Determinants of clinical response to empirical antibiotic treatment in patients with cirrhosis and bacterial and fungal infections—Results from the ICA “Global Study” (EABCIR-Global Study)

Hepatology Publish Ahead of Print
DOI:10.1097/HEP.0000000000000653

Determinants of clinical response to empirical antibiotic treatment in patients with cirrhosis and bacterial and fungal infections- Results from the ICA 'Global study' [EABCIR-Global Study]

Rakhi Maiwall[1,#], Salvatore Piano[2,#], Virendra Singh[3], Paolo Caraceni[4], Carlo Alessandria[5], Javier Fernandez[6–9], Elza Cotrim Soares[10], Dong Joon Kim[11], Sung Eun Kim[12], Monica Marino[13], Julio Vorobioff[14], Rita de Cassia Ribeiro Barea[15], Manuela Merli[16], Laure Elkrief[17], Victor Vargas[18], Aleksander Krag[19], Shivaram Prasad Singh[20], Laurentius Adrianto Lesmana[21], Claudio Toledo[22], Sebastian Marciano[23], Xavier Verhelst[24], Florence Wong[25], Nicolas Intagliata[26], Liane Rabinowich[27], Luis Colombato[28], Sang Gyune Kim[29], Alexander Gerbes[30], Francois Durand[31], Juan Pablo Roblero[32], Kalyan Ram Bhamidimarri[33], Marina Maevskaya[34], Eduardo Fassio[35], Hyoung Su Kim[36], Jae Seok Hwang[37], Pere Gines[6,7,8], Tony Bruns[38,39], Adrian Gadano[23], Paolo Angeli[2], Shiv Kumar Sarin[1] on behalf of the International Club of Ascites Global Study Group*

Affiliations

1- Department of Hepatology, Institute of Liver and Biliary Sciences, New Dehli, India

2- Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine – DIMED, University of Padova, Padova, Italy
3- Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India
4- Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy
5- Division of Gastroenterology and Hepatology, Città della Salute e della Scienza Hospital, University of Turin, Turin, Italy
6- Liver ICU, Liver Unit, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain;
7- Institut d'Investigacions Biomèdiques August-Pi-Sunyer (IDIBAPS);
8- Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHED);
9- European Foundation of Chronic Liver Failure (EF-Clif), Barcelona
10- Gastroenterology Division, Medicine Department, Faculty of Medical Sciences, University of Campinas (UNICAMP). Campinas, São Paulo, Brazil
11- Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, South Korea
12- Division of Gastroenterology and Hepatology, Department of Internal Medicine, Hallym Sacred Heart Hospital, College of Medicine, Hallym University, Anyang city, Republic of Korea
13- Liver Unit, Hospital Dr. Carlos B. Udaondo, Buenos Aires, Argentina
14- Rosario University Medical School, Rosario, Argentina
15- Serviço de Hepatologia do HRMS, Hospital Regional de Mato Grosso Do Sul-HRMS, Campo Grande, Brazil

16- Gastroenterology and Hepatology Unit, Department of Translational and Precision Medicine, Sapienza University of Rome, Rome, Italy

17- Service de Transplantation, Service d'Hépato-gastroentérologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland

18- Liver Unit, Department of Internal Medicine, Hospital Vall d'Hebron, Universitat Autònoma de Barcelona, CIBERehd, Barcelona. Spain

19- Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark

20- Department of Gastroenterology, S.C.B. Medical College, Cuttack, India

21- Digestive Disease and Oncology Centre, Medistra Hospital, Jakarta, Indonesia.

22- Gastroenterology Unit, Hospital Valdivia, Universidad Austral de Chile, Valdivia, Chile.

23- Liver Unit and Department of Research, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina

24- Department of Gastroenterology and Hepatology, Ghent University Hospital, Ghent, Belgium

25- Division of Gastroenterology, Department of Medicine, University of Toronto, Ontario, Canada

26- Division of Gastroenterology and Hepatology, University of Virginia, Charlottesville, Virginia, USA

27- Liver Unit, Department of Gastroenterology, Tel-Aviv Medical Center and Tel-Aviv University, Tel-Aviv, Israel

28- Gastroenterology Department, Buenos Aires British Hospital, Argentine Catholic University (UCA), Buenos Aires, Argentina

29- Department of Internal Medicine, Soonchunhyang University Bucheon Hospital, Bucheon, Republic of Korea.

30- Department of Medicine II, Liver Centre Munich, University Hospital, LMU Munich, Germany

31- Hepatology & Liver Intensive Care, Hospital Beaujon, Clichy, University Paris Diderot, Paris, France

32- Departamento de Medicina, Universidad de Chile Campus Centro, Hospital Clínico San Borja Arriarán, Santiago, Chile

33- Division of Gastroenterology/Hepatology, University of Miami, Miami, FL, USA

34- University of Moscow, Moscow, Russia

35- Liver Unit, Hospital Nacional Prof. Alejandro Posadas, El Palomar, Buenos Aires, Argentina

36- Department of Internal Medicine, Hallym University Kangdong Sacred Heart Hospital, Seoul, Republic of Korea.

37- Department of Internal Medicine, Keimyung University School of Medicine, Daegu, Korea.

38- Department of Internal Medicine IV, Jena University Hospital, Jena, Germany

39- Department of Medicine III, University Hospital RWTH Aachen, Aachen, Germany

Rakhi Maiwall and Salvatore Piano share co-first Authorship.

* Collaborators of the International Club of Ascites Global Study Group are listed at the end of the manuscript.

Corresponding Author:

Shiv Kumar Sarin, M.B.B.S., M.D., D.M. Department of Hepatology, Institute of Liver and Biliary Sciences, D1 Vasant Kunj, New Delhi 110070, India, E-mail: sksarin@ilbs.in, Tel.: +91-11-46300000

Paolo Angeli, M.D., Ph.D. Unit of Internal Medicine and Hepatology (UIMH), Department of Medicine – DIMED, University of Padova. Via Giustiniani 2, 35100 Padova, Italy. Telephone: 0039/0498212004, Fax: 0039/0498218676, E-mail: pangeli@unipd.it

Author Contributions:

Study concept: RM, SP, PA, SKS, VS, AdGa, AK

Study design: PA, SKS, AdGa, AK, SP, JF, TDB

Enrolment of patients and data collection: SP, VS, PC, RM, CA, JF, ES, DJK, SEK, MoMa, JV, RRB, MaMe, LE, VV, AK, SPSi, LL, CT, SM, XV, FW, NI, LR, LAC, SGK, AlGe, FD, JPR, KB, TB, MaMa, EF, HSK, JSH

Analysis and interpretation of data: RM, SP, PA, SKS, VS, AdGa, AK, FD

Drafting of the manuscript: RM, SP, PA, VS, SKS, JF

Critical revision for important intellectual content: PC, CA, JF, FW, NI, PG, AdGa, SM, AG, AK, TB, MM.

Abbreviations: MDR, multidrug-resistant; XDR- extensively drug-resistant; ICA, International club of ascites; ICU, intensive care unit; RRT, renal replacement therapy, interquartile range (p25-p75); sHR, subdistribution hazard ratio; CI, confidence interval; ICU, intensive care unit; MELD, model for end-stage liver disease; CTP, Child-Pugh; SIRS, systemic inflammatory response syndrome; CRP, C-reactive protein; EASL, European

association for the study of the liver; OR, odd's ratio; ACLF, Acute on Chronic Liver Failure; MELDNa, model for end-stage liver disease sodium; qSOFA, quick sequential organ failure assessment, IL-6, interleukin-6; SBP, spontaneous bacterial peritonitis; SOFA, sequential organ failure assessment.

Funding: The study was supported by a grant from the Italian Ministry of Education, University and Research (DOR1678487/16), and by a grant of the ISCIII, Spain (PI16/00885.)

This work was presented at the International Liver Congress in 2018

Conflicts of Interest:

Salvatore Piano consults for Plasma Protein Therapeutics Association and Resolution Therapeutics. He advises Mallinckrodt. Paolo Caraceni advises, is on the speakers' bureau, and received grants from Takeda. He advises and is on the speakers' bureau for CSL Behring. He is on the speakers' bureau and received grants from Grifols. Victor Vargas consults for GENFIT. He advises Cellaïon. He received grants from Intercept. Florence Wong consults and received grants from Ocelot Bio. She received grants from Mallinckrodt. Francois Durand consults for Eli Lilly. He received grants from Biotest. Kalyan Ram Bhamidimarri advises Albireo, eGenesis, and Mallinckrodt. Pere Gines consults and received grants from Ferring, Gilead, and Grifols. He consults for Behring, Intercept, Martin, Promethera, Sequana, and RallyBio. He received grants from Mallinckrodt. Tony Bruns consults for Grifols, Intercept, and Sofi. He is on the speakers' bureau for CSL Behring, Falk Foundation, Gore, and Merck. Paolo Angeli is on the speakers' bureau and received grants from CSL Behring. He consults for BioVie, BioMarin, and GENFIT. He is on the speakers' bureau for Grifols and Kedrion. The remaining authors have no conflicts to report.

Number of Figures: 4

Number of Tables: 4

Supplementary Tables: 5

Supplementary Figure-1

Abstract Word count- 273/275

Manuscript word count: 3688

Keywords : MDR, EDR, Sepsis, ACLF, SIRS, AKI

Graphical abstract

GA1

ABSTRACT

Background and Aims: The administration of an appropriate empirical antibiotic treatment is essential in cirrhosis and severe bacterial infections. We aimed to investigate the predictors of clinical response of empirical antibiotic treatment in a prospective cohort of patients with cirrhosis and bacterial and fungal infections included in the International Club of Ascites(ICA) “Global Study”

Methods: Hospitalized patients with cirrhosis and bacterial/fungal infection were prospectively enrolled at 46 centers. Clinical response to antibiotic treatment was defined according to changes in markers of infection/inflammation, vital signs, improvement of organ failure, and results of cultures.

Results: From October 2015 to September 2016, 1302 patients were included at 46 centres. A clinical response was achieved only 61% of cases. Independent predictors of lack of clinical response to empirical treatment were C-reactive protein (OR=1.16;95%CI=1.02–1.31),blood leukocyte count (OR=1.39;95%CI=1.09–1.77), serum albumin (OR=0.70;95%CI=0.55–0.88), nosocomial infections (OR=1.96;95%CI=1.20–2.38), pneumonia (OR=1.75;95%CI=1.22–2.53),and ineffective treatment according to antibiotic susceptibility test (OR=5.32;95%CI=3.47-8.57). Patients with lack of clinical response to first-line antibiotic treatment had a significantly lower resolution rate of infections (55%vs96%;p<0.001), a higher incidence of second infections (29%vs15%;p<0.001),shock

(35%vs7%;p<0.001) and new organ failures (52%vs19%;p<0.001) than responders. Clinical response to empirical treatment was an independent predictor of 28-day survival (sHR=0.20;95%CI=0.14-0.27). **Conclusion:** Four out of 10 patients with cirrhosis do not respond to the first-line antibiotic therapy, leading to lower resolution of infections and higher mortality. Broader-spectrum antibiotics and strategies targeting systemic inflammation may improve prognosis in patients with high degree of inflammation, low serum albumin levels and severe liver impairment.

Lay Summary

In a large, hospitalized cohort of patients with cirrhosis and infection at 46 multinational sites, lack of clinical response to empirical antibiotics was noted in four out of each ten patients. The non-response varied according to the geographic area and prevalence of multidrug/extensively drug resistant organisms with lowest response noted in the Asian countries particularly the Indian subcontinent. Severe systemic inflammation, as indicated by high white cell count, serum C-reactive protein levels low serum albumin concentration, presence of pneumonia, nosocomial infection and ineffective treatment were independent predictors of lack of clinical response to empirical antibiotic regimens. Patients with non-response to empirical regimen had worse clinical outcomes and this was identified as an independent predictor of higher in-hospital and 28-day mortality. Additional care and novel antibiotic protocols are an unmet need in cirrhosis patients, especially those with higher degree of inflammation, lower serum albumin levels and more severe liver impairment.

INTRODUCTION

Patients with cirrhosis are predisposed to develop bacterial infections[1]. Infections are seen almost two to six-fold higher in patients with cirrhosis compared to non-cirrhotics[1,2]. Infections lead to higher mortality and cause acute decompensation and organ failures[2,3]. Urinary tract infections and spontaneous bacterial peritonitis are the most common infections noted in these patients. However, with the progression of the disease, pneumonia is the most common infection in patients admitted to the intensive care unit[4]. Appropriate management of bacterial infections could be associated with improved outcomes[1,2]. Prior studies performed in patients with septic shock have shown the significance of delay in initiating the appropriate antibiotic. Each hour of delay is associated with increased mortality in these patients[5]. Therefore, initiating effective and timely antibiotics is considered a cornerstone of managing patients with severe sepsis and septic shock[5].

An alarming surge in the incidence of multidrug-resistant bacterial (MDR) infection has been reported in several studies and confirmed in a Global study[2]. We showed a striking increase in the prevalence of multidrug and extensively drug-resistant (XDR) pathogens with marked regional variation. Therefore, early and effective antibiotic treatment is imperative to prevent antibiotic failure and the development of secondary infections and prolonged ICU, and hospital stay. In the same paper, we reported an ineffective initial antibiotic as an independent predictor of worse outcomes. The empirical antibiotic regimens vary across geographic regions and should be governed by the local epidemiological pattern of microbial resistance. Most of the studies in the field have focused on epidemiology and impact of antibiotic resistance in cirrhosis. However, several host factors can influence clinical response to empirical antibiotic treatment. Currently, there is a lack of studies investigating predictors of clinical response to antibiotic treatment in patients with cirrhosis.

Therefore, in this large multicentric-multinational study, we aimed to investigate the predictors of clinical response to the empirical antibiotic treatment and its impact on clinical outcomes in patients with cirrhosis hospitalized with bacterial or fungal infections.

METHODS

The Global Study was conducted as a prospective cohort study which included patients with cirrhosis who were hospitalized with bacterial or fungal infections. The current study is a post-hoc analysis of the Global survey data conducted by the International Club of Ascites (ICA) from October 2015 to September 2016 [2]. This investigation included fifteen centres from the Asia-Pacific, fifteen from Europe, eleven from South America, and five from North America. We obtained institutional Ethics Committee approval from each centre and written informed consent from all patients included in the study. All enrolled patients were followed for 28-days or until discharge, death, or liver transplantation. We performed a record of demographics, relevant past clinical and medical history, microbiologic data, initial antibiotic, escalation, and duration of antibiotic treatment for all included patients. We also recorded the inflammatory markers, hemodynamic and liver disease severity. During follow-up, we recorded the development of new infections and organ failures[6] (use of vasopressor, renal replacement therapy, mechanical ventilation) and the need to transfer to the ICU. Microbiological data and antibiotic susceptibility testing were obtained for all enrolled patients at baseline and on developing a second infection during hospitalization. Data were collected at each participating centre using an electronic case report form (Research Electronic Data Capture Software REDCap) hosted at the Department of Medicine of the University of Padova, Italy. Data were prospectively collected in the electronic case report form for all included patients. At each participating center, management of infection was done following in accordance to the evidence-based protocols.

Patients

Patients aged more than 18 years, meeting the diagnosis of cirrhosis, and admitted with a diagnosis of a bacterial or fungal infection or developed during hospitalization were included in the study. We defined cirrhosis based on clinical (presence of ascites, jaundice, splenomegaly, etc.), biochemical, imaging (ultrasonography, computed tomography, or magnetic resonance imaging showing features of chronic liver disease), and endoscopic evidence of varices or liver histology (when available).

We excluded patients with hepatocellular carcinoma beyond the Milan criteria or extrahepatic malignancy; patients with severe comorbid diseases associated with poor outcomes (like congestive heart failure; New York Heart Association stage 3, chronic obstructive pulmonary disease, chronic kidney disease requiring renal replacement therapy; RRT); human immunodeficiency virus, patients on immunosuppressive drugs other than corticosteroids for the treatment of severe acute alcoholic hepatitis; and those with an inability to provide written informed consent.

Definitions

Microbiological effective treatment was defined based on the microbiological efficacy of the empirical treatment. The microbiological efficacy of the empirical antibiotic treatment was defined as in-vitro susceptibility of the isolated strain to at least one of the antibiotics administered.[2]

Clinical response was defined by the attending physician based on a combination of clinical and laboratory criteria in accordance with the previously published criteria:[7]

- Clinical criteria: an improvement in signs/symptoms of infection/inflammation (fever, systemic inflammatory response syndrome) and improvement in organ failures.

- Laboratory criteria: reduction in white blood leukocyte count, C-reactive protein, decrease in ascitic fluid PMN counts > 25% after 48 hours of antibiotic treatment in patients with spontaneous bacterial peritonitis.

New infections: were defined as infection developing separate from the first infection during the same hospital stay at a different site. The criteria used for defining second infection were the same as the first[2].

The details of other definitions were in accordance with the previously published criteria. (see supplementary information, http://links.lww.com/HEP/I128).

Statistical Methods

We provided descriptive statistics in the form of the median [interquartile range (p25-p75)] for non-normally distributed data and mean ± standard deviation for normally distributed data and number (%) for qualitative data. Continuous variables were compared using Mann–Whitney U-test for non-normal data and by Student's t-test for normally distributed continuous data. Categorical variables were compared using the Fisher Exact-test or Pearson's Chi-square test.

For predicting the risk factors for lack of clinical response to empirical antibiotic therapy and 28-day mortality, we performed univariate and multivariate binary logistic regression analysis using stepwise backward logistic regression analysis. Results were expressed as odds ratios (OR) and their 95% confidence intervals (95% CI)

An analysis of in-hospital and 28-day mortality was performed using a competing risk approach (liver transplantation was considered a competing risk event for death). A proportional hazard model with the Fine and Gray method was used to identify mortality predictors. Results were expressed as p-value, subdistribution hazard ratios (sHR), and their 95% CI. The Akaike Information criterion was used to get the most parsimonious model. We

did not include events that occurred during hospitalization [second infections, new organ failures, new onset of septic shock, transfer to intensive care unit (ICU) etc.] in the multivariate analysis of survival. When we included liver disease scores in the model, we excluded their components to avoid multicollinearity. Similarly, variables with a correlation>0.5 in the model were not included to avoid multicollinearity. The non-normally distributed continuous variables were log transformed for inclusion in the multivariate models. All tests were 2-tailed, and $p < 0.05$ was considered significant. We performed the statistical analysis using SPSS 24 (IBM Corp, Armonk, NY) and R 3.5.0 (R Foundation, Vienna, Austria).

RESULTS

We enrolled 1,302 hospitalized patients with cirrhosis and infection at 46 multinational sites. As previously reported, most of the included patients were males (69%) with a mean age of 57 ± 13 years. Alcohol was the most common etiology of liver cirrhosis (54%). Patients were sick with high Model for End-stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores (21 ± 8 and 10 ± 2 points, respectively). Four-hundred and five patients (31.1%) had systemic inflammatory response syndrome (SIRS). Forty-eight percent of patients (n=628) presented with community-acquired infections, while the remaining had either healthcare associated (n=338; 26%) or nosocomial episodes (n=336; 26%). The most common type of infection was spontaneous bacterial peritonitis in 354 (27%) patients, followed by urinary tract infection in 289 (22%) and pneumonia in 242 (19%). Notably, as previously reported, MDR pathogens were observed in 253 (19%) patients, while 62 (5%) patients had XDR pathogens. The prevalence of MDR and XDR pathogens showed a huge regional variation, with the highest prevalence noted in the Asia Pacific region.

Risk factors for lack of clinical response to the empirical antibiotic regimen

Seven hundred and eighty-eight (61%) patients had a clinical response to the empirical antibiotic regimen. **Table 1** summarizes the comparison of the baseline factors according to the clinical response to the empirical antibiotic regimen. The median time to antibiotic response was median 4 [interquartile range (p25-p75) 3-7] days. Patients with non-response to the empirical antibiotic regimen were younger (55± 13 vs. 57±13 years; p=0.006), predominantly males (74% vs. 66%; p=0.001) had higher MELD score (23±8 vs. 20±7; p<0.001), higher prevalence of SIRS (43% vs. 32%; p<0.001) and higher serum C-reactive protein levels at enrolment (CRP) [(46 (20-89) vs. 30 (12-64) mg/l; p<0.001]. The prevalence of extrahepatic organ failures including renal (28% vs. 17%; p<0.001), circulatory (19% vs. 10%; p<0.001), pulmonary (12% vs. 4%; p<0.001) and cerebral (18% vs. 6%; p<0.001) was significantly higher in patients with lack of clinical response to empirical antibiotic regimen. We also observed a difference in the acute on chronic liver failure (ACLF) grades in patients with lack of clinical response, showing these latter patients' higher proportions of both, overall ACLF and ACLF grade 2-3 (p<0.001). These patients more often required mechanical ventilation (10% vs. 3%; p<0.001) and vasopressors for septic shock (19% vs. 10%; p<0.001).

Interestingly, apart from the host factors, the microbiologic profile, site of infection acquisition and type of infection were also different between groups. A higher prevalence of pneumonia (26% vs. 14%; p<0.001), nosocomial episodes (31% vs. 23%; p=0.005), culture-positive infections (p=0.06) and infections caused by MDR (30% vs. 13%; p<0.001) or XDR (8% vs. 3%; p<0.001) pathogens was observed in patients with lack of clinical response to empirical treatment. A significant difference was observed in the spectrum of infections in patients with lack of clinical response. Patients without clinical response had more frequently

infections caused by gram-negative organisms (64% vs. 54%) or fungi (5% vs. 2%) (p<0.001) [Table S1, http://links.lww.com/HEP/I128 and S2, http://links.lww.com/HEP/I128] We also explored the type of empirical antibiotic treatment in patients with or without ACLF at diagnosis of infection (as a marker of sickness). Patients with ACLF more frequently received broad spectrum treatments (carbapenems, glycopeptides and antifungals). [Table S3, http://links.lww.com/HEP/I128] As expected, stratification by choice of empirical regimen showed a lower proportion of patients receiving an *in vitro,* effective regimen [30% vs. 47%; p<0.001] and lower adherence to European association for the study of the liver (EASL) recommendations [p<0.001]. The majority of these patients received third generation cephalosporins (40%) followed by classical beta-lactams plus β-lactamases inhibitors (28%) and Piperacillin-Tazobactam (24%). Interestingly, carbapenems were used in only 16% of patients as an empirical regimen. We found, among the 282 patients with no clinical response to first-line antibiotic treatment, the resolution of infections was achieved by an escalation of empirical antibiotic treatment in 274 (97.1%) patients. Only in 8 (2.8%) patients the resolution was achieved without escalating the first-line treatment. We observed that effective antibiotic rather than the number of antibiotics in the empirical regimens was associated with a clinical response to antibiotic treatment. (Figure S1, http://links.lww.com/HEP/I128)

We performed a multivariate analysis to determine the independent factors associated with lack of clinical response to the empirical antibiotic treatment. The severity of systemic inflammation represented by higher white blood leukocyte count (OR=1.39, 95%CI=1.09-1.77) and serum C-reactive protein (OR=1.16, 95%CI=1.02-1.31) were independent predictors of lack of clinical response to initial antibiotic treatment. An *in-vitro* ineffective initial antibiotic regimen was associated with the highest odds of treatment failure (OR=5.45, 95%CI=3.47-8.57). The presence of ACLF grade 3 [OR=4.08, 95%CI=2.36-7.05] and grade 2 [OR=1.58, 95%CI=1.04-2.41] compared to no ACLF (as ref. category OR=1) were

associated with a lack of clinical response to the empirical antibiotic regimen. Finally, nosocomial infection (OR=1.69, 95%CI=1.20-2.38), pneumonia (OR=1.75, 95%CI=1.22-2.53), and lower serum albumin levels (OR=0.70, 95%CI=0.55-0.88) were identified as independent factors predicting lack of response to the empirical antibiotic strategies (**Table 2, Figure 1**).

We performed a sensitivity analysis to understand the factors associated with lack of clinical response based on culture-positive and culture-negative infections. In both groups, lower serum albumin and severity of ACLF grade were risk factors, however, markers of systemic inflammation i.e., CRP and leucocyte counts, nosocomial infection and adherence to EASL regimen were risk factors for lack of clinical response in culture-negative infections while presence of pneumonia and ineffective first line antibiotic regimen were risk factors for lack of clinical response in culture-positive infections.

Comparison of clinical outcomes according to the clinical response to the empirical antibiotic regimen

Patients who had lack of clinical response to empirical antibiotic regimens had worse clinical outcomes. Among the patients transplanted during the hospitalization (n= 35), three patients were transplanted on day 5 from diagnosis of infection and all of them were considered to have had a clinical response. A higher proportion of these patients developed second infections during hospital stay (29% vs. 15%; p<0.001), had lower rates of infection resolution (55% vs. 96%; p<0.001) and increased transfer to the ICU (46% vs. 18%; p<0.001). These patients more often developed renal failure (32% vs. 9%; p<0.001), required RRT (19% vs. 4%; p<0.001), mechanical ventilation (27% vs. 5%; p<0.001) and developed septic shock (35% vs. 7%; p<0.001). These patients had prolonged hospital stay (p<0.001), higher in-hospital (44% vs. 9%; p<0.001) and 28-day mortality (47% vs. 11%; p<0.001) (**Table 3, Figure 2**).

Predictors of in-hospital and 28-day mortality

Comparison of baseline characteristics according to the survival status is shown in Table S4, http://links.lww.com/HEP/I128. On multivariate analysis, older age (OR=1.02, 95%CI=1.01-1.03), a higher MELDNa score (OR=1.58, 95%CI=1.05-1.10), presence of ACLF (OR=1.61, 95%CI=1.14-2.18), higher quick sequential organ failure assessment (qSOFA) (OR=1.33, 95%CI=0.99-1.78), white blood cell count (OR=1.52, 95%CI=1.15-2.01) and higher serum CRP levels (OR=1.18, 95% CI=1.03-1.35) were independent predictors of in-hospital mortality. We also found the clinical response to the empirical antibiotic regimen (OR=0.22, 95%CI=0.16-0.30) as an independent predictor of reduced mortality. The same factors predicting in-hospital mortality were also associated with 28-day mortality. (**Table 4, Figure 3**).

Of the total cohort, 460 (35.3%) patients had a diagnosis of ACLF. Of these patients, 176 (38.2%) had in-hospital mortality, while 180 (39.1%) died at 28-days. We performed a subgroup analysis of the predictors of in-hospital and 28-day mortality in these patients. We created two multivariable models wherein we included the CLIF-C ACLF score excluding their components age, leukocytes, scores of liver diseases and organ failures). CLIF-C ACLF score was identified as an independent predictor of both in-hospital and 28-day mortality. (Table S5, http://links.lww.com/HEP/I128) Apart from the CLIF-C ACLF score, higher CRP, and no clinical response to antibiotic treatment were identified as independent predictors of both in-hospital and 28-day mortality in ACLF patients. Lower serum albumin predicted in-hospital but not 28-day mortality in ACLF patients with infections.

Clinical response to the empirical antibiotic treatment according to geographic area

We observed a significant variation in the clinical response to the empirical antibiotic treatment according to the geographic area. Notably, it was lowest in Asia-pacific particularly

in the Indian subcontinent (n=76; 30%) followed by other Asian countries (n= 98; 59%). Response was highest in North America (n=53; 77%) and North Europe (n=105;77%) with intermediate rates in South America (n=169; 67%) and South Europe (n=287; 67%). [Table S6, http://links.lww.com/HEP/I128, **Figure 4, Figure S2).** This finding was mainly related to the rate of MDR or XDR bacterial infections.

Discussion

The current study is a post-hoc analysis of the data collected in the sizeable global study. The key finding of the study is that only 60% of patients respond to the empirical antibiotic regimen in clinical practice. We identified a combination of severity of liver disease, the host response, the strategy of antibiotic administration and the characteristics of the infecting microbe as key risk factors associated with lack of clinical response to empirical antibiotics. The severity of systemic inflammation, higher white blood counts, CRP levels, and lower serum albumin were independent predictors of a lack of clinical response to the empirical strategies. Besides, pneumonia as the primary site of infection and nosocomial acquisition were associated with higher risk of no clinical response. These patients more often received ineffective first-line antibiotic regimens. As expected, patients with lack of clinical response to empirical regimens had worse clinical outcomes, higher incidence of second infections, lower resolution of infection and increased transfer to ICU for organ support. The lack of clinical response was also an independent predictor of higher in-hospital and 28-day mortality. The response varied according to the geographic area with lowest clinical response noted in the Asian countries particularly the Indian subcontinent, feature mostly related to the huge prevalence of antibiotic resistant infections observed in these areas.

This study provides several novel findings that help to understand the clinical response to empirical antibiotic treatment in patients with cirrhosis and infection. Among infections-

related factors, as expected, the *in vitro* microbiological efficacy of empirical antimicrobials against the bacteria responsible for infection was the most important determinant of clinical response, highlighting the importance of performing cultures at the diagnosis of infection (blood, urine, ascites, respiratory samples, etc.) to guide empirical antibiotic strategies. The presence of MDR bacterial infections is a relevant risk factor for the failure of empirical antibiotic treatment and worse outcomes both in non-critically ill and critically ill patients[2,8,9]. EASL has recommended a broad-spectrum treatment in patients with risk factors for MDR bacteria[1]. Although we showed that the adherence to EASL antibiotic treatment recommendation was associated with better clinical response, the increasing spread of MDR and XDR bacteria with extreme differences among centres and countries in the predominant resistant strain makes mandatory the further implementation of protocols of empirical antibiotic treatment adapted to local epidemiology [10]. In this regard, the availability of new antibiotics, active against carbapenem resistant Gram-negative bacteria (e.g.,ceftazidime/avibactam, meropenem/varbobactam, cefiderocol) provides new weapons in particular in centres with high prevalence of XDR bacteria. Prospective studies should explore the efficacy of novel antibiotics and extended or continuous infusions of beta-lactams targeting concentrations above minimum inhibitory concentration and mutagenic window for the management of MDR/XDR infections[11]. Moreover, new technologies able to provide rapid identification of organisms and antimicrobial susceptibility test should be implemented, to allow the early adjustment of empirical antibiotic treatment. Indeed, the de-escalation of antibiotics in patients with culture-positive infections following the results of microbial susceptibility improves outcomes[12]. Among other infections related factors, well known difficult-to-treat infections such as nosocomial episodes and pneumonia were associated with clinical failure of empirical antibiotic treatment. Other studies have shown that nosocomial infections and pneumonia have poor prognosis in cirrhosis[13,14] , likely because they are

commonly caused by MDR bacteria[2,8,15] and/or because they occur in the frailest patients. The high rate of MDR and XDR pathogens observed in Asia in the Global study particularly in the Indian subcontinent,[2] explains at least partially that empirical antimicrobial strategies were frequently ineffective in Asian countries compared to American and European centers. There is an unmet need of novel drugs and empirical antibiotic strategies that incorporate antibiotics targeting the MDR and XDR pathogens predominant in each center in these regions for achieving a clinical response to the empirical strategy.

We identified serum CRP and leucocyte counts as independent predictors of lack of clinical response to empirical antibiotics and in-hospital and 28-day mortality. Patients with cirrhosis inherently have systemic inflammation secondary to low-grade endotoxemia and subclinical bacterial translocation. The CRP is synthesized in the liver in response to interleukin-6 (IL-6) release during systemic inflammation. Although leukocytes and CRP suggest a more severe systemic inflammation in patients with lack of response to treatment, it is worth noting that CRP levels are directly correlated with the expression of MERTK-expressing monocytes, which have impaired innate immune response to microbes[16]. Therefore, the severe systemic inflammation could be counterbalanced by an inappropriate anti-inflammatory response with immune paralysis. We propose CRP as an effective biomarker for identifying patients at risk of treatment failure and mortality in patients with cirrhosis and infections. However, further studies are needed to identify an appropriate CRP cut-off for its routine use in clinical practise. It would also be interesting to explore the utility of dynamic assessment with CRP in prospective studies and its correlation with clinical outcomes. As far as inflammation is concerned, increasing number of organ failures was associated with poor response to empirical antibiotic treatment. Whether this finding is due to a too advanced disease or to a state of immune paralysis is still to be determined. Indeed, several studies have found a severe immune dysfunction vis-à-vis both innate and adaptive immunity in patients with

cirrhosis and organ failure[16,17] In this regard, it has been shown that uninfected patients with higher ACLF grade have higher incidence of infections.[4] New strategies aiming at restoring immune dysfunction in patients with cirrhosis at high risk or with bacterial infection should be explored, in particular in those with multiple organ failures.

Interestingly, low serum albumin levels were associated with a higher risk of lack of response to empirical antibiotic treatment. Hypoalbuminemia has important effects on antibiotic pharmacokinetic, increasing the unbound fraction of antibiotics and volume of distribution[18]. For time-dependent β-lactam antibiotics, changes in volume of distribution and protein binding can lead to low concentrations later in the dosing interval, reaching subtherapeutic concentrations and putting patients at risk of treatment failure and of further antibiotic resistance[19]. Moreover, albumin has several immunomodulatory properties and *in vitro* and *in vivo* studies have shown that albumin may restore immune dysfunction in patients with cirrhosis[20] and modulate immune cells responses through interaction with endosomal TLR signalling[21,22]. The benefits of albumin are established in patients with high-risk SBP[23]. However, data on non-SBP infections were controversial[24-26]. Albumin has also been showed to be useful in resuscitation of patients with cirrhosis and septic shock[27]. In patients with uncomplicated ascites, albumin administration prevented SBP and non-SBP infections[28]. However, more recently, the use of albumin for a short time targeted to restore albumin concentration in patients hospitalized for any type of decompensation, did neither prevent infection nor the occurrence of acute kidney injury[29]. Moreover, patients receiving albumin developed more frequently pulmonary edema or fluid overload. Therefore, whether albumin administration could improve response to empirical antibiotic treatment in patients with cirrhosis, infections and hypoalbuminemia should be investigated[30].

Regarding predictors of mortality, clinical response to antibiotic treatment was the strongest predictor of survival. Although this was expected, it is worth noting that the use of an

microbiological effective empirical antibiotic regimen remains the most relevant modifiable factor while managing bacterial infections in cirrhosis. This is the reason why current guidelines recommend high-spectrum antibiotics covering all potential pathogens (adapted to local epidemiology) in patients with decompensated cirrhosis and sepsis, severe sepsis or shock. We also found a predominance of host factors as predictors of mortality in patients with cirrhosis and bacterial infections. Our analysis showed that the presence of organ failure(s) and the severity of liver disease (assessed by MELD-Na score) independently predicted mortality in patients with cirrhosis and infection. Moreover, we found, higher severity of systemic inflammation assessed by higher serum CRP levels and leucocyte counts as independent predictors of mortality. Those predictors (organ failures and markers of inflammation) are the hallmark of the new definition of sepsis, which is now defined as organ dysfunction secondary to a dysregulated immune response of the host to infection[31]. Whether routine incorporation of strategies targeting systemic inflammation would improve outcomes of difficult-to-treat infections requires investigation.

Our study has some limitations. The first and foremost being the lack of data on timing i.e., the time of presentation of the patient with infection and institution of a microbiological effective antibiotic and the dose of antibiotic. Second, the exact time when the antibiotics were escalated (in hours) and lack of a standardized protocol of antibiotics. This is because the study was designed as a prospective observational cohort study. Third, there is possibility of selection bias and residual confounding as only patients who were infected and hospitalized were enrolled in the analysis. Moreover, we did not analyze the data on the use of polymyxin and antibiotics like tigecycline, fosfomycin, and aztreonam to manage MDR infections. We also could not examine the impact of non-antibiotic strategies like choice, dose, and duration of albumin use, timing and modality of renal replacement therapy, and its impact on overall outcomes. We could not do a separate analysis for fungal infections

because of the small number of patients. Further, we did not collect data on procalcitonin, which may be a better biomarker for sepsis. The majority of patients had alcohol as the etiology of liver cirrhosis, however the exact proportion of patients with alcohol-associated hepatitis could not be determined and it's impact on outcomes of infections. We also could not evaluate the impact of comorbidities such as diabetes on outcomes of infection in the enrolled cohort.

Despite these limitations, our analysis performed in the largest multinational cohort of patients across the globe provides insights into risk factors of lack of clinical response to empirical antibiotic regimens in patients with cirrhosis and bacterial infections. Our data could form the basis for the development of risk stratification models for identifying patients for high risk of non-response to the empirical antibiotic regimen. Considering a recent surge in the prevalence of MDR/XDR pathogens, we reinforce the idea of developing guidelines for risk stratification and choosing an appropriate empirical regimen for the management of these difficult-to-treat organisms. In future, prospective studies should evaluate biomarker-driven approach for antibiotic use, randomized controlled trials should compare new antibiotic protocols for management of MDR/XDR pathogens and the role of adjunctive anti-inflammatory strategies for management of patients at high risk of lack of clinical response to empirical treatment.

REFERENCES

1. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60:1310-24.
2. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J et al. International Club of Ascites Global Study Group. Epidemiology and Effects of Bacterial Infections in Patients With Cirrhosis Worldwide. Gastroenterology. 2019; 156:1368-1380.e10.
3. Wong F, Piano S, Singh V, Bartoletti M, Maiwall R, Alessandria C et al; International Club of Ascites Global Study Group. Clinical features and evolution of bacterial infection-related acute-on-chronic liver failure. J Hepatol. 2021; 74:330-339.
4. Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C et al; European Foundation for the Study of Chronic Liver Failure. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut. 2018; 67:1870-1880.
5. Ferrer R, Martin-Loeches I, Phillips G, Osborn TM, Townsend S, Dellinger RP, et al. Empiric antibiotic treatment reduces mortality in severe sepsis and septic shock from the first hour: results from a guideline-based performance improvement program. Crit Care Med. 2014;42: 1749-55.
6. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J et al.; CANONIC Study Investigators of the EASL–CLIF Consortium. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013; 144:1426-37, 1437.e1-9.

7. Merli M, Lucidi C, Di Gregorio V, Lattanzi B, Giannelli V, Giusto M et al. An empirical broad spectrum antibiotic therapy in health-care-associated infections improves survival in patients with cirrhosis: A randomized trial. Hepatology. 2016; 63:1632-9
8. Fernández J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, Deulofeu C, et al; European Foundation for the Study of Chronic Liver Failure (EF-Clif). Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol. 2019;70:398-411
9. Maiwall R, Pasupuleti SSR, Chandel SS, Narayan A, Jain P, Mitra LG, et al. Co-orchestration of acute kidney injury and non-kidney organ failures in critically ill
10. Fernández J, Piano S, Bartoletti M, Wey EQ. Management of bacterial and fungal infections in cirrhosis: The MDRO challenge. J Hepatol. 2021;75 Suppl 1:S101-S117
11. Yahav D, Giske CG, Grāmatniece A, Abodakpi H, Tam VH, Leibovici L. New β-Lactam-β-Lactamase Inhibitor Combinations. Clin Microbiol Rev. 2020; 34:e00115-20.
12. Campion M, Scully G. Antibiotic Use in the Intensive Care Unit: Optimization and De-Escalation. J Intensive Care Med. 2018; 33:647-655
13. Bajaj JS, Reddy RK, Tandon P, Wong F, Kamath PS, Biggins SW, et al. Prediction of Fungal Infection Development and Their Impact on Survival Using the NACSELD Cohort. Am J Gastroenterol. 2018; 113:556-563
14. Fernández J, Bert F, Nicolas-Chanoine MH. The challenges of multi-drug-resistance in hepatology. J Hepatol. 2016;65:1043-1054.
15. Fernández J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology. 2012; 55:1551-61

16. Bernsmeier C, Pop OT, Singanayagam A, Triantafyllou E, Patel VC, Weston CJ, Curbishley S, et al. Patients with acute-on-chronic liver failure have increased numbers of regulatory immune cells expressing the receptor tyrosine kinase MERTK. Gastroenterology. 2015; 148:603-615

17. Korf H, du Plessis J, van Pelt J, De Groote S, Cassiman D, Verbeke L, et al. Inhibition of glutamine synthetase in monocytes from patients with acute-on-chronic liver failure resuscitates their antibacterial and inflammatory capacity. Gut. 2019;68:1872-1883.

18. Ulldemolins M, Roberts JA, Rello J, Paterson DL, Lipman J. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. Clin Pharmacokinet. 2011; 50:99-110.

19. Roberts JA, Abdul-Aziz MH, Lipman J, Mouton JW, Vinks AA, Felton TW et al.; International Society of Anti-Infective Pharmacology and the Pharmacokinetics and Pharmacodynamics Study Group of the European Society of Clinical Microbiology and Infectious Diseases. Individualised antibiotic dosing for patients who are critically ill: challenges and potential solutions. Lancet Infect Dis. 2014; 14:498-509

20. O'Brien AJ, Fullerton JN, Massey KA, Auld G, Sewell G, James S, et al. Immunosuppression in acutely decompensated cirrhosis is mediated by prostaglandin E2. Nat Med. 2014; 20:518-23

21. Casulleras M, Flores-Costa R, Duran-Güell M, Alcaraz-Quiles J, Sanz S, Titos E et al. Albumin internalizes and inhibits endosomal TLR signaling in leukocytes from patients with decompensated cirrhosis. Sci Transl Med. 2020;12: eaax5135

22. Fernández J, Clària J, Amorós A, Aguilar F, Castro M, Casulleras M, et al. Effects of Albumin Treatment on Systemic and Portal Hemodynamics and Systemic

Inflammation in Patients With Decompensated Cirrhosis. Gastroenterology. 2019;157:149-162.

23. Sort P, Navasa M, Arroyo V, Aldeguer X, Planas R, Ruiz-del-Arbol L, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. N Engl J Med. 1999 5; 341:403-9.
24. Guevara M, Terra C, Nazar A, Solà E, Fernández J, Pavesi M, et al. Albumin for bacterial infections other than spontaneous bacterial peritonitis in cirrhosis. A randomized, controlled study. J Hepatol. 2012; 57:759-65.
25. Fernández J, Angeli P, Trebicka J, Merli M, Gustot T, Alessandria C, et al. Efficacy of Albumin Treatment for Patients with Cirrhosis and Infections Unrelated to Spontaneous Bacterial Peritonitis. Clin Gastroenterol Hepatol. 2020;18:963-973.e14
26. Thévenot T, Bureau C, Oberti F, Anty R, Louvet A, Plessier A, et al. Effect of albumin in cirrhotic patients with infection other than spontaneous bacterial peritonitis. A randomized trial. J Hepatol. 2015;62:822-30.
27. Philips CA, Maiwall R, Sharma MK, Jindal A, Choudhury AK, Kumar G, et al. Comparison of 5% human albumin and normal saline for fluid resuscitation in sepsis induced hypotension among patients with cirrhosis (FRISC study): a randomized controlled trial. Hepatol Int. 2021;15:983-994.
28. Caraceni P, Riggio O, Angeli P, Alessandria C, Neri S, Foschi FG, et al. ANSWER Study Investigators. Long-term albumin administration in decompensated cirrhosis (ANSWER): an open-label randomised trial. Lancet. 2018 Jun 16;391(10138):2417-2429. doi: 10.1016/S0140-6736(18)30840-7. Epub 2018 Jun 1. Erratum in: Lancet. 2018 ;392:386

29. China L, Freemantle N, Forrest E, Kallis Y, Ryder SD, Wright G, et al. ATTIRE Trial Investigators. A Randomized Trial of Albumin Infusions in Hospitalized Patients with Cirrhosis. N Engl J Med. 2021;384 :808-817.

30. Bernardi M, Angeli P, Claria J, Moreau R, Gines P, Jalan R, et al. Albumin in decompensated cirrhosis: new concepts and perspectives Gut. 2020 Jun;69(6):1127-1138. doi: 10.1136/gutjnl-2019-318843.

31. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315:801-10

Table 1. Comparison of patients' characteristics according to the clinical response to empirical antibiotic treatment

Variable	Clinical response (N=788)	No clinical response (N=514)	P
Age (years) – mean (SD)	57 (13)	55 (13)	0.006
Gender (Male) – n (%)	516 (66)	382 (74)	0.001
Etiology of cirrhosis – n (%)			
Alcohol	409 (52)	288 (56)	0.161
HCV	167 (21)	69 (18)	0.166
HBV	67 (9)	33 (6)	0.203
NASH	89 (11)	57 (11)	0.980
Others	149 (19)	87 (17)	0.404
Mean arterial pressure (mmHg) – mean (SD)	82 (13)	81 (15)	0.286
Heart rate (beat/min) – mean (SD)	87 (17)	90 (17)	<0.001
Respiratory rate (breath/min) – mean (SD)	19 (4)	20 (6)	<0.001
Leukocytes (WBC; x 10^9/L) – median (p25-p75)	7.2 (4.6 – 11.8)	9.9 (6.5 – 14.2)	<0.001
C-reactive protein (mg/L) – median (p25-p75)	30 (12 – 64)	46 (20 – 89)	<0.001
Serum creatinine (mg/dl) – median (p25-p75)	1.0 (0.8 – 1.7)	1.3 (0.9 – 2.1)	<0.001
Serum bilirubin (mg/dl) – median (p25-p75)	3.3 (1.6 – 6.9)	4.4 (2.0 – 10.0)	<0.001
INR – median (IQR)	1.6 (1.3 – 2.0)	1.7 (1.4 – 2.2)	<0.001
Serum albumin (g/dl) – median (p25-p75)	2.7 (2.3 – 3.1)	2.5 (2.1 – 2.9)	<0.001
Serum sodium (mmol/L) – mean (SD)	133 (6)	132 (8)	0.001

Ascites – n (%)	604 (77)	398 (77)	0.795
Hepatic encephalopathy – n (%)	258 (33)	238 (46)	<0.001
MELD score – mean (SD)	20 (7)	23 (8)	<0.001
MELD-Na score – mean (SD)	23 (7)	26 (8)	<0.001
Child Pugh score – mean (SD)	9.6 (2.2)	10.5 (2.2)	<0.001
Acute-on-chronic liver failure grade – n (%)			
No ACLF	564 (72)	278 (54)	
Grade 1	113 (14)	77 (15)	<0.001
Grade 2	78 (10)	86 (17)	
Grade 3	33 (4)	73 (14)	
Liver failure – n (%)	102 (13)	109 (21)	<0.001
Coagulation failure – n (%)	80 (10)	89 (17)	<0.001
Renal failure – n (%)	137 (17)	145 (28)	<0.001
Brain failure – n (%)	50 (6)	90 (18)	<0.001
Circulatory failure – n (%)	77 (10)	97 (19)	<0.001
Respiratory failure – n (%)	30 (4)	61 (12)	<0.001
SIRS – n (%)	208 (32)	197 (43)	<0.001
qSOFA – n (%)	121 (18)	134 (29)	<0.001
Septic shock – n (%)	77 (10)	97 (19)	<0.001
Mechanical ventilation – n (%)	25 (3)	53 (10)	<0.001
Site of infection – n (%)			
Urinary tract infection	193 (25)	96 (19)	
Spontaneous bacterial peritonitis	226 (29)	128 (25)	
Pneumonia	108 (14)	134 (26)	<0.001
Spontaneous bacteremia	64 (8)	36 (7)	
Skin and soft tissue infection	60 (8)	41 (8)	

Other	137 (17)	79 (15)	
Type of infection – n (%)			
Community-acquired	391 (50)	237 (46)	0.005
Healthcare-associated	218 (28)	120 (23)	
Nosocomial	179 (23)	157 (31)	
Culture positive infections – n (%)	431 (55)	309 (60)	0.061
MDR bacterial infections – n (%) §	100 (13)	153 (30)	<0.001
XDR bacterial infections – n (%)§	19 (2)	43 (8)	<0.001
Fungi – n (%)	9 (1)	15 (3)	0.034
Treatment with 2 or more antibiotics – n (%)	264 (34)	185 (36)	0.386
Adherence to EASL antibiotic treatment recommendations – n (%)			
Adherent	517 (66)	279 (54)	<0.001
Weaker	164 (20)	161 (31)	
Broader	105 (13)	74 (14)	
Empirical antibiotic microbiological efficacy – n (%)			
Not effective	63 (8)	155 (30)	<0.001
Effective	368 (47)	154 (30)	
Negative cultures	357 (45)	205 (40)	

Data presented as number (percentage) for categorical variables and mean (standard deviation) for parametric or median (interquartile range) for non-parametric continuous variables. *Legend*: SIRS, systemic inflammatory response syndrome; qSOFA, quick sequential organ failure assessment; MDR, multidrug resistant; MELD model of end stage liver disease; §, only patients with positive cultures were included in this analysis; qSOFA was defined as two or more of the following criteria: altered mentation, systolic blood pressure less than 100 mmHg and respiratory rate of more than 20/min

Table 2. Independent predictors of lack of clinical response to empirical antibiotic treatment.

Variable	OR	95% CI	P
Leukocyte (WBC; x 10^9/L) #	1.39	1.09 – 1.77	0.008
C-reactive protein (mg/dl) #	1.16	1.02 – 1.31	0.019
Serum albumin (g/dl)	0.70	0.55 – 0.88	0.003
Pneumonia	1.75	1.22 – 2.53	0.003
Nosocomial infections	1.69	1.20 – 2.38	0.003
Baseline ACLF grade*			
Grade 1	1.21	0.80 – 1.82	0.369
Grade 2	1.58	1.04 – 2.41	0.033
Grade 3	4.08	2.36 – 7.05	<0.001
Empirical antibiotic microbiological efficacy °			
Not effective	5.45	3.47 – 8.57	<0.001
Negative cultures	1.03	0.74 – 1.42	0.877

Legend: OR, odds ratio; CI, confidence interval; ACLF, acute on chronic liver failure. #, variables were log transformed; *, patients without ACLF were used as reference group. °, patients receiving antibiotics effective *in vitro* were used as reference group.

Variables included in multivariate analysis: age, sex, C-reactive protein, leukocytes, SIRS, quick SOFA, MELD ACLF grade, serum albumin, nosocomial infections, pneumonia, MDR or XDR bacterial infections, microbiological efficacy of empirical antibiotic treatment.

Table 3. Comparison of clinical outcomes according to clinical response of empirical antibiotic treatment.

Variable	Clinical response (N=788)	No clinical response (N=514)	P
Resolution of infection – n (%)	756 (96)	282 (55)	<0.001
Development of new infections – n (%)	120 (15)	148 (29)	<0.001
Development of renal failure – n (%) *	61 (9)	119 (32)	<0.001
Development of septic shock during hospitalization – n (%) **	52 (7)	147 (35)	<0.001
Development of ACLF during hospitalization – n (%) ***	100 (18)	130 (47)	<0.001
Transfer to ICU – n (%) #	135 (18)	218 (46)	<0.001
Mechanical ventilation – n (%) ******	35 (5)	124 (27)	<0.001
Renal replacement therapy – n (%)	32 (4)	96 (19)	<0.001
Length of hospital stay (days) – median (p25-p75)	14 (9 – 21)	16 (10 – 27)	<0.001
In-hospital mortality – n (%) °	69 (9)	224 (44)	<0.001
28-day mortality – n (%)§	75 (11)	217 (47)	<0.001

Legend: ACLF, acute-on-chronic liver failure; *, patients with renal failure at enrolment (n=282) were excluded from this analysis; **, patients with septic shock at enrolment (n= 174) have been excluded from this analysis; ***, patients with ACLF at enrolment (n=460) have been excluded from this analysis; ****, patients with respiratory failure at enrolment (n=91) have been excluded from this analysis; °, patients transplanted during hospitalization (n=35) have been excluded from this analysis; § patients transplanted or lost to follow up (n=130) have been excluded from this analysis.

Table 4. Independent predictors of in-hospital and 28-day mortality

Variables	sHR	95% CI	P value
In-hospital mortality			
Age	1.02	1.01 – 1.03	0.002
MELD-Na score	1.58	1.05 – 1.10	<0.001
ACLF	1.61	1.14 – 2.18	0.006
Sepsis (qSOFA criteria)	1.33	0.99 – 1.78	0.058
Leukocyte (WBC; x 10^9/L) °	1.52	1.15 – 2.01	0.004
C-reactive protein (mg/l)°	1.18	1.03 – 1.35	0.015
Clinical response to empirical treatment*	0.22	0.16 – 0.30	<0.001
28-day mortality			
Age	1.02	1.01 – 1.03	0.001
MELD-Na score	1.07	1.05 – 1.10	<0.001
ACLF	1.65	1.17 – 2.34	0.005
Sepsis (qSOFA criteria)	1.42	1.05 – 1.91	0.024
C-reactive protein (mg/l)°	1.21	1.06 – 1.37	0.001
Clinical response to empirical treatment*	0.20	0.14 – 0.27	<0.001

Legend: sHR, subdistribution hazard ratio; CI, confidence interval; MELD-Na, model of end stage liver disease sodium; ACLF, acute on chronic liver failure; qSOFA, quick sequential organ failure assessment; *, no clinical response to treatment was used as reference group; °, variables were log transformed

Figure 1: Graph depicting the Odd's ratio with 95% confidence intervals of independent factors predicting no clinical response toantibiotic treatment derived from multivariate binary logistic regression analysis

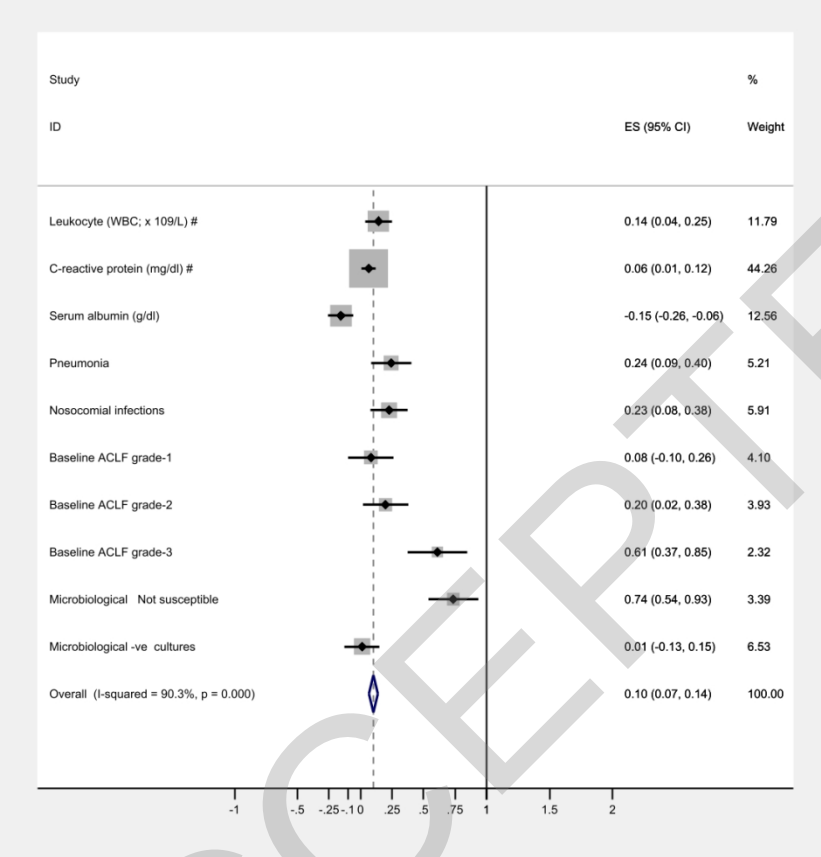


Figure 2: Incidence of clinical outcomes of patients with respect to clinical response to empirical antibiotic treatment.

Legend: *, p<0.001 vs clinical response to treatment.

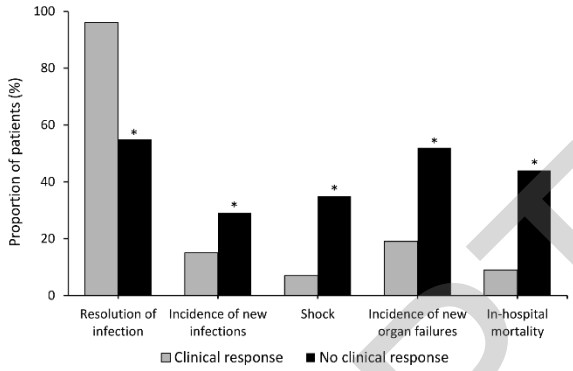


Figure 3: Competing risk survival analysis with liver transplant as competing risk stratified by clinical response to antibiotic treatment. The graph shows patients with no clinical response to treatment had worse 28-day survival compared to patients with clinical response.

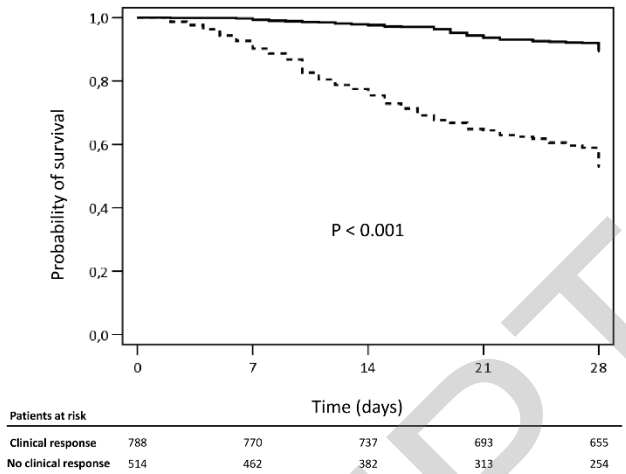
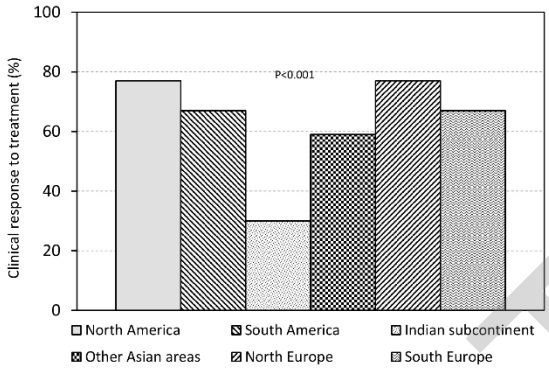


Figure 4: Depiction of the geographic variation in the clinical response to treatment with empirical antibiotics.



Appendix. International Club of Ascites GLOBAL study group collaborators:

- Michele Bartoletti, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy;
- Thomas D Boyer, Department of Medicine, University of Arizona, Tucson, Arizona, USA;
- Carlos Brodersen, Unidad en Gastroenterologia, Hospital Durand, Buenos Aires, Argentina
- Tony Bruns, Department of Internal Medicine IV, Jena University Hospital, Jena, Germany;
- Robert A. de Man, Department of Gastroenterology and Hepatology, Erasmus MC Medical Center, Rotterdam, The Netherlands;
- Annette Dam Fialla, Department of Gastroenterology and Hepatology, Odense University Hospital, Odense, Denmark;
- Carmine Gambino, Unit of Internal Medicine and Hepatology, Department of Medicine, University of Padova, Padova, Italy;
- Vikas Gautam, Postgraduate Institute of Medical Education and Research, Chandigarh, India;
- Marcos Girala, Departamento de Gastroenterología y Endoscopia Digestiva, Hospital de Clínicas, Universidad Nacional de Asunción, Asunción, Paraguay;
- Adria Juanola, Liver ICU, Liver Unit, Hospital Clínic, University of Barcelona, Barcelona, Catalonia, Spain;
- Jeong Han Kim, Konkuk University Medical Center, Seoul, South Korea;
- Tae Hun Kim, Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, Republic of Korea;
- Pramod Kumar, Department of Hepatology, Postgraduate Institute of Medical Education and Research, Chandigarh, India;

- Barbara Lattanzi, Gastroenterology and Hepatology Unit, Department of Clinical Medicine, Sapienza University of Rome, Rome, Italy;
- Tae Hee Lee, Department of Internal Medicine, Konyang University College of Medicine, Daejeon, Republic of Korea;
- Cosmas A. Rinaldi Lesmana, Digestive Disease and Oncology Centre, Medistra Hospital, Jakarta, Indonesia;
- Richard Moreau, Service d'Hépatologie, Hôpital Beaujon, AP-HP, Clichy, France;
- Preetam Nath, Department of Gastroenterology, S.C.B. Medical College, Cuttack, India;
- Gustavo Navarro, Gastroenterology Unit, Hospital Valdivia, Universidad Austral de Chile, Valdivia, Chile;
- Ji-Won Park, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Hallym Sacred Heart Hospital, College of Medicine, Hallym University, Anyang city, Republic of Korea
- Gisela Pinero, Rosario University Medical School, Rosario, Argentina;
- Nikolaos T. Pyrsopoulos, Division of Gastroenterology and Hepatology, Rutgers-New Jersey Medical School, University Hospital, Newark, NJ, USA;
- Sophie Restellini, Service d'Hépato-gastroentérologie, Hôpitaux Universitaires de Genève, Geneva, Switzerland;
- Gustavo Romero, Liver Unit, Hospital "Dr. Carlos B. Udaonod", Buenos Aires, Argentina;
- Marco Sacco, Division of Gastroenterology and Hepatology, Città della Salute e della Scienza Hospital, University of Turin, Turin, Italy;

- Tiago Sevá -Pereira, Gastroenterology Division, Medicine Department, Faculty of Medical Sciences, University of Campinas (UNICAMP). Campinas, São Paulo, Brazil;
- Macarena Simón-Talero, Liver Unit, Department of Internal Medicine, Hospital Vall d'Hebron, Barcelona, Spain;
- Do Seon Song, The Catholic University Of Korea, St.Vincent's Hospital, South Korea
- Ki Tae Suk, Department of Internal Medicine, Hallym University College of Medicine, Chuncheon, South Korea;
- Hans Van Vlierberghe, Department of Gastroenterology and Hepatology, Ghent University Hospital, Ghent, Belgium;
- Sun Young Yim, Department of Internal Medicine, Division of Gastroenterology and Hepatology, Korea University Hospital, Seoul, Republic of Korea;
- Eileen Laurel Yoon, Department of Internal Medicine, Sanggye Paik Hospital, Inje University, Seoul, Republic of Korea;
- Giacomo Zaccherini, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy.