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Effects of Antimicrobial Prophylaxis and Blood Stream Infections in Patients with Acute Liver Failure: a Retrospective Cohort Study

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Abstract

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 development of bloodstream infections and 21-day mortality.

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C.J.K. - Performed data analysis, participated in study design, drafted and revised the final manuscript.
J.C. - Participated in the design of the study, gathered data, performed data analysis, and contributed to the drafting of the manuscript.
H.B.- Participated in study design, performed statistical analysis and significantly edited the manuscript.
V.D.- Performed statistical analysis and significantly edited the manuscript.
C.S.- Was responsible for overall data retrieval, participated in the study design and editing of the manuscript.
W.M.L.- Conceived the idea of the study, participated in study design, assisted with study analysis and significantly edited the final manuscript.
All authors have reviewed and approved the final manuscript.

This work was performed jointly at the University of Texas-Southwestern (Dallas, USA) and the University of Alberta (Edmonton, Canada).

Results—In our study population, 600 patients (39%) received antimicrobial prophylaxis and 226 (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% non-prophylaxed; *P*=.12) but a greater percentage who received prophylaxis received liver transplants (28% vs 22%; *P*=.01). After adjusting for confounding factors, overall mortality within 21 days was independently associated 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 significantly associated with 21-day mortality (*P*=.004), an interaction between bloodstream infection and etiology was detected: blood stream infection affected mortality to a greater extent in non-acetaminophen 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 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 routine use of antimicrobial prophylaxis in patients with ALF.

Keywords

liver damage; APAP; antibiotic; compensatory anti-inflammatory response syndrome; systemic inflammatory response syndrome

Introduction

Patients with acute liver failure (ALF) are susceptible to infection due to multiple immunological deficits. Despite this, it is difficult to diagnose significant infections in ALF given the similarities in hemodynamic profile compared with septic shock [1]. The relationship between infection and development of the Systemic Inflammatory Response Syndrome (SIRS) and multiorgan dysfunction (MOD) in ALF have been debated [2]. The physiologic profile of SIRS is characterized by increases in both pro-inflammatory [3, 4] and anti-inflammatory cytokines [5, 6], culminating in a blunted immune response to microbial infection. Tolerance of circulating monocytes to bacterial endotoxins further impedes host immunity [7]. Reduced production of HLA-DR and pro-inflammatory cytokines, along with augmented levels of the anti-inflammatory IL-10 (compensatory anti-inflammatory response, CARS), are associated with increased incidence of infection and inferior outcomes[8].

Despite its physiological plausibility, the impact of infection in ALF patients remains to be defined. While several studies suggest poorer outcomes in ALF subjects with SIRS criteria, bloodstream infection (BSI) has not been linked to impaired survival although it is frequently assumed to be so [9–11]. Similarly, while antimicrobial prophylaxis or empirical therapy may prevent or treat early infection, no study to date has documented a clear mortality benefit.

The Acute Liver Failure Study Group (ALFSG) has collected detailed clinical and laboratory information on more than 2,000 patients with ALF over the past 13 years. We performed a retrospective, cohort study utilizing the ALFSG database to answer the following questions:

1. What is the impact of antimicrobial prophylaxis on rates of infection (particularly BSI) and 21-day survival in ALF patients?
2. What is the association between BSI and severity of illness and 21-day survival in ALF patients?

Methods

The reporting of this study followed the STROBE guideline [12].

Study Design and Setting

We performed a retrospective cohort study of 1551 patients prospectively enrolled by the U.S. ALFSG between January 1998 and November 2009. All participating centers are tertiary academic liver transplant (LT) referral centers. The Institutional Review Board at each participating center approved all protocols.

Operational Definitions

For the purposes of this study, **ALF** is defined as INR ≥ 1.5 and hepatic encephalopathy within the first 26 weeks of liver disease in a patient with an acute hepatic insult [13]. **Hepatic encephalopathy (HE) grade** is defined by the West Haven Criteria (summarized); grade 1 ~ any alteration in mentation, grade 2 being somnolent or obtunded but easily rousable or presence of asterixis, grade 3 being rousable with difficulty and, grade 4: unresponsive to deep pain[14].

Participants and variables

All patients met criteria for ALF as defined above[13]. Standardized case report forms gathering clinical, biochemical and microbiologic data were utilized and placed in a comprehensive database. Detailed data was collected for 7 days post admission to study (unless patient discharged, received LT or died before 7-days). Information regarding LT and 21-day survival were also available.

The **exposure of interest** was culture-positive infection (particularly BSI) during the first seven days in the study and the **primary outcome** assessed was 21-day overall survival. Confounding factors assessed included age, gender, severity of liver disease (MELD), severity of illness (requirement for organ support ~ vasopressors, mechanical ventilation (MV), renal replacement therapy (RRT), HE grade (West Haven Criteria[14]), requirement for LT and use of antimicrobial prophylaxis. In a secondary analysis, we examined the association between anti-microbial prophylaxis (exposure) on the subsequent development of BSI and 21-day mortality.

Data sources/measurement

As per standard intensive care unit (ICU) protocols, standard aerobic and anaerobic (2 × 10 ml of blood) paired samples were taken on admission from new central lines inserted as well as one peripheral site. Blood cultures were also taken upon clinical suspicion of BSI (presence of fever, SIRS features, hypotension, abnormalities of central line site). Urine and sputum (tracheal aspirates for intubated patients) were obtained upon admission and when clinically indicated (unexplained leukocytosis or new infiltrates on chest x-ray). Antibiotics were recorded as either prophylaxis (absence of positive cultures) or treatment on case report forms. Choice of antimicrobial regimen was individualized according to physician discretion. Culture results were documented for a maximum of 7 days after enrollment.

Positive blood, urine or sputum cultures were defined as isolation of recognized pathogenic microorganisms – both bacterial and fungal were used as the criteria for infection. The microbiological database recorded isolation of *S. aureus*, *S. pneumonia*, *E. coli*, *Klebsiella pneumoniae*, and *Candida* species. Additional organisms isolated via culture were classified as “other”; a manual review of respective case report forms to further characterize these infections was performed. The absence of urinalysis data and chest x-ray findings precluded fulfillment of diagnostic criteria for urinary tract infections and pneumonia. Use of antimicrobial therapy for prophylactic or therapeutic intent was specified on the case reporting form during the initial 7-days of study; however, the decision to use prophylactic antibiotics was made at each study site according to local protocol. Culture results and sensitivities were used to tailor antimicrobial therapy as indicated. Outcomes including survival and requirement of liver transplantation were recorded.

Statistical Methods

Statistical analyses were performed using SAS Version 9.2 (SAS Institute, Cary, NC). Descriptive statistics were used to report demographics, antimicrobial prophylaxis, presence of infection (blood, urine, sputum) and other variables describing illness severity, treatment, and outcomes. Differences in categorical variables between groups were tested using the chi-square test with one degree of freedom and a two-sided significance level of 0.05. Differences in continuous variables were determined using the Wilcoxon rank sum test and student t-test and presented as medians (Interquartile range) or means (standard deviations) after normality testing. Logistic regression analysis was used to study the effects of pre-specified prognostic variables on the a) probability of 21-day mortality and b) development of BSI. Survival was defined as dichotomous outcome - alive at 21-days after enrollment into the Registry (mortality ~ converse). Pre-specified variables included in the final model were age, etiology of ALF, HE grade on the day of admission to the registry, MELD score (admission), development of BSI during the seven-day data collection period, receiving antimicrobial prophylaxis, and receiving a transplant during the 21-days after entry to study. Etiology was collapsed into two groups: Acetaminophen toxicity (APAP) and all other etiologies (non-APAP). HE grade was categorized into two groups: low (grade 1 or 2) and high (grade 3 or 4). Variables that achieved a statistical significance of p=0.10 on univariable analysis (see Table 3) and were not collinear with other variables were included in the multivariable model. The inclusion of interaction terms were guided by clinical relevance and statistical significance of $p < 0.15$. Model performance was assessed using the

c-statistic and the Hosmer-Lemeshow test for goodness of fit. Multivariate associations are reported as odds ratios (OR) with 95% confidence limits.

Results

Review of microbiology

Baseline characteristics of 1551 enrolled ALF patients are shown in Table 1. The most common etiology was acetaminophen (n=719, 46%). A total of 531 (34%) patients experienced at least one culture-documented infection and 226 (14.6%) patients had at least one episode of bloodstream infection (BSI), 223 (14.4%) had at least one positive sputum culture/tracheal aspirate, and 258 patients (16.6%) had at least one positive urine culture. Amongst BSI ALF patients, 35.4% (n=80) were infected with a gram-positive isolate, 16.8%, (38) gram-negatives, 1% (2) were polymicrobial (gram positive/gram negative) and 9% (20) had fungemia. Eighty-six (38%) of BSI infected patients were classified as “other” and were therefore unspecified, despite manual review.

Outcomes: Impact of antimicrobial prophylaxis

Six hundred (39%) ALF patients had received antimicrobial prophylaxis at some point in their course (Table 1). More than 95% of participating sites (27/28) employed antimicrobial prophylaxis. Of the 600 ALF patients receiving prophylaxis 47% (n=283) received extended spectrum beta-lactam (e.g. piperacillin-tazobactam, ticarcillin-clavulinate), 39% (235) vancomycin, 27% (160) fluoroquinolones, and 20% (121) 3rd or 4th generation cephalosporins. 19 % (116) of patients were prophylactically on fluconazole (Supplementary File 1). On admission to study, ALF patients receiving antimicrobial prophylaxis had higher MELD score (32.4 vs. 31.3, p=0.01), bilirubin (7.9 vs. 6.9 mg/dl, p=0.01) and creatinine levels (1.8 vs. 1.5 mg/dl, p=0.02). These ‘prophylaxed’ patients were more likely to have higher coma grades (Grade III/IV 55% vs. 43%, p< 0.001) and were more likely to require organ support (MV ~ 52% vs. 42%, vasopressors 25% vs. 16%, and RRT ~ 29% vs. 16%, p<0.001 for all comparisons) on admission. There was no significant difference in the probability of having a BSI based on receiving prophylaxis (12.8%) or not (15.7% p=0.12). Likewise, there were no differences in rates of positive sputum cultures/tracheal aspirates (13.7% vs. 14.8%; p=0.53), or bacteruria (15.3% vs. 17.5%; p =0.27) respectively.

In the APAP subgroup (n=719), more patients on antimicrobial prophylaxis were listed for LT (31% vs. 21.4%, p=0.004). Overall, patients receiving antimicrobial prophylaxis were more likely to go on to LT (27.8% vs. 21.7%, p=0.006) but there was no difference in unadjusted overall 21-day survival (70% vs. 70%, p=0.88).

Association between bloodstream infection (BSI) and 21-day survival

Data on 226 ALF patients who developed BSI (14.6%) are shown in Table 2. ALF patients developing BSI had decreased 21-day survival (59% vs. 72%; p=0.0002) compared to those without BSI. This effect on 21-day survival was seen particularly amongst non-LT patients (BSI 53% vs. No BSI 65%, p=0.0013) but not in LT patients (86% vs. 91%, p=0.41, Figure 1). The difference in frequency of LT between ALF patients with and without BSI was not significant (19% vs. 25%; p=0.06).

In comparing ALF patients with BSI and without BSI (Table 2), ALF patients who went on to develop BSI had higher HE (Grade III/IV 57.5% vs. 46.2%, p=0.002) on admission and were more likely to require MV (57% vs. 44%, p<0.001).

Neither positive sputum cultures/tracheal aspirates (69% vs. 70%; p=0.70) nor urine cultures (71% vs. 70%; p=0.60) significantly impacted survival and were not analyzed further.

Multivariable analysis: Predictors of 21-day mortality

Multivariable logistic regression analysis was performed on the entire cohort of 1551 subjects to determine if the probability of mortality at three weeks was affected by pre-specified prognostic variables (Table 3). The final model (n=1452, 99 had missing data) included the following variables: age, etiology (APAP vs. Non-APAP), HE grade (low vs. high), MELD (admission), MV (admission), vasopressors (admission), antimicrobial prophylaxis, BSI and LT. After controlling for confounding, antimicrobial prophylaxis did not confer a significant effect on 21-day mortality. Furthermore, there was no significant interaction between prophylaxis and BSI (i.e. prophylaxis was not associated with decreased rates of infection). Variables which had a significant association with 21-day mortality included Age (Odds Ratio ~ 1.014 per year (95% CI 1.005– 1.024), MELD (admission) (OR 1.078 per increment (1.063–1.094), and requirement for vasopressors on admission (OR 2.499 (1.773–3.521). Low HE grade on admission (OR 0.47 (0.33–0.67) and receipt of LT (OR 0.101 (0.066–0.154)) were protective. The model c-statistic was 0.83 indicating good predictive accuracy. When site was added as a fixed effect to the multivariable model, performance did not significantly improve (c-statistic 0.84, data not shown).

While BSI did significantly impact 21-mortality (P=0.004) in the overall model, there was a statistically significant quantitative interaction between etiology (APAP/non-APAP) and presence of BSI (P=0.11). The magnitude of the association between BSI and increased 21-day mortality was greater in non-APAP ALF patients (OR 2.034(1.257–3.292)) than in APAP ALF patients (OR 1.136 (0.672–1.922)). Further exploration of the APAP population in a separate mortality model showed that BSI was not significant for predicting death (p=0.68).

Multivariate analysis: Predictors of bloodstream infection

The relationship between covariates and the development of BSI was explored with multivariable logistic regression using similar variables as included in the previous model. The model had poor fit and did not show any statistically significant relationships (data not shown).

DISCUSSION

Key findings

In this study, ALF patients who received antimicrobial prophylaxis displayed increased severity of illness on admission (MELD, HE grade and requirement for organ support). Use of antimicrobial prophylaxis did not appear either to alter rates of infection or to improve overall survival on crude or adjusted (multivariable) analysis. Nonetheless, patients who

went on to LT were more likely to have received antimicrobial prophylaxis. The presence of BSI was associated with increased severity of illness (HE grade, requirement for organ support) and 21-day mortality on univariable analysis, an effect that was more pronounced in non-acetaminophen etiologies of ALF after adjusting for confounding factors. In all ALF patients, age, MELD, and the requirement for vasopressors on admission were also independently associated with increased 21-day mortality.

Comparison with previous studies

Prior reports of the incidence of ALF-related infections have varied considerably, with bacteremia reported between 22% and 80% [15–17]. Early studies emphasized gram-positive infections likely related to pulmonary sepsis and concerns of tracheal suctioning exacerbating intracranial hypertension [18]. Studies by Rolando et al. noted the negative impact of bacteremia on survival in ALF, with attributable mortality ranging from 10 to 52% [19–21]. In contrast, two recent studies failed to demonstrate any significant impact due to infection nonetheless with a shift towards more gram-negative pathogens [11, 22]. Our study demonstrates that the development of BSI is associated with increased 21-day mortality in ALF patients, particularly in non-APAP etiologies of ALF after controlling for confounding. Non-APAP patients often follow a subacute pattern (encephalopathy >8 weeks after development of synthetic dysfunction) and are at lower risk of developing complications (cerebral edema, acute kidney injury) compared with APAP (hyperacute liver failure) patients [13]. Although not conclusively shown, the prolonged course of illness and the development of the Compensatory anti-inflammatory response (CARS); a relative state of immunosuppression may explain the increased risk of BSI in this group [2]. In contrast, for APAP patients with hyperacute liver failure (hepatic encephalopathy within seven days of hepatic dysfunction) that demonstrate a high risk of cerebral edema but also a high rate of spontaneous recovery, the severity of the ALF syndrome, and not infectious complications, may be driving mortality. Thus, BSI appears to play an important role only in slower evolving or sub-acute ALF etiologies [23].

Previous studies suggest a relationship between infection, HE grade, and outcomes in ALF. Higher rates of infection have been shown in subjects with higher HE grade and escalating number of SIRS components [9]. Vaquero et al. demonstrated a link between culture-positive infection and progression to advanced coma grade [11]. In this cohort we found an association between advanced HE grade on admission, the subsequent development of BSI and decreased 21-day survival (low coma grade was protective after adjusting for confounding factors). Coma grade would appear to be a surrogate for increased susceptibility, but this cannot be concluded from our data.

The utility of antimicrobial prophylaxis in ALF remains controversial. Previous studies have shown the use of antimicrobial prophylaxis decreases the incidence of infection in ALF patients without an effect on mortality [20, 24]. Similarly, while our results suggest that patients with an increasing burden of illness/MOD on admission are more likely to be placed on antimicrobial prophylaxis (Table 1), its use did not affect rates of BSI or 21-day mortality in ALF patients after controlling for severity of illness (organ support, MELD). While data is limited, the United States Acute Liver Failure Study Group has previously recommended

antimicrobial prophylaxis in patients with advanced HE, refractory hypotension, the presence of SIRS components and for patients listed for LT [25]. However the most recent guidelines from the American Association for the Study of Liver Disease do not advocate the routine use of prophylaxis [26].

Study limitations and strengths

This study has limitations that warrant consideration. First, while we included data from 23 liver transplant centers across the United States, it is a retrospective analysis of prospectively collected data and thus is observational in nature, potentially predisposing to bias and residual confounding. Only association and not causation can be inferred. Data on infection was only collected during the first 7-days of study and due to the retrospective format, we cannot conclusively state that all infections included in this analysis were clinically significant (colonization vs. infection). We were also unable to determine presence or duration of antibiotics prior to referral if not present on day 1 (admission) of data collection or subsequent to this day in the registry. Finally, despite a complete review of electronic and original paper charting we were unable to obtain complete microbiological information on all pathogens and as such cannot comment on changes in trends of bacterial flora (i.e., gram positive vs. gram negative). However to date, the impact of clinically significant infection on outcomes such as transplant and mortality have not been evaluated in a prospective and/or clinical trial setting. Hence there is value in replicating observational studies of this nature to assess for consistency and generalizability across studies. To our knowledge this is the largest retrospective study to date assessing the role of infection in ALF. Of interest, our study validates previous studies by Rolando, which did not show a significant benefit with antimicrobial prophylaxis [27].

Conclusions

ALF patients who received antimicrobial prophylaxis had evidence of significant organ dysfunction on admission. While antimicrobial prophylaxis did not appear to either alter rates of infection or to improve overall survival on unadjusted or adjusted (multivariable) analysis, patients who went on to LT were more likely to have received antimicrobial prophylaxis. The presence of BSI was associated with increased 21-day mortality with a greater impact in patients with non-APAP ALF patients after controlling for confounding. Age, MELD, and the requirement for vasopressors on admission were independently associated with increased 21-day mortality in all ALF patients. These findings do not support the routine use of antimicrobial prophylaxis in ALF patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALF	Acute Liver Failure
APAP	Acetaminophen
BSI	Bloodstream infection
CARS	Compensatory anti-inflammatory response syndrome
HE	Hepatic encephalopathy
ICU	Intensive care unit
LT	Liver transplantation
MELD	Model of End-stage Liver Disease score
MOD	Multiorgan dysfunction
MV	Mechanical ventilation
Non-APAP	Non-acetaminophen etiology
RRT	Renal replacement therapy
SIRS	Systemic inflammatory response syndrome
US ALFSG	United States Acute Liver Failure Study Group

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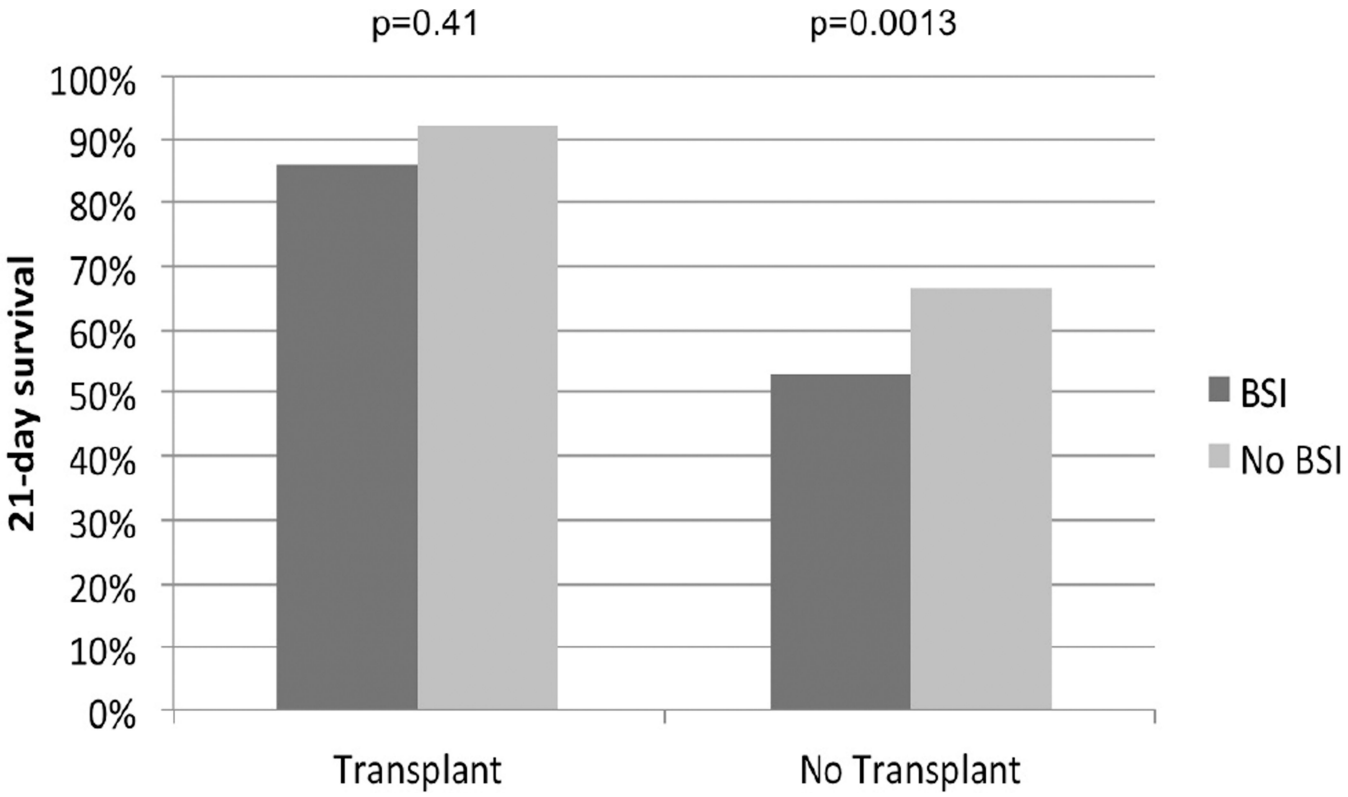

Figure 1.

Comparison of 21-day overall survival (post-transplant and transplant free) between ALF patients who did and did not acquire a BSI.

• Development of BSI conferred worse 21-day survival in non-transplanted ALF patients (53% vs. 65%, p=0.0013) but not in transplanted ALF patients (86% vs. 91%, p=0.41).

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Table 1

Baseline characteristics of 1551 ALF patients stratified for antimicrobial prophylaxis

		N	Total Cohort (N=1551)	Prophylaxis (N=600)	No Prophylaxis (N=951)	p-value
Age		1551	39.0 (29.0–50.0)	38.0 (29.0–50.0)	39.0 (29.0–51.0)	0.31
Female		1551	1066 (68.7%)	411 (68.5%)	655 (68.9%)	0.88
Etiology		1551				0.60
	APAP		719 (46.4%)	271 (45.2%)	448 (47.1%)	
	Viral Hepatitis		153 (9.9%)	65 (10.8%)	88 (9.3%)	
	DILI		174 (11.2%)	69 (11.5%)	105 (11.0%)	
	Indeterminate		206 (13.3%)	86 (14.3%)	120 (12.6%)	
	Other		299 (19.3%)	109 (18.2%)	190 (20.0%)	
Biochemistry*						
	APACHE II	430	16.0 (10.0–21.0)	N/A	16.0 (10.0–21.0)	
	MELD	1485	31.7 (24.8–38.7)	32.4 (25.5–39.8)	31.3 (24.3–37.9)	0.01
	INR	1496	2.7 (2.0–4.2)	2.7 (2.0–4.1)	2.7 (2.0–4.3)	0.49
	Bilirubin (mg/dl)	1542	7.3 (3.9–20.5)	7.9 (4.3–22.3)	6.9 (3.7–19.6)	0.01
	Creatinine (mg/dl)	1548	1.6(0.9–3.1)	1.8 (1.0–3.3)	1.5 (0.8–2.9)	0.002
	Lactate (mg/dl)	799	4.4 (2.6–9.7)	4.2 (2.6–8.7)	4.7 (2.6–10.5)	0.08
	ALT	1534	1983 (649–4510)	1944.0 (627–4305)	2003 (684–4720)	0.20
	WBC	1542	10.5 (7.1–15.2)	10.4 (6.8–15.5)	10.6 (7.2–15.1)	0.32
	Platelet Count	1539	132 (86–195)	129 (82–185)	133 (91–201)	0.03
Organ support						
	Mechanical ventilation					
	Admission*	1545	707 (45.8%)	309 (51.6%)	398 (42.1%)	<0.001
	7-days**	1551	944 (60.9%)	406 (67.7%)	538 (56.6%)	<0.001
	Vasopressors					
	Admission*	1522	293 (19.3%)	145 (24.6%)	148 (15.9%)	<0.001
	7-days**	1543	513 (33.3%)	240 (40.1%)	273 (28.9%)	<0.001

		N	Total Cohort (N=1551)	Prophylaxis (N=600)	No Prophylaxis (N=951)	p-value
	Renal Replacement Therapy					
	Admission*	1536	321 (20.9%)	175 (29.3%)	146 (15.6%)	<0.001
	7-days**	1544	522 (33.8%)	257 (42.9%)	265 (28.0%)	<0.001
Coma Grade*		1547				<0.001
	1 or 2 (Low)		807 (52.2%)	271 (45.2%)	536 (56.5%)	
	3 or 4 (High)		740 (47.8%)	328 (54.8%)	412 (43.5%)	
Infection**						
	Bloodstream	1551	226 (14.6%)	77 (12.8%)	149 (15.7%)	0.12
	Sputum	1551	223 (14.4%)	82 (13.7%)	141 (14.8%)	0.53
	Urine	1551	258 (16.6%)	92 (15.3%)	166 (17.5%)	0.27
LTx Listing	Listed for LT	1547	611 (39.5%)	263 (43.8%)	348 (36.6%)	0.0048
	Listed for LT (APAP)	719	180 (25.0%)	84/271(31.0%)	96/448 (21.4%)	0.0041
	Listed for LT (non-APAP)	828	431 (52.1%)	179/328 (54.4%)	252/500 (50.1%)	0.48
Outcomes***						
	Liver transplant	1551	373 (24.1%)	167 (27.8%)	206 (21.7%)	0.006
	Alive at 21 days	1551	1084 (69.9%)	418 (69.7%)	666 (70.0%)	0.88

- Normally distributed data presented as mean (Standard deviation)
- Non-normally distributed data presented as Median (IQR)
- Categorical data presented as percentage (chi-square test)
- 600 ALF patients received antimicrobial prophylaxis
- **~On admission, **~During 7-day inpatient phase ***~21-day post-enrollment*

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Table 2

Comparison of 226 patients with bloodstream infections with 1325 patients without BSI

		BSI (N=226)	No BSI (N=1325)	p-value
Age		40.5 (30.0–51.0)	39.0 (29.0–50.0)	0.49
Female		143 (63.3%)	923 (69.7%)	0.06
Etiology				0.30
	APAP	100 (44.3%)	619 (46.7%)	
	Viral Hepatitis	15 (6.6%)	138 (10.4%)	
	DILI	27 (12.0%)	147 (11.1%)	
	Indeterminate	34 (15.0%)	172 (13.0%)	
	Other	50 (22.1%)	249 (18.8%)	
Biochemistry*				
	APACHE II	17.0 (14.0–22.0)	15.0 (10.0–21.0)	0.02
	MELD	31.7 (26.0–38.1)	31.7 (24.5–38.8)	0.96
	INR	2.6 (1.9–4.1)	2.7 (2.0–4.2)	0.14
	Bilirubin (mg/dl)	7.6 (4.1–20.2)	7.3 (3.7–20.5)	0.50
	Creatinine (mg/dl)	1.8 (1.0–3.1)	1.6 (0.9–3.1)	0.14
	Lactate (mg/dl)	4.9 (2.8–10.9)	4.4 (2.5–9.5)	0.10
	ALT (U/L)	1461.0 (492.5–3794.5)	2076.5 (674.0–4645.0)	0.02
	WBC	10.3 (6.8–16.3)	10.5 (7.2–15.1)	0.86
	Platelet Count	120.0 (81.0–187.0)	133.0 (87.0–197.0)	0.07
Organ Support				
	Mechanical Ventilation			
	Admission*	128 (56.9%)	579 (43.9%)	<0.001
	7-days**	164 (72.6%)	780 (58.9%)	0.0001
	Vasopressors			
	Admission*	51 (23.0%)	242 (18.6%)	0.13
	7-days**	95 (42.4%)	418 (31.7%)	0.002
	Renal Replacement Therapy			

		BSI (N=226)	No BSI (N=1325)	p-value
	Admission*	50 (22.3%)	271 (20.7%)	0.57
	7-days**	79 (35.1%)	443 (33.6%)	0.65
Antimicrobial Prophylaxis**		77 (34.1%)	523 (39.5%)	0.12
Coma Grade*				0.002
	1 or 2 (Low)	96 (42.5%)	711 (53.8%)	
	3 or 4 (High)	130 (57.5%)	610 (46.2%)	

- Normally distributed data presented as mean (Standard deviation)
- Non-normally distributed data presented as Median (IQR)
- Categorical data presented as percentage (chi-square test)
- *~*On admission*
- **~*During 7-day inpatient phase*
- ***~*21-day post-enrollment*

Table 3

Multivariable analysis of 21 day mortality for 1452 patients with Acute Liver Failure

	Univariate			Multivariate (N=1452, c=0.827)			
	OR	**95% CI**	**p-value**	**Included in model?**	**OR**	**95% CI**	**p-value**
Age	1.021	1.013 – 1.028	<0.0001	Yes	1.014	1.005 – 1.024	0.003
APAP etiology*	0.693	0.556 – 0.864	0.0011	Yes			<0.0001
Low Coma grade (admission)	0.34	0.271 – 0.426	<0.0001	Yes	0.470	0.330 – 0.670	<0.0001
MELD (admission)	1.073	1.060 – 1.087	<0.0001	Yes	1.078	1.063 – 1.094	<0.0001
Mechanical Ventilation (admission)	2.967	2.366 – 3.719	<0.0001	Yes	1.398	0.970 – 2.017	0.0726
Vasopressors (admission)	4.272	3.274 – 5.574	<0.0001	Yes	2.499	1.773 – 3.521	<0.0001
Antimicrobial prophylaxis	1.017	0.814 – 1.271	0.8787	Yes	0.892	0.677 – 1.175	0.42
BSI*	1.740	1.300 – 2.327	0.0002	Yes			0.004
Transplant (during 21 days)	0.192	0.134 – 0.274	<0.0001	Yes	0.101	0.066 – 0.154	<0.0001
APAP*BSI				Yes			0.11

- Statistical significance at alpha=0.05 (p-value), OR ~ Odds Ratio, 95% CI ~ 95% Confidence Intervals.
- Abbreviations: APAP ~ Acetaminophen, BSI ~ bloodstream infection, Non-APAP ~ Non-acetaminophen
- Etiology was stratified as APAP vs. non-APAP etiologies
- Low HE grade = Grade One or Two (comparison to High HE grade (Three or Four) by West Haven Criteria[14]
- *Renal replacement therapy was not significant on univariable analysis (See Table 2).
- Etiology (APAP) and presence of BSI both significantly impacted 21-day mortality in the univariate models and there was a significant interaction in the multivariate model.
- In the presence of the interaction, BSI was independently associated with increased 21-day mortality:
  - Non-APAP ALF patients OR 2.034 (1.257–3.292)
  - APAP ALF patients OR 1.136 (0.672–1.922)
- In a separate mortality model for APAP-ALF patients, presence of BSI was NOT independently associated with 21-day mortality (p=0.68)
- 99 of 1551 patients had missing data