Title: Safety and efficacy of antibiotics among acutely decompensated cirrhosis patients

Short Running Title: Antimicrobial treatment and Acute-on-chronic Liver Failure

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None of the authors have a conflict of interest to disclose.

Acknowledgements

Authorship Contribution:
Shahid Habib: Study idea, design, data collection, statistical analysis, manuscript writing and submission.
Nehali Patel: Protocol writing and data collection.
Sandeep Yarlagadda: Protocol writing and data collection.
Chiu-Hsieh Hsu: Statistical analysis.
Sarah Patel: Protocol writing and data collection.
Lindsey Schader: Manuscript writing, statistical analysis, and submission.
Courtney Walker: Protocol writing and data collection.
Innocent A. Twesigye: Statistical analysis.

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Title: Safety and efficacy of antibiotics among acutely decompensated cirrhosis patients

Abstract

Background and Aim
Infection is a leading precipitant of acute-on-chronic liver failure. We aim to determine the safety and efficacy of antibiotics within acute-on-chronic liver failure.

Methods
Retrospective study of 457 acute-on-chronic liver failure patients, admitted to the University of Arizona Health Network between January 1 and December 31, 2014. Eligibility criteria were: at least 18 years of age and six months follow-up, data available to calculate systemic inflammatory response syndrome, and acute-on-chronic liver failure. We collected patient’s clinical features and historical data. Key data points were: infection, antibiotic use, and systemic inflammatory response syndrome. We used cox proportional hazards to model the effects of clinical factors on risk of death.

Results
521 of 1243 met the inclusion criteria, 64 had missing data, leaving 457 patients. Infection resulted in higher hazard (HR=1.6, CI: 1.1-1.3, p=0.01). Patients with infections and antibiotics, compared to non-infected patients without antibiotics, had higher hazard (HR=1.633, CI: 1.022-2.609, p=.04). Of those infected patients with antibiotics, systemic inflammatory response syndrome patients experienced higher hazard (HR=1.9, CI: 1.1-3.0, p=.007). Multivariable cox proportional hazards associated the following with higher hazard: systemic inflammatory response syndrome (HR=1.866, CI: 1.242-2.804, p=0.003), vancomycin (HR=1.640, CI: 1.119-2.405, p=0.011), Model of End-Stage Liver Disease (HR = 1.051, CI: 1.030-1.073, p<0.001), gastrointestinal bleeding (HR=1.727, CI: 1.180-2.527, p=0.005), and hepatic encephalopathy (HR=1.807, CI: 1.247-2.618, p=0.002).
Conclusion

Overall, treatment of infection with antibiotics did not improve survival, however patients not meeting SIRS criteria had better outcome and vancomycin was associated with poorer survival among acute-on-chronic liver failure patients.

Key Words: Cirrhosis, Vancomycin, Antibiotics, Infections, ACLF
Introduction

Acute-on-chronic liver failure (ACLF) is a common condition among cirrhotic patients and it carries significant mortality. ACLF is characterized by organ failure(s), acute decompensation, and a high risk of short-term mortality. Among patients with prior liver decompensation 28-day mortality and 90-day mortality of ACLF are 39.3% and 53.6% respectively. ACLF has several precipitants. These precipitants include: toxins, drug exposure, alcohol consumption, trauma, including surgical, acute kidney injury, hepatic vein or portal vein thrombosis, hepatocellular carcinoma, and infection. Infection is a leading cause of ACLF. Acute worsening could also be due to worsening of underlying chronic liver diseases such as autoimmune hepatitis, primary sclerosing cholangitis, hepatitis B viral infection and alcohol liver disease.

The main precipitant of ACLF, infection, is common among the cirrhotic patient population, and infection by viral, bacterial, fungal, or atypical organisms has been shown to lead to ACLF even in stable cirrhosis patients. A high percentage, 30%-50%, of cirrhotic patients have an infection. Furthermore, cirrhotic patients are at an increased risk of nosocomial infections, with rates of 15-35% as compared to 5-7% in non-cirrhotic patients. Among infected cirrhotic patients, drug resistance is also common. One study found that 18% of its infected cirrhotic cohort was infected with multidrug-resistant organisms (MDRO). Multiple factors have been independently associated with multi-resistant infections, including: nosocomial origin of infection (hazard ratio [HR], 4.43), long-term norfloxacin prophylaxis (HR, 2.69), recent infection by multi-resistant bacteria (HR, 2.45), and recent use of β-lactams (HR, 2.39).

A prospective case-control study detailed the natural course of infection in stable cirrhotic patients in an inpatient setting. The cohort experienced 20% mortality during the index hospital stay. A third of the cohort experienced a second infection during the index hospital stay. After discharge, almost half of the patients were readmitted with infection within 6 months. Of those readmitted, 74% had a different focus of infection, and 26% had recurrence of the prior infection. The most prevalent sites of infection were spontaneous...
bacterial peritonitis (31.1%), UTI (22.6%), and pneumonia and cellulitis (11.3%). Evidently, infection is a significant complication within the cirrhotic patient population.

Despite the high prevalence of infection resulting in high mortality among cirrhotic patients with ACLF, several clinical questions remain unanswered. Previous data has indicated that ACLF patients with infection have a higher risk of death compared to ACLF patients who do not present with an infection.\(^3\),\(^4\) It is unknown if this heightened risk of death is independent of disease severity scores, such as the Model for End-Stage Liver Disease (MELD) score. In clinical practice MELD score is used to prioritize liver transplant patients under the assumption that MELD score is predictive of short-term mortality, but the score is known to be flawed under certain clinical conditions.\(^9\) It remains unanswered whether MELD score is accurate in the presence of ACLF and infection.

The safety of antibiotic treatment within ACLF patients, in terms of effects on patient survival, is also unknown. Several antibiotics are known hepatotoxins. Amoxycillin with clavulanic acid combination is a leading cause of drug induced liver injury,\(^10\) while the Beta lactam group of antibiotics are hepatotoxic and cause cholestasis. Similarly, all anti-fungal treatments have the potential for hepatotoxicity.\(^11\) Antibiotics may also be nephrotoxic and, thereby, cause further complications for cirrhotic patients. For example, vancomycin or aminoglycosides are known nephrotoxins used to treat infections.\(^12\) Data also suggests that cirrhotic patients may be more likely to experience nephrotoxicity than the general population. One study of a non-cirrhotic patient population demonstrated that a glomular filtration rate (GFR) of less than 85% is associated with a higher risk of nephrotoxicity, and cirrhosis patients with portal hypertension tend to have GFR’s less than 85% of the normal.\(^13\) Renal deterioration, independent of underlying etiology, in advanced liver disease patients is prognostically significant, and therefore carries more weight in MELD calculation.\(^13\) One may expect that the use of such hepatotoxic and nephrotoxic antibiotics in these clinical scenarios may cause more harm than good.

Treatment of infection with antimicrobials could be deleterious in the setting of ACLF. Moreover, there is not much data to guide when to initiate antimicrobials and what antimicrobials to prescribe. Recently, goal-directed and empirical broad-spectrum antibiotics were associated with better outcomes.\(^14\),\(^15\) In this study, we aim to study the
safety and efficacy of antimicrobials in the setting of ACLF. First, we hypothesize that the effect of infection is not captured within disease severity scores, such as MELD, and that infection will lead to a higher risk of death while controlling for MELD scores. Secondly, to establish the efficacy of antimicrobials, we hypothesize that treatment of infection with antibiotics reverses the outcome equal to that of non-infected ACLF patients. Lastly, we perform an exploratory analysis to determine clinical factors associated with survival outcomes.

Methods

Study Population

Retrospective chart review was performed on patients who had ACLF and were seen at the University of Arizona Medical Center, all campuses. University of Arizona Institutional Review Board had approved the study protocol as per ethical guidelines set forth by the 1975 Declaration of Helsinki. Data was obtained from the EPIC database for all potential patients. Potential patients were defined as those who met the criteria of ACLF, were at least 18 years of age, and had a minimum of six months of follow-up following index admission. All patients were also required to have data available to calculate systemic inflammatory response syndrome (SIRS) criteria to be used as a surrogate marker for infection. 16,17 All patients included in the study were initially admitted between January 1, 2014 and December 31, 2014. Patients could only be enrolled in the study once. Patients were not re-enrolled in the study upon hospital re-admission, and the clinical data analyzed in this study is from each patient’s first admission during the study period.

The occurrence of ACLF was recorded and defined as the acute deterioration of liver function in patients with cirrhosis. 18 To meet the ACLF criteria a patient must have experienced acute deterioration of liver functions on the background of compensated or decompensated cirrhosis. Acute liver deterioration was defined as having one or any combination of the following: gastrointestinal (GI) bleeding related to portal hypertension, acute renal failure or hepato-renal syndrome (HRS), hepatic encephalopathy or altered mental status, ascites, coagulopathy of liver disease, jaundice and infection. Patients met the cirrhosis criteria if their chart contained a cirrhosis-related ICD-9 diagnosis code.
including: cirrhosis, alcohol cirrhosis, primary biliary cirrhosis, autoimmune cirrhosis, or cryptogenic cirrhosis. Diagnoses of cirrhosis were also confirmed with available imaging, hepatic histology or biochemical tests, such as Fibrosure.

Patient data was entered into an Excel data sheet. All historic characteristics and clinical features upon admission and clinical course were recorded. Infection diagnostic tests included in the dataset were paracentesis and peritoneal fluid studies (bacterial and fungal cultures, potassium hydroxide stain, gram stain, total protein, lactate dehydrogenase, glucose and albumin), bacterial and fungal blood cultures through peripheral venipuncture or other line access, Fungitell® Assay (1-3 Beta-D-Glycan Assay), coccidioidomycosis serology, urinalysis, urine cultures, and chest x-rays. Bacterial and fungal infections were based on positive culture results (blood, urine, ascites fluid), serological diagnosis, clinical diagnosis of pneumonia (imaging as reported by radiologists), and/or clinical diagnosis of spontaneous bacterial peritonitis (neutrophil granulocytes > 250 cells/µL). If a patient received a positive result for any of these diagnostic tests they were classified as infected. The type of infection was determined according to the results of these diagnostic tests and was categorized as: urinary tract infection, pneumonia, bacteremia, SBP, clostridium difficile, cellulitis, fungemia, invasive aspergillosis, cocci, esophageal candida, cutaneous candida, joint infection/septic arthritis, upper respiratory tract infection, shingles, herpes, and other. Disease severity was characterized by: AST to platelet ratio Index (APRI), Fibrosis-4 (Fib-4), Child-Turcotte Pugh (CTP) and MELD score. SIRS criteria were measured in one sitting upon admission, and patients were considered SIRS positive when at least two of four SIRS criteria were met. SIRS criteria were: temperature ≤ 36° C or > 38° C, heart rate > 90 bpm, respiratory rate > 20 breaths/min or PaCO2 < 32 mmHg, and white blood cell count > 12,000 cells/mm3, < 4,000 cells/mm3, or > 10% bands. The primary endpoint of the study was death. Outcome measures also included length of stay (LOS) in hospital, readmission rate, patient survival at 30, 90, and 365 days, and overall patient survival.

**Categorization**

The study cohort was classified into four groups according to infection status and antibiotic use (figure 1). The **study group** was defined as patients who had a positive culture, or a clinically defined infection, and received antibiotics. The control group was defined as
patients who neither had evidence of infection nor received an antibiotic during hospitalization. All other groups were considered intermediate groups and were classified as (1) the pre-emptive group - those who did not present with evidence of an infection, but received antibiotics, and (2) the untreated, infected group. The study group was further subclassified into SIRS positive and SIRS negative patients.

**Statistical Analysis**

Descriptive statistics of patient’s characteristics were derived for the overall study cohort and by the treatment groups. Specifically, mean ± standard deviation were reported for each of the continuous variables, and frequency and the associated percentage were reported for each of the categorical variables. One-way analysis of variance (ANOVA) was performed for each of the continuous variables and Chi-square test was performed for each of the categorical variables to determine whether there is any significant difference between the study groups.

Cox’s proportional hazards models were fitted to compare risk of death between the treatment groups, in which the control group was treated as the reference group. 30-day, 90-day, and 365-day mortality were used as the end-points. Both unadjusted and adjusted Cox’s proportional hazards models were fitted. The adjusted models controlled for all the patient’s characteristics, which were significantly different between the treatment groups identified in the descriptive analyses. Hazard ratio and 95% CI were reported, as well as p-value. Hypothesis tests were 2-sided. All statistical analyses were performed using SPSS® version 22. Significance level was set at 5%.

**Results**

**General Characteristics of Study Cohort**

A total of 521 out of 1243 patients met the inclusion criteria of the study. We excluded 64 patients because of incomplete records or missing data, leaving a total of 457 patient records to be used in data analysis. The mean age of the cohort was 55.5 ± 10.8 years, and 295 (65%) were male. Most of the cohort, 407 (89%), were white. We assume that the precipitating event for ACLF was infection for all patients who had evidence of infection 277/457 (61%). For the remaining patients the precipitating event is unknown. Hepatitis C
and alcohol use were the most common liver disease etiologies, 174 (39%) and 153 (34%) respectively, and the most prevalent manifestations of liver decompensation were ascites and jaundice, 202 (55%) and 183 (40%) respectively. The mean APRI score was 5.1 ± 17.57, Fib 4 score 12.09 ± 26.12, MELD score 18.7 ± 8.5, and Child-Pugh score 11.48 ± 1.45. 189 patients (41%) met SIRS criteria upon admission. Refer to figure 1 for the distribution of the study cohort based on infection and antibiotic use. Of the 277 patients with an infection, 148/277 (53%) of cases were detected based on a positive culture and the remaining 129/277 (47%) of cases were clinically defined based on blood tests (coccidioides based on IgM), clinical examination (cellulitis), radiologist’s imaging report (pneumonia), or neutrophil granulocytes > 250 cells/µL (SBP). 43/277 (16%) had a gram positive bacterial infection, 89/277 (32%) had a gram negative bacterial infection, 26/277 (9%) had a fungal infection, and the remaining 119/277 (43%) were infected with an unidentified organism. Of those infected patients with a documented type of infection 74/228 (33%) had a urinary tract infection, 61/228 (27%) pneumonia, and 51/228 (22%) bacteremia, 78/228 (34%) had multiple types of infections. Among infected patients, only 161/277 (58%) met SIRS criteria. Within the study group 152/248 (61%) met SIRS criteria.

**Characteristics of Patients Receiving Antibiotics**

Of the entire cohort, 353/457 (77%) received antibiotics regardless of indications. Indication of use of antibiotics was classified as pre-emptive for 105/353 (30%) and treatment of infection for 248/353 (70%). Of those patients receiving antibiotics, 145/353 (41%) received more than one antibiotic and 319/343 (93%) of patients received antibiotics within 24 hours of admission. The most common antibiotics were ceftriaxone, vancomycin, piperacillin-tazobactam, ciprofloxacin, and others. Vancomycin was used in conjunction with other antibiotics.

To better understand the pre-emptively treated patients group, we compared the pre-emptive and study groups. Cephalosporine was the most frequently used antibiotic for pre-emptive treatment, 84/105 (80%), and patients were significantly less likely to receive penem, penicillins, quinolones, vancomycin, azithromycin, and other antibiotics when treated pre-emptively. Only a small proportion of patients received more than one
antibiotic. The clear majority of patients received antibiotics within 24 hours of admission, and most of them received their first dose of antibiotics while in the ER.

**Characteristics of Study Groups**

The characteristics of the subgroups stratified by infection and antibiotics are displayed in table 1. Age, gender, alcohol use, and MELD were all significantly different between the groups.

**Outcome analysis (Cox Proportional Hazards Analysis)**

We performed Cox Proportional Hazards Model analysis to identify differences in risk of death. Risk of death remained higher (HR 1.6, CI - 1.1 to 1.3, p = 0.01) in patients with infection after adjustment for the severity of liver disease (MELD and CTP scores). Table 2 displays the results of the univariate and multivariable cox proportional hazards analysis of the study groups. In the unadjusted cox model, the study group had a significantly higher risk of death as compared to the control group. The Kaplan-Meier curve mortality rates at 365-days with log-log transformed 95% CIs were 36.8% (CI - 31.2% to 43.2%) and 28.4% (CI - 19.5% to 40.1%) in the study group and the control group respectively. Once the analysis was adjusted for gender, age, alcohol drinking and MELD, the hazard ratio between the two groups remained statistically significant (figure 2). For a male alcohol user with mean age 55.5 and mean MELD of 18.73, the 365-day mortality rates derived from this model were 38.2% (CI – 28.7% to 46.5%) and 24.7% (CI – 13.1% to 34.8%), in the study group and the control group respectively. Further analysis of study group, revealed that patients, who did not meet SIRS criteria had improved survival compared to those meeting SIRS criteria upon admission (HR 1.9, CI - 1.1 to 3.0. p = 0.007) (figure 3).

To identify clinical variables associated with risk of death, we performed an exploratory univariate, cox proportional hazards analysis. The following variables were significantly related to higher risk of death in univariate analysis: antibiotic use (HR 1.512, CI: 0.991-2.307, p = 0.055), vancomycin (HR 2.169, CI - 1.520 to 3.093, p < 0.001), and multiple antibiotic treatment (HR 2.14, CI: 1.499-3.055, p < 0.001 respectively). As expected MELD and CTP were also predictive of risk of death (HR 1.054, CI: 1.036-1.073, p < 0.001 and HR 1.278, CI: 1.127-1.450, p < 0.001 respectively). The following hepatic complications were
also associated with risk: gastrointestinal bleeding (HR = 1.422, CI: 0.994-2.032, p = 0.054), hepatic encephalopathy (HR 1.810, CI: 1.262-2.596, p = 0.001), ascites (HR 1.526, CI: 1.089-2.139, p = 0.014), SIRS (HR 2.188, CI: 1.551-3.086, p < 0.001), and coagulopathy (HR 1.786, CI: 1.266-2.521, p = 0.001).

We included all significant variables from the exploratory, univariate analysis in a multivariable Cox Proportional Hazards Model. The following variables were associated with higher risk: SIRS criteria (HR = 1.866, CI – 1.242 to 2.804, p = 0.003), vancomycin use (HR = 1.640, CI – 1.119 to 2.405, p = 0.011), MELD (HR = 1.051, CI - 1.030 to 1.073, p < 0.001), gastrointestinal bleeding (HR = 1.727, CI – 1.180 to 2.527, p = 0.005), and hepatic encephalopathy (HR = 1.807, CI – 1.247 to 2.618, p = 0.002).

To understand vancomycin use and the potential for multi-drug resistant organisms within our cohort we also calculated descriptive statistics on infections among the vancomycin cohort. Of the 114 patients taking vancomycin 100 (88%) had signs of an infection, 55 (48.2%) had a positive culture (blood, urine, or ascites fluid), and 12 (11%) had types of bacteria that are known for multi drug-resistance (1 MRSA, 3 Enterococcus, 1 Pseudomonas aeruginosa, 7 Staphylococcus aureus). 5 patients (4%) had an unspecified positive bacterial culture. The majority of patients taking vancomycin, 101 (89%), did not show signs of infection with drug-resistant organisms.

Discussion

The poor survival of infected decompensated patients has been well published. However, the benefits of antibiotic treatment in such patients remains largely unknown. A recent, prospective randomized controlled study of cirrhotic patients, with health-care associated infections, found that broad spectrum empiric antibiotic regimens were associated with better patient outcomes when compared to standard treatment. Another study, of infected patients in an ICU setting, associated early-goal-directed anti-microbial therapy with improved survival. The timing and the adequate regimen of antibiotic initiation is also not known. To date, this is the largest dataset studied to evaluate the impact of infection in
acutely decompensated patients and the first study to evaluate the safety and efficacy of antibiotic treatment in ACLF patients.

Our results revealed that disease severity scores do not adequately quantify risk of death in the ACLF patient population. Study and control groups experienced significantly different risks of death even when adjusted for confounding variables such as MELD and CTP scores.

Our results indicate several clinical factors that are significantly associated with survival outcomes. Within the study group, patients without SIRS had better survival outcomes compared to patients with SIRS (HR 1.9, CI - 1.1 to 3.0. p = 0.007). This result could be due to multiple factors. There could be a protective effect when antibiotics are initiated prior to the onset of SIRS. Alternatively, this result could be related to a difference in the nature or type of infection and indicate that SIRS associated infections lead to higher mortality. Prospective data would be required to determine the exact cause of this association.

Our results also associated vancomycin with higher mortality, with a HR = 1.640, CI – 1.119 to 2.405, p = 0.011 in our adjusted analysis. This result could be due to multiple factors, including nephrotoxicity or drug-resistant bacteria. Unfortunately, we did not have resistance data available in our study. We do know that within our cohort, the majority of patients taking vancomycin did not have a positive bacterial culture 58/114 (51%) and only 12/114 (11%) patients had culture results of bacteria that are associated with multi drug-resistance. This data suggests that this result was not due to drug-resistant bacteria, but more data is needed to confirm these findings.

Lastly, multiple antibiotic use was associated with higher mortality in univariable analysis with HR 2.14, CI: 1.499-3.055, p < 0.001. This result was not significant in multivariable analysis and more data is needed to support or refute this trend.

Further data is also required to quantify the effects of early versus late initiation of antibiotics on patient outcomes. Since 93% of antibiotics were given within 24 hours of patient admission, we were unable to test this factor. We did observe better survival within
our pre-emptively treated group as compared to the control group, but this result was not significant.

One unexpected result of our study was the better survival that we observed among the untreated, infected group as compared to the control group, even after controlling for disease severity scores. This result was not significant (p=0.47) and could be due to a variety of reasons such as the small sample size of untreated, infected patients (n=29). We also observed better survival of the untreated, infected group as compared to the study group. We do not know the cause of this observation. Similarly, it could be due to small sample size or a variety of clinical factors. We hypothesize that the untreated, infected patients had such minimal infections that they went clinically undetected and that some infections may not have detrimental effects in the presence of ACLF. We also hypothesize that these patients benefited from their lack of exposure to the hepato- and nephrotoxicity of antibiotics. Prior data supports that infection is detrimental in the presence of cirrhosis, and more data would be needed to test the generalizability of these observations.

Overall, we observed that treatment of established infection does not prevent death. Failure to reverse the mortality risk in the infected ACLF cohort, equal to that of the non-infected ACLF cohort in clinically matched patients could be due to a delayed initiation of antibiotics, resistant organism, hepato-nephrotoxicity of antimicrobials or an unidentified fungal infection. Above all, cirrhosis associated immune dysfunctions (CAIDS) and systemic inflammatory response triggered by infection make the clinical situation futile. It has been shown that as the degree of hepatic functions decline, the body experiences a continuous exposure to unfiltered pathogens and persistent systemic inflammatory response, which further aggravates hepatic immune dysfunctions, setting the situation into a vicious cycle. Hypothetically, reversal of this vicious cycle is only possible with restoration of hepatic immune functions, with liver transplantation or correction of deficient immune factors. Neither of the two are currently possible. Liver transplantation is contraindicated in active extra-hepatic infections. Hence, ACLF patients with SIRS criteria defines futility.

Our data provides supporting evidence that SIRS in the presence of infection leads to poor survival. It has also demonstrated that certain antibiotic regimens are associated with
poorer survival and that more data is necessary to create treatment guidelines for the unique needs of ACLF patients.

Like any retrospective study, our study has limitations. It is difficult to accurately quantify the effects of an antibiotic on risk of death when the origin of infection is not detailed. Moreover, our findings that multiple-antibiotic patients had a higher risk of death than single or no antibiotic-use patients, could be related to the severity of the patient’s infection. Our study did not include data on the resistance profile of pathogens. Furthermore, the retrospective nature of the study limited the amount of data we had on precipitating events of ACLF, re-admission rates, and infections following the first admission. Further research is necessary to investigate the effect antimicrobial treatment has on risk of death among cirrhotic patients and to determine the optimal course of antimicrobial treatment. A prospective clinical trial would be necessary to accurately quantify these effects.

**Conclusion**

Infection is a leading precipitant of ACLF in advanced liver disease patients. Infection is associated with poor survival compared to a clinically matched, non-infected ACLF cohort. Overall, treatment with antibiotics does not decrease risk of death, and vancomycin is associated with a higher risk of death. Treatment may help reduce risk and improve survival. Treatment with antibiotics of ACLF patients with SIRS does not prevent death, signifying that following the onset of SIRS it is probably too late. Pre-emptive therapy with a single antibiotic may also help improve survival. We suggest further prospective studies to confirm these findings.
References


### Table 1: Infection and Antibiotics categorization method, comparison of study groups.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Control Group (n = 75)</th>
<th>Pre-Emptive Group (n = 105)</th>
<th>Untreated, Infected Group (n = 29)</th>
<th>Study Group (n = 248)</th>
<th>P-Value</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>53.8 ± 11.82</td>
<td>52.79 ± 9.34</td>
<td>58.90 ± 11.27</td>
<td>56.78 ± 10.86</td>
<td>0.002</td>
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<tr>
<td>Gender (Male)</td>
<td>58 (77%)</td>
<td>73 (70%)</td>
<td>20 (69%)</td>
<td>144 (58%)</td>
<td>0.01</td>
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<tr>
<td>Alcohol Use</td>
<td>42 (59%)</td>
<td>84 (81%)</td>
<td>15 (56%)</td>
<td>149 (62%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Cirrhosis Types</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HCV</td>
<td>29 (39%)</td>
<td>42 (41%)</td>
<td>11 (38%)</td>
<td>92 (38%)</td>
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<tr>
<td>NASH</td>
<td>8 (11%)</td>
<td>10 (10%)</td>
<td>4 (14%)</td>
<td>29 (12%)</td>
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<tr>
<td>AIH</td>
<td>1 (1%)</td>
<td>1 (1%)</td>
<td>2 (7%)</td>
<td>6 (3%)</td>
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<tr>
<td>Other</td>
<td>1 (1%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
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<tr>
<td>Fib-4</td>
<td>9.73 ± 12.70</td>
<td>11.90 ± 30.76</td>
<td>8.79 ± 7.74</td>
<td>13.28 ± 28.33</td>
<td>0.66</td>
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<tr>
<td>Ascites</td>
<td>31 (41%)</td>
<td>44 (42%)</td>
<td>16 (55%)</td>
<td>111 (45%)</td>
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<td>Hepatic Encephalopathy</td>
<td>18 (24%)</td>
<td>22 (21%)</td>
<td>7 (25%)</td>
<td>73 (30%)</td>
<td>0.34</td>
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<td>MELD</td>
<td>16.78 ± 7.87</td>
<td>17.27 ± 8.01</td>
<td>17.99 ± 6.67</td>
<td>20.08 ± 8.92</td>
<td>0.005</td>
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<td>CTP</td>
<td>11.29 ± 1.47</td>
<td>11.41 ± 1.35</td>
<td>11.52 ± 1.24</td>
<td>11.56 ± 1.52</td>
<td>0.52</td>
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</table>
**Table 2:** Infection and antibiotics categorization method, Cox Proportional Hazards Model results. The control group served as the comparison group in this analysis. The adjusted model included age, sex, alcohol use, and MELD.

<table>
<thead>
<tr>
<th></th>
<th>Unadjusted Analysis</th>
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<th>Adjusted Analysis</th>
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<td>95% CI for Exp(B)</td>
<td>p-value</td>
<td>Hazard Ratio</td>
</tr>
<tr>
<td></td>
<td>Lower</td>
<td>Upper</td>
<td>Lower</td>
<td>Upper</td>
</tr>
<tr>
<td>Pre-emptive Group</td>
<td>0.637</td>
<td>0.345</td>
<td>1.175</td>
<td>0.15</td>
</tr>
<tr>
<td>Untreated, Infected Group</td>
<td>0.55</td>
<td>0.207</td>
<td>1.459</td>
<td>0.23</td>
</tr>
<tr>
<td>Study Group</td>
<td>1.633</td>
<td>1.022</td>
<td>2.609</td>
<td>0.04</td>
</tr>
</tbody>
</table>
Figure 1. Distribution of study cohort based on infection and antibiotics usage. Patients were categorized by infection and antibiotics use. The study group was further categorized by systemic inflammatory response syndrome (SIRS).
Figure 2. Adjusted cox proportional hazards model predicting risk of death after index admission, all cohort subgroups. Age, gender, alcohol use, and MELD were controlled for in this model.
Figure 3. Adjusted cox proportional hazards model predicting risk of death after index admission, study group stratified by SIRS. Age, gender, alcohol use, and MELD were controlled for in this model.