Antibiotics in Acute Liver Failure (ALF)

Abstract 1

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BACKGROUND & AIMS: We investigated whether antimicrobial prophylaxis alters the incidence of bloodstream infection in patients with acute liver failure (ALF), and whether bloodstream infections affect overall mortality within 21 days after development of ALF.

METHODS: We performed a retrospective cohort analysis of 1551 patients with ALF enrolled by the US Acute Liver Failure Study Group from January 1998 through November 2009. We analyzed data on infections in the first 7 days after admission and the effects of prophylaxis with antimicrobial drugs on the development of bloodstream infections and 21-day mortality.

RESULTS: In our study population, 600 patients (39%) received antimicrobial prophylaxis and 226 patients (14.6%) developed at least 1 bloodstream infection. Exposure to antimicrobial drugs did not affect the proportion of patients who developed bloodstream infections (12.8% in patients with prophylaxis vs 15.7% in nonprophylaxed patients; $P = .12$), but a greater percentage of patients who received prophylaxis received liver transplants (28% vs 22%; $P = .01$). After adjusting for confounding factors, overall mortality within 21 days was associated independently with age (odds ratio [OR], 1.014), Model for End-stage Liver Disease score at admission (OR, 1.078), and vasopressor administration at admission (OR, 2.499). Low grade of coma (OR, 0.47) and liver transplantation (OR, 0.101) reduced mortality. Although bloodstream infection was associated significantly with 21-day mortal-

ity ($P = .004$), an interaction between bloodstream infection and etiology was detected: blood stream infection affected mortality to a greater extent in nonacetaminophen ALF patients (OR, 2.03) than in acetaminophen ALF patients (OR, 1.14).

CONCLUSIONS: Based on a large, observational study, antimicrobial prophylaxis does not reduce the incidence of bloodstream infection or mortality within 21 days of ALF. However, bloodstream infections were associated with increased 21-day mortality in patients with ALF—to a greater extent in patients without than with acetaminophen-associated ALF. Our findings do not support the routine use of antimicrobial prophylaxis in patients with ALF.

Abstract 2

Constantine J. Karvellas,^{1,2} R. Todd Stravitz,³ Holly Battenhouse,⁴ William M. Lee,⁵ and Michael L. Schilsky,⁶ for the US Acute Liver Failure Study Group. Therapeutic Hypothermia in Acute Liver Failure: A Multicenter Retrospective Cohort Analysis. Liver Transpl 21:4–12, 2015.

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The benefit of therapeutic hypothermia (TH) in acute liver failure (ALF) has not been previously demonstrated in a controlled fashion. This study sought to determine the impact of TH on 21-day survival and complications in ALF patients at high risk for cerebral edema. This was a retrospective cohort study of ALF patients in the US Acute Liver Failure Study Group with grade III or IV hepatic encephalopathy. TH (32 °C–35 °C) was used in 97 patients (8%); 1135 (92%) who were not cooled were controls. Intracranial pressure was monitored in 38 TH ALF patients (39.2% versus 22% of controls, $P < 0.001$). Rates of bleeding (12% for both) and bloodstream (17% versus 18%) and tracheal infections (21% versus 23%, $P > 0.5$ for all) were similar. Unadjusted 21-day overall (62% versus 60%) and transplant-free survival rates (45% versus 39%, $P > 0.4$ for both) were similar. Multivariate models were created for acetaminophen (APAP) patients ($n = 582$) and non-APAP patients ($n = 613$). For APAP patients, the Model for End-Stage Liver Disease [MELD; odds ratio (OR) 0.91 per increment, 95% confidence interval (CI) 0.89–0.94, $P < 0.001$] and vasopressors (OR 0.16, 95% CI 0.11–0.24, $P < 0.001$) were associated with decreased 21-day spontaneous survival. Survival was improved with TH in APAP patients who were <25 years old (age of 25 years: OR = 2.735, 95% CI = 1.001–7.467) but worsened

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Abbreviation: ALF: Acute liver failure; CBF: Cerebral blood flow; MELD: Model for end stage liver disease; TH: Therapeutic hypothermia
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for APAP patients who were 64 years old or older (age of 64 years: OR = 0.167, 95% CI 0.028–0.999). For non-APAP patients, MELD (OR = 0.93 per increment, 95% CI = 0.91–0.95, $P < 0.001$) and vasopressors (OR = 0.60, 95% CI 0.40–0.90, $P = 0.01$) were associated with worse outcomes, whereas TH had no impact ($P = 0.93$). In conclusion, TH in ALF was not associated with increased bleeding or infections. Although young APAP ALF patients may benefit, TH did not consistently affect 21-day survival. A prospective trial is required to clarify the utility of TH in ALF patients.

COMMENTS

Liver is an important component of the immune system. In ALF, rapid immune paralysis is well known and overt sepsis has been reported in 55%–90% of patients.¹ The reasons for this propensity to develop sepsis include abnormal opsonisation due to reduced hepatic synthesis of proteins like fibronectin, impaired Kupffer cell function, decrease in complement synthesis and neutrophil dysfunction.² The occurrence of infection is associated with worsening of encephalopathy in patients with ALF.^{3,4} In a prospective evaluation of 96 acetaminophen induced ALF cases with early encephalopathy, occurrence of infection was associated with progression of encephalopathy to deeper grades in about 80% of the individuals.⁵ In this study, ALF patients without evidence of overt infection ($n = 168$), who progressed from early to advanced encephalopathy, had a number of components of SIRS.⁵ Fifty percent of those with 2–3 components of SIRS progressed to advanced encephalopathy in contrast to 25% of the patients without any component of SIRS. Elevated ammonia in patients with ALF is associated with increased complications and mortality.⁶ Kumar et al in a prospective study reported that infections in ALF are independently associated with persistent hyperammonemia, and such patients develop more complications and have higher mortality than those without hyperammonemia.⁷ The results suggest that infections are associated with poor outcome in these patients. Once infection occurs, a vicious circle begins—of increased ammonia, which causes neutrophil dysfunction, which further increases the risk of sepsis.

In ALF, majority of bacterial infections occur within 72 h of admission. Hence, there is a role of prophylactic broad spectrum parenteral antibiotics, which are used to prevent and treat infection in these patients. Infections and cerebral edema are the leading cause of death in these patients. Rolando et al reported that infection causing organisms were bacteria in 80% and fungal in 32% of their cases,⁸ whereas Acharya et al³ reported infection in 52% of ALF cases. Among the patients with positive culture, 43% had gram negative infections and 25% had *Aspergillus*.³ In more recent reports, the predominant organisms reported are Gram-negative.⁹ The prophylactic antibiotic

regimen used includes those acting against gram negative and gram positive bacteria, and anti-fungals. Addition of oral non-absorbable antibiotics does not confer any advantage over parenterally administered antibiotics.¹⁰

Any unexplained decrease in blood pressure, drop in urinary output, worsening encephalopathy, and development of severe acidosis or disseminated intravascular coagulation should be considered as signs of sepsis. Fungal infection should be strongly considered in the setting of unresponsive fever, leukocytosis, deterioration of neurologic status after initial improvement, and presence of renal failure.

Moderate hypothermia (32 °C–35 °C) using cooling blankets leads to a reduction in cerebral blood flow (CBF), cerebral metabolism, ammonia uptake by the brain, and glutamine synthesis; and reduces intracranial pressure in patients with ALF.¹¹ Data from studies in patients undergoing liver transplantation for ALF suggests that increases in intracranial pressure can be prevented during the dissection and reperfusion phases of the operation if the patients are maintained hypothermic during surgery.¹² However, hypothermia as a therapy has not shown any improvement in survival among patients with ALF, instead, has been used as a therapeutic bridge to transplantation.¹³ Hypothermia in the above mentioned studies has been used for not more than 8 h, and prolonged hypothermia is well known to cause cardiac arrhythmia and coagulopathy. Possibly, hypothermia for short duration may be of help in patients with ALF.

In these two retrospective analysis by the US ALFSG, authors assessed the role of prophylactic antibiotics¹⁴ and therapeutic hypothermia¹⁵ in a cohort of ALF patients. The authors documented increased age, high model for end stage liver disease (MELD) score, vasopressor requirement and advanced grades of coma to be associated with increased mortality. Similar proportion of patients developed infection among the group which received antibiotics as compared to those who did not. The authors concluded that antimicrobial prophylaxis did not reduce either the occurrence of infections or mortality. A total of 600 (39%) patients received antibiotics—sicker patients likely received prophylactic antibiotics, although the indications are not clearly spelt. The predominant etiology of ALF was acetaminophen. In the other study, the authors concluded that hypothermia was not associated with increased survival in patients with ALF,¹⁵ the results corroborated the existing evidence. A number of limitations in the study prevent its findings from being generalized across the globe. The commonest cause of ALF in the East is hepatitis viruses. Infections are common and lead to high mortality in these patients. Prevention and early treatment of infection is essential to reduce mortality. Contemplating antibiotics only after establishing positive culture reports leads to loss of vital time. These patients have high short term mortality, and if prevention/treatment of infection is not done at the early stages of illness, they will invariably develop

infection and die. The reasons for selective use of antibiotics are not clear from this retrospective study. The decisions were made independently by the treating physicians at each center. The included cohort was heterogeneous in terms of etiology and indications of starting prophylactic antibiotics/therapeutic hypothermia. A well designed prospective study with definitive inclusion, exclusion criteria and end points will better define the role of prophylactic antibiotics. Our experience suggests that infections are a major cause of mortality in ALF patients and we routinely use prophylactic antibiotics in all our patients.

CONFLICTS OF INTEREST

The author has none to declare.

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