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Posted Date: 13 August 2024

doi: 10.20944/preprints202408.0936.v1

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 doi:10.20944/preprints202408.0936.v1

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Bacterial Infections Features in Alcohol-Associated Hepatitis: Review of a 2016–2021 Cohort

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Abstract: Background/Objectives: Bacterial infections (BI) are a major cause of mortality in patients with alcohol-associated hepatitis (AH); however, only a few studies have investigated BI in AH in the last decade. Therefore, we aimed to assess the features and outcomes of BI in patients with AH. **Methods:** This observational descriptive study included patients with AH admitted to a tertiary academic hospital between 2016–2021. Clinical and complete microbiological data were recorded and complications, including acute-on-chronic liver failure (ACLF), and mortality over 90-days were compared between infected and non-infected patients. **Results:** Overall, 115 patients with AH were recruited and 75 had severe AH; among them, 66 started corticosteroid treatment. We identified 69 cases of BI in 44 patients; the incidence of BI at hospital discharge was 32.2%, which reached 38.2% at 90 days. The predominant infection site was the chest (35%). Among the identified bacteria (52.1%), half were gram-positive and half gram-negative. A low rate of multidrug-resistant bacteria (14%) was also noted. Infected patients during hospitalization (n=37) exhibited higher rates of hepatic decompensation and ACLF p=0.001) and lower survival (81.8% vs. 95.8%, p=0.015) than did non-infected patients (n=78). In-hospital infected patients (n=22) exhibited worse survival (72.7%) than did those infected upon admission (93.3%) or non-infected patients (94.9%) (p=0.009). Corticosteroid-treated patients displayed a nonsignificant increase in the total number of BI; however, without greater mortality. **Conclusions:** BI were common in our cohort of patients with AH. Patients with in-hospital infections commonly experienced serious complications, including high ACLF and death rates. Infections diagnosed upon admission were treated without affecting survival.

Keywords: bacterial infections; alcoholic hepatitis; alcohol-associated hepatitis; risk factors; acute-on-chronic liver failure; corticosteroids

1. Introduction

Alcohol-related liver disease (ArLD) is the main cause of chronic liver disease worldwide, contributing to 41.7% of cirrhosis-related deaths [1,2]. It comprises a clinical–histological spectrum, including fatty liver, alcohol-associated hepatitis (AH), and cirrhosis with associated complications. AH is characterized by abrupt jaundice, malaise, and liver-related decompensation [3]. Patients with AH are relatively susceptible to infection [4,5]; some studies have reported up to 49% of infections [4,6]. Both Infections and AH potentially lead to acute-on-chronic liver failure (ACLF) with an incidence rate as high as 20–50% at 3 months [7,8].

Studies with the largest cohorts of patients with AH and concomitant infection were conducted more than 10 years ago, and all studies did not identify the causative agent [6,9–13]. Moreover, the concept of ACLF was defined in the last decade. Thus, although both AH and infections are the main

 doi:10.20944/preprints202408.0936.v1

causes of ACLF, few studies [14,15] have specifically investigated the role of infections in ACLF development in AH.

Therefore, this observational, single center study endeavored to evaluate the emergence and course of infection in patients with AH. Ultimately, it aimed to describe the characteristics, causative microorganisms, severity, complications and risk factors of bacterial infections (BI) in patients with AH.

2. Materials and Methods

2.1. Study Design and Population

This observational descriptive study included patients with AH consecutively admitted to Hospital Vall d' Hebron liver unit between January 2016 and December 2021 who were followed-up for 90 days or until death. Inclusion criteria were age > 18 years, patients with bilirubin level ≥ 3 mg/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) values < 400 IU/L, AST/ALT ratio > 1.5 and active alcohol consumption of > 40 g/day in women or > 60 g/day in men for ≥ 6 months with less than 60 days of abstinence prior to inclusion according to National Institute on Alcohol Abuse and Alcoholism (NIAAA) AH consortia or a confirmatory biopsy. Exclusion criteria followed the NIAAA recommendations for the diagnosis of a probable AH with more than one etiology of liver disease, sepsis defined by the presence of systemic inflammatory response syndrome (SIRS) and infection at baseline (defined as infections diagnosed within the first 48 h of admission), patients with any type of shock at baseline, defined by the use of vasoactive substances at admission (excluding those specifically used for bleeding control), cocaine use or recent use of a drug with drug-induced liver injury potential within 30 days, and patients with comorbidities encompassing high short-term mortality including either hepatocellular carcinoma out of Milan criteria or extrahepatic neoplasia.

For each patient, the following data were collected upon admission: epidemiological and demographic data such as age; sex; body mass index; history of alcohol intake, history of liver disease including previous decompensations and other underlying diseases, such as arterial hypertension, diabetes mellitus, dyslipidemia, metabolic syndrome, obesity, chronic renal disease, ischemic heart disease, and chronic obstructive pulmonary disease. On admission, infections; hepatic decompensations (HD); acute kidney injury (AKI); ACLF and severity scores were registered (i.e Maddrey, Model for End-Stage Liver Disease (MELD), MELD Na, MELD 3.0, and Child–Pugh). Physical examination, routine laboratory and microbiological examinations, and concurrent medications (prophylactic antibiotic) usage data were also collected. During hospitalization, the following data were recorded: development of infections, HD, AKI, transjugular intrahepatic portosystemic shunt insertion, vasoactive support required, intensive care unit (ICU) support, ACLF development, and mortality. After hospital discharge, only new infections and mortality were recorded. Patients were followed up for 90 days or up to death.

The following information was recorded for infections at any time point: type and location, nosocomial or community acquired infection, type of bacteria or fungus, antibiotic resistance and treatment, antibiotic escalating and deescalating.

2.2 Definitions

Hepatic decompensation was defined as the acute development of ascites, upper gastrointestinal bleeding (GIB), hepatic encephalopathy (HE), or any combination of the foregoing, requiring prolonged or new hospitalization [17]. ACLF was defined as a clinical syndrome occurring in patients with cirrhosis characterized by acute deterioration, organ failure, and high short-term mortality, according to the European Foundation for the Study of Chronic Liver Failure criteria [18]. Proven infection (criteria defined by the NACSELD consortium) [4] was established in the following cases: 1) spontaneous bacteremia: positive blood cultures without a source of infection; 2) spontaneous bacterial peritonitis (SBP): ascitic fluid polymorphonuclear cells > 250/μL with or without a positive fluid culture; 3) lower respiratory tract infections: new pulmonary infiltrate on chest radiograph in

 doi:10.20944/preprints202408.0936.v1

the presence of compatible clinical criteria, at least one respiratory symptom (cough, sputum production, dyspnea, and/or pleuritic pain), and/or at least one finding on auscultation (rales or crepitation) or sign of infection (e.g., fever and leukocytosis); 4) bacterial enterocolitis: diarrhea or dysentery with a positive stool culture for pathogenic bacteria (e.g., *Salmonella*, *Shigella*, *Yersinia*, *Campylobacter*, and *Escherichia coli*); 5) *Clostridium difficile*: diarrhea with a positive toxigenic *C. difficile* test result; 6) skin infection: cellulitis; 7) urinary tract infection: urinary white blood cell count > 20 per field with positive urinary culture findings in a symptomatic patient; 8) intra-abdominal infections (e.g., diverticulitis, appendicitis, cholangitis, and secondary bacterial peritonitis); and 9) healthcare–associated infections (e.g., catheter-related bloodstream infection [CRBSI]). Multidrug-resistant bacteria (MRB) were defined as nonsusceptibility to at least one agent in at least three antimicrobial categories. Nosocomial infection (in-hospital infection) was defined as the novo infection after 72 hours of hospitalization.

2.3 Statistical Analysis

Descriptive statistics were used to summarize data. Quantitative variables are expressed as the mean ± standard deviation and normally and non-normally distributed data are expressed as median (interquartile range). Percentages were calculated using categorical data. Qualitative variables are presented as frequencies and percentages. Between-group differences for categorical and quantitative variables were evaluated using the chi-square or Fisher's exact test and the Student's t-test or the Mann–Whitney U test as appropriate. Survival times were compared using the Kaplan–Meier curves and log-rank tests. All statistical analyses were performed using IBM SPSS Statistics (version 22) software.

3. Results

3.1 Study Population

In total, 115 patients with AH were admitted to our hospital and met our eligibility criteria. Their characteristics are shown in Table 1. In summary, 76.5% were men, the median age was 50 years old, and 85% were Caucasians.

Table 1. Baseline clinical and biological characteristics.

	n=115
Medical History	
Sex (male), n(%)	88 (76.5%)
Age, median (IQR) P 25-75	50 (44-58)
Race, n(%)	Caucasian 98 (85%)
BMI, median (IQR) P 25-75	27 (24-31)
Arterial hypertension, n(%)	35 (30.4%)
Diabetes, n(%)	15 (13%)
Dyslipidemia, n(%)	23 (20%)
Metabolic syndrome, n(%)	16 (14%)
Obesity, n(%)	28 (24%)
Chronic renal failure, n(%)	0 (0%)
Ischemic heart disease, n(%)	4 (3.4%)
Chronic obstructive pulmonary disease, n(%)	7 (6%)
Hepatic cirrhosis, n(%)	68 (59%)

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History of hepatic decompensation, n(%)	28 (24%)
Previous alcohol-related hepatitis, n(%)	23 (20%)
Hepatocellular carcinoma, n(%)	0 (0%)
Prophylactic antibiotics, n(%)	2 (1.7%)
Hospital admission (BASELINE)	
Hepatic cirrhosis, n(%)	81 (70%)
Hepatic decompensation, n(%)	64 (56%)
Infection, n(%)	18 (16%)
Ascites, n(%)	59 (51%)
Hepatic encephalopathy, n (%)	15 (13%)
Gastrointestinal bleeding, n (%)	7 (6%)
Acute kidney injury, n(%)	13 (11%)
Acute on chronic liver failure, n(%)	7 (6%)
Maddrey score, median (IQR) P 25-75	40 (20-50)
MELD score, median (IQR) P 25-75	19 (16-22)
MELD Na score, median (IQR) P 25-75	22 (19-22)
MELD 3.0 score, median (IQR) P 25-75	23 (20-26)
Child-Pugh score, median (IQR) P 25-75	10 (9-11)
Bilirubin (mg/dL), median (IQR) P 25-75	7.4 (4.8-12)
INR, median (IQR) P 25-75	1.5 (1.2-1.8)
Albumin (g/dL), median (IQR) P 25-75	2.7 (2.4-3.1)
Creatinine (mg/dL), median (IQR) P 25-75	0.7 (0,5-0.9)
AST (UI/L), median (IQR) P 25-75	147 (102-264)
ALT (UI/L), median (IQR) P 25-75	61 (35-89)
GGT (UI/L), median (IQR) P 25-75	593 (223-1461)
ALP (UI/L), median (IQR) P 25-75	204 (150-328)
CRP (mg/dL), median (IQR) P 25-75	2.5 (1-5.5)
Leucocytes (10^9/L), median (IQR) P 25-75	8.2 (6.1-11.6)
Platelets 10^9/L	104 (64-153)

IQR: interquartile range, BMI: body mass index, MELD: Model for End-stage Liver Disease, INR: international normalized ratio, AST: Aspartate transaminase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl Transferase, ALP: Alkaline Phosphatase, CRP: C-reactive protein.

On admission, 70% patients were diagnosed with hepatic cirrhosis and 56% exhibited a liver-related decompensation, with ascites being the most common one accounting for up to half of the patients, and 7 (6%) patients fulfilled ACLF criteria. The median (interquartile range) Maddrey, MELD, and Child–Pugh scores were 40 (20–50), 19 (16–22), and 10 (9–11), respectively.

Overall, 75 (65%) patients met the criteria for severe AH (Maddrey score > 32 points); among them, 66 started corticosteroids CS treatment, whereas 9 did not receive CS because of ongoing severe infection and GIB (6 and 3 patients, respectively).

 doi:10.20944/preprints202408.0936.v1

3.2 Infections

In the AH cohort, we identified 69 infections in 44 patients (38.2% of all patients with AH) during the 90-day study period. On admission, 20 infections were present in 18 patients (15.6% of all patients with AH).

During hospitalization, 30 infections occurred in 22 patients (19.1% of all patients with AH), among whom 3 had infections upon admission.

From hospital discharge to the end of follow-up, 19 infections developed in 14 patients (13.2% of 106 living patients), among whom 7 had a previous infection (6 patients had a preexisting infection upon admission, and 1 developed an infection during hospitalization).

3.3 Bacteria and Sites of Infection

Among the 69 detected infections, 40 bacteria were identified and isolated from cultures of 36 infections (52.1%). The cultured organisms are listed in Table 2. Overall, gram-positive and gram-negative bacteria were equally represented. Gram-negative bacteria accounted for 50% of the isolated organisms, and *E. coli* and *Klebsiella pneumoniae* were the predominantly isolated organisms (17% and 15% of all isolated organisms, respectively). Gram-positive bacteria also accounted for 50% of the isolated organisms, and *Staphylococcus aureus* was the most isolated organism (20% of all isolated organisms). MRB were rare in this series of patients; only five MRBs (*S. aureus*, *S. haemolyticus*, *K. pneumoniae* (×2), and *Enterococcus faecalis*) were identified among the 36 identified infections (14%).

Table 2. Site infection and bacteria classification (gram stain).

Site	Number of infections, (%)	Positive cultures	Bacteria, (n)	Gram positive or gram negative, (n)
Chest	24 (35%)	3	*Streptoccocus pneumoniae, Staphylococcus aureus, Clamydia pneumoniae*	Gram positive (2) Gram negative (1)
Skin	14 (20%)	3	*Staphylococcus aureus (2) Staphylococcus aureus**	Gram positive (3)
Blood	11 (16%)	11	*Acinetobacter baumannii Staphylococcus hemolyticus (2) Staphylococcus hemolyticus* Staphylococcus epidermidis (4) Enterococcus faecalis*, Klebsiella oxytoca, Staphylococcus aureus, Escherichia coli, Klebsiella pneumoniae, Enterococcus faecium*	Gram-positive (10) Gram-negative (4)
Abdominal (Ascites)	11 (16%)	10	*Staphylococcus aureus (2) Acinetobacter baumannii Staphylococcus hemolyticus Escherichia coli, Enterobacter cloacae, Klebsiella pneumoniae* Enterococcus faecium, Serratia marcenses, Acinetobacter pittii*	Gram-positive (4) Gram-negative (6)

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Urinary tract	9 (13%)	9	*Escherichia coli (5), Klebsiella pneumoniae (2), Klebsiella pneumoniae* Enterococcus faecalis, Klebsiella aerogenes*	Gram-positive (1) Gram-negative (9)
TOTAL	69	36	40	Gram-positive (20) Gram-negative (20)

*Multidrug-resistant bacteria

The infection sites are summarized in Table 2. The chest was the most common infection site, with 24 cases (35%) of pneumonia, followed by the skin (14 (20%)), blood (11 (16%): bacteremia (8) and CRBSI (3)), abdomen (ascites (SBP)) (11 (16%)), and urinary tract (9 (13%)).

3.4 Infections upon Admission

On admission, 20 infections were detected in 18 patients, whereas no infection was detected in 97 patients. Two patients had two different infections; one had coexistent SBP, caused by *S. haemolyticus*, and bacteriemia, caused by *Acinetobacter baumannii*, whereas the second had cellulitis and aspiration pneumonia. The most frequently associated infections were chest infections (7 (35%)) and cellulitis (7 (35%)), whereas urinary tract infections (3 (15%)), SBP (2), and bacteremia (1) were the least frequent. In 11 infections (55%), especially pneumonia and cellulitis, the microorganisms were not identified (clinical diagnosis). Additionally, upon diagnosis, nine (45%) patients had associated SIRS, whereas three (16.6%) met the ACLF criteria. Infection characteristics upon admission and during the course of the disease are shown in Table 3-a.

Table 3. a. Characteristics of bacterial infections at admission.

ID-Episode	Infection	Bacteria	SIRS	ACLF	Resolution infection	Antibiotics	MRB
P4- 1	SBP	*Staphylococcus aureus*	Yes	No	Yes	Cefazolin	
P6- 2	Cellulitis	Non-isolated bacteria	Yes	No	Yes	Levofloxacin + Clindamycin	
P8- 3	Aspiration Pneumonia	Non-isolated bacteria	Yes	No	Yes	Amoxicillin-Clavulanate	
P17- 4	Cellulitis	Non-isolated bacteria	No	No	Yes	Amoxicillin-Clavulanate	
P19- 5	Pneumonia	Non-isolated bacteria	Yes	No	Yes	Amoxicillin-Clavulanate	
P33- 6	Bacteremia SBP	*Acinetobacter baumannii* + *Staphylococcus haemolyticus*	Yes	No	Yes	Ciprofloxacin	
P62- 7	Cellulitis	Non-isolated bacteria	No	No	Yes	Amoxicillin-Clavulanate	
P69- 8	Cellulitis	Non-isolated bacteria	Yes	No	Yes	Amoxicillin-Clavulanate	
P74- 9	UTI	*Escherichia coli*	No	No	Yes	Ceftriaxone	

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P76- 10	Pneumonia	*Streptococcus pneumoniae*	Yes	Yes	Yes	Cefotaxime + Azithromycin	
P79- 11	Pneumonia	*Chlamydia pneumoniae*	No	No	Yes	Levofloxacin	
P82- 12	UTI	*Klebsiella pneumoniae*	Yes	Yes	Yes	Meropenem	
P86- 13	Pneumonia	Non-isolated bacteria	No	No	Yes	Amoxicillin-Clavulanate	
P26- 14	Aspiration Pneumonia	Non-isolated bacteria	No	No	Yes	Piperacillin-Tazobactam	
P27- 15	Cellulitis	Staphylococcus aureus	No	No	Yes	Amoxicillin-Clavulanate	
P89- 16	Aspiration Pneumonia	Non-isolated bacteria	Yes	Yes	Yes	Piperacillin-Tazobactam	
	Cellulitis	Non-isolated bacteria					
P99- 17	Cellulitis	Non-isolated bacteria	No	No	Yes	Amoxicillin-Clavulanate	
P107-18	UTI	*Escherichia coli* + *Enterococcus faecalis*	No	No	Yes	Amoxicillin-Clavulanate	

SBP: spontaneous bacterial peritonitis, UTI: urinary tract infection, MRB: multi-drug resistant bacteria.

3.5. Infections during Follow-Up

During hospitalization and at follow-up (90 days after diagnosis), 49 infections were detected in 36 patients. Ten patients developed more than one infection upon admission or during follow-up; eight who had a preexisting infection upon admission were later reinfected (three were infected during hospitalization and five after hospital discharge), and the other two patients developed an infection during hospitalization and were later reinfected after hospital discharge.

Chest infections (17 (35%)), blood infections (10 (20%)), and SBP (9 (18%)) were predominantly associated with infections during follow-up. Microorganisms were identified in a significant proportion of patients (30 out of 49 (61.2%)); half of the isolated organisms were gram-positive bacteria (14 isolations of *Staphylococcus spp*. and three of *Enterococcus spp*.), whereas the other half were gram-negative bacteria (mostly *Enterobacteriaceae*: five isolations of *E. coli* and five of *K. pneumoniae*) (Table 2).

3.6. Liver Related Decompensations and ACLF in Infected Patients Compared with Non-Infected Patients.

On admission, infected patients (n=18) yielded higher prognostic scores than did non-infected patients (n=97). The presence of HD, such as ascites (78% vs. 46%, p=0.029) and HE (50% vs. 6%, p=0.001), was more frequent in infected patients than in non-infected patients. Infected patients exhibited higher prognostic scores than did non-infected patients: Maddrey (48 vs. 38, p=0.02), MELD (22 vs. 19, p=0.01), MELD Na (24.5 vs. 22, p=0.03), MELD 3.0 (25.5 vs. 23, p=0.01), Child–Pugh (11 vs. 10, p=0.001), and ABIC (11 vs. 10; p=0001). Furthermore, infected patients displayed a higher ACLF incidence (16.6% vs. 4.1%, p=0.041) than did non-infected patients. The complete clinical characteristics are shown in Table 4. Notably, infections diagnosed upon admission were cured with antibiotics, thus having no impact on survival.

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Table 4. Clinical and biological characteristics at admission.

	Infected patients n=18	No infected patients N=97	p
Sex (male), n(%)	12 (66.6%)	75 (77,3%)	0.28
Age, median (IQR) P 25-75	45 (41.7- 55.7)	51 (44–58)	0.43
Clinical History			
BMI, median (IQR) P 25-75	27.3 (23-31.2)	27.2 (24-31.7)	0.86
Arterial hypertension, n(%)	5 (28%)	30 (31%)	0.79
Diabetes, n(%)	2 (11%)	13 (13.4%)	0.80
Metabolic syndrome, n(%)	2 (11%)	14 (14.4%)	0.70
Obesity, n(%)	7 (39%)	21 (22%)	0.11
Chronic renal failure, n(%)	0	4 (4%)	0.91
History of HD, n(%)	6 (33.3%)	22(22.6%)	0.33
Previous AH, n(%)	5 (28%)	18 (18.5%)	0.36
Prophylactic antibiotics, n(%)	1 (5%)	1 (1%)	0.17
BASELINE			
HC diagnosis, n(%)	16 (88%)	65 (67%)	0.062
HD, n(%)	16 (88%)	48 (49.5%)	**0.005**
Ascites, n(%)	14 (78%)	45 (46,4%)	**0.029**
HE, n (%)	9 (50%)	6 (6.2%)	**0.001**
GIB, n (%)	0	7 (7.2%)	0.25
AKI, n(%)	3 (16.6%)	10 (10.3%)	0.43
ACLF, n(%)	3 (16.6%)	4 (4.1%)	**0.041**
Maddrey score, median (IQR) P 25-75	48 (32–68.5)	38 (18–51)	**0.022**
MELD score, median (IQR) P 25-75	22 (19-25)	19 (15-21)	**0.012**
MELD Na score, median (IQR) P 25-75	24 (22-29)	22 (19-26)	**0.037**
MELD 3.0 score, median (IQR) P 25-75	25 (25-28)	23 (20-25)	**0.013**
Child-Pugh score, median (IQR) P 25-75	11 (11–12)	10 (9–11)	**0.011**
Bilirubin serum (mg/dL), median (IQR) P 25-75	9.89 (6.96–16.31)	7.16 (4.53–11.62)	0.084
INR, median (IQR) P 25-75	1.8 (1.4–1.95)	1.5 (1.15–1.8)	0.027
Creatinine (mg/dL), median (IQR) P 25-75	0.63 (0.55–0.87)	0.67 (0.54–0.88)	0.81
Albumin (g/dl), median (IQR) P25–P75	2.5 (2.3–2.7)	2.8 (2.4–3.2)	**0.038**
CRP (mg/dL), median (IQR) P 25-75	3 (1.5-9.5)	2.4 (0.9-5.2)	0.31
Leucocytes (10^9/L), median (IQR) P 25-75	8.2 (5.8–10.7)	10.3 (6.6–13.2)	0.26

IQR: interquartile range, BMI: body mass index, HC: hepatic cirrhosis, GIB: gastrointestinal bleeding, HD: hepatic decompensations, AH: alcohol-associated hepatitis, HE: hepatic encephalopathy, AKI: acute kidney injury, ACLF: acute-on-chronic liver failure, MELD: Model for end-stage Liver Disease, INR: international normalized ratio, CRP: C-reactive protein.

Comparison of the clinical course of the infected (admission + hospitalization) and non-infected patients (n=37 vs. n=78) revealed significant differences. Infected patients (n=37) developed more cases of HD (62% vs. 28%, p=0.001), especially ascites (43% vs. 23%, p=0.046) and HE (41% vs. 13%, p=0.001), than did non-infected patients. They also presented with ACLF more frequently (32% vs.

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6%, p=0.001), requiring vasoactive (16% vs. 1.3%, p=0.002) and ICU (27% vs. 2.5%, p=0.001) support. Finally, patients with infections had a higher mortality rate (6/37, 16% vs. 3/78, 4%; p=0.021) than did non-infected patients. Table 5 compares the clinical characteristics of the infected and non-infected patients. Of the 22 in-hospital infected patients, 10 had infection-associated SIRS, nine developed ACLF, and five died of ACLF (Table 3-b). These 22 patients had higher incidence rates of HD (59% vs. 34.4%, p=0.033) and ACLF (36.3% vs. 9.6%, p=0.002) than did the non-infected patients during hospitalization.

Table 5. BASELINE AND COMPLICATIONS, PATIENTS IN HOSPITALIZATION.

	INFECTED PATIENTS N=37	**NO INFECTED PATIENTS N=78**	**p**
Sex (male), n(%)	25 (67.5%)	63 (81%)	0.12
Age, median (IQR) P 25-75	50 (43- 57)	51 (44–58)	0.87
Race, n(%)	Caucasian, 30 (87%)	Caucasian, 68 (87%)	0.91
BASELINE			
Maddrey score, median (IQR) P 25-75	45 (31.5–61.5)	37 (18–51)	**0.020**
MELD score, median (IQR) P 25-75	21 (18-25)	18 (15-21)	**0.002**
Child-Pugh score, median (IQR) P 25-75	11 (10–12)	10 (9-11)	**0.001**
Bilirubin serum (mg/dL), median (IQR) P 25-75	10.4 (5.4-17.5)	6.5 (4.4-10.5)	**0.010**
INR, median (IQR) P 25-75	1.63 (1.4-1.84)	1.48 (1.14-1.80)	**0.047**
Albumin (g/dl), median (IQR) P25–P75	2.5 (2.3-2.75)	2.8 (2.5-3.4)	**0.002**
Creatinine (mg/dL), median (IQR) P 25-75	0.7 (0.6-1.0)	0.65 (0.53-0.86)	0.45
COMPLICATIONS			
HD, n(%)	23 (62%)	22 (28%)	**0.001**
Ascites, n(%)	16 (43%)	18 (23%)	**0.046**
HE, n (%)	15 (41%)	10 (13%)	**0.001**
GIB, n (%)	4 (11%)	5(6.4%)	0.41
AKI, n(%)	6 (16%)	5 (6.4%)	0.095
Vasoactive support	6 (16%)	1 (1.3%)	**0.002**
ICU, n (%)	10 (27%)	2 (2.5%)	**0.001**
ACLF, n(%)	12 (32.4%)	5 (6.4%)	**0.001**
Death, n (%)	6 (16%)	3 (4%)	**0.021**

IQR: interquartile range, HD: hepatic decompensations, HE: hepatic encephalopathy, GIB: gastrointestinal bleeding, AKI: acute kidney injury, ICU: intensive care unit, ACLF: acute-on-chronic liver failure,

During hospitalization, the assessment focused solely on infections and complications, as not all patients recorded complete analytical values, nor was sufficient clinical information available after discharge.

Table 3b. Characteristics of infections in hospitalization.

ID-Episode	**CE**	**Infection**	**Bacteria**	**SIRS**	**ACLF**	**Resolution infection**	**Cause of death**	**Antibiotic**	**MRB**

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P2- 1	Yes	CRBSI	*Staphylococcus epidermidis*	Yes	Yes	Yes	ACLF	Meropenem	
P4- 2	Yes	UTI	*Klebsiella aerogenes*	Yes	Yes	Yes		Cefazolin	
		Cellulitis	*Staphylococcus aureus*					Cloxacillin	
		CRBSI	*Enterococcus faecalis, Staphylococcus epidermidis, Staphylococcus haemolyticus*					Piperacillin-Tazobactam	
P5- 3	Yes	UTI	*Escherichia coli*	No	No	Yes		Ceftriaxone	
P6- 4	Yes	Aspiration Pneumonia	Non-isolated bacteria	No	No	Yes		Meropenem	
P20- 5	No	UTI	*Escherichia coli*	No	No	Yes		Amoxicillin-Clavulanate	
P21- 6	Yes	Aspiration Pneumonia	Non-isolated bacteria	Yes	Yes	Yes	ACLF	Ceftazidime	
P28- 7	Yes	Pneumonia	Non-isolated bacteria	No	No	Yes		Amoxicillin-Clavulanate	
P38- 8	No	Cellulitis	*Staphylococcus aureus*	No	No	Yes		Linezolid	Yes
P44- 9	No	Pneumonia	Non-isolated bacteria	No	No	Yes		Amoxicillin-Clavulanate	
P50-10	Yes	Bacteremia	*Klebsiella oxytoca*	Yes	No	Yes		Amoxicillin-Clavulanate	
P51-11	Yes	Pneumonia	Non-isolated bacteria	No	No	Yes		Piperacillin-Tazobactam	
P25-12	No	SBP	*Staphylococcus aureus*	Yes	Yes	Yes		Ceftriaxone	
		Bacteremia	*Staphylococcus aureus*					Cefazolin	
		Aspiration Pneumonia	Non-isolated bacteria					Piperacillin-Tazobactam	
P61-13	Yes	Pneumonia	Non-isolated bacteria	Yes	Yes	Yes	ACLF	Piperacillin-Tazobactam	
P63-14	No	SBP	*Escherichia coli*	No	No	Yes		Ceftriaxone	
		Pneumonia	Non-isolated bacteria						
P68-15	Yes	Bacteriemia	*Escherichia coli*	Yes	No	Yes		Piperacillin-Tazobactam	

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P73-16	No	Aspiration Pneumonia	Non-isolated bacteria	No	No	Yes		Amoxicillin-Clavulanate		
P78-17	Yes	SBP	*Enterobacter cloacae*	Yes	Yes	No	SBP, ACLF	Ceftriaxone		
		Aspiration Pneumonia	Non-isolated bacteria					Amoxicillin-Clavulanate		
		SBP	*Klebsiella pneumoniae*					Meropenem + Daptomycin		Yes
P82-18	No	Pneumonia	Non-isolated bacteria	Yes	Yes	No	ACLF	Meropenem		
		CRBSI	*Staphylococcus hemolyticus, Staphylococcus epidermidis. *Candida albicans*					Meropenem + Daptomycin, *Anidulafungin		Yes
P87-19	No	Aspiration Pneumonia	Non-isolated bacteria	No	No	Yes		Amoxicillin-Clavulanate		
P102-20	No	Pneumonia	Non-isolated bacteria	No	No	Yes		Ceftriaxone		
P103-21	Yes	Pneumonia	Non-isolated bacteria	Yes	Yes	Yes		Piperacillin-Tazobactam		
P106-22	No	Aspiration Pneumonia	Non-isolated bacteria	No	No	Yes		Piperacillin-Tazobactam		

CE: corticosteroids, SBP: spontaneous bacterial peritonitis, CRBSI: catheter-related bloodstream infection, UTI: urinary tract infection, ACLF: acute-on-chronic liver failure, MRB: multi-drug resistant bacteria.

We did not identify any significant differences in the incidence rates of infections or liver complications between CS-treated and non-CS-treated patients during hospitalization (Table 6). After discharge, CS-treated patients developed more infections (26% vs. 6%, p=0.09) and had a greater frequency of infection-associated SIRS, compared with non-CS-treated patients, but without significant differences. Complete data are provided in Tables 6 and 3-c.

Table 6. Clinical characteristics, corticosteroid treatment vs. non treated patients.

	Corticosteroids n= 49	**No Corticosteroids n= 66**	**p**
Baseline			
Male, n (%)	36 (73.5%)	51 (77%)	0.63
Age median (IQR) P 25-75	51 (44-58)	48 (43-56)	0.16
Maddrey score, median (IQR) P 25-75	34 (18-50)	41 (28-58)	0.27
MELD score, median (IQR) P 25-75	19 (15-22)	19 (16-22)	0.88
Child-Pugh score, median (IQR) P 25-75	10 (9-11)	10 (9-11)	0.44
Complications during hospitalization			
Infections, n (%)	9 (18%)	13 (20%)	0.76

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HD, n(%)	18 (36%)	27 (40%)	0.65
Ascites, n(%)	14 (28%)	20 (30%)	0.89
HE, n (%)	10 (20%)	15 (22%)	0.73
GIB, n (%)	2 (4%)	7 (10%)	0.19
AKI, n(%)	7 (14%)	4 (6%)	0.14
Vasoactive support, n (%)	3 (6%)	4 (6%)	0.98
ICU, n (%)	5 (10%)	7 (11%)	0.94
ACLF, n(%)	4 (8%)	13 (20%)	0.08
Death, n (%)	4 (8%)	5 (7.5%)	0.92
Follow up 90 days			
Infections, n (%)	3 de 45 (6%)	11 de 61 (18%)	0.08
Number of infections, n (%)	3 de 45 (6%)	16 de 61 (26%)	0.09
Death, n (%)	1 (2%)	1 (1.5%)	0.82

IQR: interquartile range, MELD: Model for end-stage Liver Disease, HD: hepatic decompensations, HE: hepatic encephalopathy, GIB: gastrointestinal bleeding, AKI: acute kidney injury, ICU: intensive care unit, ACLF: acute-on-chronic liver failure.

Table 3. b. Characteristics of infections after hospital discharge.

ID- Episode	**CE**	**Infection**	**Bacteria**	**SIRS**	**ACLF**	**Resolution infection**	**Cause of death**	**Antibiotic**	**MRB**
P5- 1	Yes	Bacteremia	*Staphylococcus epidermidis*	No	No	Yes		Ceftriaxone	
P19-2	Yes	Cellulitis	Non-isolated bacteria	No	No	Yes		Ceftriaxone, Teicoplanin	
P28-3	Yes	Pneumonia	*Staphylococcus aureus*	Yes	Yes	No	Septic Shock	Meropenem Linezolid	+
		Intra-abdominal	Non-isolated bacteria						
P33-4	Yes	SBP	*Enterococcus faecium*	Yes	No	Yes		Piperacillin-Tazobactam	
P39-5	Yes	Cellulitis	Non-isolated bacteria	No	No	Yes		Amoxicillin-Clavulanate	
P45-6	Yes	Bacteriemia	*Klebsiella pneumoniae*	Yes	Yes	Yes		Meropenem, Teicoplanin	
		Bacteremia	*Enterococcus faecium*						Yes
P47-7	Yes	SBP	*Serratia marcescens*	No	No	Yes		Ceftriaxone	
P26-8	No	Bacteremia	*Staphylococcus aureus*	No	No	Yes		Amoxicillin-Clavulanate	

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P74-9	Yes	UTI	*Escherichia coli*	No	No	Yes		Ceftriaxone
P76-10	No	Cellulitis	Non-isolated bacteria	No	No	Yes		Cefadroxil
P83-11	No	Cellulitis	Non-isolated bacteria	No	No	Yes		Amoxicillin-Clavulanate
P92-12	Yes	SBP	*Klebsiella pneumoniae*	No	No	Yes		Ceftriaxone
		UTI	*Klebsiella pneumoniae*	No	No	Yes		Ciprofloxacin
		UTI	*Klebsiella pneumoniae*	Yes	Yes	yes		Cefotaxime + Clindamycin Yes
		Cellulitis	Non-isolated bacteria	No	No	Yes		Amoxicillin-Clavulanate
P105-13	Yes	Pneumonia	Non-isolated bacteria	No	No	Yes		Piperacillin-Tazobactam
P108-14	Yes	SBP	*Acinetobacter pitti*	Yes	Yes	Yes	ACLF	Meropenem

CE: corticosteroids, SBP: spontaneous bacterial peritonitis, UTI: urinary tract infection, ACLF: acute-on-chronic liver failure, MRB: multi-drug resistant bacteria.

3.7 Mortality and Predictors of Mortality in Infected Patients

The 90-day survival was higher in non-infected patients (71) than in infected patients (44) (95.8 ± 2.4% vs. 81.8 ± 5.8%, p=0.015; Figure 1). In-hospital infected patients exhibited worse survival (72.7 ± 9.5%) than did those infected upon admission (93.3 ± 6.4%) or non-infected patients (94.9 ± 2.5%) (p=0.009; Figure 2).

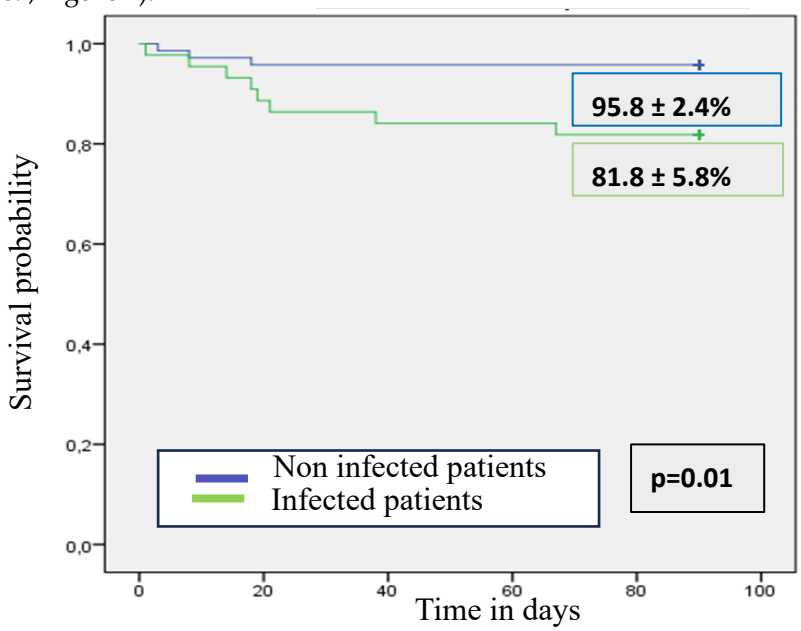

Figure 1. Impact survival according to the infection.

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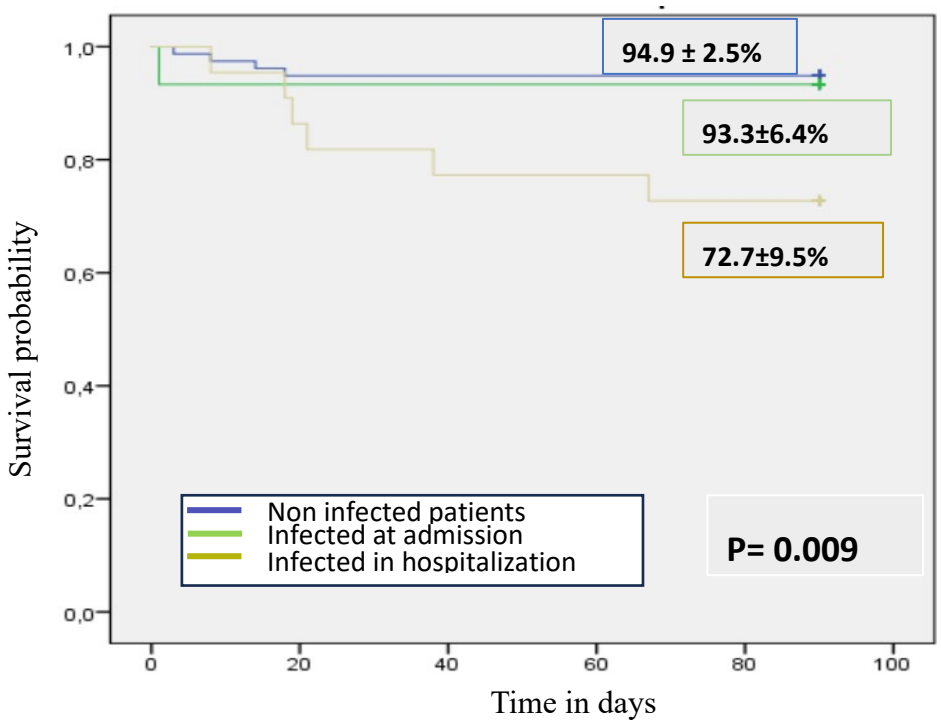

Figure 2. Survival according to the time of the acquisition of infection.

4. Discussion

In this study, we prospectively reviewed patients who were diagnosed with AH at our academic tertiary hospital and were registered in a national database. Among them, 70% had cirrhosis, 65% had a Maddrey score > 32, and 57% received CS treatment.

In our cohort, we identified 69 infections in 44 patients, among whom the incidence of infection at hospital discharge was 32.2%, reaching 38.2% at 90 days post-discharge. On admission, 15.6% of patients had infections; however, 19.1% developed in-hospital infections. This incidence was slightly lower than that reported in previous studies. Parker [6] reported a global incidence of 49% for in-hospital infections, whereas Louvet et al. [9] and Michelena et al. [10] reported incidence rates of 25.6% and 23.1%, respectively, among patients infected upon admission, compared with 23% and 43.8%, respectively, among those infected during hospitalization. The incidence of in-hospital infections reported in this study (19.1%) was considerably similar to that observed in a meta-analysis by Hmoud et al. [13], who reported that 20% of CS-treated patients with AH developed in-hospital infections. In contrast, the "Steroids or Pentoxifylline for Alcoholic Hepatitis" study [11] reported that only 10% patients were infected during hospitalization; however, they accounted for 24% of the deaths in their study.

The predominant infections upon admission were lower respiratory tract infections (7/20) and cellulitis (7/20). Both represent frequent locations of outpatient infections in patients with chronic liver disease. On admission, these infections occurred in patients with more deteriorated liver function; notably, in our series, other common locations, such as the abdomen (ascites) and urinary tract, were underreported. Additionally, in a multicenter study led by Parker [6], patients who acquired in-hospital infections in Spain exhibited relatively few cases of urinary tract infections. In our cohort infections (pneumonia) were the most frequent in patients with AH who had acquired the infection during hospitalization or follow-up; however, the blood (bacteremia) and abdomen (ascites [SBP]) appeared to be important locations, consistent with other studies [20]. The appearance of these locations is attributable to not only a severe immunological deterioration of patients with AH but also hospitalization (nosocomial infections), prolonged hospital stay, and HD. Ascites and HE predispose to SBP and HE to lower respiratory tract infections (aspiration), respectively.

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Moreover, secondary mechanical effects on respiratory function owing to abdominal ascites or hydrothorax predispose patients to pulmonary infection [6].

From our infection data, we identified the bacteria responsible for 51% of the infections by culture, displaying consistency with a large multinational study [6] that identified the causative bacteria in 53% infections. Additionally, we found similar proportions of gram-negative and gram-positive bacteria (50%). Generally, gram-positive bacteria are predominant in skin, chest, and blood infections (catheter-related), whereas gram-negative bacteria are predominant in urinary tract infections and ascites. In our study, the most frequent gram-positive cocci were *S. aureus* and *S. epidermidis*, whereas the predominant gram-negative bacteria were *E. coli* and *K. pneumoniae*. In contrast to previous study [21] wherein *Enterococcus* was identified as the pathogen, this species was only isolated in three of our patients. Notably, at our center, we found a low incidence of MRB (14%) and only one fungal infection associated with another bacterial infection (CRBSI). This potentially reflects the effectiveness of the antibiotics administered at our center [22,23].

Patients with AH often develop SIRS and immune dysfunction, favoring BI [7,24,25]. Excessive alcohol consumption can induce gut dysbiosis and increase the permeability of the intestinal barrier, inducing bacterial translocation and resulting in endogenous inflammation [26]. Additionally, treatment with CS potentially increases the risk of infection in AH [12,20,27]. Moreover, in a significant proportion of patients with AH, hepatic cirrhosis can also predispose to infection via different mechanisms (immune dysfunction, intestinal dysbiosis, and bacterial translocation) [5,28]. Both situations possibly explain the presence of infections in AH (38% of patients in our study). In our study, BI resulted in a poor prognosis for patients with AH. Infected patients had worse survival rates and more instances of HD, especially ascites and HE, compared with non-infected patients. However, infection favored ACLF development in patients with AH. ACLF is associated with a high risk of short-term death (i.e., death < 28 days after hospital admission) in patients with acutely decompensated cirrhosis. In the context of intense systemic inflammation, it frequently develops in close temporal relationships with proinflammatory precipitating events and is associated with single- or multiple-organ failure [29,30]. Among the most frequent proinflammatory precipitation events in Europe are infection and AH [31]. In our study, the coexistence of infection with AH induced a high rate (32%) of ACLF with a severe course of ICU admission in several cases. Considering the prognostic implications of ACLF, this is an important finding since most previous studies did not consider the presence of ACLF because the syndrome had not been defined or used yet.

CS treatment in patients with AH seems to increase susceptibility to infection [9,11,12,20] ; nevertheless, CS use is safe once the infection is under control. A meta-analysis of 12 randomized trials reported a 12% cumulative incidence of infection in patients with AH during CS therapy [13]. Although the treatment groups (CS and non-CS) in our study were not comparable, CS-treated and non-CS-treated patients presented no differences in the incidence of infections or mortality rate. This is consistent with the findings of Hmoud et al. [13], who found CS did not increase BI-related mortality in patients with severe AH.

Similar to other studies, we categorized infections based on onset time and peri- and post-admission diagnoses (in-hospital and follow-up infections). However, our data on follow-up infections were limited to those available in the registry; therefore, they were not included in the analysis. Nonetheless, infections upon admission in our study had two remarkable characteristics. First, on admission, infected patients had more advanced liver disease than did non-infected patients, based on the HD, Child–Pugh, and MELD scores. According to the PREDICT [30] and other studies on cirrhosis, infection and liver impairment are followed by greater susceptibility to HD and ACLF. This characteristic was not observed in previous studies, such as Louvet et al. [9]. Second, the infection upon admission exhibited favorable evolution. In our cohort, all infections upon admission resolved with adequate antibiotic treatment, and no deaths were recorded. In these patients, infection cure, outcome, and survival were similar to those in non-infected patients. However, not all series have made similar observations; in a multicenter study, Parker et al. [6] did not identify any differences in survival between infected patients upon admission and those infected during hospitalization.

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Consistent with the study by Michelena et al. [10], one of the most important findings in our study was that patients infected during hospitalization presented a greater number of complications and yielded a higher mortality rate than did non-infected patients. The reason for this poor evolution is that infections develop concurrently with proinflammation, leading to immune paralysis and predisposing to severe infections [25]. Additionally, CS use and infections with a risk of aggressive bacterial resistance potentially contribute to infection severity. ACLF was the clinical complication that conferred the poorest prognosis to these patients; in fact, out of 22 in-hospital infected patients, eight (36.4%) developed ACLF, and five died. The fact that in-hospital infections have the worst prognostic value suggests the possibility of considering the use of antibiotic prophylaxis upon admission [14,32,33].

Despite the positive results, this study has some limitations. First, although we collected data of all clinical events, the biochemical data recorded during hospitalization was only collected at baseline. Second, we lacked information after hospital discharge as only two post-discharge clinical events were recorded: infections and death. Thus, no biochemical information was available to evaluate prognostic scores or other liver-related complications. Finally, we did not obtain information on alcohol consumption after discharge.

5. Conclusions

Infections were common in a cohort of patients with AH admitted to a tertiary academic hospital. The most frequent site of infection was the chest. Among the identified bacteria, half of the isolated organisms were gram-positive and the other half gram-negative. The number of infections caused by enteric bacteria predominantly gram-negative (in abdomen: ascites, UTI) was evenly equaled among chest, blood, and skin infections, with gram-positive bacteria predominating in these sites. Infections diagnosed upon admission were cured with antibiotics and had no impact on survival. Our findings suggest that in-hospital infections are commonly associated with serious complications in patients with AH, including a high rate of ACLF and death. Corticosteroid-treated patients displayed a nonsignificant increase in the total number of infections; and this was not accompanied by greater mortality.

Author Contributions: Victor Vargas, Meritxell Ventura-Cots and Cesar Jimenez conceived the study. Aina Martí-Carretero, Ares Villagrasa, Anna Aguilar and María Pérez acquired the data. Victor Vargas and Cesar Jimenez drafted the manuscript. All authors critically reviewed and gave final approval of the manuscript.
Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki, and approved by the Local Ethics Committee for Clinical Research (CEIC), Vall d'Hebron University Hospital (project number: PR(AG)569-2023 date approval march 2023).
Conflicts of Interest: The authors declare no conflicts of interest.

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