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Risk factors of cellulitis in cirrhosis and antibiotic prophylaxis in preventing recurrence

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Abstract

Background Cellulitis is a commonly encountered bacterial infection among cirrhotic patients apart from spontaneous bacterial peritonitis, urinary tract and respiratory infections. This study aimed to determine the risk factors of cellulitis in cirrhosis and whether antibiotic prophylaxis helps prevent recurrence of cellulitis.

Methods The study was conducted in two phases. In phase 1, all cirrhotic patients admitted with cellulitis from August 2011 to August 2013 were taken as cases (n=70) and cirrhotic patients without cellulitis were included as controls (n=73). Baseline demographic data, comorbidities and investigations were noted and compared. In phase 2, the cases of phase 1 were divided into two groups, based on initiation of antibiotic prophylaxis at the time of discharge and were followed up for six months for recurrence of cellulitis.

Results The main etiology of cirrhosis was alcohol and 68% of cases were Child C. Factors which showed significance in univariate analysis were presence of diabetes mellitus, hepatic encephalopathy, platelet count, albumin level and model for end-stage liver disease (MELD) score. Using logistic regression, hepatic encephalopathy (OR 2.95, CI 1.01-8.45), albumin level <2.5 g/dL (OR 2.80, CI 1.32-5.92) and MELD >15 (OR 2.95, CI 1.39-6.27) emerged as significant factors associated with cellulitis. Cellulitis recurred in 20% and recurrence was significantly low among antibiotic prophylaxis group (15% vs. 50% P=0.048).

Conclusions Hypoalbuminemia, and high MELD score are the risk factors for cellulitis in cirrhosis. Antibiotic prophylaxis can reduce the recurrence of cellulitis as in the case of spontaneous bacterial peritonitis.

Keywords Cellulitis, cirrhosis, risk factors, recurrence, antibiotic prophylaxis

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Introduction

Cirrhotic patients are more prone to serious bacterial infections [1]. These infections precipitate decompensation of cirrhosis and thus lead to increased morbidity and mortality [2]. The increased infections in cirrhotic patients are due to the defect in the immune system which includes both humoral and cellular immunity [3-6]. Cellulitis is one of the major bacterial infections seen in cirrhosis apart from spontaneous bacterial peritonitis (SBP), urinary and respiratory tract infections. The prevalence of cellulitis in cirrhosis is 10.5-12.5% [7,8]. A nationwide population based study in Taiwan has shown that cirrhotic patients are at increased risk of cellulitis than non-cirrhotics [6].

Cellulitis in cirrhotic patients is different from that of the general population regarding microorganisms, pathogenesis and prognosis. Bacterial translocation (BT) from gut is postulated to be a major source of infections in cirrhosis [9]. As opposed to cellulitis in the general population, where the major etiological organisms are gram positive bacteria (Group A *streptococci* and *Staphylococcus aureus*) [10,11] cellulitis due to gram negative organisms are frequently reported in cirrhotic patients [12,13]. This suggests that, as in the case of SBP [3], BT from the gut may play a major role in pathogenesis of cellulitis in cirrhosis. Norfloxacin prophylaxis has helped reduce the

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Conflict of Interest: None

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one-year probability of developing SBP from 61% to 7% [14] and recurrence of SBP decreased from 68 to 20% [15]. We hypothesize that in cirrhotic patients with cellulitis antibiotic prophylaxis might help prevent the recurrence of cellulitis. The present study aimed to identify the risk factors of cellulitis in cirrhosis and to assess the role of antibiotic prophylaxis in preventing the recurrence of cellulitis.

Patients and methods

Study design and setting

The study was conducted in two phases (Phase 1 and Phase 2), in the Medical Gastroenterology department of a tertiary care hospital in South India. Phase 1 was a case control study to identify the risk factors of cellulitis in cirrhosis. Consecutive patients admitted with cirrhosis and cellulitis (n=70), between August 2011 and August 2013 were included as cases. Controls were age- and sex-matched cirrhotic patients without cellulitis or without past history of cellulitis, selected from the same center (n=73). Patients with a history of significant trauma and known cases of filariasis were excluded. Cellulitis was diagnosed by the presence of erythema, warmth and swelling of the affected area [16]. Doppler ultrasound was used to exclude deep vein thrombosis in suspicious cases.

Phase 2 was a cohort study to look for the role of antibiotics in preventing recurrence of cellulitis in cirrhosis. Of the 70 cases with cellulitis in phase 1, five died during admission, four were lost to follow up, and the rest of the 61 cases were included in phase 2.

Method of patient evaluation

In phase 1, data regarding age, sex, etiology of cirrhosis, comorbidities, duration of liver disease, site of cellulitis, Child-Turcotte-Pugh (CTP) score, model for end-stage liver disease (MELD) score, presence of edema, ascites, SBP, hepatorenal syndrome (HRS), acute kidney injury (AKI), alcoholic hepatitis (AH), hepatic encephalopathy (HE), hemoglobin (Hb) level, platelet count, erythrocyte sedimentation rate, international normalized ratio, serum creatinine, bilirubin, albumin, and sodium levels were collected and compared with those of controls. Report of blood culture or culture from the infected skin was also noted.

In phase 2, two cohorts were identified from cellulitis cases of phase 1 based on the initiation of antibiotic (norfloxacin or rifaximin) at the time of discharge (as primary or secondary prophylaxis for SBP, or for HE). Those who were initiated on antibiotic prophylaxis were assigned to group 1 and those who were not initiated on antibiotic prophylaxis were assigned to group 2. Both groups were followed up and data regarding recurrence of cellulitis within six months were collected. We compared the recurrence of cellulitis between the two groups.

The study was approved by the institutional ethics committee and the hospital review board.

Statistical analysis

Continuous variables were described by mean ± SD; categorical variables were described by percentages. Association between study variables were assessed by t-test, Chi square test and Mann Whitney U test depending upon the nature of study variables. The logistic regression was done to identify the risk factors. Odds ratio (OR) and confidence interval (CI) were calculated. Relative Risk and number needed to treat (NNT) were calculated to assess the effect of antibiotic prophylaxis. Statistical analysis was done using SPSS ver. 17.

Results

There were 70 patients with cellulitis (cases) and 73 patients without cellulitis (controls). Univariate analysis of various parameters of cases and controls is shown in Tables 1 and 2. Among the cases, 61 (87%) were males and 9 (13%) were females. Mean age was 51.7 years. Etiology of cirrhosis were alcoholic liver disease in 47 (67%) patients, nonalcoholic steatohepatitis in 9 (12.8%), chronic hepatitis B in 8 (11.4%), chronic hepatitis C in 5 (7.1%), and Wilson disease in 1 (1.4%). Forty eight (68%) were Child C, 20 (29%) were Child B and 2 (3%) were Child A. Mean duration between diagnosis of cirrhosis and development of cellulitis was 19.3 months. Twenty seven (39%) were diabetics. Ascites was present in 54 (77%) and SBP was present in 25 (36%). Twenty one cases (30%) had HE, 14 (22%) had AKI, 14 (22%) had AH, 6 (8.6%) had hepatocellular carcinoma, and 5 (4%) developed HRS. Fifty four patients had edema of lower limbs, and 7 had scrotal edema. Sixty cases (85%) presented with cellulitis of lower limbs, 9 (13%) had scrotal cellulitis, and one had anterior abdominal wall cellulitis. Culture was positive in 31% (22/70) either from blood or from skin aspirates (10 from blood, 9 from skin, and 3 from both). 73% of culture (16/22) showed growth of gram negative organisms. The organisms were *Klebsiella pneumoniae* in 6 (27%) patients, *Pseudomonas aeruginosa* in 6 (27%) and *Escherichia coli* in 4 (18%) cases. Twenty seven percent (6/22) had *Staphylococcus aureus* of which two were methicillin-resistant *Staphylococcus aureus* (MRSA). Out of 45 cellulitis patients without SBP, 10 had culture positivity of which 8 were gram negative organisms (2 *Pseudomonas*, 4 *Klebsiella*, 2 *E. coli*) and 2 were gram positive (*Staphylococcus*). Of the 9 cellulitis cases where the skin culture was positive, 8 cases showed growth of gram negative organisms.

Treatment

The patients were initially treated with intravenous cefotaxime. Nineteen patients (27%) were switched over to

Table 1 Clinical characteristics of patients with and without cellulitis

Variable	With cellulitis (N=70)	Without cellulitis (N=73)	P
Age (mean±SD) years	51.7±11.2	53.3±9.9	0.383
Sex			
Male (%)	61 (87.1)	71 (97.3)	0.23
Female (%)	9 (12.9)	2 (2.7)	
Child			
A (%)	2 (2.9)	4 (5.5)	
B (%)	20 (28.6)	26 (35.6)	
C (%)	48 (68.6)	43 (58.9)	0.436
CTP (mean±SD)	10.42±1.8	9.8±2	0.171
Etiology of cirrhosis			
HBV	8 (11)	16 (22)	0.093
Alcohol	47 (67)	57 (78)	0.142
HCV	5 (7.1)	3 (4.1)	0.43
NASH	9 (13)	4 (5.5)	0.125
Complications			
Ascites	54 (77)	62 (88)	0.234
SBP	25 (36)	31 (43)	0.408
HRS	5 (7.1)	4 (5.5)	0.682
HE	21 (30)	6 (8.6)	0.001
DM	27 (39)	17 (23)	0.048
AKI	14 (22)	7 (9.6)	0.079
HRS	5 (7.1)	4 (5.5)	0.682
Alcoholic hepatitis	14 (20)	18 (25)	0.504

AKI, acute kidney injury; CTP, child-Turcotte-Pugh score; HBV, hepatitis B virus; HCV, hepatitis C virus; HRS, hepatorenal syndrome; NASH, nonalcoholic steatohepatitis; SBP, spontaneous bacterial peritonitis; HE, hepatic encephalopathy; DM, diabetes mellitus

Table 2 Laboratory parameters (Univariate analysis)

Parameter	Cellulitis (N=70)	Without cellulitis (N=73)	P value
Hemoglobin in g/dL	9.7±1.8	9.8±2.2	0.94
Leukocyte count in cmm.	12056.2±2096	7935.9±4417	0.103
Platelet count in cmm	0.98±0.6	1.27±5.4	0.016
Bilirubin in mg/dL	3.7±2.9	4±3.8	0.578
AST in U/L	85.3±63.1	98±63.4	0.231
ALT in U/L	46.8±29.8	53.1±36.2	0.258
Albumin in g/dL	2.6±0.6	2.8±0.5	0.027
INR	1.9±0.7	1.7±0.7	0.096
S. Creatinine in mg/dL	1.2±0.6	1.1±0.6	0.163
Sodium in mmol/L	133.2±6.4	134.2±5.4	0.327
MELD score	17 (13-21)	13 (10-18)	0.005*

*Mann Whitney U test, Data are expressed as mean±SD (according to distribution)
AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; MELD, model for end-stage liver disease

Table 3 Logistic regression analysis for the risk factors of cellulitis

Parameter	B	SE	P	OR	95% CI for OR	
					Lower	Upper
HE	1.073	0.542	0.048	2.925	1.012	8.458
DM	0.675	0.409	0.099	1.963	0.88	4.379
MELD>15	1.085	0.38	0.005	2.958	1.395	6.27
Platelet	0.285	0.402	0.478	1.33	0.605	0.922
Albumin<2.5	1.03	0.381	0.007	2.804	1.328	5.922

HE, hepatic encephalopathy; DM, diabetes Mellitus; MELD, model for end-stage liver disease; CI, confidence interval; OR, odds ratio

piperacillin- tazobactam due to poor response to cefotaxime. Ceftazidime was initiated for one patient with *Pseudomonas* infection, linezolid was given to patients with MRSA and cefoperazone for 2 patients with *Klebsiella* infection as per culture and sensitivity. There was a significant difference in the mean number of days of hospitalization, among cases (6.4 days) and controls (5 days) P=013.

Risk factors of cellulitis

On univariate analysis, presence of diabetes, HE, platelet count, serum albumin level, and MELD score showed a significant difference between cases and controls. On logistic regression (Table 3), HE (P=0.048, OR 2.925, C.I 1.012-8.458), albumin <2.5 g/dL (P=0.007, OR 2.804, CI 1.328-5.922), and MELD score >15 (P=0.005, OR 2.958, CI 1.395-6.27) showed significant differences between the two groups.

Recurrence and mortality

On follow up in phase 2, out of 61 cellulitis cases, 12 (20%) had recurrence of cellulitis within 6 months. Of these, 51 were in group 1 (those patients who were started on antibiotic prophylaxis at the time of discharge) and 10 patients were in group 2 (discharged without antibiotic prophylaxis). The recurrence rate in group 1 was 14% (7/51) whereas in group 2 it was 50% (5/10) which was statistically significant (P=0.048), with a relative risk of 0.27 and the NNT was 3. Table 4 shows baseline characteristics of group 1 and group 2. In univariate analysis none of the other variables showed a significant difference between these two groups. Logistic regression showed that antibiotic prophylaxis significantly reduced the recurrence of cellulitis (P=0.011, OR 0.099, CI 0.017-0.583) (Table 5).

Mortality of the follow up cases of cellulitis (n=61) was at 1 month 15.7%, at 3 months 27.1% and at 6 months 32.8%. Of the 23 patients who expired during the follow up period, 18 belonged to the antibiotic prophylaxis group (18/51, 35%),

Table 4 Baseline characteristics of the follow-up group

Variable	Antibiotic Px (N=51)	Without antibiotic Px (N=10)	P
Age (mean±SD) years	51.7±8.6	53.3±9.1	0.433
Sex			
Male (%)	44 (86.3)	8 (80)	0.981
Female (%)	7 (13.7)	2 (20)	
Child			
B (%)	13 (25.5)	3 (30)	
C (%)	38 (74.5)	7 (70)	1.000
CTP (mean±SD)	10.7±2.0	10.4±1.7	0.643
MELD (mean±SD)	17.4±6.0	14.4±5.8	0.178
Ascites	39 (76.5)	8 (80)	1.000
HE	17 (33.3)	3 (30)	1.000
DM	25 (49)	3 (30)	0.449
Alcoholic hepatitis	11 (21.6)	2 (20)	1.000
HCC	4 (7.8)	0	0.828
Edema	39 (76.5)	8 (80)	0.808
Albumin (mean±SD)	2.61±0.55	2.49±0.63	0.551

CTP, child-Turcotte-Pugh score; DM, diabetes mellitus; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; MELD, model for end stage liver disease; Px, prophylaxis

Table 5 Logistic regression of factors associated with recurrence of cellulitis

					95% C.I. for OR	
Variable	B	S.E.	P	OR	Lower	Upper
Edema	1.705	1.400	0.223	5.501	0.354	85.493
Albumin	1.341	0.930	0.149	3.824	0.618	23.672
DM	−0.458	0.843	0.587	0.633	0.121	3.300
MELD	0.058	0.067	0.385	1.06	0.930	1.207
Child	−1.236	1.014	0.223	0.291	0.040	2.118
Prophylaxis	-2.311	0.904	0.011	0.099	0.017	0.583
SBP	−0.619	0.938	0.509	0.539	0.086	3.384

DM, diabetes mellitus; MELD, model for end stage liver disease; SBP, spontaneous bacterial peritonitis

while 5 belonged to the no-prophylaxis group (5/10, 50%). The causes of death were sepsis in 9 (5 related to cellulitis, and 4 unrelated to cellulitis), uncontrolled upper GI bleeding in 6, severe alcoholic hepatitis in 4, HCC in 3, and HRS in 1.

Discussion

To date, there are only very few studies in the literature conducted to assess the risk factors of cellulitis in cirrhotic patients. In this hospital-based case-control study we found that hypoalbuminemia, high MELD score, and HE are the factors significantly associated with cellulitis in cirrhotic patients.

In our study, MELD score >15 (OR 2.95, CI 1.39-6.27) was observed as a significant risk factor for cellulitis. Poor liver function results in increased susceptibility to infection due to immune system defects, including the defective bactericidal function of immunoglobulin, decreased polymorphonuclear leukocyte activity, complement deficiency, and reduced number of Kupffer cells [17]. The majority of cellulitis patients (68%) belonged to Child C status. Gut BT is found to be significantly increased in Child C than in Child A and B patients [9]. However, our study did not show Child to be a significant variable. This could be due to the fact that the control group were selected from the patients who were admitted with complications of cirrhosis (other than cellulitis), which might have reflected as high CTP score in the control group.

Our data showed that low serum albumin (<2.5 g/dL, OR 2.80, CI 1.32-5.92) is significantly associated with the development of cellulitis. This finding is comparable with the observation in another south Indian study [7]. This finding also points to the fact that poor functional status of the liver is the predisposing factor for cellulitis in cirrhosis. Other studies have shown that in cellulitis patients, hypoalbuminemia is significantly associated with mortality in cirrhotic patients as well as the general population [18,19].

In our study, HE was significantly associated with cellulitis in cirrhotic patients (OR 2.95, CI 1.01-8.45). This association of HE with cellulitis could be either a cause or an effect. Cellulitis may be the predisposing factor for HE. Bacterial translocation is considered to be important in the pathogenesis of both HE [20] and cellulitis [21]. The gut mucosa of cirrhotic patients is more permeable to bacteria than normal mucosa [22]. Portal systemic shunt circulation in cirrhotic patients will help the organism that gained access to the gastrointestinal tract to escape phagocytosis by hepatic reticuloendothelial system, thereby establishing systemic bacteremia [18]. This bacteremia may result either in primary septicemia or localized infections like cellulitis. Likewise, because of the hepatocyte dysfunction and portosystemic shunting there are increased circulating levels of ammonia, primarily produced in the colon, which is the major neurotoxin involved in HE. On the other hand, HE in cirrhotic patients may predispose them to minor injuries of the lower limbs, of which the patient may be unaware, or they may neglect it due to encephalopathy. These injuries serve as an entry port of bacteria and subsequently develop cellulitis. Our patients had both cellulitis and HE on admission and we could not establish which event occurred first.

In our study, 77% of cellulitis patients had ascites, and 36% had SBP. This shows that cellulitis can occur independently in patients with cirrhosis without ascites or SBP. Gram-positive bacteria are the predominant organism isolated from cellulitis patients of the general population. But gram-negative bacteria are the major organism involved in cellulitis of cirrhotic patients [7,12,13]. In our study, 73% of culture from blood or pus showed growth of gram-negative bacilli (*Klebsiella*, *Pseudomonas* and *E. coli*), and 27% showed growth of *Staphylococcus*. The predominance of gut flora in the cultures from cellulitis patients with cirrhosis is probably related to

intestinal bacterial overgrowth and increased BT [23]. Though diabetes mellitus is a risk factor for cellulitis in the general population, surprisingly, our study did not find diabetes as a risk factor in cirrhotic patients.

This is the first study to assess the role of antibiotics in preventing recurrence of cellulitis in cirrhosis. On follow up 20% of cases had recurrence of cellulitis within 6 months which is comparable with 21.4% recurrence rate reported by Catherine *et al* [24]. The follow-up group showed decreased recurrence of cellulitis among patients who were started on antibiotic prophylaxis compared with those who were not on prophylaxis (15% vs. 50%, P=0.048). The NNT was 3. Logistic regression analysis showed that antibiotic prophylaxis independently reduced the rate of cellulitis recurrence. This novel finding suggests that the administration of prophylactic antibiotics in cirrhotic patients with cellulitis will help decrease the recurrence of cellulitis. However this should be analyzed in further larger prospective studies. Another hypothesis, we would like to suggest is that antibiotic prophylaxis may help prevent the development of cellulitis in at risk cirrhotic patients, with albumin <2.5 g/dL and MELD score >15.

Our study has certain strengths and limitations. This is the first study to assess the role of antibiotics in preventing recurrence of cellulitis in cirrhosis and is one of the very few case control studies which looked into the risk factors of cellulitis in cirrhotic patients. The study has demonstrated the novel finding that antibiotic prophylaxis is useful in preventing recurrence of cellulitis. This finding has important clinical implications, because it may help to reduce repeated hospital admissions in these patients. The limitation of the study is that as the data are collected from inpatients of a tertiary care center, the sample may not exactly represent the general population of cirrhotic patients. The number of patients in group 2 in the follow-up phase was lower. Since most of the patient had indication for initiation of SBP prophylaxis (primary or secondary prophylaxis) based on AASLD recommendations, we were bound to start antibiotics. Also many patients had HE, for which antibiotics were needed. Thus patients in the non prophylactic group became less in number. Even though the number is small, the statistical significance suggests that the association is relevant. Another limitation of our study is that we could not retrieve the data regarding antibiotic exposure prior to development of cellulitis.

In conclusion, our study demonstrated that hypoalbuminemia and high MELD score are the risk factors for cellulitis in cirrhosis. Antibiotic prophylaxis in cirrhotic patients with cellulitis will help prevent recurrence of cellulitis. This also points to the need for further studies which will guide for primary or secondary antibiotic prophylaxis for cellulitis in cirrhotic patients who have high-risk factors.

Summary Box

What is already known:

- Cellulitis is one of the major bacterial infections seen in cirrhosis apart from spontaneous bacterial peritonitis (SBP), urinary and respiratory tract infections
- Bacterial translocation from gut is postulated to be a major source of infection in cirrhosis
- Norfloxacin prophylaxis has helped to reduce the one-year probability of developing SBP and recurrence of SBP
- The role of antibiotic prophylaxis in preventing the recurrence of cellulitis is not known to date

What the new findings are:

- Model for end-stage liver disease score >15 and hypoalbuminemia are observed as significant risk factors for cellulitis in cirrhosis
- Administration of prophylactic antibiotics in cirrhotic patients with cellulitis will help decrease the recurrence of cellulitis

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