbidity in severe acute pancreatitis (SAP). There is limited information regarding the predisposing factors, Candida species distribution and in vitro susceptibility. Methodology: Current data have been derived from a larger prospective nonintervention study conducted on 200 critically ill patients which was done to study the antifungal prescription practices, collect epidemiological data, and perform an external validation of risk prediction models for IC under senior research associateship program of Council of Scientific and Industrial Research New Delhi. Of these critically ill patients, thirty had SAP and were included for analysis. Results: There were 23 males and 7 females. Out of eight patients (27%) who developed IC, three had isolated candidemia, two had isolated deep-seated candidiasis while three had both candidemia and deep-seated candidiasis. SAP patients with IC had a longer duration of Intensive Care Unit stay, hospital stay, days on mechanical ventilation and duration of shock. Mortality was not different between SAP patients with or without IC. Conclusion: There is a high rate of Candida infection in SAP. More studies are needed to generate epidemiological data and develop antifungal stewardship in this subset of high-risk population.

Key words: Candidemia, invasive candidiasis, severe acute pancreatitis

INTRODUCTION

Severe acute pancreatitis (SAP) is a life-threatening condition which is frequently complicated by intra-abdominal sepsis. The disease is characterized by initial inflammatory phase followed by resolution or progression to infective/noninfective complications.[1] Infection correlates with the extend of necrosis, as necrotic tissue promotes microbial translocation from the gastrointestinal tract. Fungal infections in SAP patients is associated with increased morbidity as compared to isolated bacterial infection.[2] Candida is the most common fungal pathogen in SAP patients.

Pancreatic Candida infection is considered primary when it occurs in patients without any previous intervention, while it is considered secondary when cultures are positive in patients with previous surgical intervention. Pathogenesis of invasive Candida infection in SAP is polyfactorial. Translocation of microorganisms from gut, breach in continuity of normal barriers during placement of lines and drainage tubes, progressive colonization with increased duration of hospitalization and broad spectrum antibiotic use are some of the mechanisms predisposing for invasive candidiasis (IC).

Schmidt et al. studied the microorganisms infecting the walled-off pancreatic necrosis in 78 patients who underwent endoscopic transmural drainage and necrosectomy.[3] Fungi was found more frequently in patients with antibiotic exposure as compared to those not exposed to antibiotics (20% vs. 4%; P = 0.07). Hall et al. found Candida colonization as an independent risk factor Candida infection in a study involving 101 SAP patients.[4] The current study was undertaken to study the epidemiology of SAP in a tertiary care teaching hospital in North India.

METHODOLOGY

Our data for IC in SAP have been derived from a larger prospective observational study done under senior research associateship program of Council of Scientific and Industrial Research New Delhi. Of these critically ill patients, thirty had SAP and were included for analysis.

Results: There were 23 males and 7 females. Out of eight patients (27%) who developed IC, three had isolated candidemia, two had isolated deep-seated candidiasis while three had both candidemia and deep-seated candidiasis. SAP patients with IC had a longer duration of Intensive Care Unit stay, hospital stay, days on mechanical ventilation and duration of shock. Mortality was not different between SAP patients with or without IC.

Conclusion: There is a high rate of Candida infection in SAP. More studies are needed to generate epidemiological data and develop antifungal stewardship in this subset of high-risk population.

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Research New Delhi. It was nonintervention, a single center study conducted on 200 critically ill patients to study the antifungal prescription practices, collect epidemiological data, and perform an external validation of risk prediction scores for IC. Out of these thirty patients were of SAP.

**Study design**

A prospective single center study was conducted at 12 bedded medical/surgical Intensive Care Unit (ICU) of a tertiary care teaching hospital in North India. The study was approved by the ethics committee of the institute. Informed consent was taken by the patient/nearest relative of the patient.

**Table 1: Clinical characteristics of the patients with severe acute pancreatitis**

|                          | Total (n=30) | Invasive candidiasis group (n=8) | Noninvasive candidiasis group (n=22) | P  |
|--------------------------|-------------|---------------------------------|-------------------------------------|----|
| **Age**                  |             |                                 |                                     |    |
| Mean±SD                  | 38±13.5     | 35±10.9                         | 39±8                                | 0.467|
| Median (IQR 25-75)       | 36 (26-50)  | 33.5 (27-39)                    | 37.5 (26-51)                        |    |
| **Gender (male/female)** | 23/7        | 4/4                             | 19/3                                | 0.037|
| **Etiology**             |             |                                 |                                     |    |
| Biliary (stone/s visualised) | 7          | 4                               | 3                                   |    |
| Alcoholic                | 4           | 1                               | 3                                   |    |
| Hypertriglyceridemia     | 1           | 0                               | 1                                   |    |
| Traumatic                | 2           | 1                               | 1                                   |    |
| Hypercalcaemia           | 1           | 0                               | 1                                   |    |
| Post-ERCP                | 1           | 0                               | 1                                   |    |
| Postcholecystectomy      | 1           | 0                               | 1                                   |    |
| Suspected biliary/unknown etiology | 13 | 2 | 11 |    |
| Pre-ICU days of hospitalization | | | | |
| Median (IQR 25-75)       | 7 (3-13)    | 13.5 (7-31)                     | 5 (2-11)                            | 0.004|
| Days of ICU stay         |             |                                 |                                     |    |
| Median (IQR 25-75)       | 13 (8-31.5) | 32 (13-43)                      | 10.5 (6-18)                         | 0.010|
| Days of hospital stay    |             |                                 |                                     |    |
| Median (IQR 25-75)       | 36 (15-46)  | 47 (41-68)                      | 21.5 (12-38)                        | 0.001|
| Medical/surgical         | 22/8        | 3/5                             | 19/3                                | 0.037|
| APACHE II at admission   | 12 (8-16)   | 11 (9-17)                       | 12 (8-16)                           | 0.925|
| SOFA at admission        | 8 (4-12)    | 5.5 (4-10)                      | 9 (3-12)                            | 0.556|
| 28 days mortality (%)    | 13 (43)     | 3 (37)                          | 10 (45)                             | 0.697|
| Mortality at discharge from ICU (%) | 16 (53) | 5 (62) | 11 (50) | 0.544|
| Total/partial parenteral nutrition (%) | 28 (93) | 8 (100) | 20 (90) | 0.531|
| Mechanical ventilation (%)| 24 (80)    | 7 (87)                          | 17 (77)                             | 0.536|
| Duration of mechanical ventilation | | | | |
| Median (IQR 25-75)       | 10.5 (5.5-16) | 25 (12-47) | 8 (0.75-12) | 0.008|
| Shock at admission (%)   | 17 (57)     | 6 (75)                          | 11 (50)                             | 0.212|
| Duration of shock        |             |                                 |                                     |    |
| Median (IQR 25-75)       | 6 (0-13.25) | 18 (11-28)                      | 5 (0-8)                             | 0.003|
| AKI at admission (%)     | 20 (67)     | 6 (75)                          | 14 (63)                             | 0.835|
| RRT use (%)              | 14 (47)     | 4 (50)                          | 10 (45)                             | 0.574|
| Number of catheters      | 4.5 (4-6)   | 6 (5-7)                         | 4 (4-5)                             | 0.003|
| Duration of antibiotic therapy | | | | |
| Median (IQR 25-75)       | 13.5 (7.75-31.5) | 32 (13-43) | 11 (7-17) | 0.011|
| Multifocal colonization (%) | 24 (80) | 8 (100) | 16 (72) | 0.099|
| Antifungal therapy (%)   | 20 (67)     | 8 (100)                         | 12 (54)                             | 0.020|

SD: Standard deviation; IQR: Inter quartile range; AKI: Acute kidney injury; RRT: Renal replacement therapy; ICU: Intensive Care Unit; SOFA: Sequential Organ Failure Assessment; ERCP: Endoscopic retrograde cholangiopancreatography

**Patient population**

All patients admitted to the unit with the diagnosis of SAP from July 2013 to November 2014 were included in the study. Patients with age <18 years, neutropenia (absolute neutrophil count <0.5 × 10⁹/L at admission or during their stay in ICU), bone marrow transplant, hematological malignancy were excluded. Patients who died within 48 h of ICU admission were also excluded from this study.

**Clinical and mycological data**

For all patients of SAP, demographic data, disease severity scores, risk factors for IC, length of ICU stay, and hospital
stay were recorded. Blood culture samples were collected at admission and then as advised by the treating physician. Samples were also taken from necrosum at the time of open laparotomy and drain fluids at the time of placement of percutaneous drain. Blood cultures were processed using BACTEC system (Becton Dickinson Diagnostic Instrument system). Phenotypic species identification was done using germ tube testing, sugar assimilation, chrome agar, and tetrazolium reduction medium. Candidemia isolates were sent for matrix-assisted laser desorption ionization-time of flight (MALDI Biotyper, Bruker Daltonik, Microlabs, Coimbatore) analysis.

Antifungal sensitivity was done using E strips (BioMerieux, SGPGIMS, Lucknow). It is an agar-based method for determining minimum inhibitory concentration. The standard broth dilution method as per Clinical and Laboratory Standard Institute or European Committee on Antibiotic Susceptibility Testing could not be used due to limited finances.

**Definitions**
IC was defined as per definition given by of European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group/National Institute of Allergy and Infectious Diseases Mycoses Study Group Consensus Group. Only patients who had proven candidiasis (positive blood culture/necrosum collected during surgery/drain sample collected at the time of insertion of a new percutaneous catheter drainage) were taken as cases.

Multispecies candidemia was defined as isolation of more than one Candida species in the same blood culture bottle or samples obtained within a 72-h period.

SAP was defined as radiologically proven acute pancreatitis with one or more organ failure. Severity grading was done using contrast-enhanced computed tomography severity index (CTSI). SAP was defined as CTSI >7.

**Statistics**
Patients were divided into two groups; those with invasive candidiasis and those without IC (non-IC). Statistical analysis was done using SPSS version 17 (IBM). Variables were expressed as mean with standard deviations and medians with interquartile range (IQR). The two groups were compared using Chi-square test for discrete variables and Mann–Whitney test for continuous variables.

**Results**

**Patient characteristics**
Among the 200 patients enrolled for the observational study on antifungal prescription from July 2013 to November 2014, thirty patients were of SAP See Table 1. There were 23 males and 7 females. Eight patients developed IC giving an infection rate of 14/1000 days (8/571 days). Female gender, longer pre-ICU days of hospitalization, surgical interventions were factors significantly associated with IC (P < 0.05). The median duration from onset of pancreatitis to IC was 23 days (IQR 13.25–37.5).

**Mycological data**
Out of eight patients who developed IC, 3 had isolated candidemia, 2 had isolated deep-seated candidiasis while 3 had both candidemia and deep-seated candidiasis See Figure 1. Species identification was done for isolates obtained from the blood. Two patients developed multispecies candidemia.

![Diagram showing distribution of invasive candidiasis in severe acute pancreatitis patients.](image-url)

**Table 2: Candida species distribution and antifungal sensitivity in candidemia patients with severe acute pancreatitis**

| Species          | Number of patients with positive blood culture | Patient number*** | Fluconazole | Amphotericin B | Caspofungin | Micafungin | Anidulafungin | Voriconazole |
|------------------|-----------------------------------------------|-------------------|------------|----------------|-------------|------------|---------------|-------------|
| Candida albicans | 2                                             | 79                | S          | S              | S           | S          | S             | S           |
|                  | 190                                           |                   | S          | S              | S           | S          | S             | S           |
| Candida tropicalis| 2                                             | 24                | S          | S              | S           | S          | S             | S           |
|                  | 168                                           |                   | S          | S              | S           | S          | S             | S           |
| Candida parapsilosis| 2                                         | 75                | R          | S              | S           | S          | S             | S           |
|                  | 190                                           |                   | S          | S              | S           | S          | S             | S           |
| Candida glabrata | 1                                             | 168               | R          | R              | S           | S          | S             | S           |
| Candida auris    | 1                                             | 136               | R          | S              | S           | S          | S             | S           |

***Patient number as per the database of 200 critically ill patients
Table 2 shows the *Candida* species distribution along with sensitivity for candidemia patients.

**Outcome**
ICU mortality was not different among the two groups, but IC patients had a longer duration of ICU stay, hospital stay, days on mechanical ventilation and duration of shock.

**Antifungal therapy**
Out of 30 patients with SAP 20 (7 in IC group and 12 in non-IC group) received antifungal therapy [Tables 3 and 4]. Data on antifungal therapy of one patient in IC group were not available as she was shifted to ward by the time culture results came positive. Among the non-IC patients two received prophylactic antifungal therapy (risk factor driven) while ten received empirical antifungal therapy (fever driven). In IC group targeted therapy (microbiology driven) was given to three patients, while rest of the four patients received empirical therapy followed by treatment modulation once the culture/sensitivity report was available.

**DISCUSSION**
IC is a significant problem in SAP. The true incidence of IC in SAP remains unknown as differentiation between *Candida* colonization, and infection is not always clearly demarcated, and many of these patients receive prophylactic/empirical antifungal therapy. Blood culture sensitivity for IC has been reported between 25% and 70% in autopsy studies. The rate of *Candida* infection in pancreatitis ranges between 5% and 68.5% in previous studies depending on the study population (acute vs. severe acute; ICU patients vs. global). We found a rate of 27% in our study population.

Although the sample size of our cohort was small, among the various risk factors studied surgery and prolonged hospitalization before ICU admission were found to be significantly different between IC and non-IC group. Surgery is a well-known risk factor for *Candida* infection and has been included in the derivation of a number of risk prediction models for IC in critically ill patients, for example, *Candida* score,

| Table 3: The details of antifungal therapy in invasive candidiasis patients |
|-----------------------------|----------------------|----------------------|-----------------------------|-------------------|-----------------------------|
| Patient number*** | Type of invasive candidiasis | Duration of ICU stay | Duration of antifungal therapy | Days of antifungal therapy | Type of antifungal therapy | Antifungal agent | Outcome |
| 24 | Candidemia | 31 | 22 | 9-17 | Fluconazole; caspofungin | Nonsurvivor |
|  | | | | 18-22 | | |
|  | | | | 23-31 | | |
| 75 | Candidemia | 44 | 38 | 7-17 | Amphotericin B; voriconazole | Nonsurvivor |
|  | | | | 18-29 | | |
|  | | | | 29-44 | | |
| 79 | Candidemia | 60 | 45 | 5-9 | Amphotericin B; caspofungin | Survivor |
|  | | | | 9-23 | | |
|  | | | | 23-30 | | |
|  | | | | 30-50 | | |
| 136 | Candidemia | 41 | 21 | 5 and 6 | Fluconazole | Survivor |
|  | | | | 7-28 | | |
| 139 | Intra-abdominal candidiasis | 12 | 12 | 1-12 | Fluconazole | Survivor |
| 168 | Candidemia | 33 | 30 | 3-33 | Amphotericin B | Nonsurvivor |
| 182 | Intra-abdominal candidiasis | 13 | 13 | 1-3 | Fluconazole; amphotericin B | Nonsurvivor |
| 190 | Candidemia | 14 | 15 | 1-4 | Fluconazole; amphotericin B | Nonsurvivor |

***Patient number as per the database of 200 critically ill patients. ICU: Intensive Care Unit
Ostrosky’s clinical prediction rule, etc. In agreement with our findings, pre-ICU hospitalization was found as a risk factor for IC in a retrospective case–control study conducted on 352 ICU patients. There were more females in IC group (50%) as compared to non-IC group (13%) in our study. Somewhat similar to our findings, Dupont et al. also reported female gender as a risk factor for yeast isolation in peritoneal fluid in a study on 221 peritonitis patients admitted to surgical intensive care but gender has not been found as a risk factor for Candida infection in other studies.

Our study did not show any difference in mortality between the two groups, but SAP patients with IC suffered increased morbidity (longer duration of hospital stay, ICU stay, mechanical ventilation and shock). These findings are consistent with recently published largest case series of 207 SAP patients, out of which 14.5% had intra-abdominal fungal infection along with concomitant bacterial infection, 38% had intra-abdominal bacterial infection, and 48% had no intra-abdominal infection. Patients with fungal infection had higher ICU stay, hospital stay and higher rates of organ failure but similar mortality when compared with patients with intra-abdominal bacterial infection only.

Geographical variation in the distribution of Candida species is a well-known fact and has been extensively studied by SENTRY antimicrobial surveillance program. Chakrabarti et al. reported Candida tropicalis (43.9%) as the most common fungal pathogen in a study on 335 patients of acute pancreatitis from the Indian subcontinent. As shown in Table 2, nonalbicans Candida was more common as compared to Candida albicans in our study population.

Two patients showed growth of more than one Candida species in their blood (Table 2). These findings are important because such patients may require combination antifungal therapy for appropriate management. Thirty-seven percent (3 out of 8) of the isolates from candidemia cases were resistant to fluconazole. One patient showed growth of Candida glabrata which was resistant both to fluconazole and amphotericin B. Our study also showed high use of antifungal therapy in the study population (66%). Antifungal stewardship is necessary for optimization and appropriate use if antifungal therapy.

The study is limited by its small sample size. As already mention the true rate of IC remains unknown as many patients received prophylactic/empirical antifungal therapy.

**Conclusion**

Our study shows that Candida infection is frequently seen in SAP patients and such infections are associated with increased morbidity. There is need do conduct larger multicenter studies in the field and develop antifungal stewardship programs.

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**Table 4: The details of antifungal therapy in noninvasive candidiasis group**

| Patient number*** | Duration of ICU stay | Duration of antifungal therapy | Days of antifungal therapy | Type of antifungal therapy | Antifungal agent | Outcome |
|-------------------|----------------------|--------------------------------|-----------------------------|----------------------------|-----------------|---------|
| 6                 | 3                    | 0                              | 0                           | -                          | -               | Survivor |
| 10                | 9                    | 5                              | 4-9                         | Caspofungin                | Empirical       | Nonsurvivor |
| 26                | 6                    | 6                              | 1-6                         | Amphotericin B             | Empirical       | Nonsurvivor |
| 34                | 25                   | 14                             | 1-14                        | Fluconazole                | Empirical       | Survivor   |
| 35                | 33                   | 23                             | 10-17                       | Fluconazole                | Empirical       | Nonsurvivor |
|                   |                      |                                | 18-33                       | Amphotericin B             | Empirical       | Nonsurvivor |
| 40                | 8                    | 12                             | 4-8                         | Caspofungin                | Empirical       | Nonsurvivor |
| 43                | 7                    | 0                              | 0                           | -                          | -               | Survivor   |
| 71                | 8                    | 0                              | 0                           | -                          | -               | Survivor   |
| 74                | 11                   | 11                             | 1-3                         | Fluconazole                | Prophylaxis     | Nonsurvivor |
|                   |                      |                                | 8-11                        | Amphotericin B             | Empirical       | Nonsurvivor |
| 82                | 2                    | 0                              | 0                           | -                          | -               | Nonsurvivor |
| 96                | 51                   | 20                             | 18-38                       | Amphotericin B             | Prophylaxis     | Survivor   |
| 99                | 17                   | 0                              | 0                           | -                          | -               | Survivor   |
| 119               | 16                   | 0                              | 0                           | -                          | -               | Survivor   |
| 121               | 10                   | 8                              | 3-10                        | Caspofungin                | Empirical       | Nonsurvivor |
| 125               | 24                   | 0                              | 0                           | -                          | -               | Survivor   |
| 128               | 11                   | 8                              | 4-11                        | Amphotericin B             | Empirical       | Nonsurvivor |
| 144               | 4                    | 0                              | 0                           | -                          | -               | Survivor   |
| 147               | 36                   | 11                             | 15-25                       | Caspofungin                | Empirical       | Survivor   |
| 187               | 13                   | 2                              | 12-13                       | Micafungin                 | Empirical       | Nonsurvivor |
| 194               | 5                    | 0                              | 0                           | -                          | -               | Nonsurvivor |
| 195               | 10                   | 0                              | 0                           | -                          | -               | Survivor   |
| 200               | 15                   | 14                             | 1-2                         | Fluconazole                | Empirical       | Survivor   |

***Patient number as per the database of 200 critically ill patients. ICU: Intensive Care Unit

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**Conclusion**

Our study shows that Candida infection is frequently seen in SAP patients and such infections are associated with increased morbidity. There is need do conduct larger multicenter studies in the field and develop antifungal stewardship programs.
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Conflicts of interest
There are no conflicts of interest.

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