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Infections in Patients with Severe Alcoholic Hepatitis: A Retrospective Study

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Abstract

Introduction Severe alcoholic hepatitis (SAH) is the severest type of alcohol-related liver disease and is fraught with risk of infectious complications. The present study was done to determine the frequency and types of infections noted in patients with SAH at baseline evaluation.

Methods This is a retrospective analysis of patients with alcoholic hepatitis treated at our center between 2019 and 2022. Details of age, gender, baseline laboratory parameters, and clinical presentation were noted. All patients were screened for infections to ascertain the suitability for steroid use as per protocol. Diagnosis of infections was done as per the North American Consortium for the Study of End Stage Liver Disease (NACSELD) criteria. In culture-positive infections, the details of the microorganisms that were isolated and antibiotic susceptibility patterns were recorded.

Results A total of 66 patients with SAH formed the study cohort (median age: 42 years; 100% males). The majority of them had underlying cirrhosis (33 [50%]) and 26 had acute-on-chronic liver failure. Twenty-eight (42.4%) cases had bacterial infections. Spontaneous bacterial peritonitis (10 [35.7%]) was the commonest infection, followed by urinary tract infection (8 [28.5%]), lower respiratory infections (7 [25%]), and skin infections (3 [10.7%]). Culture positivity was noted in 12 cases (42.9%). The commonest organism cultured was *Escherichia coli* (6 cases), followed by *Klebsiella pneumoniae* (cases). Multidrug-resistant (MDR) infections were noted in nine (13.6%) cases. Two patients had tuberculosis.

Conclusion In all, 42.4% of patients with SAH had bacterial infections at baseline evaluation. Spontaneous bacterial peritonitis was the commonest infection. MDR bacterial infections were noted in nine cases (13.6%).

Keywords
- alcoholic cirrhosis
- alcoholic hepatitis
- Asia
- cirrhosis
- peritonitis

Introduction

Immune system dysfunction in cirrhosis is characterized by deranged phagocytic function, defective opsonization, and dysfunctional neutrophils. This leads to increased risk of bacterial infections including tuberculosis.[1,2] Severe alcoholic hepatitis (SAH) is the severest type of alcohol-related liver disease. Most patients with SAH in India have underlying cirrhosis or acute-on-chronic liver failure (ACLF).[3] They have profound immune paresis that predisposes them to

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acquire infectious complications resulting in poor short-term outcomes. It is, therefore, important to recognize and treat infections appropriately to improve outcomes in such patients.[4,5]

The present study was done to determine the frequency and types of infections noted in patients with SAH at baseline evaluation.

Methods

This is a retrospective analysis of a prospectively maintained database of patients with alcoholic hepatitis (AH) treated at our center between 2019 and 2022. We screened all the patients with liver disease and excluded those with non-alcohol-related liver diseases. Among those with alcohol-related liver diseases, we identified patients with AH based on clinical presentation and laboratory parameters. Patients with incomplete data and mild AH as per study definitions were excluded.

Definitions Used

AH was defined as per the National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria: history of significant alcohol intake, abstinence of <2 months prior to jaundice onset, hyperbilirubinemia (>3 mg/dL) with elevated aminotransferases (but not >400 IU/mL), and an aspartate-to-alanine aminotransferase (AST/ALT) ratio of >1.5. Histology was not done in any patient.[6] *SAH* was diagnosed if Maddrey's discriminant function (MDF) score was >32 and the Model for End-Stage Liver Disease (MELD) score was >20.[7]

Cirrhosis was diagnosed as usual on the basis of a combination of clinical findings (icterus, ascites, altered sensorium, portal hypertension-related bleed), biochemical tests (elevated bilirubin, hypoalbuminemia, prolonged prothrombin time or altered liver enzymes, and AST/ALT >1), and imaging showing altered liver size with changes in echotexture and irregular surface, splenomegaly, ascites, and presence of varices or portal hypertensive gastropathy on endoscopy.[3] *ACLF* was diagnosed as per the Asian Pacific Association for the Study of the Liver (APASL) criteria.[8]

Data Collection

The following details were obtained for patients with SAH: age, gender, baseline laboratory parameters, history of antibiotic use in preceding 4 weeks, and clinical presentation. All patients were screened for infections to ascertain suitability for steroid use as per protocol. The screening tests included hemogram, blood biochemistry, blood culture, urine culture, ascitic fluid examination, ascitic fluid culture, urine culture and, X-ray of the chest. Blood samples of 10 mL were collected from two different sites for blood culture. These were inoculated in aerobic and anaerobic culture bottles at bedside. Similarly, 10-mL ascitic fluid was inoculated in blood culture bottle at bedside for culture. Sputum was collected in symptomatic patients and processed as per the standard protocol. Serological tests for hepatotropic viruses were done in all cases. Those detected with HBsAg (hepatitis B surface antigen) and/or anti-Hbc (anti-hepatitis B core antibody) positivity were further investigated with using appropriate tests.

Diagnosis of infections was done as per the North American Consortium for the Study of End Stage Liver Disease (NACSELD) criteria.[9,10] The infections were classified into the following broad categories:

- *Spontaneous bacteremia:* a growth detected on blood culture without any identifiable source of infection.
- **Spontaneous bacterial peritonitis (SBP):** ascitic fluid cytology with >250 polymorphonuclear cells.
- **Lower respiratory tract infection:** pulmonary infiltrate, at least one respiratory symptom, that is, rales/crepitations, or one sign of infection—temperature <36°C or >38°C, leucocytosis (>10,000/mm^3), or leukopenia (<4,000/mm^3) in the absence of antibiotic intake.
- ***Clostridioides difficile* infection:** symptoms of diarrhea with a positive *C. difficile* assay.
- **Bacterial enterocolitis:** characterized by diarrhea or dysentery and positive stool culture.
- Skin infections (cellulitis).
- **Urinary tract infections:** urine examination showing more than 15 WBCs/high power field (hpf); Gram stain positivity in urine sample, or positive culture growth in a symptomatic patient.
- Intra-abdominal infections like appendicitis and diverticulitis.
- **Secondary bacterial peritonitis:** >250 polymorphonuclear cells/μL of ascitic fluid with intra-abdominal source of peritonitis; polymicrobial growth on fluid culture.

In culture-positive infections, the microbial organism that was isolated and the antibiotic susceptibility pattern were recorded. Multidrug-resistant (MDR) bacteria were defined as those bacteria that are resistant to three or more of the principal antibiotic families, including β-lactams, for example, extended-spectrum β-lactamase (ESBL) producing *Escherichia coli*, carbapenemase-producing *Klebsiella* (CPK), and others.[11]

Statistical analysis: The collected data were tabulated in a Microsoft Excel sheet. Continuous variables were analyzed as median ± standard deviation and range depending on normality of distribution. Categorical variables were interpreted using percentages. A comparison of medians was done using the Mann–Whitney *U* test. A *p*-value of <0.05 was considered significant. The institutional ethics committee approved the study and provided a waiver of informed consent.

Results

A total of 66 patients (median age of 42 years, 100% males, 56 admitted) with SAH formed the study cohort. Of these 66 cases, 33 (50%) had cirrhosis, 26 had ACLF (39.4%), and 7 (10.6%) had AH. The baseline demographic characteristics, clinical features, and laboratory parameters of the group are shown in ►**Table 1**.

All the patients were screened for infections prior to starting steroids. It was noted that 28 (42.4%) cases had

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Table 1 Baseline characteristics of study cohort

Parameters	
Total no. of cases	66
Age in years, median (range)	42 (28–62)
Sex (males)	66 (100%)
Alcohol consumption	
> 80 g/d 60–80 g/d	60 (91%) 6 (9%)
Tobacco consumption/smoking	
Active Past None	48 (72.7%) 16 (24.3%) 2 (3%)
Clinical findings	
Ascites Jaundice Hepatic encephalopathy ≥ grade 2	56 (84.8%) 66 (100%) 20 (30.3%)
Laboratory parameters	
Serum bilirubin (mg/dL) Serum albumin (g/dL) Aspartate aminotransferase (IU/mL) Alanine aminotransferase (IU/mL) Gamma glutamyl transferase (IU/L) International normalized ratio	8.2 ± 6.2 (6–38) 2.5 ± 0.6 (1.4–3.8) 97.2 ± 18.2 (43–158) 49 ± 10.6(24–130) 115.7 ± 15.8 (85–344) 1.8 ± 0.4 (1.5–2.8)
Antibiotic use in preceding 4 wk	48 (72.7%)
Discriminant function (DF), median (range)	60 (36–98)
Model for end-stage liver disease (MELD) score, median (range)	25 (21–30)

bacterial infections and 2 (3%) had hepatitis B infection. As hepatitis B infection was not related to SAH, it has not been included in further analysis. Two cases (3%) with lower respiratory tract infections had sputum positivity for acid-fast bacilli suggesting pulmonary tuberculosis.

Bacterial infections (28 cases): SBP (10 [35.7%]) was the commonest infection, followed by urinary tract infection (8 [28.5%]), lower respiratory tract infection (7 [25%]), and skin infection (3 [10.7%]). Culture positivity was noted in 12 cases (42.85%): 7 from blood culture, 4 from urine culture, and 1 from sputum culture. None of the ascitic fluid samples showed growth of microorganisms. The commonest organism cultured was *E. coli* (6 cases), followed by *K. pneumoniae* in 4 cases. *Streptococcus pneumoniae* infection was noted in two cases. MDR organisms were detected in nine cases: ESBL in six cases and CPK in three cases. The details of cultures are highlighted in ►**Table 2**. Culture negativity rates were 57.1%.

On comparing patients with ($n = 28$) and without infections ($n = 38$), it was noted that the median DF was significantly higher in patients with infection (68 [48–98] vs. 54 [36–84], $p = 0.02$) and there was no significant difference in the MELD scores (26 [21–30] vs. 24 [21–30], $p = 0.09$). On comparing patients with culture-positive infections ($n = 12$) and those without culture-positive infections ($n = 16$), no significant difference was noted in the DF (56 [41–78] vs. 62 [36–98], $p = 0.10$) and MELD scores (24 [21–30] vs. 26 [21–30], $p = 0.14$).

Discussion

The present study noted that at baseline evaluation, 42.4% of patients with SAH had bacterial infections. SBP was the commonest infection, followed by urinary tract infection and lower respiratory tract infection. MDR bacterial infections were noted in nine cases (13.6%).

A study by Louvet et al noted that one-fourth of cases presented with infection at the time of SAH diagnosis.[12] Similarly, in another study from Denmark, 37% of patients were infected at admission.[13] Our series had a higher infection rate at baseline evaluation. This is likely as majority of our patients had cirrhosis or ACLF and, hence, were more susceptible to infections. A rising trend of infection has been noted on follow-up and treatment across various studies.[12,14] Louvet et al distinguished infections at admission from those during treatment and follow-up. At baseline, SBP was common (44%), followed by urinary tract infection (32%) and respiratory (13%) and cutaneous (11%) infections. We noted a similar pattern in our study cohort. After or during corticosteroid treatment, an increased occurrence of respiratory infections was noted.[12] Similar findings were reported by Altamirano et al[15] and a meta-analysis.[16] The Steroids or pentoxifylline for alcoholic hepatitis (STOPAH) trial also reported that respiratory infections accounted for up to 50% of all infections during follow-up.[17] This sharp rise in

Table 2 Details of culture reports and antibiotic susceptibility

Escherichia coli ($n = 6$) Blood culture (3) Urine culture (2) Sputum culture (1)	ESBL (6) Type A (4) Types A and C (2)	Resistant to penicillins, all cephalosporins, aztreonam Sensitive to aminoglycosides (5 [83.3%]) and carbapenems (3 [50%])
Klebsiella pneumonia ($n = 4$) Blood culture (2) Urine culture (2)	CPK (3)	Resistant to penicillins, cephalosporins, fluoroquinolones, Septran, and carbapenems Sensitive to aminoglycosides (2 [50%]), polymyxin(3 [75%]), and vancomycin (3 [75%])
Streptococcus pneumoniae Blood culture (2)		Sensitive to aminoglycosides, vancomycin, piperacillin/tazobactam, and carbapenems

Abbreviations: CPK, carbapenemase-producing *Klebsiella*; ESBL, extended spectrum beta lactamase.

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respiratory infections during treatment may be related to corticosteroid use, nosocomial origin of infections, and intensive care unit stay including ventilator support.

Culture-positive infections were noted in 12 cases (42.9%) and 9 patients had MDR bacterial infections. This may be related to high rate of antibiotic exposure in preceding 4 weeks and immune dysfunction. MDR infections are increasingly being reported in Indian patients with advanced liver disease[18,19] and adversely affect outcomes of patients.

It is interesting to note that two cases had active pulmonary tuberculosis. It is well known that prevalence of tuberculosis is higher in cirrhosis, more so in alcoholics.[2] In India, tuberculosis is still prevalent and needs to be ruled out before starting steroids.

The limitations of this study are being a single-center experience, small sample size, and the retrospective design. Earlier studies have shown that serum procalcitonin is a useful marker for diagnosing sepsis in patients with AH.[20] However, this test was done in only 22 cases in the present cohort and, thus, not included in the analysis.

Despite these shortcomings, the present study highlights a rarely studied aspect of infections in SAH in the Indian setting.

Consent and Ethical Clearance

Ethical clearance was obtained via letter no. AHRC/IEC/2022/6. The need for informed consent was waived due to the retrospective nature of the study.

Authors' Contribution

All the authors contributed equally to the article.

Data Availability

Data can be shared by the author on a reasonable request.

Conflict of Interest

None declared.

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