Risk Prediction of Nosocomial and Posthospital Discharge Infections in Alcohol-Associated Hepatitis

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Alcohol-associated hepatitis (AAH) is a severe form of liver injury with mortality as high as 30%-40% at 90 days. As a result of altered immune function in AAH, bacterial infections are common and are associated with poor outcomes. However, determining the risk and subsequent development of infection in patients with AAH remain challenging. We performed a retrospective study of consecutive patients admitted with a diagnosis of AAH at two independent tertiary centers from 1998 to 2018 (test cohort, n = 286) who developed infections following hospitalization. The diagnosis of AAH was confirmed by manual chart review according to the recent National Institute on Alcohol Abuse and Alcoholism definition. Infections were categorized by location and time of diagnosis as hospital-acquired infection (48 hours after admission until discharge) and posthospital infections (up to 6 months following discharge). The cohort was 66% men, and the median age was 48 (21-83) years. Corticosteroids were used in 32% of all patients with AAH. The overall infection rate was 24%. Of those with infections, 46% were hospital acquired and 54% were acquired after hospitalization. Variables found to be significant risk factors for bacterial infection included the presence of ascites on admission (hazard ratio [HR], 2.06), corticosteroid administration (HR, 1.70), Model for End-Stage Liver Disease (MELD) >23 (HR, 2.61), and white blood cell (WBC) count on admission per point (HR, 1.02).

Conclusion: In this multicenter cohort study of patients hospitalized with AAH, MELD score, ascites, WBC count, and use of corticosteroids were identified as significant predictors of the development of bacterial infection. We created a novel predictive equation that may be used to aid in the identification of patients with AAH at high risk of infection. (Hepatology Communications 2021;5:2096-2103).

Alcohol-associated hepatitis (AAH) is a serious form of alcohol-associated liver disease, estimated to occur in up to 35% of patients with alcohol use disorder. (1) Severe cases of AAH are characterized by new onset jaundice and are classified by the Maddrey’s discriminant function (MDF) or the Model for End-Stage Liver Disease (MELD). (1-3) Infections are common in severe AAH, with approximately 25% of patients presenting with community-acquired infection and a similar percentage found to develop nosocomial infections. (4) The high rates of sepsis observed in AAH may be explained by...
the impact of alcohol excess on the immune system. Chronic alcohol consumption alters the structure of epithelial cells, allowing gut bacteria-derived products into the portal circulation,\(^5\) and also impairs T-cell function.\(^6\) These negative effects of alcohol are amplified in patients with AAH and cirrhosis.\(^5\)

Mortality in severe AAH has been shown to increase a further 30% in patients who develop infection.\(^7\) Previous studies have found as many as 24% of all deaths from severe AAH to be infection related.\(^1\) Additionally, patients treated with prednisolone who develop infection have been shown to have increased 90-day mortality independent of MELD or Lille score.\(^4\)

Treatment of AAH may further exacerbate the immune dysfunction observed in these patients. Corticosteroids remain the only pharmacologic therapy available found to reduce short-term mortality.\(^8,9\) However, the benefit appears to be marginal and comes at the cost of increased risk of infections.\(^10,11\) While the search for more effective therapies for AAH continues, they still largely target the immune system and will likely continue to result in an increased risk of infection. The role of antibiotic prophylaxis in AAH remains largely unexplored despite widespread use of antibiotics for other indications in patients with cirrhosis, such as gastrointestinal bleeding.\(^12\)

Furthermore, the recognition of sepsis in AAH constitutes a diagnostic challenge due to shared clinical and laboratory features between the two conditions. As a consequence, the diagnostic performances of otherwise well-validated tools for early detection of sepsis in the general population, such as the Systemic Inflammatory Response Syndrome criteria or the Sequential Organ Failure Assessment score, remain suboptimal at best in patients with AAH.\(^13\)

Therefore, identification of patients with AAH at highest risk for the development of infection may allow for closer surveillance, lowered threshold for antibiotic administration for suspected infection, or infection prophylaxis in this known critically ill patient population wherein treatment is primarily supportive at this time. The aim of this study is to identify risk factors for the development of bacterial infections in patients admitted to the hospital with AAH.

**Patients and Methods**

**PATIENT COHORTS**

The patient cohort (n = 286) was derived retrospectively from consecutive patients admitted with AAH at the Mayo Clinic (Rochester, MN) between 1998 and 2016 and at Virginia Commonwealth University (VCU; Richmond, VA) between 2013 and 2018. The study was approved by the institutional review boards at both institutions.

**DEFINITION OF AAH**

Patients were diagnosed with AAH based on the clinical criteria for probable AAH established by the National Institute on Alcohol Abuse and Alcoholism (NIAAA). Inclusion criteria established by the NIAAA included ongoing consumption of 40 g/day (women) or 60 g/day (men) for a minimum of 6 months, onset of jaundice within the prior 8 weeks, aspartate aminotransferase (AST) >50, aspartate aminotransferase/alanine aminotransferase (ALT) ratio >1.5, AST/ALT <400 IU/L, and serum bilirubin (total) >3.0 mg/dL. When the diagnosis of AAH remained unclear, a

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liver biopsy was obtained for confirmation. Patients in whom cirrhosis was suspected or confirmed were included if they otherwise met inclusion criteria for AAH. Additionally, patients with hepatitis B and hepatitis C virus markers were included. Patients were excluded from the study if they carried a current or previous diagnosis of autoimmune hepatitis, hemochromatosis, or Wilson disease (Fig. 1). Patients were considered to have received steroids if they received prednisolone at any point during their hospitalization for AAH.

**DEFINITION OF INFECTION**

Infections were categorized by type and time of infection. A community-acquired infection was one that occurred up to 48 hours after admission, a hospital-acquired infection was one that occurred 48 hours after admission until the discharge date, and posthospital infections were classified as infections that occurred up to 6 months after the discharge date.

Types of infection were categorized as a urinary tract infection (UTI), bloodstream infection (BSI), pneumonia (PNA), spontaneous bacterial peritonitis (SBP), and *Clostridium difficile* (*C. diff*). UTI was defined by the presence of typical UTI symptoms (dysuria, frequency, urgency) and a positive urine culture. BSI was defined by a positive culture result in blood cultures from more than one site. PNA was defined by a positive culture result in blood cultures from more than one site. PNA was defined by clinical symptoms of PNA along with positive sputum culture, chest x-ray findings, or a BSI with consolidation on chest imaging. SBP was defined as >250 white blood cell (WBC) count in the peritoneal fluid, with or without positive cultures, and *C. diff* infection was defined as a positive stool culture for *C. difficile*.

**STATISTICAL ANALYSIS**

Descriptive statistics are reported using mean ± SD for continuous data or frequencies and percentages for categorical data. Univariate analysis was used to identify variables significantly associated with the development of infection. Multivariate analysis was then employed on the variables found to be significant on univariate analysis to develop an equation to predict infection risk at 7, 30, and 180 days in this patient population. Infection risk equation was developed using these variables by logistic regression. Survival analyses, including the Kaplan–Meier method and Cox proportional hazards regression, were used to assess the time-to-event outcomes of infection and death. Associations between these outcomes and risk factors were summarized using hazard ratios (HRs) and 95% confidence intervals (CIs). The analysis for infections was from 48 hours after admission (i.e., excluded those with a community-acquired infection) to infection, last follow-up, death, or 6 months after discharge (whichever happened first). For the Cox proportional hazards model for death, the start time was hospital discharge and patients were followed to last follow-up or death (whichever happened first). Infection was treated as a time-dependent covariate in this model in order to incorporate postdischarge infections. Kaplan–Meier curves comparing the different infection timings on death were landmark time at 30 days postdischarge (i.e., the start time was 30 days after discharge, and patients were followed forward based on their infection grouping at that time). All tests were two sided, and *P* ≤ 0.05 was considered statistically significant. Analyses were performed using R version 3.6.2.

**Results**

**PATIENT CHARACTERISTICS**

A cohort of 286 adult patients hospitalized with AAH from 1998 to 2018 was identified (193 from the Mayo Clinic and 96 from VCU). Baseline characteristics of the cohort are presented in Supporting Table S1. Overall, 32.1% of patients received steroids during their hospitalization. The median duration of steroid administration in the Mayo cohort was 9 days. Among the 36 Mayo patients receiving steroids, only 19.4% of patients (n = 7) completed a 28-day course of steroids.
INFECTION IN AAH

The overall incidence of infection in our cohort was 36% (n = 102). We then excluded those who presented to the hospital with community-acquired infection, which was 12% (n = 34) of patients. Baseline characteristics based on timing of infection are presented in Table 1. The most common sources of infection at presentation were UTI (12), BSI (10), lower respiratory (6), SBP (3), and \textit{C. diff} (3), and the most commonly identified organisms included \textit{Escherichia coli} (8) and \textit{Staphylococcus aureus} (6). Of those who developed an infection while hospitalized (31/286), the most common infection sources included lower respiratory tract infections (10), BSI (7), SBP (6), UTI (6), and \textit{C. diff} (2). Finally, the most common sources in those who developed an infection within 6 months of hospital discharge (37/286) included UTI (15), SBP (9), lower respiratory tract infection (8), BSI (3), and \textit{C. diff} (2) (Supporting Table S2).

Analysis for significant predictors of development of infection in our multicenter cohort identified the following variables: MELD score (HR, 1.05; 95% CI, 1.02–1.09; \(P = 0.002\)), ascites (HR, 2.06; 95% CI, 1.26–3.36; \(P = 0.004\)), WBC count (HR, 1.02; 95% CI, 1.00–1.05; \(P = 0.048\)), and use of prednisolone (HR, 1.70; 95% CI, 1.05–2.75; \(P = 0.031\)) (Table 2). While prednisolone use did not increase the risk of hospital-acquired infection (HR, 0.82; 95% CI, 0.39–1.7; \(P = 0.59\)), the administration of prednisolone was associated with posthospital infection (HR, 1.98; 95% CI, 1.03–3.81; \(P = 0.039\)).

MORTALITY

The second aim of the study was to examine the extent to which infection impacted mortality. The Mayo cohort notably spans 20 years; as such, we divided the cohort into two groups by 10-year period to determine if there were changes in practice over time that would lead to differences in mortality. The cohorts were split into two groups to compare mortality from different time periods. Those in our cohort with hospitalizations from 1998 to 2008

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### TABLE 1. BASELINE CHARACTERISTICS OF PATIENTS BASED ON SPECIFIC TIMING OF INFECTION

| Location | No Infection (n = 184) | Community (n = 34) | Hospital (n = 31) | Posthospital (n = 37) | Total (n = 286) |
|----------|------------------------|--------------------|------------------|----------------------|----------------|
| VCU      | 62 (33.7%)             | 8 (23.5%)          | 12 (38.7%)       | 14 (37.8%)           | 96 (33.6%)     |
| Mayo     | 122 (66.3%)            | 26 (76.5%)         | 19 (61.3%)       | 23 (62.2%)           | 190 (66.4%)    |
| Sex      |                        |                    |                  |                      |                |
| Female   | 55 (29.9%)             | 16 (47.1%)         | 11 (35.5%)       | 20 (54.1%)           | 102 (35.7%)    |
| Male     | 129 (70.1%)            | 18 (52.9%)         | 20 (64.5%)       | 17 (45.9%)           | 184 (64.3%)    |
| MELD on admission |                 |                    |                  |                      |                |
| Number   | 181                    | 33                 | 31               | 37                   | 282            |
| Mean (SD) | 23.7 (7.9)            | 26.2 (8.8)         | 26.7 (7.2)       | 25.2 (5.5)           | 24.5 (7.7)     |
| Median   | 22.0                   | 24.0               | 25.0             | 26.0                 | 24.0           |
| Q1, Q3   | 18.0, 29.0             | 20.0, 30.0         | 21.0, 33.0       | 23.0, 30.0           | 19.0, 29.0     |
| Range    | (9.0–57.0)             | (10.0–46.0)        | (15.0–45.0)      | (11.0–37.0)          | (9.0–57.0)     |
| Ascites on admission |                 |                    |                  |                      |                |
| No       | 104 (56.5%)            | 17 (50.0%)         | 9 (29.0%)        | 17 (45.9%)           | 147 (51.4%)    |
| Yes      | 80 (43.5%)             | 17 (50.0%)         | 22 (71.0%)       | 20 (54.1%)           | 139 (48.6%)    |
| WBC on admission |                 |                    |                  |                      |                |
| Mean (SD) | 11.7 (8.7)            | 11.8 (7.3)         | 14.1 (7.7)       | 13.0 (7.3)           | 12.1 (8.2)     |
| Median   | 9.5                    | 10.0               | 13.0             | 11.3                 | 10.0           |
| Q1, Q3   | 6.5, 13.3              | 5.6, 16.5          | 9.0, 16.1        | 8.2, 16.9            | 6.7, 14.8      |
| Range    | (1.6–58.1)             | (1.7–27.9)         | (3.8–37.8)       | (3.0–28.4)           | (1.6–58.1)     |
| Steroids during admission |             |                    |                  |                      |                |
| No       | 129 (70.1%)            | 26 (76.5%)         | 18 (58.1%)       | 21 (56.8%)           | 194 (67.8%)    |
| Yes      | 55 (29.9%)             | 8 (23.5%)          | 13 (41.9%)       | 16 (43.2%)           | 92 (32.2%)     |

Abbreviation: Q1/Q3, quartile 1/3.
were compared to those with hospitalizations from 2009 to 2018, and we found no significant difference in mortality \( P = 0.2192 \). Survival in the combined cohort was determined for community, hospital, and posthospital-acquired infections. Patients with posthospital-acquired infection had increased overall mortality compared to those without infection \( HR = 4.27; 95\% CI, 2.65-6.88; \) \( P < 0.001 \). However, no difference in survival was observed in those with community and hospital-acquired infections (Table 3). Kaplan-Meyer curves for long-term survival with landmark time at 30 days posthospital discharge were determined (Fig. 2). Mortality was also evaluated based on type of infection. Patients with lower respiratory tract infection \( HR = 2.97; 95\% CI, 1.64-5.37; \) \( P < 0.001 \), SBP \( HR = 2.94; 95\% CI, 1.65-5.25; \) \( P < 0.001 \), and UTI \( HR = 2.19; 95\% CI, 1.34-3.57; \) \( P = 0.002 \) were noted to have increased mortality compared to those patients without infection. Those with spontaneous BSI did not have a higher mortality rate compared to those without infection \( HR = 1.27; 95\% CI, 0.63-2.54; \) \( P = 0.51 \) (Table 4). Time from infection to death was also analysed, and SBP, lower respiratory tract infection, and UTIs had decreased survival at 5 years compared to BSIs (Fig. 3).

### A SCORING SYSTEM TO PREDICT INFECTION

The variables found to be significant predictors of infection on univariate analysis were admission WBC count, MELD score, presence of ascites, and use of prednisolone. Using multivariate logistic regression with the variables identified on univariate analysis, the following risk score was calculated: \( 1.03 \times \text{MELD} + 1.61 \times (\text{ascites} = \text{yes}) + 1 \times \text{WBC} + 1.28 \times (\text{prednisolone} = \text{yes}) \). Using this scoring system, we were able to determine risk of infection within 7, 30, and 180 days of diagnosis. These scores with corresponding risk of infection are listed in Table 5. This newly proposed model has a C statistic of 0.634 and was cross-validated using leave-one-out, with a resulting C statistic of 0.634 (95% CI, 0.631-0.639).

### Discussion

The development of infection in severe AAH is a significant cause of mortality, with infections accounting for approximately 25% of all deaths in AAH.\(^{11}\) A previous meta-analysis of 12 studies comprising 1,062 patients with severe AAH found an infection rate of 20%.\(^{11}\) In our cohort, we found a much higher rate of infection of 36%. Louvet et al.\(^{7}\) evaluated timing of infection in AAH in a cohort of 246 patients. They found that 26% of patients presented with an infection at the time of diagnosis with another 22% developing infection during the 2-month follow-up period. In our cohort of 286 patients of whom 102 were found to have infection, we further characterized the timing of infection. We found that 33% (34/102) presented with infection at time of diagnosis, 30% (31/102) were diagnosed with infection while hospitalized, and 36% (37/102) developed infection during the 6-month follow-up period after discharge from the hospital.
The Steroids or Pentoxifylline for Alcoholic Hepatitis (STOPAH) trial identified 418 patients who developed infection, with the most common types being pulmonary (45%), SBP (18%), urinary (16%), and BSI (11%). In our study, we observed similar rates of SBP and BSI but lower numbers of pulmonary infection, which is possibly due to more stringent definitions of bacterial PNA in our study.

Development of *C. diff* infection in patients with AAH has been shown to carry a higher mortality risk and require a longer hospital stay. In our study, isolated *C. diff* infection was not found to be an independent risk factor for death; however, development of superimposed *C. diff* infection in patients with AAH with another documented infection significantly increased mortality. This has important implications for the use of antibiotics in AAH. There is currently a clinical trial underway evaluating the efficacy of antibiotic therapy in patients treated with prednisolone. Further studies are needed to assess the potential benefits of more liberal antibiotic administration in patients with AAH against the increased risk of *C. diff* infection.

The prediction of infection in AAH remains a clinical challenge, and previous studies have examined the relationship between severe AAH and the development of nosocomial infections. Factors previously associated with infection include age, baseline liver function, and renal function. Additionally, a recent study has demonstrated an increased risk of

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**TABLE 4. MORTALITY BASED ON TYPE OF INFECTION**

| Group (Time Dependent) | HR (95% CI)     | P Value |
|------------------------|-----------------|---------|
| No infection Reference |                 |         |
| Lower respiratory      | 2.97 (1.64, 5.37) | <0.001  |
| SBP                    | 2.94 (1.65, 5.25) | <0.001  |
| BSI                    | 1.27 (0.63, 2.54) | 0.51    |
| UTI                    | 2.19 (1.34, 3.57) | 0.002   |
| Other (including combinations) | 4.66 (1.86, 11.64) | 0.001   |

Abbreviation: SBP, spontaneous bacterial peritonitis.
severe infections in patients with AAH given prednisolone compared to those who were not given steroids. Thus, risk assessment in previous studies has been limited due to a disproportional number of patients with AAH receiving treatment with steroids. The cohort in our study is unique because less than one third of patients received treatment with corticosteroids. This practice difference has allowed our analysis to explore the rate of infections in patients with AAH regardless of their treatment status. This multicenter cohort study demonstrates that the risk of bacterial infection in AAH remains significantly high, independent of the use of steroids (35% in those treated and 23% in those not treated with prednisolone). Vergis et al. found there was no correlation between baseline infection and mortality; however, they found that development of incident infection was associated with increased mortality in patients treated with prednisolone but not in patients not receiving prednisolone. Thus, due to the marginal short-term survival benefit and increased risk of infections with prednisolone, the search for novel effective therapies for AAH continues.

It has been demonstrated that signs associated with liver decompensation, such as encephalopathy, ascites, and variceal bleeding, increase the risk of mortality in those with cirrhosis. However, the presence of ascites has not previously been shown to be an indicator for risk of future infection. We found 49% (139/286) of patients in our cohort to have ascites on initial presentation. Approximately 42% (59/139) of patients presenting with ascites either presented with infection or went on to develop infection as opposed to 29% (43/104) of patients without ascites. Thus, presence of ascites on admission was found to be a significant factor in predicting infection in our cohort. Vergis et al. has also found both MELD score and peripheral WBC count to be strongly associated with subsequent risk of infection. Our cohort yielded similar findings for MELD score and WBC count on hospital admission in the prediction of infection development.

Sarcopenia has also recently been shown to be associated with a longer hospital stay and worsening outcomes in AAH. Further studies are needed to explore sarcopenia and its impact on infection risk in AAH.

The main limitation of this study relates to the inherent difficulty in recognizing infection in this population. AAH often presents with systemic inflammatory response syndrome, making the diagnosis of infection a clinical challenge. The ultimate goal of predicting infection risk in AAH is the ability for early identification of infection in these patients so that targeted therapy can be initiated as soon as possible.

**Table 5. Risk of Infection at Various Time Points Based on Newly Developed Score**

| Score | Risk of Infection Within 7 days | 30 days | 180 days |
|-------|-------------------------------|---------|----------|
| 15    | 3.4%                          | 11.0%   | 19.1%    |
| 20    | 3.8%                          | 12.3%   | 21.2%    |
| 25    | 4.3%                          | 13.7%   | 23.5%    |
| 30    | 4.8%                          | 15.3%   | 26.0%    |
| 35    | 5.4%                          | 17.0%   | 28.8%    |
| 40    | 6.1%                          | 18.9%   | 31.7%    |
| 45    | 6.8%                          | 21.0%   | 34.9%    |
| 50    | 7.6%                          | 23.3%   | 38.3%    |
| 55    | 8.5%                          | 25.8%   | 41.9%    |
| 60    | 9.5%                          | 28.5%   | 45.7%    |
| 65    | 10.7%                         | 31.4%   | 49.7%    |
| 70    | 11.9%                         | 34.6%   | 53.9%    |
| 75    | 13.3%                         | 38.0%   | 58.1%    |
| 80    | 14.8%                         | 41.5%   | 62.4%    |
| 85    | 16.5%                         | 45.3%   | 66.8%    |

**Fig. 3.** Kaplan–Meyer curve for long-term survival based on infection type.
possible as well as infection prevention, potentially by prophylactic antibiotic administration.

The novel risk prediction model we present here differs from the multitude of existing prognostication models for outcomes in patients with AAH as it focuses on risk of bacterial infections. Furthermore, previous attempts at improving on the prognostication abilities of the MELD score and MDF in patients with an AAH score have proved difficult. While our prediction model has a modest performance in its current form, we anticipate that it can be improved by incorporating novel biomarkers in the future, such as circulating serum bacterial DNA, endotoxin, or bacterial 16S ribosomal DNA. Until such biomarkers are further validated and become widely available, our prediction model may indeed be a useful tool to aid in guiding clinical decision making. This model employs routine laboratory parameters obtained in patients who present with AAH and is therefore practical. Pending further studies, this model may alert clinicians to have higher clinical suspicion and consider closer surveillance for the development of infection as well as a lower threshold to start empiric or targeted therapy for suspected infection. Future prospective studies should investigate whether such an approach might improve survival in AAH.

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Supporting Information

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