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Prevalence of Sepsis and Role of Prophylactic Antibiotics in Acute Liver Failure

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Abstract

Sepsis is a major cause of death in ALF accounting for 24- 49% of death in Indian patients which is in fact more common than renal failure or GI bleed. We aimed to study the prevalence of sepsis in ALF and the role of prophylactic antibiotics in limiting the incidence of infections in ALF and improving related mortality. 46 patients of ALF were stratified into 2 main groups with SIRS>=2 and SIRS<2 on admission based on the number of SIRS components. Patients with SIRS>=2 were studied for the prevalence of sepsis in ALF. Patients with SIRS<2 were studied for the incidence of sepsis and the role of prophylactic antibiotics in ALF dividing them further into control group who received prophylactic antibiotics and the Test group who were given antibiotics only on worsening due to sepsis or there were evidence of infection. SIRS was documented regularly and on every episode of worsening. Prevalence of sepsis was studied by observing day1 infections. Role of prophylactic antibiotics was studied by documenting subsequent infections and related mortality in control group and comparing with the test group without prophylactic antibiotics. 70% of infected patients expressed more than 2 SIRS components whereas 27.3% infected patients never expressed more than 1 SIRS component. 50% infection rate was noted with expression of more than 2 SIRS components as compared to 14.3% who remained SIRS<2 without deterioration. Prevalence of sepsis was 64%. Mortality in the infected was 69% compared to 30% in the non infected. 71.4% infections with 40% related mortality was observed in the control group on prophylactic antibiotics whereas in the test group without antibiotic prophylaxis 75% infection were observed with 66.7% related mortality. This prospective evaluation points to SIRS being closely associated with infections. Use of prophylactic antibiotics may limit the incidence of infection and reduce sepsis related mortality in ALF.

Keywords: Sepsis; Prophylactic Antibiotics.

Introduction

ALF is a relatively uncommon condition that encompasses both fulminant and subfulminant hepatic failure marked by rapid impairment of liver function characterized by jaundice and subsequent altered mental state and coagulopathy. Mortality in ALF has been reported as 40%-95% and sepsis remains a major cause [1]. The most widely accepted definition of ALF includes evidence of coagulation abnormality suggested by prolongation of prothrombin time ≥ 15 secs or INR ≥ 1.5 and any degree of mental alteration in a patient with clinically evident liver disease of less than 26 weeks duration in the absence of pre-existing liver disease [2,3,4].

O'Grady and colleagues from King's college hospital in London defined ALF as onset of jaundice and subsequent encephalopathy between 8 and 28

days [1,4,5,6,7]. This was proposed after reviewing the data on 538 patients seen in the liver failure unit of King's college in London between 1972 and 1985 [1,5,6,7].

In Indian study, liver failure occurring after 4 weeks of onset of jaundice usually presented with ascites, encephalopathy being an extremely rare manifestation at this stage. These patients were quite different from ALF cases and were identified as subacute liver failure and these patients do not survive beyond 6 months [8,9].

Acute liver failure in India always presents with encephalopathy within 4 weeks of onset of jaundice [8,9]. It was noted that the rapidity of onset of encephalopathy had no influence on survival in these patients with ALF. Hence further classification with hyperacute, acute and subacute was not relevent [6,8].

There is a close interplay between ALF and the components of SIRS and when there is an infective process resulting in SIRS, it is called sepsis [8,10,11]. Definitions of sepsis includes the components of SIRS [12]. Presence of 2 or more components of SIRS when due to infection is termed sepsis [13].

Sepsis as a cause of death has been identified in 24%-49% of Indian patients with ALF and is documented as second most common cause of death after cerebral edema [10,14,15]. Early studies on ALF had reported sepsis in 11% of patients but more recent studies have found a 50% association with bacteraemia [5,16]. About 10-37% of mortalities in ALF can be attributed to bacterial infections and 10-80% experience bacterial infections sometimes in course of illness [13,17,18,19].

The role of prophylactic antibiotics in ALF has always been debatable. Some studies have supported its use and some groups do not advocate its use in view of resistant infections in about 10% of patients [20,21]. Clinically in the setting of ALF, or otherwise, sepsis is suspected when there is fever, tachycardia, leucocytosis and patients are investigated accordingly.

An analysis of 50 patients for prospective study of bacterial infections in ALF showed 80% infection rate with 70% gram positive infections commonly respiratory tract, urinary tract and central venous lines [5,18]. Another study 57% gram negative bacteria as the commonest and some had bacteraemia of unknown source [5,18].

Etiology of ALF in India has been observed as Hepatitis-E-38%,Hepatitis B31%, seronegative hepatitis-24%, drug reactions 5% and Hepatitis A 2% [22,23]. The demographic characteristics noted in India are: a) mostly young patients(mean age 29.5), b) less than 50% are females, pregnant women constitute 1/3rd of such patients.

Aims and Objectives

The integrated multidisciplinary supports involving liver transplant is not yet easily available/ affordable in the Eastern part of the country, hence intensive medical management including prevention and treatment of sepsis and its deleterious outcome remains the mainstay of treatment in ALF.

Pathophysiology of Sepsis in ALF

The reduced complement levels, impaired phagocytic functions and increased need for invasive procedures make patients of ALF more susceptible to infections. Gram negative sepsis with endotoxaemia resulting in microcirculatory failure and tissue hypoxia contributes to multiorgan failure [24]. A retrospective study from King's college group on acetoaminophen related ALF highlighted the association of SIRS and infection with progression of encephalopathy [11]. This was also expressed in an analysis of 887 patients reducing the chances of OLT [11,13,25]. When transplant provides the only chance of survival in severe cases of ALF, about 20-50% patients enlisted for OLT die before the transplant due to cerebral edema or sepsis [13,26,27].

Concept of Prophylactic Antibiotics in ALF

The criteria for SIRS is fulfilled by about 60% of ALF patients though 1/3rd of patients fail to express SIRS even when clinical sepsis is evident. In a study 74% of all infections occurred before day 10; 25 out of 35 patients died as compared to 7 out of 46 non-infected patients [14]. A vast majority of bacterial infections occurred early within 72 hours of admission. Pneumonia accounting for 50% of the infections developed at a median of 5 days after onset of ALF whereas bacteraemia and urinary tract infections occurred at a median of 3 and 2 days respectively [5,28]. Bacteriological evidence of infections has been recorded up to 80% and fungal infections, predominantly candidiasis in 32% [29].

Considering the early timing of infections in ALF and associated high mortality it may be unwise to await development of fever and leucocytosis to support evidence of infection or for positive cultures prior to initiation of antibiotics [24]. The concept of use of prophylactic antibiotics in ALF patients remains unproven and the subject needs more

research with a very high number of patients in reference to poor survival rates [2,20,30].

Material and Methods

A small scale prospective case control study was carried out on 46 patients of ALF who fulfilled the diagnostic criteria of ALF as laid down by O'Grady and colleagues [6,9,28,29]. Period of study was between January 2007 to September 2009.

Inclusion Criteria

- Patients above 10 yrs of age
- Jaundice with subsequent encephalopathy within 8-28 days
- Coagulopathy with INR ≥1.5

Exclusion Criteria

- History of illness>4 weeks
- Pre-existing liver disease
- Alcoholism >10 years
- Encephalopathy due to non-hepatic causes
- Evidence of portal hypertension

Sampling Strategy

46 patients were first categorized into groups with SIRS ≥ 2 and SIRS < 2.

SIRS ≥ 2 (20 patients) were considered to have clinical sepsis and were studied for prevalence of sepsis.

Patients with SIRS <2 (26 patients) formed the study group who were further divided into

- Control (13 patients), on prophylactic antibiotics
- Test (13 patients), who were not given prophylactic antibiotics.

SIRS components studied were

pulse rate>90/min

total leucocyte count<4000/>12000

temperature <36°c/>38°c

respiration rate>24/min

Observations

SIRS in ALF

Our aim was to observe whether SIRS can be considered as a true representation of clinical sepsis to justify the use of prophylactic antibiotics in the presence of more than 2 SIRS components.

Of the 20 patients with SIRS ≥ 2, 70% (14/20) had evidence of either radiological or microbiological infections. When SIRS<2, 42.3%(11/26) had evidence of infection whereas 27.3% (3/11) with documented infections expressed only 0-1 SIRS components.

Out of 26 patients with SIRS < 2 of the study group, subsequent observation and monitoring of SIRS components showed that by day 2-3, 12 patients(8 from the test group without prophylactic antibiotics and 4 from the control group on antibiotic prophylaxis) developing more than 2 SIRS components, 50% (6/12) had become infected as compared to 14.3% (2/14) infections in the remaining 14 patients who never expressed more than 1 SIRS components (significant at $p \leq 0.05$ after following Z test). Therefore initial SIRS assessment did not correlate with prevalence of infection in the study group but subsequent increase in SIRS components correlated well with acquisition of infections.

Events of ongoing sepsis as observed in SIRS ≥ 2 was 80% and SIRS < 2 was 57.7%. A statistically significant observation was that, presence of worsening factors was associated with 67.8% infections whereas in absence of such factors only 26.6% were infected.

Infections in ALF

Rate of infections observed was 54.3%(25/46).

In SIRS ≥ 2, 70%(14/20) were infected with 64.3% (9/14) mortality in the infected.

In SIRS < 2, 42.3%(11/26) were infected with 54.5%(6/11) mortality in the infected.

Mortality in the non-infected was 30%(not significant at $p \leq 0.05$).

Prevalence of infections in ALF as determined by observing day1 infections was 64%(16/25) of which 93% infections was prevalent in SIRS ≥ 2 and 27.3%(3/11) in SIRS < 2 (significant at $p \leq 0.05$ after performing the Z test).

Respiratory tract infections accounted for 64%(17/25) and 41.2%(7/17) had microbiological documentation as Klebsiella 57%(4/7); E.coli 28.5%(2/7) and Acinetobacter 14% (1/7) isolated from sputum or E-tube cultures.

In our study, the most significant organism was Pseudomonas 33.3%; E.coli 27.8%; Klebsiella 22.2%;

Staphylococcus, Acinetobacter and Candida was 5.5% each.

Urosepsis 44.4% (8/18) were predominantly caused by E.coli 62.5% (5/8) and Pseudomonas 37.5% (3/8). Bacteraemia was caused by Pseudomonas and Staphylococcus. E.coli infections were documented in first 2 days of illness suggesting E.coli prevalence in ALF.

Infections and Mortality in ALF

Mortality in ALF is multifactorial. Therefore in this study we compared mortality in infected to non-infected with or without prophylactic antibiotics.

Mortality in the studied group of ALF was 52.2%

Mortality in SIRS < 2 was 42.3% and SIRS ≥ 2 was 60%.

In SIRS ≥ 2, microbiologically documented infections were reported in 25% (5/20) and evidence of chest infections clinically and imaging without microbiological confirmation was present in 65% (13/20). Whether sepsis was directly related to death was difficult to ascertain as these patients were mostly in grade III-IV encephalopathy with concommitene factors like G.I bleed, cerebral edema, respiratory failure and renal dysfunction. Role of prophylactic antibiotics in ALF was studied by documenting infections those occurred from day2 onwards in the study group.

Control: Total infections including at time of admission was 53.8% (7/13)

Day 2 onwards documented infections was 71.4% (5/7) with mortality 40% (2/5)

In Test group(without antibiotic prophylaxis) 61.5% (8/13) deteriorated from day2-3 onwards with clinical signs of sepsis. 25% (2/8) attributed to microbiological sepsis and chest infections. 38.5% (5/13) did not deteriorate but documented urosepsis in 40% (2/5). Documented infections were 30.7% (4/13) of which day 2 onwards infections were 75% (3/4) and associated mortality was 66.7% (2/3). This showed that prophylactic antibiotics could reduce the mortality in the infected to 40% from 66.7% when antibiotic prophylaxis was not used.(statistically not significant at $p \leq 0.05$ after following Z test).

Discussion

ALF is a rare catastrophic illness involving almost all organ system. Where integrated supports involving liver transplant are lacking, prevention of sepsis and its disastrous outcome remains the mainstay of treatment.

This small scale retrospective study was carried out on 46 ALF patients after they fulfilled the diagnostic criteria as laid down by O'Grady and colleagues [1,5,6,7].

SIRS and infections in ALF

SIRS as a response to inflammation and infwection was expressed in 70%(14/20) of cases as SIRS ≥ 2 components whereas 27.3% (3/11) who had documented infections either microbiological or radiological did not express >1 SIRS component. Several studies had reported that about 60% of ALF patients fulfill the criteria for SIRS though clinical signs such as fever and high leucocyte count are absent in 30% of cases [2,31,32,33]. The hypodyanamic circulation, tachycardia, leucocytosis and acidosis with tachypnoea may be a reflection of the disease itself, thereby often masking the clinical signs of infections [13,16,34,35]. In this study, in SIRS ≥ 2, 70% (14/20) infection rate was noted as compared to 42.3% (11/26) infection rate with SIRS < 2.

When SIRS was recorded in each episode of worsening and infections, it was observed that 30.8% (4/13) from the control group and 61.5% (8/13) from the test group deteriorated and expressed more than 2 SIRS components from day3. Microbiological and radiological documented infections were present in 14.3% (2/14) in SIRS < 2 and 50% (6/12) in SIRS ≥ 2. Thus SIRS can be a good bedside marker and determinant for starting antibiotics. The absence of SIRS or late expression of SIRS as noted in 27% in our study and also noted in several other studies re-emphasise the fact that infections may be present in ALF without triggering the immune response.

Worsening Factors and Infections

The factors suggesting ongoing sepsis such as unexplained hypotension, decreasing urine output, worsening encephalopathy, severe acidosis and disseminated intravascular coagulation was observed in 80% of cases with SIRS ≥ 2 and only 57.7% in SIRS < 2. It was observed that presence of worsening factors was associated with 67.8% infections whereas in absence of such factors only 28.6% patients were infected. This association was found to be statistically significant. Hence it can be said that in presence of worsening factors, probability of ongoing sepsis always prevails and use of prophylactic antibiotics may have a favorable outcome.

Infections in ALF

Recent Indian studies have reported clinical evidence of severe sepsis or positive cultures in 52% of ALF patients [10]. We observed an infection rate of 54.3% (25/46) in our study. Sepsis remains a major cause of death in ALF accounting for 24-49% of Indian patients which is in fact more than renal failure and gastrointestinal bleed [10]. When outcome was compared between infected and non-infected, with 70% (14/20) infections 64.3% (9/14) died in SIRS ≥2 group whereas in SIRS<2 with 42.3% (11/26) infections 54.5% (6/11) expired. Mortality in the non-infected was only 30%.

Prevalence of sepsis in ALF as determined by observing the infections on admission both in SIRS ≥ 2 and SIRS < 2 categories was 64%.

There were 18 episodes of microbiologically documented sepsis in 13 cases out if 25 infected patients and the other 12 had clinical and radiological evident infection. A considerable number of cases had concomitant infections in 2 or more sites. Respiratory tract infections accounted for 64%(17/25) of the total ALF case and occurred very early during the course of illness. 41.2%(7/17) had microbiological documentation. The causative organisms were Klebsiella 57%(4/7), E.coli 28.5%(2/7) and Acinetobacter 14%(1/7) isolated from sputum/e-tube cultures unlike the hospital infection surveillance data(HISD) where pseudomonas infections were more common (37-38%).

Gram negative bacteria have long been recognized as a cause of sepsis and septic shock [13]. In this study Pseudomonas emerge as the most significant pathogen accounting for 33.3% of septicaemia followed by E.coli 27.8% and Klebsiella 22.2%. Staphylococcus, Acinetobacter and Candida infections were found in 5.5% each. Candida or oher fungal cultures was 5-6% in our hospital HISD records. Urinary sepsis was found in 44.4%(8/18) of the infections which were predominantly caused by E.coli 62.5%(5/8) and Pseudomonas 37.5%(3/8). The HISD documented urinary sepsis in 42.6% in general infected patients.

Bacteraemia was seen to be caused mainly by Pseudomonas and Staphylococcus.

E.coli sepsis was documented mainly in first 2 days of illness which suggests its prevalence in ALF and empiric antibiotics sensitive to these organisms might improve outcome in such patients.

Role of Prophylactic Antibiotics in ALF

Role of prophylactic antibiotics in ALF was studied by documenting infections those occurred after day1 and their outcome was compared between control group where prophylactic antibiotics were used and the test group where prophylactic antibiotics were not used. It was seen that only 2 out of 18 episodes of microbiological sepsis were documented in the first 2 days of illness and thereafter incidence of sepsis increased with increasing duration of illness. Therefore there may be a role prophylactic antibiotics in arresting the acquisition of infection during the course of illness and the deleterious outcome of sepsis in ALF.

No significant difference was observed with the use of prophylactic antibiotics and empiric antibiotics used after deterioration with clinical sepsis. Subsequent clinical deterioration occurred in 46.2%(12/26) amongst whom 50%(6/12) had documented infection. When compared to other 14/26 who did not deteriorate, only 14.3% (2/14) were infected. This implied a good correlation between deterioration and acquisition of infection. Therefore it may not be always wise to wait for clinical signs of sepsis to appear as it has already been shown that 27.3% of infected patients in our study never expressed more than 1 SIRS component. The restrictions in the definition of infection and sepsis to microbiological documentation may underestimate the true incidence of infection and its deleterious influence in ALF which might in fact have started long before a positive culture is obtained [11].

A recovery rate of 80% with 40% infections was seen in the control group with lower grades of encephalopathy with prophylactic antibiotic as compared to 69.2% recovery with 30.8% infections in the test group without antibiotic prophylaxis though this observation was not statistically significant. Lower grades of encephalopathy therefore carried lesser risks of infections and related mortality and better survival with prophylactic antibiotics. There are several studies too where the efficacy of prophylactic antibiotics could not be established [36,37].

The role of prophylactic antibiotic was finally studied by comparing the outcome in subsequently acquired infections in the control and the test group. 40% (2/5) mortality was observed with 71.4%(5/7) infections in the control group on prophylactic antibiotic versus 66.6% (2/3) mortality with 75% (3/4) infections in those without antibiotic prophylaxis.

The result of this study suggests that prophylaxis against gram negative sepsis needs to be emphasized in ALF. Daily assessment of clinical deterioration with expression of SIRS correlated

well with acquisition of infections in our study.

It can thus be recommended that antibiotics in those with clinical infections (SIRS) may be beneficial.

The observations in this study suggest an antibiotic regime of 3rd generation Cephalosporins to curb the incidence of sepsis and related mortality in ALF. A statistical significance could not established in this study probably owing to the small number of cases but a trend towards improvement was evident with prophylactic antibiotics.

References

1. Emette B. Keeffe, MD. Acute liver failure : In: Friedman SL, McQuard KR, Grendell JH. Current Diagnosis and treatment in Gastroenterology. vol.2; 2nd Ed: 2004.pp.536-545.
2. Polson Julie and Lee William M. AASLD position paper: The management of Acute liver failure. Hepatology. 2005;41(5):1179-97.
3. Tandon BN, Bernauau J, O'Grady J et al: Recommendation of International Association for the study of liver. Subcommittee on nomenclature of acute and subacute liver failure. J Gastroenterol Hepatol 1999;14:403-4.
4. Bernau J, Rueff B, Benhamov J.Fulminant and subfulminant liver failure: Definitions and causes. Semin liver Dis 1986;6:97-106.
5. Sanyal Arun J, Stravitz Todd R. Acute liver failure, In hepatology, a textbook of liver diseases, Zakim & Boyer, 4th ed. Vol.1, 2003.pp.445-480.
6. Lee WM, Sorrel MF. Developing a world view towards acute liver failure. Hepatology 1996;24: 270-1.
7. O'Grady JG, Schalm SW, Williams R. Acute liver failure: Redifining the syndromes. Lancet 1993;342: 273-275.
8. Acharya SK, Panda SK, Saxena A and Duttagupta S. Acute hepatic failure in India; a perspective from the East: Journal of gastroenterology and Hepatology 2000;15(5):473-479.
9. Acharya SK, Panda SK, Saxena A et al. Acute liver failure in India, a prospective from the East. J. Gastroenterol Hepatol 2000;15:473-79.
10. Anand AC. Management of acute liver failure. Gastroenterology Annual 2002.pp.118-137.
11. Vaquero J, Polson J et al.- the US Acute liver failure study group: Infection and progression of hepatic encephalopathy in acute liver failure. Gastroenterology. 2003;125(3):755-64.
12. Members of the American College of Chest Physicians/ Society of critical care medicine consensus conference committee; Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Critical care med. 1992;20:864-874.
13. Rolando N, Wade J, Davalos M, Wendou J, Philpott Howard J, Williams R. The systemic inflammatory response syndrome in Acute liver failure, Hepatology 2000;32(4):734-39.
14. Schiodt FV, Atillasoy E, Shakil AO et al. Etiology and outcome for 295 patients with Acute liver failure in the United States, Liver transplant surg. 1999;5:29-34.
15. Paul Richardson and John O'Grady. Acute liver disease. Hospital pharmacist; 2002;9:131-34.
16. Bhatia V; Acute liver failure: Infections and their management. Hepatology 2005;41:1179-97.
17. Larson Anne M. Diagnosis and management of Acute liver failure. Current opinion in Gastroenterology 2010;26(3):214-221.
18. Nancy Rolando, Harvey F, Brahm J, Philpott. Howard J, Alexander G, et al. Perspective study of bacterial infection in acute liver failure: An ana. Perspective study of bacterial infection in acute liver failure: An analysis of 50 patients. Hepatology. 1990.pp.49-53.
19. Rolando N, Wade JJ, Stangou A. et al. Prospective study comparing the efficacy of prophylactic parenteral antimicrobials with or without enteral decontamination in patients with acute liver failure: Liver transplant surgery, 1996;2(1):8-13.
20. Herrera Jorge. Management of Acute liver failure: Digestive diseases 1998;16;274-83.
21. O'Grady JG. Acute liver failure. Postgraduate Med. J. 2005;81:148-54.
22. Cheng V. Current issues and treatment of fulminant hepatic failure including transplantation in Hong Kong and in the Far East, semin liver disease 2003;23:239-50.
23. Wyke RJ, Canalese JC, Gimson AF et al. Bacteraemia in patients with fulminant hepatic failure. Liver 1982;2:45.
24. Santiago J Munoz. Difficult management problems in Fulminant hepatic failure: Seminars in liver diseases. 1993;13(4):395-410.
25. Riordan SM, Kurtovic J, Williams R. Fulminant hepatic failure; In: Schiff's diseases of the liver, Lipincott Williams & Wilkins, 10th ed. Vol 1. 2007.pp.601-614.
26. Lee WM. Acute liver failure in the United States; Seminars in liver disease, 2003;23(30):217-26.
27. Lee WM. Acute liver failure, N. England J Med. 1993; 329:1862-72.
28. Rolando N Philpott, Howard J. Bacterial and fungal infectins in acute liver failure. Semin liver dis 1996; 16:389.
29. Bansal S, Dhawan A. Acute liver failure. Indian journal pediatrics gastroenterology & hepatology III 2006;73(10):931-934.

30. Khuroo MS. Acute liver failure. Annals of Saudi medicine. 1998;18(4):318-26.

31. Acharya SK, Dorothy S, Kumar TL et al. Fulminant hepatitis in a tropical population: Clinical course and early predictors of outcome. Hepatology. 1996;23: 1448-55.

32. Kelly DA. Managing liver failure: Postgraduate Med J. 2002;78:660-67.

33. Todd Stravitz R & David J Kramer. Management of acute liver failure: Nature reviews gastroenterology and hepatology. 2009;(6):542-553.

34. O'Grady JG, Alexander GJ, Hayllar KM, William R. Early indicators of prognosis in fulminant hepatic failure, Gastroenterology 1989;97(2);439-445.

35. Rolando N, Philpott- Howard J, Williams R. Bacterial and fungal infections in acute liver failure. Semin liver disease.1996;16:389-402.

36. Lee WM, Williams R. Acute liver failure- Infections and their management: Medical, 1997;160-169.

37. H.assoun Z, Fournier C, Tessier G, Villeneuve E, Villeneuve JP. Prophylactic intravenous antibiotics do not influence the outcome of Acute liver failure: Journal of Hepatology; 2006;44(suppl 2):S70-S71.

38. Fisher RA, Yates F. Statistical table for biological agriculture and medical research, 6th ed, Oliver and Boyd, Edinburgh 1963.

39. Greenwood PE, Nikulin MS. A guide to chi-square testing, Wiley, New York,1996.