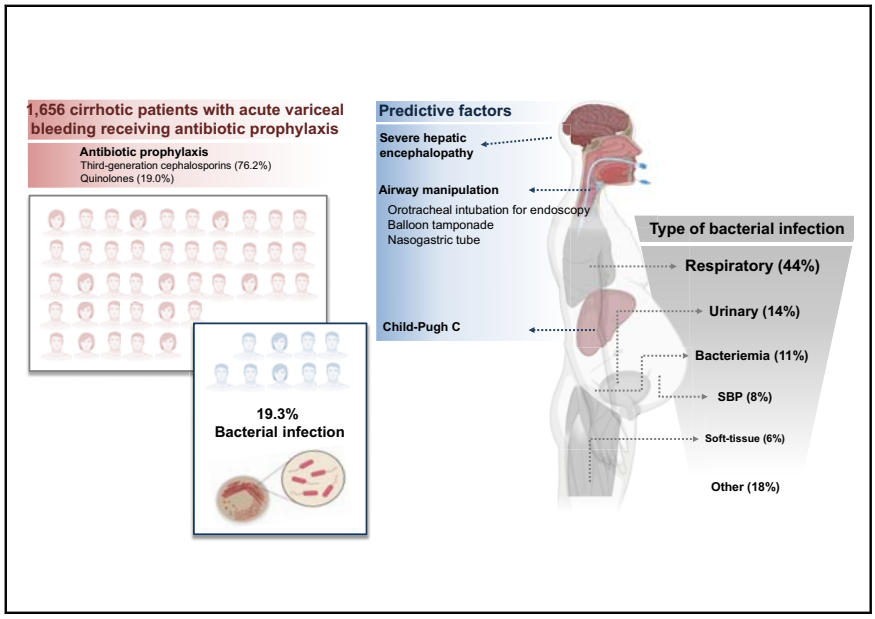
Research Article
Cirrhosis and Liver Failure

JOURNAL
OF HEPATOLOGY

Bacterial infections in patients with acute variceal bleeding in the era of antibiotic prophylaxis

Graphical abstract



Highlights

- Bacterial infections still occur in around one-fifth of patients with cirrhosis and acute variceal bleeding despite antibiotic prophylaxis.
- Respiratory bacterial infections are the most frequent, occurring early after admission.
- Respiratory infections are related to the severity of cirrhosis, presence of severe hepatic encephalopathy and airway manipulation.
- Over 50% of the bacteria isolated in this series were resistant to third-generation cephalosporines.

Authors

Javier Martínez, Virginia Hernández-Gea, Enrique Rodríguez-de-Santiago, …, Jaime Bosch, Juan Carlos García-Pagán, Agustín Albillos

Correspondence

agustin.albillos@uah.es (A. Albillos).

Lay summary

Bacterial infections develop during hospitalization in close to 20% of patients with acute variceal bleeding despite antibiotic prophylaxis. Respiratory bacterial infections are the most frequent and occur early after admission. Respiratory infection is associated with advanced liver disease, severe hepatic encephalopathy and a need for a nasogastric tube, orotracheal intubation for endoscopy or esophageal balloon tamponade.

https://doi.org/10.1016/j.jhep.2021.03.026
© 2021 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Research Article
Cirrhosis and Liver Failure

JOURNAL OF HEPATOLOGY

Bacterial infections in patients with acute variceal bleeding in the era of antibiotic prophylaxis

Javier Martínez[1,2], Virginia Hernández-Gea[2,3,†], Enrique Rodríguez-de-Santiago[1,2], Luis Téllez[1,2], Bogdan Procopet[4], Álvaro Giráldez[5], Lucio Amitrano[6], Candid Villanueva[2,7,8], Dominique Thabut[9,10], Luis Ibañez-Samaniego[11], Gilberto Silva-Junior[3], Joan Genescà[2,12], Christophe Bureau[13], Jonel Trebicka[14,15], Rafael Bañares[2,11], Aleksander Krag[16], Elba Llop[2,17], Wim Laleman[18,†], Jose María Palazon[19], Jose Castellote[20], Susana Rodrigues[21], Lise L. Gluud[22], Carlos Noronha-Ferreira[23], Nuria Cañete[24], Manuel Rodríguez[25], Arnulf Ferlitsch[26], Remy Schwarzer[26], Jose Luis Mundi[27], Henning Gronbaek[28,†], Manuel Hernández-Guerra[29], Romano Sassatelli[30], Alessandra Dell'Era[31], Marco Senzolo[32,†], Juan G. Abraldes[33], Manuel Romero-Gomez[34], Alexander Zipprich[35], Meritxell Casas[36], Helena Masnou[37], Massimo Primignani[38,†], Frederik Nevens[18], Jose Luis Calleja[2,17], Christian Jansen[39], Marie Angèle Robic[13], Irene Conejo[2,12], Maria Vega Catalina[2,11], Marika Rudler[8,10], Edilmar Alvarado[2,7,8], Valeria Perez-Campuzano[3], Maria Anna Guardascione[6], Petra Fischer[4], Jaime Bosch[2,3,40,†], Juan Carlos García-Pagán[2,3,†], Agustín Albillos [1,2,*], for International Variceal Bleeding Observational Study Group and Baveno Cooperation

[1]*Servicio de Gastroenterología y Hepatología, Hospital Universitario Ramón y Cajal, Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS), Universidad de Alcalá, Madrid, Spain;* [2]*Centro de Investigación Biomédica Red de Enfermedades Hepáticas y Digestivas (CIBEREHD), Madrid, Spain;* [3]*Barcelona Hepatic Hemodynamic Laboratory, Liver Unit, Hospital Clinic, Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS), University of Barcelona, Barcelona, Spain;* [4]*Regional Institute of Gastroenterology and Hepatology "Octavian Fodor", Hepatology Department and "Iuliu Hatieganu" University of Medicine and Pharmacy, 3rd Medical Clinic, Cluj-Napoca, Romania;* [5]*Unit for the Clinical Management of Digestive Diseases, Virgen del Rocío University Hospital, Instituto de Biomedicina de Sevilla (IBIS), Liver Diseases, Seville, Spain;* [6]*Gastroenterology Unit, Ospedale A Cardarelli, Naples, Italy;* [7]*Department of Gastroenterology and Institut de Recerca, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain;* [8]*Universitat Autònoma de Barcelona, Bellaterra (Cerdanyola del Vallès), Barcelona, Spain;* [9]*Groupement Hospitalier Pitié-Salpêtrière-Charles Foix, Paris, France;* [10]*Sorbonne Université, INSERM, Centre de Recherche Saint-Antoine (CRSA), Institute of Cardiometabolism and Nutrition (ICAN), Paris, France;* [11]*Servicio de Medicina de Aparato Digestivo Gregorio Marañón, Hospital General Universitario Gregorio Marañón, CIBERehd, Madrid, Spain;* [12]*Liver Unit, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institute of Research (VHIR), Universitat Autònoma de Barcelona and CIBERehd, Barcelona, Spain;* [13]*Department of Hepato-Gastroenterology, Purpan Hospital, CHU Toulouse, INSERM U858, University of Toulouse, Toulouse, France;* [14]*Department of Internal Medicine I, Goethe University Frankfurt, Frankfurt, Germany;* [15]*European Foundation for the Study of Chronic Liver Failure (EF-Clif), Barcelona, Spain;* [16]*Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark;* [17]*Liver Unit, Hospital Universitario Puerta de Hierro. Universidad Autónoma de Madrid, CIBERehd, Madrid, Spain;* [18]*Department Gastroenterology and Hepatology. Division of Liver and Biliopancreatic Disorders, University Hospitals Leuven – KU Leuven, Leuven, Belgium;* [19]*Hospital General Universitario de Alicante, Alicante, Spain;* [20]*Gastroenterology Department, Hepatology Unit, Hospital Universitari de Bellvitge, IDIBELL, Universitat de Barcelona, Barcelona, Spain;* [21]*Gastroenterology and Hepatology Department, Centro Hospitalar São João, Porto, Portugal;* [22]*Gastro unit, Medical Division, University Hospital of Hvidovre, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark;* [23]*Serviço de Gastroenterología e Hepatologia, Hospital de Santa Maria – Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal;* [24]*Liver Section, Gastroenterology Department, Hospital del Mar, Universitat Autònoma de Barcelona, Barcelona, Spain;* [25]*Department of Gastroenterology, Hospital Central de Asturias, Oviedo, Spain;* [26]*Department of Internal Medicine III, Division of Gastroenterology and Hepatology, Medical University of Vienna, Vienna, Austria;* [27]*Department of Gastroenterology, University Hospital San Cecilio, Granada, Spain;* [28]*Department of Hepatology and Gastroenterology, Aarhus University Hospital, Aarhus, Denmark;* [29]*Gastroenterology Department, University Hospital of the Canary Islands, La Laguna, Tenerife, Spain;* [30]*Unit of Gastroenterology and Digestive Endoscopy, Arcispedale Santa Maria Nuova IRCCS,Reggio Emilia, Italy;* [31]*Gastroenterology Unit, ASST Fatebenefratelli Sacco, Department of Clinical and Biomedical Sciences 'Luigi Sacco', University of Milan, Milan, Italy;* [32]*Multivisceral Transplant Unit, Gastroenterology, Department of Surgery, Oncology and Gastroenterology, University*

Keywords: Cirrhosis; Acute variceal bleeding; Antibiotic prophylaxis; Bacterial infection; Respiratory infection.
Received 16 August 2020; received in revised form 23 March 2021; accepted 25 March 2021; available online 12 June 2021
* Corresponding author. Address: Servicio de Gastroenterología y Hepatología, Hospital Universitario Ramón y Cajal. M-607, km. 9,100. 28034 Madrid.
E-mail address: agustin.albillos@uah.es (A. Albillos).
† Health Care Provider of the European Reference Network on Rare Liver Disorders (ERN-Liver).
https://doi.org/10.1016/j.jhep.2021.03.026

Hospital of Padua, Padua, Italy; [33]Division of Gastroenterology (Liver Unit), University of Alberta, Edmonton, Canada; [34]Unidad de Hepatología, Hospital Universitario de Valme, CIBERehd, Sevilla, Spain; [35]First Department of Internal Medicine, Martin Luther University Halle-Wittenberg, Halle (Saale), Germany; [36]Hepatology Unit, Digestive Disease Department Hospital de Sabadell, Universitat Autónoma de Barcelona, Sabadell, Spain; [37]Hospital Universitari Germans Trias i Pujol, Universitat Autònoma Barcelona, Badalona, Spain; [38]Division of Gastroenterology and Hepatology, IRCCSCa'Granda Maggiore Hospital Foundation, University of Milan, Milan, Italy; [39]Department of Internal Medicine I, Universitiy of Bonn, Bonn, Germany; [40]Department of Biomedical research, Bern University, Hepatology, Inselspital, Bern, Switzerland

Background & Aims: Antibiotic prophylaxis reduces the risk of infection and mortality in patients with cirrhosis and acute variceal bleeding (AVB). This study examines the incidence of, and risk factors for, bacterial infections during hospitalization in patients with AVB on antibiotic prophylaxis.

Methods: A *post hoc* analysis was performed using the database of an international, multicenter, observational study designed to examine the role of pre-emptive transjugular intrahepatic portosystemic shunts in patients with cirrhosis and AVB. Data were collected on patients with cirrhosis hospitalized for AVB (n = 2,138) from a prospective cohort (October 2013-May 2015) at 34 referral centers, and a retrospective cohort (October 2011-September 2013) at 19 of these centers. The primary outcome was incidence of bacterial infection during hospitalization.

Results: A total of 1,656 patients out of 1,770 (93.6%) received antibiotic prophylaxis; third-generation cephalosporins (76.2%) and quinolones (19.0%) were used most frequently. Of the patients on antibiotic prophylaxis, 320 patients developed bacterial infection during hospitalization. Respiratory infection accounted for 43.6% of infections and for 49.7% of infected patients, and occurred early after admission (median 3 days, IQR 1-6). On multivariate analysis, respiratory infection was independently associated with Child-Pugh C (odds ratio [OR] 3.1; 95% CI 1.4-6.7), grade III-IV encephalopathy (OR 2.8; 95% CI 1.8-4.4), orotracheal intubation for endoscopy (OR 2.6; 95% CI 1.8-3.8), nasogastric tube placement (OR 1.7; 95% CI 1.2-2.4) or esophageal balloon tamponade (OR 2.4; 95% CI 1.2-4.9).

Conclusion: Bacterial infections develop in almost one-fifth of patients with AVB despite antibiotic prophylaxis. Respiratory infection is the most frequent, is an early event after admission, and is associated with advanced liver failure, severe hepatic encephalopathy and use of nasogastric tube, orotracheal intubation for endoscopy or esophageal balloon tamponade.

Lay summary: Bacterial infections develop during hospitalization in close to 20% of patients with acute variceal bleeding despite antibiotic prophylaxis. Respiratory bacterial infections are the most frequent and occur early after admission. Respiratory infection is associated with advanced liver disease, severe hepatic encephalopathy and a need for a nasogastric tube, orotracheal intubation for endoscopy or esophageal balloon tamponade.

© 2021 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Bacterial infection is a major complication in patients with cirrhosis presenting with acute variceal bleeding (AVB). In the absence of antibiotic prophylaxis, 35-66% of these patients develop bacterial infections within the first 5-7 days of a bleeding episode, and this risk is particularly high in Child-Pugh C patients.[1–3] Infections are associated with an increased risk of failure to control variceal bleeding, rebleeding and death.[1,2,4] Antibiotic prophylaxis reduces the incidence of bacterial infections to 10-20%, improves control of bleeding, decreases rebleeding and increases survival.[1,2,5] Based on these confirmed benefits, antibiotic prophylaxis is a component of the standard of care for patients with AVB and should be initiated on admission to hospital.[6,7] However, adherence to antibiotic prophylaxis recommendations in some recent series was lower than 50%.[8]

When antibiotic prophylaxis was first proposed, spontaneous bacterial peritonitis and bacteremia caused by enteric Gram-negative bacilli were the most frequent infections in patients with AVB.[3] In consequence, initial prophylaxis regimens targeted enteric bacteria and included non-absorbable antibiotics and oral quinolones.[1,6,9] Thereafter, intravenous third-generation cephalosporins (TGC) were recommended because of increasing prevalence of Gram-negative bacilli and non-enteric streptococci resistant to quinolones, and also because the parenteral route is more effective in patients with advanced cirrhosis.[10] It is conceivable that the efficacy of prophylaxis is likely to fluctuate as infections could occur at sites not targeted by current prophylaxis. This situation is aggravated by increases in both antibiotic exposure and the invasiveness of current medical practice. We considered that the analysis of a large cohort of patients with AVB admitted to tertiary and academic centers could provide valuable information regarding the efficacy of current guidelines on antibiotic prophylaxis in real-world clinical practice.

The participants of the present study were all patients with cirrhosis hospitalized for AVB from 2011 to 2015 in 34 referral centers across Europe and Canada. Our main objectives were to assess i) the effectiveness of currently recommended antibiotic prophylaxis to prevent bacterial infection during admission in patients with AVB, and ii) the types of, and risk factors for, bacterial infections in this population.

Patients and methods

Study design and patients

This was a *post hoc* analysis of the database of an international, multicenter, observational study designed to examine the role of pre-emptive transjugular intrahepatic portosystemic shunt (TIPS) in patients with cirrhosis and AVB (Fig. 1). The study was conducted by the Baveno Cooperation at 34 referral centers (33 in Europe and 1 in Canada) from October 2011 to May 2015.[11] All patients with cirrhosis admitted to a participating center for AVB during the study period were registered in the database. The database included 2,138 patients admitted with AVB from 2 cohorts: i) a prospective cohort of 1,334 patients from October 2013 to May 2015 at the 34 participating centers, and ii) a retrospective cohort of 804 patients with data prospectively registered from October 2011 to October 2013 at 19 of the 34 centers. For the purpose of this study, we excluded patients diagnosed with a bacterial infection at the time of admission (n = 368), and patients that did not receive antibiotic prophylaxis (n = 114).

After being specifically asked, all participating centers mentioned that they followed the guidelines of the Baveno V

consensus, which recommend the use of antibiotic prophylaxis (oral quinolones or intravenous ceftriaxone) from admission in all patients with cirrhosis and upper gastrointestinal bleeding.[12]

The primary outcome of this ancillary study was to analyze the incidence of bacterial infection during hospitalization. Secondary outcomes were: i) predictive factors of bacterial and respiratory infection, ii) survival at 6 weeks, and iii) adherence to current antibiotic prophylaxis recommendations.

The Health Research Ethics Committees of all participating hospitals approved the protocol and the patients included signed a written informed consent to be registered and for the use of their clinical data. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee.

Data management

All data were gathered in the context of standard practice from patients' clinical records. To improve the quality of data, we included a unified capture system and a steering committee, as described.[11] Data were recorded, encrypted and managed using the Research Electronic Data Capture (REDcap) system. A steering committee was created to regularly check for inconsistencies or errors in the data. Any queries requiring resolution by the local investigators were sent to each center. The steering committee was responsible for validating all reported clinical variables before their statistical treatment.

Data in the database collected at the time of AVB included information related to: i) Medical history: demographics, comorbidities, etiology and severity (Child-Pugh score) of liver disease, active alcoholism, previous decompensation, previous medications (outpatient antibiotic prophylaxis, non-selective beta-blockers, diuretics, anticoagulants, statins); ii) Index bleed: clinical manifestations, use of nasogastric tube at admission, need for sedation and/or orotracheal intubation for upper gastrointestinal endoscopy, need for esophageal balloon tamponade; iii) Physical signs at admission: temperature, arterial pressure, respiratory and heart rate, encephalopathy, ascites, jaundice; iv) Laboratory results on admission: hemoglobin, platelet count, white blood cell count, international normalized ratio, bilirubin, albumin, creatinine; and v) Initial hemostatic treatment: vasoactive drugs, endoscopic therapy, balloon tamponade or esophageal stent, route (oral, intravenous) and type of antibiotic prophylaxis, timing of TIPS, and transfusion of red blood cells or platelets. Data on in-hospital and 6-week mortality were also collected.

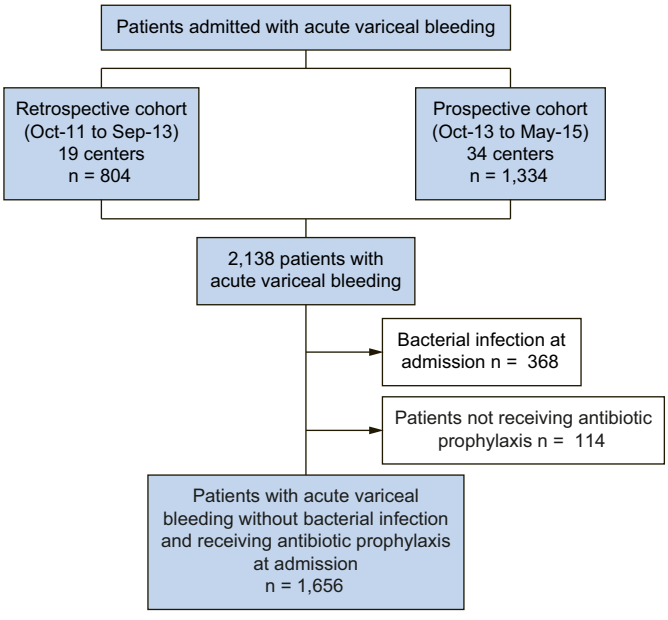


Fig. 1. Flow chart of the patients included in and excluded from the study.

For the purpose of this study, we considered bacterial infections reported by the attending physician in the clinical records at admission and during hospitalization. Centers were requested to retrospectively revise the timing and type of bacterial infection reported in the original dataset according to conventional criteria.[13,14] Briefly, the diagnosis of bacterial infection was based on clinical and laboratory findings, as follows: Spontaneous bacterial peritonitis: ascites polymorphonuclear cell count ≥250 cells/mm^3; Pneumonia: new or progressive infiltrates on chest X-ray and clinical signs of infection; Ventilator-associated tracheobronchitis: positive bronchial aspirate or sputum culture, absence of infiltrates on X-ray and clinical signs of infection in a patient on mechanical ventilation; Urinary tract infection: abnormal urinary sediment (>10 leukocytes/field) and positive urinary culture or uncountable leukocytes per field if cultures prove negative, and presence of urinary tract infection symptoms or positive blood culture; Skin and soft tissue infections: clinical signs of infection associated with swelling, erythema, heat and tenderness in the skin; Primary bacteremia: positive blood cultures, no cause of bacteremia and clinical signs of infection. Common skin contaminants were not considered as contaminants unless blood cultures were positive on 2 separate occasions or in the presence of clinical signs of infection; Catheter-related infection: positive blood and catheter cultures; *Clostridium difficile* infection: stool positive for the toxin in a patient with diarrhea.

Statistical analysis

The study followed Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational studies.[15] Categorical data are provided as frequencies and percentages. Continuous data are provided as the mean and SD when normally distributed, and median and IQR when skewed. Data were compared using the Chi-squared or Fisher's exact test for categorical variables, and the *t* test and Mann-Whitney test for ordinal and non-Gaussian continuous variables. Missing data for each variable are shown in Table S1. Only those variables previously reported as predictive factors or with a plausible pathophysiological relationship with bacterial infection were included in the univariate analysis. Multivariate analysis was performed by backward stepwise, binomial, unconditional logistic regression. Variables with p values <0.05 in the univariate analysis were considered for the logistic regression models. The AUROC was calculated to assess the discriminative ability of the logistic models. Goodness-of-fit was assessed using the Hosmer-Lemeshow test and calibration plots. Multi-colinearity was explored via the variance inflation factor, Spearman correlation coefficient and contingency tables.[16] First-order interactions were assessed in a global likelihood-ratio test. Models were validated internally using the resampling validation method with 200 bootstrap re-samples. Additionally, we performed a sensitivity time-to-event analysis through Kaplan-Meier estimates and Cox regression to explore the incidence and predictive factors of infection in a survival data framework.

The association between bacterial infection and mortality was examined through Cox regression. For this analysis, we adjusted for confounding variables with a known mortality impact (age, creatinine, Child-Pugh class, pre-emptive TIPS, antibiotics).

Significance was set at the 2-sided 5% level. All statistical analyses were performed using STATA software version 14.1 (StataCorp. Texas, USA).

Results

The final dataset therefore included 1,656 patients with cirrhosis and AVB who received antibiotic prophylaxis and did not have a bacterial infection at the time of admission (Fig. 1). Of the 1,656 participants (733 from the retrospective and 923 from the prospective cohort), 320 (19.3%) developed a bacterial infection during hospitalization.

Table 1. Characteristics of the patients without and with bacterial infection.

	All Patients	Without bacterial infection	With bacterial infection	
Variable	**n = 1,656**	**n = 1,336**	**n = 320**	***p* value**
Age, years	59.1 (12.4)	59.2 (12.4)	58.8 (12.6)	0.61
Sex, male	1,225 (74.0)	980 (73.4)	245 (76.6)	0.24
Etiology of cirrhosis, alcohol	895 (54.1)	697 (52.2)	198 (61.9)	**<0.01**
Active alcohol use	584 (35.3)	451 (33.8)	133 (41.6)	**<0.01**
Previous antibiotics	203 (12.3)	159 (11.9)	44 (13.8)	0.27
Diabetes	510 (30.8)	419 (31.4)	91 (28.4)	0.31
Severity of cirrhosis				
Child-Pugh				**<0.01**
A	230 (13.9)	212 (15.9)	18 (5.6)	
B	984 (59.4)	801 (60.0)	183 (57.2)	
C	442 (26.7)	323 (24.2)	119 (37.2)	
Hepatic encephalopathy				**<0.01**
No	1,177 (71.1)	1,000 (74.9)	177 (55.3)	
Grade I-II	307 (18.5)	233 (17.4)	74 (23.1)	
Grade III-IV	172 (10.4)	103 (7.7)	69 (21.6)	
Bilirubin, mg/dl	2.8 (3.8)	2.7 (3.6)	3.2 (4.3)	**0.02**
Albumin, g/dl	2.8 (0.6)	2.8 (0.6)	2.7 (0.6)	**<0.01**
INR	1.6 (0.5)	1.5 (0.5)	1.7 (0.6)	**<0.01**
Index bleed: severity				
Hematemesis	1,260 (76.1)	1,019 (76.3)	241 (75.3)	0.72
Active bleeding at endoscopy	528 (31.9)	422 (31.6)	106 (33.1)	0.60
Shock	454 (27.4)	350 (26.2)	104 (32.5)	**0.03**
Hemoglobin, g/dl	9.1 (2.2)	9.2 (2.2)	8.8 (2.2)	**0.01**
Number of packed red blood cells	2.1 (2.0)	1.7 (2.0)	2.1 (1.9)	**0.01**
Index bleed: management				
Antibiotic prophylaxis				**<0.01**
TGC	1,262 (76.2)	1,026 (76.8)	236 (73.8)	
Quinolones	314 (19.0)	260 (19.5)	54 (16.9)	
Amoxicillin/clavulanic	48 (2.9)	35 (2.6)	13 (4.1)	
Others	32 (1.9)	15 (1.1)	17 (5.3)	
Nasogastric tube	532 (32.1)	407 (30.5)	125 (39.1)	**<0.01**
Sedation for endoscopy	1,143 (69.0)	921 (68.9)	222 (69.4)	0.55
Orotracheal intubation for endoscopy	323 (19.5)	221 (16.5)	102 (31.9)	**<0.01**
Time to endoscopy				0.15
<12 h	1,386 (83.7)	1,103 (82.6)	283 (88.4)	
12-24 h	129 (7.8)	111 (8.3)	18 (5.6)	
>24 h	59 (3.6)	47(3.5)	12 (3.8)	
Initial hemostatic treatment				
Drugs plus endoscopy	1,422 (85.9)	1,137 (85.1)	285 (89.1)	0.53
Drugs alone	166 (10.0)	128 (9.6)	38 (11.9)	0.42
Endoscopy alone	54 (3.3)	47 (3.5)	7 (2.2)	0.26
Balloon tamponade	50 (3.0)	32 (2.4)	18 (5.6)	**<0.01**
Esophageal stent	2 (0.1)	2 (0.1)	0 (0.0)	1
Endoscopic treatment				
Ligation	1,225 (74.0)	989 (74.0)	236 (73.8)	0.23
Sclerotherapy	159 (9.6)	119 (8.9)	40 (12.5)	0.12
Tissue glue injection	111 (6.7)	87 (6.5)	24 (7.5)	0.76
Other	43 (2.6)	31 (2.3)	12 (3.8)	0.24
Pre-emptive TIPS	53 (3.2)	42 (3.1)	11 (3.4)	0.23
Hospitalization and mortality				
Length, days	10.1 (7.7)	8.8 (7.1)	15.7 (9.5)	**<0.01**
Intensive care unit admission	471 (28.4)	325 (24.3)	146 (45.6)	**<0.01**
In-hospital mortality	164 (9.9)	109 (8.2)	55 (17.2)	**0.01**
Mortality at 6-weeks	220 (13.3)	156 (11.7)	64 (20.0)	**0.01**

p value is a comparison of patients with and without infection. Values in bold denote statistical significance.
Continuous variables are expressed as mean (SD) or as median (IQR). Categorical variables are expressed as n (%). INR, international normalized ratio; TIPS, transjugular intrahepatic portosystemic shunt.

Patient characteristics at admission

Table 1 shows the characteristics of the study participants. Patients developing bacterial infection more frequently had alcohol-related cirrhosis, active alcohol use, and worse liver function compared to those that did not. Severe (grade III-IV) hepatic encephalopathy on admission occurred 3 times more often in patients with infection (21.6% *vs.* 7.7%, $p < 0.01$). At admission, 292 patients (17.6%) had acute-on-chronic liver failure (ACLF) according to EASL-CLIF criteria (grade 1: 39.6%; grade 2: 38.8%; grade 3: 21.6%).

Management of AVB and hospitalization course

The severity of AVB was greater in patients developing infection, as shown by a higher rate of shock on admission (defined as a systolic arterial pressure <90 mmHg), a lower hemoglobin level, and greater need for blood transfusion. Use of nasogastric tube, orotracheal intubation for endoscopy or need for balloon tamponade at index bleed were more frequent in patients that developed bacterial infection. Orotracheal intubation was undertaken in 323 patients (19.5%), and severe encephalopathy was present in 67 of these patients (20.7%).

The most frequent antibiotics used for prophylaxis were TGC (1,262; 76.2%) followed by quinolones (314; 19.0%). Remarkably, TGC were the antibiotic of choice in 939 out of the 1,214 Child-Pugh A and B patients (77.3%), whereas quinolones were used in 57 out of the 442 Child-Pugh C patients (12.9%). Only 4.8% of the cohort received other broad-spectrum antibiotics such as penicillins (48; 2.9%) or others (32; 1.9%).

Initial hemostasis was achieved by vasoactive drugs and endoscopic therapy in 85.9% of patients, band ligation being the endotherapy used in most cases (74.0%). Pre-emptive TIPS was used with similar frequency in patients with and without infection. In patients that developed bacterial infection, hospitalization was longer (15.7 *vs.* 8.8 days, $p < 0.01$), and they were more frequently admitted to the intensive care unit (45.6% *vs.* 24.3%, $p < 0.01$).

There were no differences between the 2 groups in terms of previous decompensation episodes, previous use of drugs such as antibiotics, beta-blockers, anticoagulants, simvastatin or diuretics, or the presence of hepatocellular carcinoma or portal vein thrombosis (Table S2).

The characteristics of the patients included in the retrospective (2011-2013) and prospective (2013-2015) cohorts are shown in Table S3. In spite of a similar severity of the index bleeding episode, patients in the prospective cohort received a lower ($p = 0.02$) number of packed red blood cells, and less often required placement of a nasogastric tube ($p < 0.01$) or orotracheal intubation for endoscopy. Patients in the prospective cohort had a lower number of total (17.8% *vs.* 21.3%, $p < 0.01$) and respiratory (8.7% *vs.* 10.8%, $p = 0.08$) bacterial infections. There was a trend for patients in the prospective cohort to more often receive TGC than oral quinolones as prophylaxis. The characteristics of the patients and outcomes were otherwise similar between the 2 cohorts.

Incidence and types of bacterial infection

Three hundred and twenty (19.3%, 95% CI 16.6%–20.6%) of the 1,656 patients developed 365 episodes of bacterial infection (Table 2). Thirty-one (9.7%) and 7 (2.2%) patients developed 2 and 3 episodes of infection, respectively. Bacterial infection occurred at a median of 4 days (IQR 2–8) from admission. The cumulative incidence of bacterial infection at days 3, 7 and 14 determined by Kaplan-Meier analysis was 9% (95% CI 7.5%–10.4%), 14.9% (95% CI 13.2%–16.8%) and 23.0% (95% CI 20.4%–25.9%), respectively (Fig. 2A). Only 23 patients (7.2%) developed bacterial infection after day 14.

Respiratory infection was the most frequent bacterial infection, accounting for 43.6% of all infections reported and for 49.7%

Table 2. Bacterial infections and isolates during admission.

Type of infection	n (%)	Time to infection (days), median (IQR)	Infections with positive cultures	Bacterial isolates: n
Respiratory	159 (43.6)	3 (1-6)	23 (14.5)	*P. aeruginosa: 8* *E. coli: 2* *K. pneumoniae: 3* *E. cloacae:2* *S. pneumoniae: 3* *S.aureus: 4* *A. woffi: 1*
Urinary tract	50 (13.7)	5 (3-7)	17 (34.0)	*P. aeruginosa: 2* *E. coli: 4* *K. pneumoniae: 3* *E. faecium: 6* *E. fecalis: 2* *E. cloacae: 1*
Primary bacteremia	39 (10.7)	3 (1-4)	39 (100)	*P. aeruginosa: 3* *E. coli: 15* *K. pneumoniae: 4* *E. faecium: 5* *E. fecalis: 7* *S. pneumoniae: 2* *S. aureus: 2* *A. baumanii: 1*
Spontaneous bacterial peritonitis	29 (7.9)	3 (2-4)	5 (17.2)	*E. coli: 2* *E. faecium: 2* *S. pneumoniae: 1*
Soft tissue	23 (6.3)	5 (3-8)	1 (4.3)	*S. epidermidis*: 1
Other	65 (17.8)	5 (2-7)	3 (4.6)	*C. difficile: 3*

Continuous variables are expressed as median (IQR). Categorical variables are expressed as n (%).

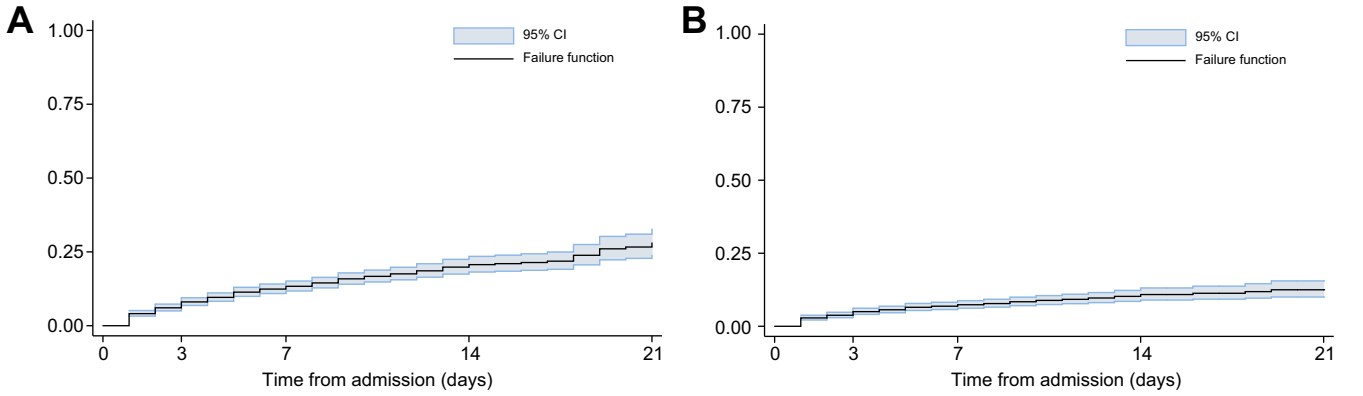


Fig. 2. Cumulative incidence of infections during hospitalization. (A) Bacterial infection. (B) Respiratory infection. Kaplan-Meier analysis (95% CI).

of all infected patients (Table 2, Table S4). Respiratory infections occurred at a median of 3 days (IQR 1-6) from admission. The cumulative incidence of respiratory bacterial infection on days 3, 7 and 14 determined by Kaplan-Meier analysis was 5.5% (95% CI 4.5%–6.7%), 8.1% (95% CI 6.9%–9.6%) and 12.1% (95% CI 10.0%–14.4%), respectively (Fig. 2B). Eight patients (5.0%) developed respiratory infection after day 14. Forty out of the 162 episodes of respiratory infection were classed as ventilator-associated, either pneumonia or tracheobronchitis.

Urinary tract was the second most frequent infection (13.7%) followed by primary bacteremia (10.7%). Spontaneous bacterial peritonitis was diagnosed in 29 patients (7.9%), and soft tissue infection in 23 (6.3%). Sixty-five patients (17.8%) had other infections (*e.g.*, *Clostridium difficile* enterocolitis, catheter-related phlebitis, periodontitis).

Bacteria were cultured in 88 out of 365 episodes of infection (24.1%), and 44.3% of these isolations corresponded to the 39 episodes of primary bacteremia (Table 2). Bacteria were isolated in 23 of the 159 (14.5%) respiratory infections. Gram-negative bacteria accounted for 69.6% and 59.0% of the isolates of respiratory and primary bacteremia infections, respectively. Antibiotic susceptibility information was available for 78 bacterial isolates from 64 infections (Table S5). Forty-six and thirty-six out of the 78 isolates were resistant to TGC (59.0%), and to quinolones (46.2%), respectively. The same figures in the 23 respiratory isolates were 15 (65.2%) and 6 (26.1%), respectively.

Factors predictive of bacterial infection

We thereafter analyzed the variables associated with the development of any bacterial infection. In the univariate analysis, alcoholic etiology, decompensated liver disease (defined as Child-Pugh B/C), hepatic encephalopathy, antibiotic prophylaxis, nasogastric tube, orotracheal intubation for endoscopy or balloon tamponade were associated with infection development. Factors independently associated with bacterial infection by multivariate logistic regression were Child-Pugh B and C, severe (grade III-IV) hepatic encephalopathy, nasogastric tube or orotracheal intubation for endoscopy (Table 3). This model showed an AUROC = 0.66 and a p value calibration by Hosmer-Lemeshow test of 0.85. The same variables were found to be independently associated with bacterial infection in the sensitivity time-to-event analysis (Table S6).

Factors predictive of respiratory infection

We then identified the factors predictive of respiratory infection (Table 3, Table S4). In multivariate logistic regression analysis, factors independently associated with respiratory infection were Child-Pugh C (odds ratio [OR] 3.1; 95% CI 1.4–6.7; $p < 0.01$), severe (grade III-IV) hepatic encephalopathy (OR 2.8; 95% CI 1.8–4.4; $p < 0.01$), nasogastric tube (OR 1.7; 95% CI 1.2–2.4; $p < 0.01$), orotracheal intubation for endoscopy (OR 2.6; 95% CI 1.8–3.8; $p < 0.01$) or esophageal balloon tamponade (OR 2.4; 95% CI 1.2–4.9; $p = 0.02$). This model showed adequate discrimination (AUROC = 0.74) and calibration (Hosmer-Lemeshow test $p = 0.31$). The estimated AUROC after bootstrapping was 0.70 (optimism = 0.04). We found no significant interaction between severe encephalopathy and the remaining variables included in the final model (likelihood-ratio test p value >0.10). Neither did we find collinearity between the use of nasogastric tube, orotracheal intubation for endoscopy or esophageal balloon tamponade. The same variables were found to be independently associated with respiratory infection in the sensitivity time-to-event analysis (Table S6).

Survival analysis: 6-week mortality

Two hundred and twenty of the patients (13.3%) died within 6 weeks of the index bleed. Of those, 61 (27.7%) had developed bacterial infection during their hospitalization. Bacterial

Table 3. Multivariate regression analysis of variables associated with development of bacterial and respiratory infection.

	Bacterial infection			Respiratory infection		
Variable	**OR**	**95% CI**	***p* value**	**OR**	**95% CI**	***p* value**
Child-Pugh A		Ref.			Ref.	
Child-Pugh B	2.2	1.3–1.7	<0.01			
Child-Pugh C	2.9	1.7–5.0	<0.01	3.1	1.4–6.7	<0.01
Severe (grade III-IV) hepatic encephalopathy	2.3	1.6-3.3	<0.01	2.8	1.8–4.4	<0.01
Nasogastric tube	1.4	1.1–1.8	0.01	1.7	1.2–2.4	<0.01
Orotracheal intubation for endoscopy	2.0	1.5–2.6	0.01	2.6	1.8–3.8	<0.01
Esophageal balloon tamponade				2.4	1.2–4.9	0.02

infection emerged as a predictor of mortality in the univariate (hazard ratio [HR] 1.7; 95% CI 1.3–2.3) but not in the multivariate analysis (Table S7). Independent factors related to 6-week mortality in the multivariate analysis were age (HR 1.1; 95% CI 1.1–1.2), Child-Pugh B (HR 2.2; 95% CI 1.1–4.4), Child-Pugh C (HR 7.6; 95% CI 3.8–15.1), active bleeding on endoscopy (HR 1.5; 95% CI 1.2–2.0), and shock on admission (HR 2.1; 95% CI 1.6–2.7), whereas pre-emptive TIPS reduced the mortality risk (HR 0.3; 95% CI 0.2–0.5).

Discussion

In this *post hoc* analysis of data compiled in a multicenter, observational study examining the role of pre-emptive TIPS in a large series of patients with AVB, we addressed the incidence of bacterial infections, predictive factors and adherence to antibiotic prophylaxis recommendations in real-world clinical practice. Our findings revealed that i) bacterial infection developed in close to 20% of patients with AVB despite the widespread use of recommended antibiotic prophylaxis; ii) respiratory infections were the most frequent, occurring early after admission; and iii) respiratory infection was associated with advanced liver disease, severe hepatic encephalopathy and the need for a nasogastric tube, orotracheal intubation or balloon tamponade.

Our study confirms that bacterial infection occurs in around one-fifth (~19%) of patients with AVB despite antibiotic prophylaxis. This residual rate of bacterial infection is similar to the 15% rate reported in other recent series of patients with AVB[8,17] and to the 14% rate detected in a meta-analysis by Bernard *et al.* addressing the efficacy of antibiotic prophylaxis in preventing bacterial infection in patients with cirrhosis.[1] These figures reflect the similar global efficacy of antibiotic prophylaxis over the last 20 years. Our results also indicate that current prophylaxis recommendations are far from optimal for preventing bacterial infection in patients with AVB, especially Child-Pugh B/C patients, who were most affected in our study. It should be underscored that bacterial infection is a risk factor for failure to control bleeding, rebleeding and death in patients with AVB, and efforts should be made to prevent this complication.[3,4] In effect, in our series, bacterial infection was found to be a risk factor for 6-week mortality in the univariate analysis, although it was not identified as an independent predictor.

Respiratory infection accounted for almost 50% of all the infections observed in our patients, similar to rates reported in other recently published series.[17] In contrast, spontaneous bacterial peritonitis, which was the most frequent infection encountered in the pre-prophylaxis era, only represented 8% of infections in our series, and likely reflects the high efficacy of current prophylaxis against gut microbes. Bacterial, and more specifically, respiratory infections were an early event during hospitalization (occurring at a median of 3 days), which strongly indicates an association between its appearance and the maneuvers used within the first hours of admission. Indeed, Child-Pugh C, severe (grade III-IV) hepatic encephalopathy, and maneuvers involving nasopharyngeal or orotracheal manipulation emerged as independent risk factors for respiratory infections. As respiratory infections were the most common bacterial infections observed, overlap between risk factors for all infections and respiratory infections is not surprising. Severe hepatic encephalopathy on admission was linked to a 3-fold increase in the risk of respiratory infection – this association remained unchanged when other variables (*e.g.* orotracheal intubation) were included in the final model, as shown by the absence of significant interactions. This suggests that the augmented risk of respiratory infection (probably related to aspiration pneumonia) conferred by severe encephalopathy was independent of a need for orotracheal intubation for endoscopy.

Despite the limited antibiotic susceptibility data available, we found that over 50% of our bacterial isolates were resistant to TGC, which is currently the most frequently used prophylactic agent in these patients. In the case of respiratory infections, this percentage was 65%. Further, the overall rate of resistance to quinolones was 46%. These figures fall within the range recently reported in Europe for patients with cirrhosis, and suggest an increasing prevalence of resistant strains.[17,18] Such concerns should make us revise current recommendations for the prophylaxis of bacterial infections in AVB. It is also important to remark that, in the case of respiratory infections, all patients with isolates sensitive to TGC or quinolones had at least 1 risk factor for respiratory infection other than Child-Pugh C class (data not shown). Besides a need to address bacterial susceptibility to antibiotics, this observation highlights that efforts are also needed to minimize identified risk factors to reduce the incidence of respiratory infections in these patients.

Our findings indicate that the rate of respiratory infections observed here could be reduced by minimizing maneuvers associated with an increased risk of these infections. We detected no collinearity among orotracheal intubation, nasogastric tubing and balloon tamponade, which suggests the independent behavior of each risk factor. Prophylactic intubation for endoscopy conferred an increased risk of respiratory infection. Twenty percent of intubations were recorded in patients with severe encephalopathy, and other intubations were probably related to massive bleeding. Our results are in agreement with those of recent meta-analyses in which systematic prophylactic orotracheal intubation to achieve a stable airway for ease of intervention was found to increase the risk of pneumonia and death in patients with upper gastrointestinal bleeding, particularly AVB, compared to endoscopy without intubation.[19,20] Our findings emphasize the importance of limiting orotracheal intubation to highly selected patients, such as those with a low level of consciousness or massive hemorrhage. The routine use of nasogastric aspiration is neither recommended, as so far the available evidence suggests no benefit for patient outcomes.[21] In uncontrolled variceal hemorrhage, balloon tamponade can be replaced with an expandable esophageal stent, which is more effective for the temporary control of bleeding and gives rise to a much lower rate of aspiration pneumonia.[22] The frequency of respiratory infections was lower in the prospective than in the retrospective cohort, which is partly related to a lower use of nasogastric tube or orotracheal intubation for endoscopy. Finally, an option that deserves special attention is the design of new regimens of antibiotic prophylaxis for use in specific subsets of patients with AVB.

Antibiotic prophylaxis recommendations were not followed in only 114 out of 1,770 patients without a bacterial infection at admission (6.4%), which is half the rate of non-adherence (12%) reported in a recent French audit on AVB for the same period.[23] It remains speculative whether these differences could be due to a higher number of academic centers involved in our study compared to the French one. Our study also indicates that TGC has become the standard of antibiotic prophylaxis in AVB, even in the Child-Pugh A and B patients of both cohorts. This result

contrasts with the information provided by the centers, which mostly reported adherence to the Baveno V consensus guidelines that recommend oral quinolones for most patients (reserving TGC for those with advanced cirrhosis).[6] However, considering the increasing prevalence of resistance to quinolones, a greater number of infections could have been expected in case of strict adherence to Baveno V consensus.[18] On the other hand, oral quinolones – a prophylaxis with demonstrated lower efficacy than TGC to prevent bacterial infection in this patient subset – were used in up to 12.9% of Child-Pugh C patients.[10]

The main strength of our study lies in its large sample size, involving 34 European academic centers with wide experience in the management of cirrhosis. Its main limitation is that it is a *post hoc* analysis of a study designed for other purposes. Another limitation was the lack of prespecified criteria of infection in the initial dataset, although infections were prospectively collected in the second cohort. This limitation was partly overcome by the retrospective re-assessment of bacterial infection diagnoses according to standard criteria. The rather low number of bacterial isolates with antibiogram information is another limitation of the study. Finally, a shorter interval between last data collection and the present would have increased the strength and timeliness of the study.

Taken together, our data identified a group of patients with cirrhosis and AVB at special risk of developing respiratory bacterial infection early after admission despite receiving recommended antibiotic prophylaxis. This risk is particularly high in patients with severe hepatic encephalopathy on admission and was extended to patients undergoing orotracheal intubation for endoscopy, receiving a nasogastric tube or requiring balloon tamponade. Consequently, we believe these procedures should be minimized when possible. Physicians should actively search for a respiratory infection in cases of clinical deterioration of patients with any of these risk factors, especially severe encephalopathy. Tailoring antibiotic prophylaxis to patients with risk factors for respiratory infection not covered by current recommendations remains a relevant topic for further research.

Abbreviations

ACLF, acute-on-chronic liver failure; AVB, acute variceal bleeding; HR, hazard ratio; INR, international normalized ratio; OR, odds ratio; TGC, third-generation cephalosporins; TIPS, transjugular intrahepatic portosystemic shunt.

Financial support

Supported by grants from the Spanish Ministry of Science and Innovation (SAF-2016-75767-R to JC.G-P, SAF 2017-86343-R awarded to A.A, Instituto de Salud Carlos III PIE 15/00027 to JC.G-P, PI17/00398 to V.H.G, PI18/01901 to R.B and PI20/01302 to A.A, and Commissioner for Universities and Research of the Generalitat de Catalunya (AGAUR SGR 2017 awarded to JC.G-P). CIBEREHD is funded by the Instituto de Salud Carlos III with grants cofinanced by the European Development Regional Fund "A way to achieve Europe" (EDRF).

Conflicts of interest

Juan Carlos Garcia-Pagan has consultant fees for GORE, Shionogi and Cook grants from GORE and Novartis. Álvaro Giráldez has served as speaker for Gore.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

JM, VHG, JB, JCGP and AA contributed to the study concept and design. JM, ERS, LT, and AA contributed to the analysis and interpretation of data and drafted the manuscript. All authors contributed to the acquisition of data. JM, VHG, ERS, LT, JB, JCGP and AA contributed to the critical revision of the manuscript for important intellectual content. All authors approved the final manuscript prior to submission.

Data availability statement

Data were recorded, encrypted and managed using the Research Electronic Data Capture (REDcap) system. The access to this database was private and limited to the authors and investigators of each hospital.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2021.03.026.

References

[1] Bernard B, Grange JD, Khac EN, Amiot X, Opolon P, Poynard T. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. Hepatology 1999 Jun;29(6):1655–1661. PubMed PMID: 10347104.

[2] Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila FI, Soares-Weiser K, Uribe M. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. Cochrane database Syst Rev 2010 Sep 8;(9):CD002907. PubMed PMID: 20824832. Pubmed Central PMCID: 7138054.

[3] Bernard B, Cadranel JF, Valla D, Escolano S, Jarlier V, Opolon P. Prognostic significance of bacterial infection in bleeding cirrhotic patients: a prospective study. Gastroenterology 1995 Jun;108(6):1828–1834. PubMed PMID: 7768389.

[4] Goulis J, Armonis A, Patch D, Sabin C, Greenslade L, Burroughs AK. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. Hepatology 1998 May;27(5):1207–1212. PubMed PMID: 9581672.

[5] Chavez-Tapia NC, Barrientos-Gutierrez T, Tellez-Avila F, Soares-Weiser K, Mendez-Sanchez N, Gluud C, et al. Meta-analysis: antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding - an updated cochrane review. Aliment Pharmacol Ther 2011 Sep;34(5):509–518. PubMed PMID: 21707680.

[6] de Franchis R, Baveno VIF. Expanding consensus in portal hypertension: report of the Baveno VI consensus workshop: stratifying risk and individualizing care for portal hypertension. J Hepatol 2015 Sep;63(3):743–752. PubMed PMID: 26047908.

[7] Electronic address eee, European Association for the Study of the L European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol 2018 Aug;69(2):406–460. PubMed PMID: 29653741.

[8] Tandon P, Abraldes JG, Keough A, Bastiampillai R, Jayakumar S, Carbonneau M, et al. Risk of bacterial infection in patients with cirrhosis and acute variceal hemorrhage, based on child-pugh class, and effects of antibiotics. Clin Gastroenterol Hepatol: Off Clin Pract J Am Gastroenterological Assoc 2015 Jun;13(6). 1189-11896 e2. PubMed PMID: 25460564.

[9] Rimola A, Salmeron JM, Clemente G, Rodrigo L, Obrador A, Miranda ML, et al. Two different dosages of cefotaxime in the treatment of spontaneous bacterial peritonitis in cirrhosis: results of a prospective, randomized, multicenter study. Hepatology 1995 Mar;21(3):674–679. PubMed PMID: 7875666.

[10] Fernandez J, Ruiz del Arbol L, Gomez C, Durandez R, Serradilla R, Guarner C, et al. Norfloxacin *vs.* ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. Gastroenterology 2006 Oct;131(4):1049–1056. quiz 285. PubMed PMID: 17030175.

[11] Hernandez-Gea V, Procopet B, Giraldez A, Amitrano L, Villanueva C, Thabut D, et al. Preemptive-TIPS improves outcome in high-risk variceal bleeding: an observational study. Hepatology 2019 Jan;69(1):282–293. PubMed PMID: 30014519.

[12] de Franchis R, Baveno VF. Revising consensus in portal hypertension: report of the Baveno V consensus workshop on methodology of diagnosis

and therapy in portal hypertension. J Hepatol 2010 Oct;53(4):762–768. PubMed PMID: 20638742.
[13] Horan TC, Andrus M, Dudeck MA. CDC/NHSN surveillance definition of health care-associated infection and criteria for specific types of infections in the acute care setting. Am J Infect Control 2008 Jun;36(5):309–332. PubMed PMID: 18538699.
[14] Fernandez J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, et al. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut 2018 Oct;67(10):1870–1880. PubMed PMID: 28847867.
[15] von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol 2008 Apr;61(4):344–349. PubMed PMID: 18313558.
[16] Marcoulides KM, Raykov T. Evaluation of variance inflation factors in regression models using latent variable modeling methods. Educ Psychol Meas 2019 Oct;79(5):874–882. PubMed PMID: 31488917. Pubmed Central PMCID: 6713981.
[17] Lee S, Saxinger L, Ma M, Prado V, Fernandez J, Kumar D, et al. Bacterial infections in acute variceal hemorrhage despite antibiotics-a multicenter study of predictors and clinical impact. United Eur Gastroenterol J 2017 Dec;5(8):1090–1099. PubMed PMID: 29238587. Pubmed Central PMCID: 5721982.
[18] Fernandez J, Bert F, Nicolas-Chanoine MH. The challenges of multi-drug-resistance in hepatology. J Hepatol 2016 Nov;65(5):1043–1054. PubMed PMID: 27544545.
[19] Almashhrawi AA, Rahman R, Jersak ST, Asombang AW, Hinds AM, Hammad HT, et al. Prophylactic tracheal intubation for upper GI bleeding: a meta-analysis. World J meta-analysis 2015 Feb 26;3(1):4–10. PubMed PMID: 25741509. Pubmed Central PMCID: 4346140.
[20] Chaudhuri D, Bishay K, Tandon P, Trivedi V, James PD, Kelly EM, et al. Prophylactic endotracheal intubation in critically ill patients with upper gastrointestinal bleed: a systematic review and meta-analysis. JGH Open: Open Access J Gastroenterol Hepatol 2020 Feb;4(1):22–28. PubMed PMID: 32055693. Pubmed Central PMCID: 7008165.
[21] Karakonstantis S, Tzagkarakis E, Kalemaki D, Lydakis C, Paspatis G. Nasogastric aspiration/lavage in patients with gastrointestinal bleeding: a review of the evidence. Expert Rev Gastroenterol Hepatol 2018 Jan;12(1):63–72. PubMed PMID: 29098897.
[22] Escorsell A, Pavel O, Cardenas A, Morillas R, Llop E, Villanueva C, et al. Esophageal balloon tamponade versus esophageal stent in controlling acute refractory variceal bleeding: a multicenter randomized, controlled trial. Hepatology 2016 Jun;63(6):1957–1967. PubMed PMID: 26600191.
[23] Thabut D, Pauwels A, Carbonell N, Remy AJ, Nahon P, Causse X, et al. Cirrhotic patients with portal hypertension-related bleeding and an indication for early-TIPS: a large multicentre audit with real-life results. J Hepatol 2017 Dec 14;68(1):73–81. PubMed PMID: 28918131.