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).

Access this article online

Quick Response Code:

Website: www.ijccm.org

DOI: 10.4103/0972-5229.198325

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

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How to cite this article: Baronia AK, Azim A, Ahmed A, Gurjar M, Marak RS, Yadav R, *et al*. Invasive candidiasis in severe acute pancreatitis: Experience from a tertiary care teaching hospital. Indian J Crit Care Med 2017;21:40-5.

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				
Median (IQR 25-75)	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

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.

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 $<0.5 \times 10^9$/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.

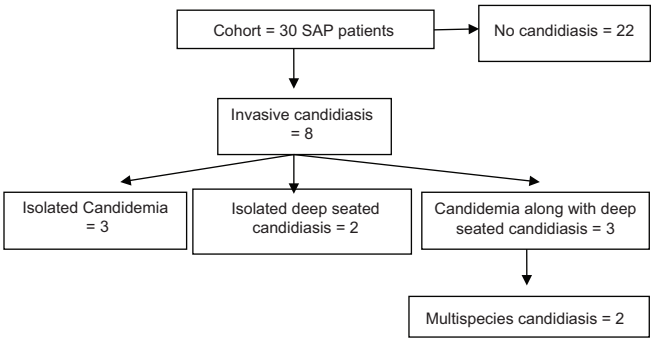

Figure 1: Diagram showing distribution of invasive candidiasis in severe acute pancreatitis patients.

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.[5] 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).[6] 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 18-22 23-31	Fluconazole Caspofungin Amphotericin B	Initially on empirical fluconazole; developed breakthrough candidemia on day 13 and therapy was escalated to echinocandin	Nonsurvivor
75	Candidemia	44	38	7-17 18-29 29-44	Amphotericin B Voriconazole Amphotericin B	Targeted therapy was started on day 7 when the culture came positive. Therapy was deescalated to azole after 10 days but again changed to amphotericin B in view of clinical deterioration	Nonsurvivor
79	Candidemia	60	45	5-9 9-23 23-30 30-50	Amphotericin B Caspofungin Amphotericin B Caspofungin	Targeted therapy was started on day 5 with amphotericin B but was escalated to caspofungin in view of clinical deterioration. Antifungal therapy was continued up to day 50 in view of ongoing risk of invasive candidiasis	Survivor
136	Candidemia	41	21	5 and 6 7-28	Fluconazole Caspofungin	Fluconazole prophylaxis was started on day 5. Therapy empirically escalated to caspofungin in view of clinical deterioration	Survivor
139	Intra-abdominal candidiasis	12	12	1-12	Fluconazole	Empirical given during ICU stay; her drain fluid came positive a few weeks after discharge to ward (antifungal records of the ward not available)	Survivor
168	Candidemia	33	30	3-33	Amphotericin B	Targeted therapy started on day 3 when culture came positive Further evaluation showed multispecies candidemia. Echinocandins could not be added due to financial constraints	Nonsurvivor
182	Intra-abdominal candidiasis	13	13	1-3 4-13	Fluconazole Amphotericin B	Empirical antifungal started on day 1, escalated to amphotericin B in view of clinical deterioration	Nonsurvivor
190	Candidemia	14	15	1-4 4-13	Fluconazole Amphotericin B	Empirical Targeted	Nonsurvivor

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

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		
40	8	12	4-8	Caspofungin	Empirical	Nonsurvivor
43	7	0	0	-	-	Nonsurvivor
71	8	0	0	-	-	Survivor
74	11	11	1-3	Fluconazole	Prophylaxis	Nonsurvivor
			8-11	Amphotericin B	Empirical	
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
			2-14	Caspofungin		

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

Ostrosky's clinical prediction rule, etc.[7,8] 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.[9] 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.[10]

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.[2] 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.[11] 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.[12] 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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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