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CLINICAL—LIVER

Epidemiology and Effects of Bacterial Infections in Patients With Cirrhosis Worldwide

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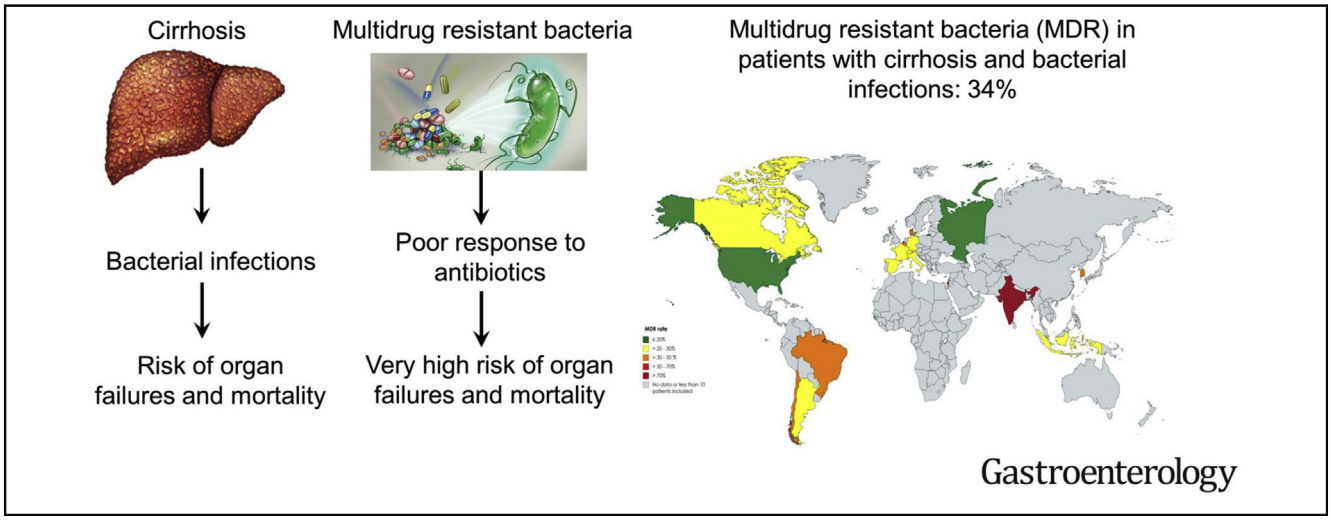

BACKGROUND & AIMS: Bacterial infections are common and life-threatening in patients with cirrhosis. Little is known about the epidemiology of bacterial infections in different regions. We performed a multicenter prospective intercontinental study to assess the prevalence and outcomes of bacterial and fungal infections in patients with cirrhosis. **METHODS:** We collected data from 1302 hospitalized patients with cirrhosis and bacterial or fungal infections at 46 centers (15 in Asia, 15 in Europe, 11 in South America, and 5 in North America) from October 2015 through September 2016. We obtained demographic, clinical, microbiology, and treatment data at time of diagnosis of infection and during hospitalization. Patients were followed until death, liver transplantation, or discharge. **RESULTS:** The global prevalence of multidrug-resistant (MDR) bacteria was 34% (95% confidence interval 31%–37%). The prevalence of MDR bacteria differed significantly among geographic areas, with the greatest prevalence in Asia. Independent risk factors for infection with MDR bacteria were infection in Asia (particularly in India), use of antibiotics in the 3 months before hospitalization, prior health care exposure, and site of infection. Infections caused by MDR bacteria were associated with a lower rate of resolution of infection, a higher incidence of shock and new organ failures, and higher in-hospital mortality than those caused by non-MDR bacteria. Administration of adequate empirical antibiotic treatment was independently associated with improved in-hospital and 28-day survival. **CONCLUSIONS:** In a worldwide study of hospitalized patients, we found a high prevalence of infection with MDR bacteria in patients with cirrhosis. Differences in the prevalence of MDR bacterial infections in different global regions indicate the need for different empirical antibiotic strategies in different continents and countries. While we await new antibiotics, effort should be made to decrease the spread of MDR bacteria in patients with cirrhosis.

Keywords: Global; Resistance; Sepsis; Stewardship.

Bacterial infections are very common in patients with cirrhosis and are associated with the development of complications and high short-term mortality.[1,2] The negative impact of bacterial infections in cirrhosis is clinically relevant at any stage of liver disease.[3–5] In addition, although the risk of dying of some major complications of cirrhosis, such as hepatorenal syndrome, gastrointestinal bleeding, or hepatocellular carcinoma, has progressively decreased over time, that from sepsis has increased.[6] This finding is alarming and has occurred despite the ongoing "surviving sepsis campaign."[7] The reasons are not clear, but the increasing spread of multidrug-resistant (MDR) bacteria and the lack of new effective antibiotics likely have a relevant role. The problem of antimicrobial resistance is so important that during the 68th World Health Assembly, the World Health Organization adopted a resolution and a global action plan to counteract the spread of MDR strains.[8] Among the main aims of this plan, 2 should be highlighted: (1) to strengthen the knowledge and evidence base through surveillance and research and (2) to optimize the use of antimicrobial medicines in human and animal health. For the former aim, it should be highlighted that large epidemiologic studies are lacking in patients with cirrhosis and/or are limited to single-center experiences.[9–14] For the latter, the European Association for the Study of the Liver (EASL) recommended specific antibiotic regimens for patients with cirrhosis and bacterial infections.[1] However, these recommendations are based on expert opinion and the clinical impact of adherence to these recommendations has never been evaluated.

Thus, the International Club of Ascites planned a prospective, multicenter, intercontinental, cross-sectional study

Abbreviations used in this paper: **ACLF, acute-on-chronic liver failure; EASL, European Association for the Study of the Liver; HCA, health care associated; ICU, intensive care unit; MDR, multi drug resistant; MELD, model of end-stage liver disease; MELD-Na, model of end-stage liver disease–sodium; qSOFA, quick sequential organ failure assessment; RRT, renal replacement therapy; SBP, spontaneous bacterial peritonitis; sHR, sub-distribution hazard ratio; UTI, urinary tract infection; XDR, extensively drug resistant.**

Most current article

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WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Mortality for bacterial infections is increasing in patients with cirrhosis and the spread of multi-drug resistant (MDR) bacteria may be responsible for these findings. Regional differences on the prevalence and clinical impact of MDR bacterial infections are not clearly defined.

NEW FINDINGS

In patient with cirrhosis, one third of infections are due to MDR bacteria, with relevant regional differences. The prevalence of MDR infections is very high in Asia and these infections are associated with poor outcomes.

LIMITATIONS

Some geographic areas, such as Africa and China, were not included. Specific genetic resistance rates of isolated bacteria were not tested.

IMPACT

The identification of risk factors for MDR infections may help clinicians in optimizing the selection of empiric antibiotic treatment. Measures to limit the spread of MDR bacteria should be implemented in parallel with research to identify new antibiotics.

to assess (1) the epidemiology of bacterial infections in hospitalized patients with cirrhosis and (2) the impact of bacterial infections on clinical outcomes in these patients according to the antibiotic treatment empirically administered.

Methods

Patients

From October 2015 to September 2016, 1302 consecutive hospitalized patients with cirrhosis and bacterial or fungal infections were included at 46 centers (15 from Asia, 15 from Europe, 11 from South America, and 5 from North America). Inclusion criteria were (1) a diagnosis of cirrhosis; (2) a diagnosis of bacterial and/or fungal infection at admission or during hospitalization; and (3) age >18 years. Exclusion criteria were (1) hepatocellular carcinoma beyond the Milan criteria; (2) extrahepatic malignancy; (3) severe extrahepatic disease (congestive heart failure [New York Heart Association stage ≥3], chronic obstructive pulmonary disease [Global Initiative for Chronic Obstructive Lung Disease stage ≥3]; chronic kidney disease requiring renal replacement therapy [RRT]); (4) previous solid organ transplantation; (5) human immunodeficiency viral infection; (6) use of immunosuppressive drugs other than corticosteroids for the treatment of severe acute alcoholic hepatitis; and (7) inability to provide written informed consent.

The protocol was approved by the local ethics committee at each center and patients provided written informed consent.

Design of Study

At study enrollment, physical examination and routine laboratory and microbiological analyses were performed. Demographic, clinical, laboratory, and microbiological data and treatment administered were collected. Information about concurrent medications (quinolone prophylaxis, rifaximin, and β-blockers) also was collected. The following potential risk factors for the development of MDR infections were collected: (1) antibiotic treatment for at least 5 days in the previous 3 months; (2) isolation of MDR bacteria in the previous 6 months; (3) invasive procedures (surgery, central venous catheterization, bladder catheterization, paracentesis, etc) in the month before hospitalization; and (4) exposure to health care facilities.

Cirrhosis was diagnosed according to histologic, clinical, biochemical, ultrasound, and/or endoscopic findings. Bacterial and fungal infections were diagnosed according to conventional criteria, which are reported in detail in the Supplementary Materials. Bacterial and fungal infections were classified as community-acquired, health care-associated (HCA), and nosocomial infections as previously described.[9]

Microbiological cultures and antibiotic susceptibility tests were performed according to standard international criteria. Patients were followed until death, liver transplantation, and/or discharge. Patients discharged before 28 days were followed until 28 days since the diagnosis of infection. Data on the development of new bacterial and fungal infections, septic shock, acute kidney injury, acute-on-chronic liver failure (ACLF), transfer to the intensive care unit (ICU), use of vasopressors, mechanical ventilation, and/or RRT during hospitalization were collected. When a second infection developed during hospitalization, microbiological cultures and antibiotic susceptibility tests were repeated. Data were collected using an electronic case report form using the Research Electronic Data Capture Software REDCap[15] hosted at the Department of Medicine of the University of Padova (Padova, Italy).

Definitions

MDR bacteria were defined as nonsusceptibility to at least 1 agent in at least 3 antimicrobial categories.[16] Extensively drug-resistant (XDR) bacteria were defined as nonsusceptibility to at least 1 agent in all but less than 2 antimicrobial categories (ie, bacterial isolates remain susceptible to only 1 or 2 categories).[16] For the assessment of MDR and XDR definitions, intrinsic resistance was not considered (eg, enterococci are constitutively resistant to cephalosporins). In vitro resistance was established according to either EUCAST or CLSI minimal inhibitory concentration breakpoints, according to local policy.

For this study, the microbiological efficacy of the empirical antibiotic treatment was defined as in vitro susceptibility of the isolated strain to at least 1 of the antibiotics administered. Then, the first-line empirical antibiotic treatment was evaluated according to the following criteria. When a monotherapy was recommended by the EASL, the treatment was considered "adherent" if at least 1 of the recommended antibiotics was administered. When a combination of 2 antibiotics was recommended by the EASL, the treatment was considered "adherent" when the patients received 1 of the recommended combinations (Supplementary Table 1). Nonadherent treatments were subclassified as "weaker" when the antibiotic(s) administered had a narrower spectrum than those recommended and "broader" when the antibiotic(s) administered had a broader spectrum than those recommended. Escalation was defined by the add-on of at least 1 new antibiotic to the empirical treatment and/or the switch of antibiotic(s) to a molecule(s) with broader antibiotic spectrum. Conversely, de-

escalation was defined by the decrease in number of antibiotics administered or the switch of the empirical antibiotic(s) to a narrower spectrum molecule(s) within 5 days.

Acute kidney injury and ACLF were defined according to the International Club of Ascites and the EASL Consortium for the Study of Liver Failure, respectively, which are reported in the Supplementary Materials.[17,18]

Likewise, the criteria to define the presence of systemic inflammatory response syndrome and a positive quick sequential organ failure assessment (qSOFA) are reported in the Supplementary Materials.

Management of Infections

The empirical antibiotic treatment was prescribed by the attending physicians and changed according to antibiotic susceptibility test result and/or clinical evolution. Accordingly, the judgment on its clinical efficacy was entrusted to the attending physician according to clinical and laboratory improvement and microbiological test results. All other decisions concerning the management of patients, including transfer to the ICU, were made by the attending physicians according to the patient's conditions and to standard recommendations.[19,20]

Study Oversight

Investigators at each center enrolled patients, ensured adherence to the protocol, and completed the electronic case report forms. A 3-level strategy was adopted to guarantee the quality of data: (1) during completion of the electronic case report form, automatic alerts were developed for variables of a pre-established expected range and missing data at the time of saving forms; (2) an automatic check of data quality was performed using the REDCap (missing values, outliers, multiple choice fields with invalid values, incorrect data type, etc) and researchers were asked by e-mail to confirm or give an explanation for these queries; and (3) all electronic case report forms were carefully reviewed and researchers were asked by e-mail to provide an explanation to the further queries raised. S.P. was responsible for study oversight under the supervision of P.A.

Statistical Analysis

The primary end point of the study was the prevalence of MDR and XDR infections. Secondary end points were in-hospital mortality, 28-day mortality, development of ACLF, septic shock, transfer to ICU, and need for organ support (mechanical ventilation or RRT) during hospitalization. Normally distributed continuous variables were reported as mean ± standard deviation and compared using Student t test or 1-way analysis of variance, and non-normally distributed continuous variables were reported as median with interquartile range and compared using Mann-Whitney U test or Kruskal-Wallis test. Categorical variables were reported as proportions and compared with χ^2 or Fisher exact test. For patients with more than 1 strain isolated, only the strain with the broader antibiotic resistance was considered for assessing predictors of MDR. Variables found to be associated with MDR and XDR bacteria with a P value <0.1 in univariate analysis were included in a multivariate stepwise logistic regression analysis, with backward elimination (entry $P < .05$; drop $P > .1$). Odds ratios and their 95% confidence intervals were calculated. Analysis of in-hospital and 28-day mortality was performed using a competing risk approach. Cumulative incidence of death was estimated considering liver transplantation as a competing risk for death. The cumulative incidence curves were compared using the Gray test. The Fine and Gray method was used to identify the sub-distribution hazard function for death, considering liver transplantation as a competing risk for death. A proportional hazard model with the Fine and Gray method was used to identify independent predictors of mortality and results were expressed P values, sub-distribution hazard ratios (sHR), and their 95% confidence intervals. The Akaike information criterion was used to develop the most parsimonious model. Events during hospitalization (second infections, new organ failures, new onset of septic shock, transfer to ICU, etc) were not included in multivariate analysis of survival. When scores of liver disease were included in the model, their components were excluded to avoid multicollinearity. Similarly, for a correlation >0.5 between variables and/or scores, they were not included in the model to avoid multicollinearity. Non-normally distributed continuous variables were log-transformed to be included in the multivariate models. All statistical tests were 2-tailed and P values $<.05$ were considered significant. Statistical analysis was performed using SPSS 24 (IBM Corp, Armonk, NY) and R 3.5.0 (R Foundation, Vienna, Austria).

Results

Study Population

During the study period 1302 patients were enrolled, 565 (43%) from Europe, 416 (32%) from Asia, and 321 (25%) from America. The number of patients included in each center is presented in Supplementary Table 2. Demographic and clinical characteristics of patients included in the study are presented in Table 1. The number of missing data for each variable is presented in Supplementary Table 3. Most patients were men (69%) and their mean age was 57 ± 13 years. Alcohol was the most common cause of cirrhosis followed by hepatitis C viral infection and nonalcoholic steatohepatitis. Patients had advanced liver disease as shown by the high prevalence of ascites (77%), hepatic encephalopathy (38%), mean model of end-stage liver disease (MELD) score (21 ± 8), MELD sodium (MELD-Na) score (24 ± 8), and Child-Turcotte-Pugh score (10 ± 2). Notably, 35% of patients had ACLF at the diagnosis of infection. The characteristics of bacterial infections are listed in Table 2. Infection was classified as community acquired, HCA, and nosocomial in 48%, 26%, and 26%, respectively. The most common infections were spontaneous bacterial peritonitis (SBP; 27%), urinary tract infection (UTI; 22%), and pneumonia (19%). Systemic inflammatory response syndrome and a positive qSOFA were found in 36% and 23% of patients, respectively. At the diagnosis of infection, 174 patients (14%) had septic shock. Microbiological cultures were positive in 57% of patients, and globally 959 bacteria were isolated (299 from urine cultures, 271 from blood cultures, 136 from ascites, 141 from bronchoalveolar lavage and sputum cultures, 11 from pleural fluid, and 101 from other sites). Gram-negative

Table 1. Characteristics of Patients Included in the Study at Infection Diagnosis

Variable	Global (N = 1302)	America (n = 321)	Asia (n = 416)	Europe (n = 565)	*P* value
Age (*y*), mean (SD)	57 (13)	56 (12)	51 (13)	61 (12)	<.001
Men, n (%)	898 (69)	222 (69)	321 (77)	355 (63)	<.001
Etiology, n (%)[a]					
Alcohol	697 (54)	176 (55)	236 (57)	285 (50)	.129
HCV	259 (20)	62 (19)	31 (8)	166 (29)	<.001
HBV	100 (8)	9 (3)	58 (14)	33 (6)	<.001
NASH	146 (11)	46 (14)	49 (12)	51 (9)	.050
Other	236 (18)	56 (17)	68 (16)	112 (20)	.353
Mean arterial pressure (*mm Hg*), mean (SD)	82 (13)	81 (13)	83 (13)	82 (13)	.064
Heart rate (*bpm*), mean (SD)	88 (17)	87 (15)	93 (18)	85 (17)	<.001
Body temperature (°*C*), mean (SD)	37.0 (0.9)	36.9 (0.9)	37.3 (0.8)	36.9 (0.9)	<.001
Respiratory rate (*breaths/min*), mean (SD)	19 (5)	19 (6)	20 (3)	19 (5)	<.001
SpO_2/FiO_2 ratio, median (IQR)	462 (452–467)	462 (452–467)	467 (457–471)	462 (452–467)	<.001
β-Blocker use, n (%)	423 (33)	116 (36)	73 (18)	234 (41)	<.001
Treatment with vasopressors, n (%)	174 (13)	45 (14)	68 (16)	61 (11)	.038
Ascites, n (%)	1002 (77)	247 (77)	348 (84)	407 (72)	<.001
Hepatic encephalopathy, n (%)	496 (38)	152 (47)	159 (38)	185 (33)	<.001
Grades 1–2	356 (27)	108 (34)	96 (23)	152 (27)	
Grades 3-4	140 (11)	44 (14)	63 (15)	33 (6)	
ACLF, n (%)	460 (35)	117 (36)	193 (46)	150 (27)	<.001
MELD score, mean (SD)	21 (8)	21 (7)	23 (9)	20 (7)	<.001
MELD-Na score, mean (SD)	24 (8)	24 (7)	26 (8)	22 (7)	<.001
Child-Pugh score, mean (SD)	10 (2)	10 (2)	10 (2)	9 (2)	<.001
INR, median (IQR)	1.6 (1.3–2.1)	1.6 (1.4–2.1)	1.8 (1.4–2.31)	1.5 (1.3–1.9)	<.001
Bilirubin (*mg/dL*), median (IQR)	3.7 (1.7–8.0)	3.3 (1.8–6.8)	4.6 (2.0–10.3)	3.3 (1.6–7.0)	<.001
Albumin (*g/dL*), median (IQR)	2.6 (2.2–3.0)	2.4 (2.0–2.8)	2.4 (2.1–2.9)	2.8 (2.5–3.2)	<.001
Serum creatinine (*μmol/L*), median (IQR)	1.1 (0.8–1.9)	1.1 (0.8–1.9)	1.3 (0.8–2.1)	1.1 (0.8–1.7)	.001
Serum sodium (*mmol/L*), mean (SD)	133 (7)	133 (7)	132 (8)	134 (6)	<.001
Leukocytes ($\times 10^9$/L), median (IQR)	8.4 (5.2–13.0)	8.5 (5.3–13.1)	9.4 (6.2–13.9)	7.2 (4.5–11.8)	<.001
C-reactive protein (*mg/L*), median (IQR)[b]	35 (15–77)	48 (20–83)	31 (12–72)	34 (15–74)	.051

FiO_2, fraction of inspired oxygen; HBV, hepatitis B virus; HCV, hepatitis C virus; INR, international normalized ratio; IQR, interquartile range; NASH, nonalcoholic steatohepatitis; SD, standard deviation; SpO_2, pulse oximetric saturation.
[a]One hundred twenty-nine patients had more than 1 etiology of cirrhosis.
[b]Available in 1102 patients.

bacteria were the most common isolates (57%), and gram-positive bacteria accounted for 38% of positive cultures. Only 4% of cultures were positive for fungi.

Tables 1 and 2 present a comparison of continents. A higher prevalence of pneumonia and UTI and a lower prevalence of SBP were detected in Asian centers compared with American and European centers. The highest prevalence of infections by gram-negative bacteria was found in Asian centers, and the highest prevalence of infections by gram-positive bacteria was found in European centers. Remarkably, the highest prevalence of ACLF and septic shock was found in Asian centers (Table 2).

Among gram-negative bacteria, the most commonly isolated were *Enterobacteriaceae*, such as *Escherichia coli* and *Klebsiella pneumoniae*, and *Staphylococcus aureus* and enterococci were the most common among gram-positive bacteria. Overall, 322 MDR bacteria were isolated in 253 patients. This means that MDR bacteria were isolated in 34% of patients with a positive culture. The most commonly isolated MDR bacteria were extended spectrum β-lactamase producing *Enterobacteriaceae*, methicillin-resistant *S aureus*, vancomycin-resistant enterococci, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* (Supplementary Table 4). Overall, 73 XDR bacteria were isolated in 62 patients (8% of those with positive cultures). The most common XDR bacteria were carbapenem-producing *Enterobacteriaceae*, *P aeruginosa*, and *A baumannii* (Supplementary Table 4).

Prevalence of MDR and XDR Bacteria Across Different Countries

Relevant differences were observed in the prevalence of MDR and XDR bacteria across the different centers. Remarkably, MDR bacterial infections were very common in Indian centers (73% of isolates), whereas their prevalence was quite low in North American centers (16% in United States and 24% in Canada). The prevalence of MDR was quite high in South American and other Asian centers (Figure 1), whereas there was a relevant variability across Europe (from 57% in Israel to 17% in Russia; Supplementary Table 4). Similarly, the prevalence of XDR infections was strikingly high in Indian centers (33% of isolates) but was 0%–16% in the other countries. Relevant differences were observed among countries, particularly for the prevalence of carbapenem-resistant *Enterobacteriaceae* and *A baumannii*. The latter was highly prevalent in Asian

Table 2. Clinical and Microbiological Characteristics of the First Infection

Variable	Global (N = 1302)	America (n = 321)	Asia (n = 416)	Europe (n = 565)	*P* value
Site of infection, n (%)					<.001
UTI	289 (22)	86 (27)	60 (14)	143 (25)	
SBP	354 (27)	99 (31)	144 (35)	111 (20)	
Pneumonia	242 (19)	36 (11)	116 (28)	90 (16)	
Spontaneous bacteremia	100 (8)	30 (9)	21 (5)	49 (9)	
Skin and soft tissue infections	101 (8)	30 (9)	30 (7)	41 (7)	
Other[a]	216 (17)	40 (13)	45 (11)	131 (23)	
Type of infection, n (%)					<.001
Community acquired	628 (48)	153 (48)	234 (56)	241 (43)	
HCA	336 (26)	99 (31)	98 (24)	141 (25)	
Nosocomial	338 (26)	69 (22)	84 (20)	183 (32)	
SIRS, n (%)[b]	405 (36)	86 (28)	163 (41)	156 (38)	.001
qSOFA, n (%)[b]	255 (23)	76 (24)	94 (23)	85 (21)	.538
Septic shock, n (%)	174 (13)	45 (14)	68 (16)	61 (11)	.038
Patients with positive cultures, n (%)	740 (57)	192 (60)	191 (46)	357 (63)	<.001
Bacteria per patient, n (%)					<.001
1	592 (80)	148 (77)	174 (91)	270 (76)	
>1	148 (20)	44 (23)	17 (9)	87 (24)	
Strains isolated, n	959	244	248	467	—
Type of strain isolated, n (%)					<.001
Gram negative	561 (59)	137 (56)	174 (70)	250 (54)	
Gram positive	360 (38)	91 (37)	69 (28)	200 (43)	
Fungi	38 (4)	16 (7)	5 (2)	17 (4)	
Most frequently isolated bacteria, n (%)					
Escherichia coli	266 (28)	78 (32)	61 (25)	127 (27)	.176
Klebsiella pneumoniae	143 (15)	32 (13)	60 (24)	51 (11)	<.001
Staphylococcus aureus	78 (8)	15 (6)	26 (11)	37 (8)	.207
Enterococcus faecalis	52 (5)	12 (5)	4 (2)	36 (8)	.003
Enterococcus faecium	53 (5)	9 (4)	5 (2)	39 (8)	.001
MDR bacteria, n (%)[c]	322 (35)	66 (27)	124 (50)	132 (28)	<.001
XDR bacteria, n (%)[d]	73 (8)	10 (4)	39 (16)	24 (5)	<.001

SIRS, systemic inflammatory response syndrome.
[a]Cholangitis (n = 37), secondary bacteremia (n = 32), *Clostridium difficile* infection (n = 31), signs of sepsis without focus (n = 20), secondary bacterial peritonitis (n = 17), upper respiratory infection (n = 14), bone or joint infection (n = 13), pleural empyema (n = 12), and other (n = 40).
[b]Patients with at least 2 SIRS or qSOFA criteria; data available in 1,119 patients.
[c]In 253 patients (34%).
[d]In 62 patients (8%).

centers. Supplementary Table 5 presents the rate of resistance to specific antibiotics for the most commonly isolated strains.

According to these epidemiologic findings, patients were classified in 6 geographic areas (India, other Asian countries, South Europe, North Europe, South America, and North America) for further analyses.

Risk Factors for MDR and XDR Bacterial Infections

Table 3 presents a comparison between patients with and without MDR bacteria. Infections caused by MDR bacteria were more common in young patients, men, and those with worse liver function according to MELD-Na and Child-Turcotte-Pugh scores. Among known risk factors for MDR bacteria, the use of systemic antibiotics for the treatment of a bacterial infection for at least 5 days in the previous 3 months, invasive procedures in the previous month, and exposure to health care (HCA and nosocomial infections) were more frequent in those with MDR bacteria than in those without.

Previous administration of an antibiotic prophylaxis for SBP with quinolones was not found to be more frequent in patients with MDR infections. The lack of an association between quinolone prophylaxis and MDR infections was confirmed when the data were analyzed across different geographic areas (Supplementary Figure 1). MDR infections were more commonly observed in patients with UTI, pneumonia, and skin and soft tissues infections than in those with SBP or spontaneous bacteremia. In multivariate analysis, patients from India, other Asian centers, and South America had an increased risk of infections sustained by MDR bacteria (Table 4). Other independent predictors were exposure to treatment with systemic antibiotics for at least 5 days in the previous 3 months, exposure to health care

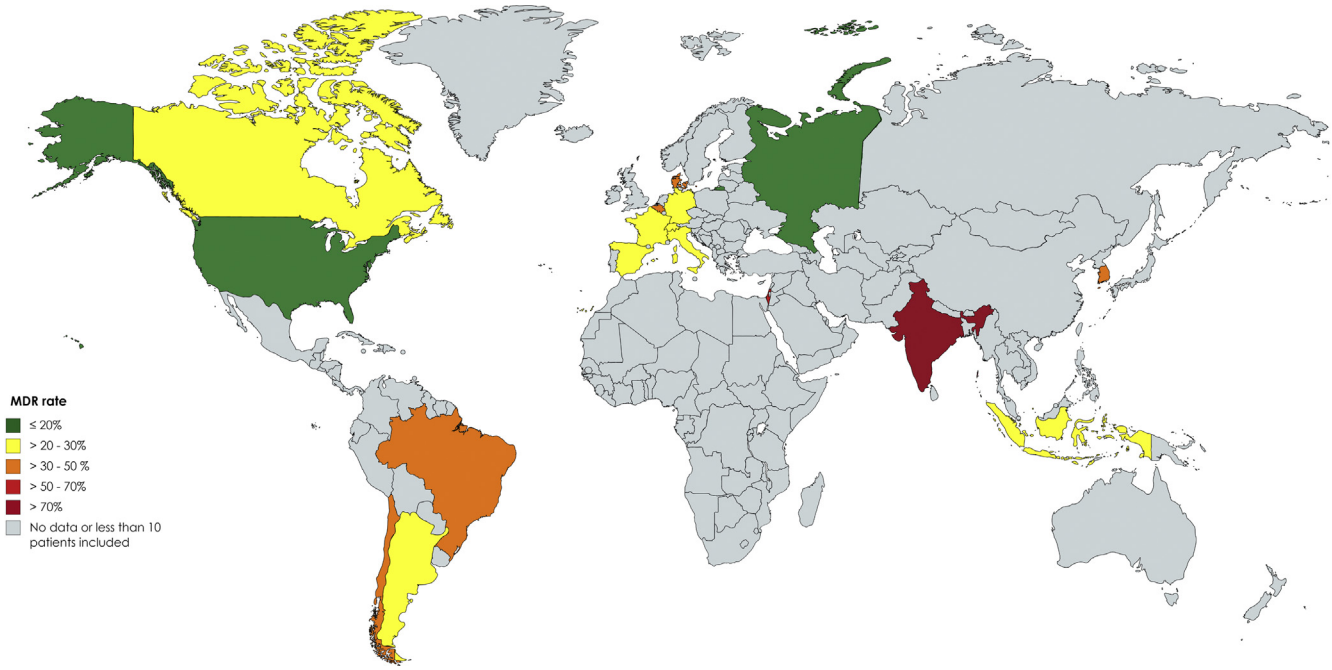

Figure 1. Prevalence of MDR bacteria across the world. Different colors represent different rates of prevalence of MDR bacterial infections. Relevant differences were found in the prevalence of MDR bacteria among the different countries.

(HCA and nosocomial infection), and site of infection (UTI, pneumonia, skin and soft tissues infections). Analysis of predictors of XDR bacteria showed similar findings (Table 4).

Antibiotic Treatment and Clinical Course of Infections

Sixty-six percent of patients received only 1 antibiotic as empirical treatment, whereas 34% received a combination of at least 2 antibiotics. Overall, the most commonly used antibiotics were third-generation cephalosporins (40%), classic β-lactams and β-lactamase inhibitors (28%), piperacillin–tazobactam (22%), and carbapenems (16%; Supplementary Table 6). The isolated strains were susceptible to empirical antibiotics in 71% of patients. The microbiological efficacy was significantly higher in patients who were judged as clinical responders than in those who were not (85% vs 50%; $P < .001$). The first-line antibiotic treatment was adherent to EASL recommendations in only 61% of patients. In patients who received a "nonadherent" antibiotic treatment (39%), it was weaker in 65% and broader in 35%. Antibiotic treatment was escalated, de-escalated, or unchanged in 37%, 8%, and 56% of patients, respectively. De-escalation of antibiotic treatment was associated with similar outcomes as continuation of empirical antibiotic treatment (Supplementary Table 7).

During hospitalization, 268 patients (21%) developed a second infection. The main type and etiology of second infections are presented in Supplementary Table 8. Pneumonia, UTI, and SBP were the most common second infections. Cultures were positive in 60% of patients with a second infection, showing different bacteria than the first infection in most cases (85%). The rate of fungal infections increased in second infections (11% vs 4%; $P < .001$) as did the rate of MDR and XDR infections (50% vs 34%; $P < .001$; and 17% vs 8%; $P < .001$, respectively).

Clinical Impact of MDR Infections

MDR bacterial infections were associated with a lower efficacy of empirical antibiotic treatment, a more frequent need to escalate antibiotic treatment, a longer duration of antibiotic treatment, and a lower rate of resolution of the infection than non-MDR bacterial infections (Supplementary Table 9). In addition, patients with MDR bacterial infections had a higher incidence of septic shock, need to be transferred to the ICU, and need for mechanical ventilation or RRT than those with non-MDR bacterial infections. Length of hospital stay was significantly longer in patients with MDR bacterial infections than in those without. Most important, patients with MDR infections had a significantly higher in-hospital and 28-day mortality rate. Cumulative incidence of mortality at 28 days was significantly higher in patients with MDR infections than in those without (29% vs 20%; $P = .014$; Supplementary Figure 2). Notably, administration of a microbiologically effective empirical antibiotic treatment also significantly improved the outcomes of MDR bacterial infections (Supplementary Table 9).

Predictors of In-Hospital Mortality

During hospitalization, 293 patients (23%) died, 35 (3%) underwent transplantation, and 974 (75%) survived. Supplementary Table 10 presents a comparison of

Table 3. Comparison of Patients' Characteristics According to Presence or Absence of Infection From MDR Bacteria

Variable	No MDR (n = 487)	MDR (n = 253)	*P* value
Geographic area, n (%)			<.001
India	23 (5)	63 (25)	
Other Asian centers	71 (15)	34 (13)	
North Europe	62 (13)	27 (11)	
South Europe	191 (39)	77 (30)	
North America	45 (10)	9 (4)	
South America	95 (20)	42 (17)	
Age (*y*), mean (SD)	58 (13)	56 (13)	.003
Men, n (%)	305 (63)	177 (70)	.057
Mean arterial pressure (*mm Hg*), mean (SD)	81 (13)	82 (14)	.560
Quinolone prophylaxis, n (%)	45 (9)	21 (8)	.772
Treatment with rifaximin, n (%)	147 (30)	81 (32)	.669
Antibiotic treatment in previous 3 mo, n (%)	186 (38)	156 (62)	<.001
Invasive procedures in previous month, n (%)[a]	188 (39)	143 (57)	<.001
Isolation of MDR bacteria in previous 6 mo, n (%)[a]	29 (6)	22 (9)	.214
ACLF, n (%)	161 (33)	87 (34)	.779
MELD-Na score, mean (SD)	23 (7)	25 (7)	.046
Child-Pugh score, mean (SD)	9.7 (2.2)	10.2 (2.3)	.016
Site of infection, n (%)			<.001
UTI	157 (32)	90 (36)	
SBP	94 (19)	28 (11)	
Pneumonia	47 (10)	58 (23)	
Spontaneous bacteremia	72 (15)	22 (9)	
Skin and soft tissue infection	25 (5)	19 (8)	
Other	92 (19)	36 (14)	
Type of infection, n (%)			<.001
Community acquired	242 (50)	75 (30)	
HCA	123 (25)	77 (30)	
Nosocomial	122 (25)	101 (40)	
SIRS, n (%)	158 (40)	75 (34)	.138
qSOFA, n (%)	89 (23)	53 (24)	.802
Septic shock, n (%)	64 (13)	41 (16)	.307
Leukocytes ($\times 10^9$/L), median (IQR)	7.7 (4.4–12.1)	8.8 (5.6–13.4)	.003
C-reactive protein (mg/L), median (IQR)	32 (12–80)	37 (17–74)	.396

IQR, interquartile range; SD, standard deviation; SIRS, systemic inflammatory response syndrome.
[a]Comparator combined patients without the variable of interest and those with missing data.

Table 4. Independent Predictors of Infection by MDR and XDR Bacteria

Variable	OR	95% CI	*P* value
MDR bacteria			
Geographic area, n (%)[a]			
South America	2.23	0.99–5.00	.053
India	7.94	3.30–19.11	<.001
Other Asian centers	2.79	1.20–6.46	.017
North Europe	1.91	0.82–4.48	.136
South Europe	1.64	0.77–3.49	.197
Antibiotic treatment in previous 3 mo	1.92	1.32–2.80	.001
Site of infection[b]			
UTI	2.48	1.59–3.87	<.001
Pneumonia	3.20	1.83–5.59	<.001
Skin and soft tissue infection	2.92	1.41–6.09	.004
Other infections	1.45	0.85–2.49	.175
Type of infection[c]			
HCA	1.62	1.04–2.52	.032
Nosocomial	2.65	1.75–4.01	<.001
XDR bacteria			
Geographic area, n (%)[a]			
South America	2.82	0.34–23.54	.339
India	13.57	1.71–107.96	.014
Other Asian centers	3.13	0.34–28.49	.312
North Europe	2.00	0.21–18.74	.545
South Europe	2.67	0.34–20.89	.350
Antibiotic treatment in previous 3 mo	1.91	0.94–3.90	.074
Site of infection[b]			
UTI	2.14	1.08–4.24	.029
Pneumonia	2.71	1.29–5.70	.009
Type of infection[c]			
HCA	2.55	1.05–6.16	.038
Nosocomial	5.10	2.24–11.59	<.001

CI, confidence interval; OR, odds ratio.
[a]North American patients were used as the reference group.
[b]All other infections were used as the reference group.
[c]Community-acquired infections were used as the reference group.

baseline characteristics between survivors and nonsurvivors. Nonsurvivors had more advanced liver disease and a higher prevalence of systemic inflammatory response syndrome, positive qSOFA, septic shock, and ACLF than survivors. Nosocomial infections, pneumonia, and SBP were more prevalent in nonsurvivors. Nonsurvivors were less likely to receive a microbiologically effective first-line empirical antibiotic treatment than survivors. In multivariate analysis, independent predictors of in-hospital mortality were age (sHR 1.02; $P = .016$), MELD-Na score (sHR 1.08; $P < .001$), ACLF (sHR 1.51; $P = .012$), a positive qSOFA (sHR 1.49; $P = 0.005$), leukocyte count (sHR 1.40; $P = .011$), C-reactive protein (sHR 1.21; $P = .004$), and microbiological efficacy of empirical antibiotic treatment (sHR 0.52; $P = .001$). At 28 days, 292 patients (22%) died, 38 (3%) underwent transplantation, 880 (68%) survived, and 92 (7%) were lost to follow-up. Median follow-up was 28 days (interquartile range 25–28). The analysis of predictors of 28-day mortality showed similar results (Table 5). An alternative model is presented in Supplementary Table 11, in which the clinical efficacy instead of the microbiological efficacy was used. The clinical efficacy was found to be an independent predictor of in-hospital and 28-day mortality. The proportion of transplant recipients was larger in European

Table 5. Independent Predictors of In-Hospital and 28-Day Mortality

Variables	sHR	95% CI	*P* value
In-hospital mortality			
Age	1.02	1.00–1.03	.016
MELD-Na score	1.08	1.05–1.10	<.001
ACLF	1.51	1.10–2.02	.012
Positive qSOFA	1.49	1.13–1.98	.005
Leukocytes ($\times 10^3$)[a]	1.40	1.08–1.81	.011
C-reactive protein (*mg/L*)[a]	1.21	1.06–1.38	.004
Nosocomial infection	0.78	0.57–1.07	.120
Microbiological efficacy of empirical treatment[b]			
Effective treatment	0.52	0.36–0.76	.001
Negative cultures	0.80	0.13–1.13	.210
28-d mortality			
Age	1.02	1.01–1.03	.004
MELD-Na score	1.08	1.05–1.10	<.001
ACLF	1.65	1.18–2.31	.004
Positive qSOFA	1.58	1.19–2.10	.002
Leukocytes ($\times 10^3$)[a]	1.26	0.98–1.61	.067
C-reactive protein (*mg/L*)[a]	1.25	1.10–1.42	.001
Nosocomial infection	1.35	1.19–2.10	.047
Microbiological efficacy of empirical treatment[b]			
Effective treatment	0.59	0.42–0.84	.004
Negative cultures	0.61	0.43–0.86	.005

CI, confidence interval.
[a]Variables were log-transformed.
[b]Ineffective treatment was used as the reference group.

and American centers than in Asian centers during hospitalization (4.2%, 3.1%, and 0.2%, respectively; $P = .001$) and at 28 days (4.6%, 2.5%, and 1%, respectively; $P = .003$).

Adherence to EASL Antibiotic Treatment Recommendations and Impacts on Clinical Outcomes

Adherence to EASL antibiotic treatment varied greatly among centers, from 70% in South America to 46% in North America (Supplementary Table 12). Microbiological efficacy was significantly higher in patients who received a treatment adherent to EASL recommendations than in those who did not (75% vs 64%; $P = .001$). As expected, this gap was further increased after comparing patients receiving a treatment adherent to EASL recommendations with those who received a "weaker" treatment (75% vs 50%; $P < .001$).

Bacteria isolated in Asian centers had a lower antimicrobial susceptibility to antibiotics suggested by EASL recommendations than the other centers (58% vs 80%; $P < .001$). The rate of in vitro antimicrobial susceptibility to different antibiotics and combinations suggested by EASL recommendations for bacteria isolated in HCA and nosocomial infections is presented in Figure 2. Significant differences were found among geographic areas. After adjusting for age, ACLF, MELD-Na score, qSOFA, leukocyte count, C-reactive protein, and nosocomial infections, the administration of empirical antibiotics "weaker" than EASL recommendations was associated with in-hospital mortality (sHR 1.44; $P = .023$).

Discussion

The main aim of this study was to provide a worldwide view of the epidemiology of bacterial infections in patients with cirrhosis. Indeed, most studies in this field come from single centers or limited geographic areas. The global nature of our study showed remarkable differences in demographic and clinical characteristics of patients among different geographic areas. As expected, the etiology of cirrhosis differed, with hepatitis B viral infection being more frequent in Asia than in Europe and America, where hepatitic C virus was more frequent. Our study proved that community-acquired infections were more common than HCA or nosocomial infections in all continents, particularly in Asia. Nevertheless, it should be highlighted that in almost 50% of patients, the bacterial infection developed after exposure to health care facilities.

Another main aim of the study was to show the epidemiology of infections sustained by MDR or XDR bacteria across the world. Strikingly, the global prevalence of infections sustained by MDR bacteria was 34%, quite higher than that observed in previous studies.[9,11–14] Even more strikingly, relevant differences were found in the prevalence of infections sustained by MDR and XDR bacteria across the continents, with the highest prevalence in Asia and the lowest in America. Furthermore, huge differences were found in the prevalence of infections sustained by MDR and XDR bacteria among different geographic areas, with the highest rate in Indian centers (73% and 33%, respectively) and the lowest in North American centers (18% and 2%, respectively). These results are well in keeping with other epidemiologic studies showing a very high prevalence of infections sustained by MDR bacteria in Asia, and particularly India, in the general population.[21] Two potential reasons are responsible for this finding, namely (1) over-the-counter access to antibiotics in the community and (2) the presence of antibiotics in the environment.[22] For the former, it should be considered that, in 2010, India was the world's largest consumer of antibiotics for human health at 12.9×10^9 units (10.7 units per person).[23] Thus, although strategies aiming to restrict over-the-counter access to antibiotics should be promoted, such strategies should take into account that a significant proportion of the population lacks access to doctors and that a lack of access to effective antibiotics still kills more children than antibiotic resistance.[24] For environmental exposure to antibiotics, 3 factors should be considered: (1) use of antibiotics in livestock, (2) lack of regulations governing discharge of expired antibiotics, and/or (3) waste water treatment plants serving antibiotic manufacturing facilities.[22] All these have been associated with the transfer of resistance genes into the human microbiota[22] and should be counteracted with specific government policies. In keeping with all these observations, the high prevalence of MDR and XDR bacteria in India also occurred in community-acquired infections (88%

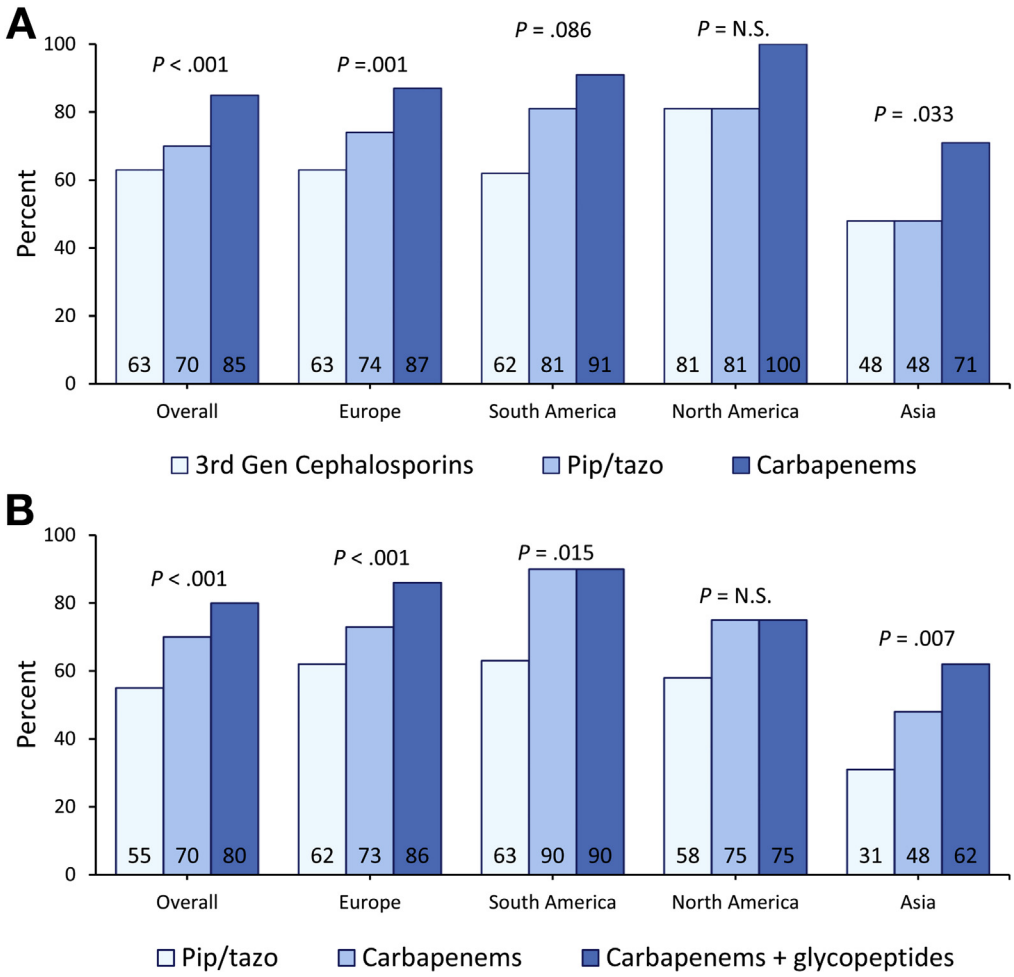

Figure 2. In vitro antimicrobial susceptibility to different antibiotics and combinations suggested for treatment of HCA infections (*A*) and nosocomial infections (*B*). Infections analyzed were UTIs, SBP, pneumonia, and spontaneous bacteremia. Relevant differences were found in the rate of antimicrobial susceptibility to tested antibiotics among the different geographic areas. 3rd Gen, third-generation; N.S., not significant; Pip/Tazo, piperacillin–tazobactam.

and 12%, respectively). When the prevalence of MDR and XDR was adjusted for confounding factors, other geographic areas were associated with an increased risk of MDR bacterial infection. Beyond geographic areas, other independent predictors of MDR and XDR bacterial infections were exposure to systemic antibiotics or health care facilities and types of infection. One could argue these results just confirm previous findings in this field. However, for once, the most striking result is a negative one. Indeed, unexpectedly, SBP prophylaxis with quinolones was not among the predictors of MDR bacterial infections. This is in contrast with most previous studies performed in this field, which considered quinolone prophylaxis one of the main drivers of the spread of MDR infections in cirrhosis.[9,12,13] Our findings were confirmed when a sub-analysis was made within different geographic areas (Supplementary Figure 1). A possible explanation of the discrepancy with the previous study could be the low rate of patients who received quinolone prophylaxis on one side (10%) and the potential role of environmental antibiotics on the other side. In addition, our results are in keeping with findings of a randomized controlled trial comparing norfloxacin with placebo in 291 patients with decompensated cirrhosis, showing that the risk of developing infections from MDR bacteria was not higher in patients receiving norfloxacin than in those who received placebo.[25] Therefore, while waiting for nonantibiotic options for SBP prophylaxis, the most important message that can be drawn from this finding is that patients with an indication for primary or secondary SBP prophylaxis should be treated with quinolones.[26]

The identification of risk factors for MDR bacterial infections could help physicians optimize empirical antibiotic treatment. In fact, our study confirms that infections sustained by MDR and XDR bacteria are more difficult to treat, being associated with a high risk of lack of infection resolution, organ failures, septic shock, and, most remarkably, in-hospital and 28-day mortality, as previously suggested by studies in smaller cohorts of patients with cirrhosis.[4,9]

As expected, the efficacy of empirical antibiotic treatment was found to be an independent predictor of in-hospital and 28-day mortality. We explored 2 prognostic models, 1 including the clinical efficacy of antibiotic treatment (ie, clinical improvement during treatment) and 1 including microbiological efficacy (ie, in vitro susceptibility of bacteria to empirical antibiotic treatment). Although previous studies showed that clinical efficacy of treatment was an independent predictor of mortality in patients with cirrhosis and bacterial infections,[4,27,28] microbiological

efficacy was preferred, because the clinical improvement during treatment of an infection depends not only on the choice of an effective empirical antibiotic treatment, but also on other factors, such as severity and type of infection, severity of liver disease, presence of organ failures, ability of the host to provide an adequate immune response, and nonantibiotic treatments. In addition, the expected susceptibility of bacteria to antimicrobial agents is one of the most relevant factors in the selection of the empirical antibiotic treatment to be administered. The microbiological efficacy of empirical antibiotic treatment was found to be a strong independent predictor of mortality beyond age, degree of inflammation, MELD-Na score, presence of ACLF, and new qSOFA score.[2,4,29] Remarkably, it was the only potentially modifiable predictor of mortality.

The marked differences in the distribution and type of MDR and XDR bacteria among geographic areas suggest that it is not possible to develop empirical antibiotic treatment schemes that can be applied worldwide. These schemes need to be adapted to national, regional, or even local microbiological epidemiology. However, it does not mean the scientific societies should renounce a priori their mission to provide international recommendations on antibiotic treatment. Indeed, our study showed that a treatment weaker than the EASL recommendations was an independent predictor of mortality. Thus, international recommendations on empirical antibiotic treatment could be a good starting point on which to build national, regional, or even local guidelines. The choice of the most appropriate empirical antibiotic treatment should consider the balance between the need for an adequate broad-spectrum antibiotic and the risk of developing further resistance. In this difficult task, the role of rapid de-escalation of the initial antibiotic treatment should not be overlooked. Our study proved that this strategy also can be applied successfully in patients with cirrhosis. In future, the widespread use of rapid antimicrobial susceptibility tests (matrix-assisted laser desorption/ionization mass spectrometry combined with the VITEK 2 [bioMérieux, St Laurent, QC, Canada], automated microscopy of bacterial cells, and nanotechnology partnered with microfluidics)[30–32] should be implemented, because they can speed up the administration of an appropriate antibiotic treatment and/or de-escalation and shorten the overall duration of antibiotic treatment.[30] In addition, antibiotic stewardship programs should be enhanced to rationalize the use of antibiotics in hospital and community settings. In high-risk patients (those admitted to the ICU as and those discharged from the ICU, other hospitals, or nursing home residency, or those with a previous MDR isolate), active screening (rectal and nasal swabs) for colonization with MDR bacteria is needed. It allows identification of carriers of MDR bacteria and the application of contact precautions and hand hygiene to prevent the further spread of these organisms.[33]

Our study has several strengths; it is the largest and first global study assessing the epidemiology and clinical impact of infections in patients with cirrhosis. It also has some limitations; it was not possible to enroll centers from Africa or other geographic areas because of the lack of manpower and/or willingness to participate in the study. In addition, tools for the detection of specific genetic resistance were not provided.

In conclusion, our study showed that the spread of MDR and XDR bacterial infections is a relevant threat for the health of patients with cirrhosis. Efforts should be made to limit the spread of MDR and XDR bacteria in patients with cirrhosis involving all stakeholders. Considering the huge differences in the prevalence of MDR and XDR infections across the different geographic areas, empirical antibiotic treatment needs to be adapted to national, regional, or even local microbiological epidemiology. In addition, considering the limited available options for treating MDR and XDR bacterial infections, new antibiotics should be developed.

Appendix

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Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2018.12.005.

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Collaborators of the International Club of Ascites Global Study Group are presented in the Appendix.

Author contributions: Paolo Angeli, Shiv Kumar Sarin, Virendra Singh, Adrian Gadano, and Aleksander Krag devised the study. Paolo Angeli, Shiv Kumar Sarin, Adrian Gadano, Aleksander Krag, Salvatore Piano, Javier Fernandez, and Thomas D. Boyer designed the study. Salvatore Piano, Virendra Singh, Paolo Caraceni, Rakhi Maiwall, Carlo Alessandria, Javier Fernandez, Elza Cotrim Soares, Dong Joon Kim, Sung Eun Kim, Monica Marino, Julio Vorobioff, Rita de Cassia Ribeiro Barea, Manuela Merli, Laure Elkrief, Victor Vargas, Aleksander Krag, Shivaram Prasad Singh, Laurentius Adrianto Lesmana, Claudio Toledo, Sebastian Marciano, Xavier Verhelst, Florence Wong, Nicolas Intagliata, Liane Rabinowich, Luis Colombato, Sang Gyune Kim, Alexander Gerbes, Francois Durand, Juan Pablo Roblero, Kalyan Ram Bhamidimarri, Thomas D. Boyer, Marina Maevskaya, Eduardo Fassio, Hyoung Su Kim, and Jae Seok Hwang enrolled patients and collected data. Salvatore Piano, Paolo Angeli, Shiv Kumar Sarin, Virendra Singh, Adrian Gadano, Aleksander Krag, and Francois Durand analyzed and interpreted the data. Salvatore Piano, Paolo Angeli, Virendra Singh, Shiv Kumar Sarin, Rakhi Maiwall, Adrian Gadano, Sebastian Marciano, Aleksander Krag, and Francois Durand drafted the manuscript. Paolo Caraceni, Carlo Alessandria, Javier Fernandez, Florence Wong, Nicolas Intagliata, and Pere Gines critically revised the manuscript for important intellectual content.

Conflicts of interest
Authors declare they have no conflict of interest regarding the content of this article.

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Supplementary methods

Bacterial infections were diagnosed according to the following criteria.

SBP: Polymorphonuclear cell count in ascitic fluid $\geq$250/mm^3.[1]

UTI: Patient had at least 1 of the following signs or symptoms (fever $\geq$38°C, urgency, frequency, dysuria, or suprapubic tenderness) and a positive urine culture or at least 2 of the following signs or symptoms (fever $\geq$38°C, urgency, frequency, dysuria, or suprapubic tenderness) and more than 10 leukocytes/μL in urine.[2]

Pneumonia: Radiologic evidence of a new or progression of a previous pulmonary infiltrate, consolidation, or cavitation plus at least 1 of the following criteria (fever $\geq$38°C, leucocyte count $>$12,000/mm^3 or $<$4,000/mm^3) plus at least 1 of the following symptoms (new onset of purulent sputum or change in character of sputum, new onset of cough, dyspnea or tachypnea $>$20 breaths per minute, rales or bronchial breath sounds, or worsening of gas exchange) and/or organisms cultured from blood, pleural fluid, or a specimen obtained by transtracheal, aspirate, bronchoalveolar lavage, or biopsy.

Spontaneous bacteremia: At least 1 of the following signs or symptoms: fever ($\geq$38°C), chills, or hypotension and a positive blood culture ($\geq$2 positive blood cultures for common skin contaminant) in the absence of a known source of infection.

Other infections were diagnosed according to the Centers for Disease Control and Prevention criteria.[2]

Supplementary Definitions

Organ failures (liver, kidney, coagulation, brain, circulation, and lungs) were defined according to the Chronic Liver Failure–Sequential Organ Failure Assessment score.[3] Briefly, liver failure was defined as a serum bilirubin level $\geq$12 mg/dL, kidney failure was defined as a serum creatinine (SCr) level $\geq$2 mg/dL, coagulation failure was defined as an international normalized ratio $\geq$2.5, brain failure was defined as hepatic encephalopathy grade 3 or 4 according to West Haven grading, circulatory failure as hypotension requiring vasopressors, and lung failure was defined as a ratio of oxygen saturation to fraction of inspired oxygen $\leq$214.

ACLF was defined according to the EASL–Chronic Liver Failure consortium definition[3]:

Grade 1: Patients with SCr $\geq$2 mg/dL; patients with single failure of the liver, coagulation, circulation, or respiration who had a SCr level of 1.5–1.9 mg/dL and/or mild to moderate hepatic encephalopathy (grade 1 or 2 according to West Haven criteria); and patients with single cerebral failure who had a SCr level of 1.5–1.9 mg/dL

Grade 2: Patients with 2 organ failures

Grade 3: Patients with $\geq$3 organ failures

Acute kidney injury was defined as an increase in SCr level $\geq$0.3 mg/dL within 48 hours or an increase in SCr level $\geq$50% from baseline within 7 days, according to International Club of Ascites acute kidney injury criteria.[4]

The qSOFA was considered positive when at least 2 of the following criteria were present: alteration of consciousness; respiratory rate $\geq$22 breaths per minute; and systolic blood pressure $\leq$100 mm Hg.[5]

Systemic inflammatory response syndrome was defined by the presence of at least 2 of the following criteria: body temperature $<$36°C or $>$38°C, heart rate $>$90 beats per minute, respiratory rate $>$20 breaths per minute, white blood cell count $<$4000/μL or $>$12,000/μL, or immature neutrophil count $>$10%.

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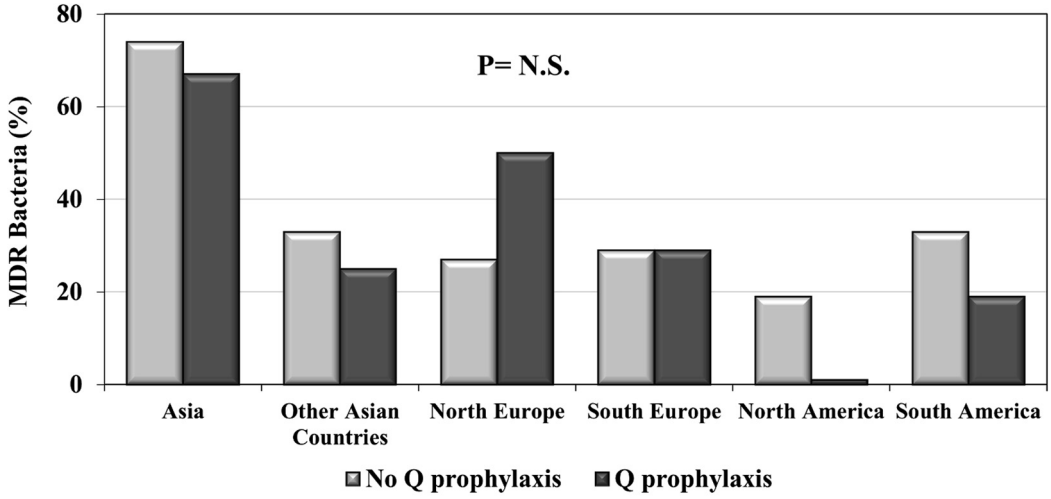
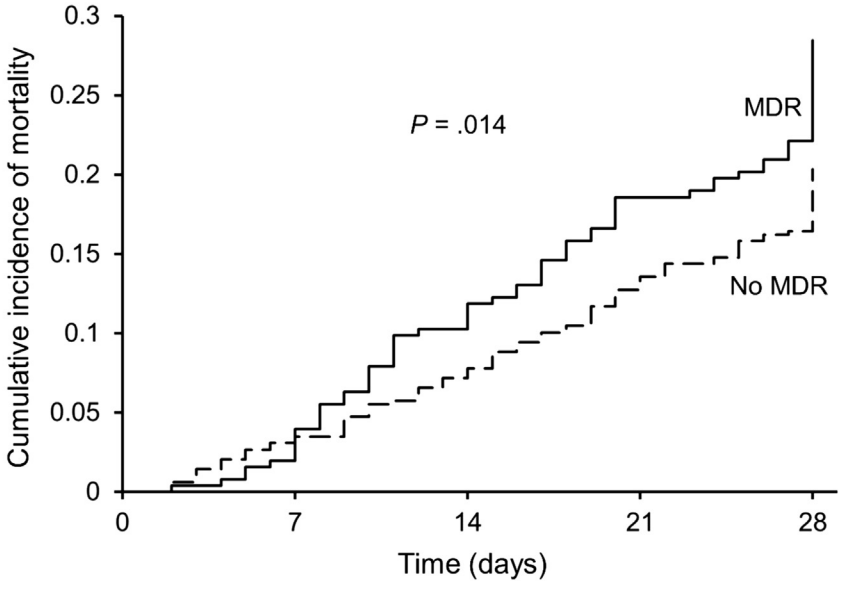


Legend: MDR, multi drug resistant; Q, quinolone; P>0.05 for all geographic areas

Supplementary Figure 1. Prevalence of MDR bacteria in patients treated or not with Q prophylaxis before the development of infections. $P > .05$ for all geographic areas. NS, not significant; Q, quinolone.



Legend: MDR, multi drug resistant; Cumulative incidence of 28-day mortality was 29% in MDR group and 20% in No MDR group.

Supplementary Figure 2. Cumulative incidence of 28-day mortality between patients with and without MDR bacterial infections (n = 740). Cumulative incidence of 28-day mortality was 29% in the MDR group and 20% in the no-MDR group.

Supplementary Table 1. EASL Empirical Antibiotic Treatment Recommendations for Community-Acquired and Nosocomial Bacterial Infections in Cirrhosis

Type of infection	Community-acquired infections	Nosocomial infections[a]
SBP, SBE, and spontaneous bacteremia	Cefotaxime or ceftriaxone or amoxicillin–clavulanic acid	Piperacillin–tazobactamΔ or meropenem[b] ± glycopeptide[c]
UTI		
Uncomplicated	Ciprofloxacin or cotrimoxazole	Nitrofurantoin or fosfomycin
For sepsis	Cefotaxime or ceftriaxone or amoxicillin–clavulanic acid	Piperacillin–tazobactam[d] or meropenem ± glycopeptide[c]
Pneumonia	Amoxicillin–clavulanic acid or ceftriaxone + macrolide or levofloxacin or moxifloxacin	Piperacillin–tazobactam[d] or meropenem–ceftazidime + ciprofloxacin ± glycopeptide[c] should be added in patients with risk factors for MRSA[b]
Cellulitis	Amoxicillin–clavulanic acid or ceftriaxone + oxacillin	Meropenem–ceftazidime + oxacillin or glycopeptides[c]

MRSA, methicillin-resistant *Staphylococcus aureus*; SBE, spontaneous bacterial empyema.
[a]Recommended empirical treatment also for HCA UTIs and pneumonia. Empirical antibiotic treatment of HCA spontaneous infections and cellulitis is decided based on the severity of infection (patients with severe sepsis should receive the regimen proposed for nosocomial infections) and local prevalence of MDR bacteria in HCA infections.
[b]Ventilator-associated pneumonia, previous antibiotic therapy, and nasal MRSA carriage.
[c]Intravenous vancomycin or teicoplanin in areas with a high prevalence of MRSA and vancomycin-susceptible enterococci. Glycopeptides must be replaced by linezolid in areas with a high prevalence of vancomycin-resistant enterococci.
[d]In areas with a low prevalence of MDR bacteria.

Supplementary Table 2. Patients Included in Each of the 46 Study Centers

Center	Patients, n
Hospital Britanico, Buenos Aires (Argentina)	17
Hospital Durand, Buenos Aires (Argentina)	3
Hospital Italiano, Buenos Aires (Argentina)	22
Hospital Posadas, Buenos Aires (Argentina)	11
Hospital Udaondo, Buenos Aires (Argentina)	38
Rosario (Argentina)	37
Ghent (Belgium)	20
Campinas (Brazil)	46
Campo Grande (Brazil)	35
Toronto (Canada)	19
Santiago (Chile)	14
Valdivia (Chile)	23
Odense (Denmark)	27
Paris (France)	15
Jena (Germany)	9
Munich (Germany)	16
Chandigarh (India)	123
New Delhi (India)	101
Cuttack (India)	26
Jakarta (Indonesia)	24
Tel-Aviv (Israel)	18
Bologna (Italy)	103
Padova (Italy)	102
Rome (Italy)	35
Turin (Italy)	69
Rotterdam (Netherlands)	4
Asuncion (Paraguay)	6
Bucheon (Republic of Korea)	17
Chuncheon (Republic of Korea)	29
Daegu, Keimyung (Republic of Korea)	10
Daejeon (Republic of Korea)	6
Anyang (Republic of Korea)	41
KUH, Seoul (Republic of Korea)	6
Inje, Seoul (Republic of Korea)	8
Kangdong, Seoul (Republic of Korea)	10
Konkuk, Seoul (Republic of Korea)	5
Ewha Womans, Seoul (Republic of Korea)	6
Suwon (Republic of Korea)	4
Moscow (Russia)	12
Hospital Clinic, Barcelona (Spain)	68
Vall d'Hebron, Barcelona (Spain)	33
Geneva (Switzerland)	34
Charlottesville, Virginia (USA)	19
Miami, Florida (USA)	13
Newark, New Jersey (USA)	6
Tucson, Arizona (USA)	12

USA, United States of America.

Supplementary Table 3. Number and Proportion of Missing Data in Study Cohort (N = 1302)

Variable	Missing, n (%)
Age	0 (0)
Sex	0 (0)
Etiology[a]	1 (0.1)
Mean arterial pressure	7 (0.5)
Heart rate	6 (0.5)
Body temperature	17 (1.3)
Respiratory rate	178 (13.7)
SpO_2/FiO_2 ratio	41 (3.2)
β-Blocker use	0 (0)
Treatment with rifaximin	0 (0)
Quinolones prophylaxis	2 (0.2)
Antibiotic treatment in previous 3 mo	8 (0.6)
Invasive procedures in previous month	137 (10.5)
Isolation of MDR bacteria in previous 6 mo	185 (14.2)
Treatment with vasopressors	17 (1.3)
Mechanical ventilation	10 (0.8)
Ascites	0 (0)
Hepatic encephalopathy	0 (0)
MELD score	4 (0.3)
MELD-Na score	5 (0.4)
Child-Pugh score	39 (3.0)
INR	4 (0.3)
Bilirubin	0 (0)
Albumin	36 (2.8)
Serum creatinine	0 (0)
Serum sodium	1 (0.1)
Leukocytes	0 (0)
C-reactive protein	200 (15.4)
SIRS	183 (14.1)
qSOFA	183 (14.1)
Septic shock	17 (1.3)
Site of infection	0 (0)
Type of infection	0 (0)
Positive cultures	0 (0)
Empirical antibiotic treatment	2 (0.2)
Duration of antibiotic treatment	22 (1.7)
Clinical efficacy of first-line treatment	5 (0.4)
Second bacterial infections	0 (0)
Resolution of infection	2 (0.2)
Length of hospital stay	7 (0.5)
In-hospital mortality	0 (0)
28-d mortality	0 (0)[a]

FiO_2, fraction of inspired oxygen; INR, international normalized ratio; SIRS, systemic inflammatory response syndrome; SpO_2, pulse oximetric saturation.
[a]Ninety-two patients were lost to follow-up after discharge.

Supplementary Table 4. Prevalence of MDR and XDR Bacteria Across Different Countries[a]

Country	MDR	XDR	ESBL *Enterobacteriaceae*	CRE	*Acinetobacter baumannii*	MRSA	VRE
Overall, n (%)	253 (34)	62 (8)	89 (12)	35 (5)	19 (3)	14 (2)	16 (2)
Asia, n (%)	97 (51)	33 (17)	26 (14)	20 (11)	14 (7)	6 (3)	5 (3)
India	63 (73)	28 (33)	18 (21)	19 (22)	11 (13)	2 (2)	3 (4)
Indonesia	3 (25)	0 (0)	1 (8)	0 (0)	1 (8)	0 (0)	0 (0)
South Korea	31 (33)	5 (5)	7 (8)	1 (1)	2 (2)	4 (4)	2 (2)
Europe, n (%)	104 (29)	20 (6)	31 (9)	13 (4)	4 (1)	8 (2)	6 (2)
Belgium	5 (33)	0 (0)	2 (13)	0 (0)	0 (0)	0 (0)	0 (0)
Denmark	6 (50)	2 (17)	2 (17)	2 (17)	0 (0)	1 (8)	0 (0)
France	3 (30)	1 (10)	0 (0)	1 (10)	0 (0)	0 (0)	0 (0)
Germany	5 (26)	1 (5)	2 (11)	1 (5)	0 (0)	0 (0)	0 (0)
Israel	4 (57)	0 (0)	3 (43)	0 (0)	0 (0)	0 (0)	0 (0)
Italy	57 (30)	14 (7)	15 (8)	7 (4)	2 (1)	5 (3)	6 (3)
Russia[b]	1 (17)	0 (0)	1 (17)	0 (0)	0 (0)	0 (0)	0 (0)
Spain	16 (23)	2 (3)	4 (6)	2 (3)	1 (1)	2 (3)	0 (0)
Switzerland	6 (26)	0 (0)	2 (9)	0 (0)	0 (0)	0 (0)	0 (0)
America, n (%)	52 (27)	9 (5)	32 (17)	2 (1)	1 (1)	0 (0)	5 (3)
Canada	4 (24)	0 (0)	3 (18)	0 (0)	0 (0)	0 (0)	0 (0)
United States	6 (16)	1 (3)	4 (11)	0 (0)	0 (0)	0 (0)	1 (5)
Argentina	22 (27)	2 (3)	14 (17)	0 (0)	0 (0)	0 (0)	2 (11)
Brazil	10 (31)	5 (16)	4 (13)	2 (6)	1 (3)	0 (0)	1 (4)
Chile	9 (39)	1 (4)	6 (26)	0 (0)	0 (0)	0 (0)	1 (3)

CRE, carbapenem-resistant *Enterobacteriaceae*; ESBL, extended spectrum β-lactamase producing; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci.
[a]Only patients with positive cultures (n = 740) were included in this analysis.
[b]European Russia. Only countries with at least 10 patients included were reported.

Supplementary Table 5. Prevalence of Specific Antibiotic Resistance of *Enterobacteriaceae*, *Staphylococcus aureus,* and Enterococci

	Enterobacteriaceae (n = 372)				*Staphylococcus aureus* (n = 54)	Enterococci (n = 91)	
Antibiotic	3GC	Quinolones	Pip-Tazo	Carbapenem	Methicillin–oxacillin	Ampicillin	Glycopeptides
Overall	131 (35)	149 (40)	89 (24)	35 (9)	14 (24)	38 (42)	16 (18)
Asia, n (%)	51 (50)	49 (48)	35 (34)	20 (20)	6 (35)	6 (43)	5 (36)
India	39 (74)	36 (68)	30 (57)	19 (36)	2 (33)	1 (25)	3 (75)
Indonesia	1 (13)	3 (38)	1 (13)	0 (0)	0 (0)	—	—
South Korea	11 (27)	10 (24)	4 (10)	1 (2)	4 (40)	5 (50)	2 (20)
Europe, n (%)	45 (27)	56 (33)	37 (22)	13 (8)	8 (26)	27 (47)	6 (11)
Belgium	2 (15)	6 (46)	3 (23)	0 (0)	0 (0)	—	—
Denmark	4 (44)	2 (22)	3 (33)	2 (22)	1 (50)	—	—
France	0 (0)	0 (0)	1 (14)	1 (14)	0 (0)	2 (100)	0 (0)
Germany	3 (27)	3 (27)	2 (18)	1 (9)	0 (0)	1 (50)	0 (0)
Israel	3 (100)	2 (67)	2 (67)	0 (0)	0 (0)	1 (100)	0 (0)
Italy	24 (28)	29 (34)	22 (26)	7 (8)	5 (31)	20 (54)	6 (16)
Russia	1 (33)	1 (33)	0 (4)	0 (0)	0 (0)	1 (50)	0 (0)
Spain	6 (34)	9 (47)	3 (16)	2 (11)	2 (25)	1 (10)	0 (0)
Switzerland	2 (14)	2 (14)	1 (7)	0 (0)	0 (0)	1 (33)	0 (0)
America, n (%)	35 (34)	44 (43)	17 (17)	2 (2)	0 (0)	5 (25)	5 (25)
Canada	3 (60)	2 (40)	3 (60)	0 (0)	0 (0)	—	—
United States	4 (29)	6 (43)	1 (7)	0 (0)	0 (0)	1 (20)	1 (20)
Argentina	14 (30)	20 (43)	8 (17)	0 (0)	0 (0)	1 (13)	2 (25)
Brazil	6 (33)	5 (28)	4 (22)	2 (11)	0 (0)	2 (67)	1 (33)
Chile	7 (41)	10 (59)	1 (6)	0 (0)	0 (0)	1 (25)	1 (25)

3GC, third-generation cephalosporins; Pip-Tazo, piperacillin–tazobactam.

Supplementary Table 6. Data on Empirical Antibiotic Treatment, Antibiotic Changes, and Microbiological and Clinical Efficacy

Variable	
Treatment with ≥2 antibiotics, n (%)	448 (34)
Antibiotic class used, n (%)	
Classic β-lactams plus β-lactamase inhibitors[a]	365 (28)
Piperacillin–tazobactam	288 (22)
Third-generation cephalosporins	523 (40)
Quinolones	180 (14)
Carbapenems	204 (16)
Glycopeptides	166 (13)
Lipopeptides	17 (1)
Tigecycline	20 (2)
Linezolid	25 (2)
Others[b]	244 (19)
Antifungal treatment, n (%)	
Azoles	34 (3)
Echinocandins	11 (1)
Adherence to EASL antibiotic treatment recommendations, n (%)	
Adherent	796 (61)
Weaker	325 (25)
Broader	179 (14)
Microbiological efficacy of empirical antibiotic treatment, n (%)[c]	522 (71)
Clinical efficacy of empirical antibiotic treatment, n (%)	788 (61)
Changes of antibiotic treatment, n (%)	
Escalation	477 (37)
De-escalation	102 (8)
No changes	723 (56)
Duration of antibiotic treatment (*d*), median (IQR)	10 (7–15)
Development of new infections, n (%)[d]	268 (21)
Resolution of infection, n (%)	1038 (80)

IQR, interquartile range.
[a]Amoxicillin–clavulanic acid or ampicillin–sulbactam.
[b]Other antibiotics included other β-lactams, other cephalosporins, cefepime, colistin, aminoglycosides, macrolides, and tetracyclines.
[c]Only patients with positive cultures were included in this analysis.
[d]Pneumonia (n = 73), UTIs (n = 53), SBP (n = 35), spontaneous bacteremia (n = 25), skin and soft tissues infections (n = 18), and others (n = 64).

Supplementary Table 7. Comparison of Clinical Outcomes According to De-escalation or Continuation of Empirical Antibiotic Treatment[a]

Variable	De-escalation (n = 102)	No changes (n = 723)	*P* value
Resolution of infection, n (%)	91 (89)	662 (92)	.432
Development of ACLF during hospitalization, n (%)[b]	17 (24)	89 (18)	.258
Development of septic shock during hospitalization, n (%)[c]	8 (9)	50 (8)	.841
In-hospital mortality, n (%)[d]	13 (13)	80 (12)	.759
28-d mortality, n (%)[e]	11 (11)	95 (15)	.483

[a]Patients with escalation of antibiotic treatment during hospitalization (n = 477) were excluded from this analysis.
[b]Patients with ACLF at inclusion (n = 248) were excluded from this analysis.
[c]Patients with septic shock at inclusion (n = 90) were excluded from this analysis.
[d]Patients who received a transplant during hospitalization (n = 30) were excluded from this analysis.
[e]Patients who received a transplant or were lost to follow-up (n = 86) were excluded from this analysis.

Supplementary Table 8. Characteristics of Second Infection

Variable	n = 268
Site of infection, n (%)	
UTI	53 (20)
SBP	35 (13)
Pneumonia	73 (27)
Spontaneous bacteremia	26 (10)
Skin and soft tissue infections	18 (7)
Other[a]	63 (24)
Different site of second infection, n (%)[b]	217 (81)
Patients with positive cultures, n (%)	160 (60)
Bacteria per patient, n (%)	
1	146 (91)
>1	14 (9)
Strains isolated, n	176
Type of strain isolated, n (%)	
Gram negative	97 (55)
Gram positive	60 (34)
Fungi	19 (11)
Most frequently isolated bacteria, n (%)	
Escherichia coli	25 (14)
Klebsiella pneumoniae	34 (19)
Staphylococcus aureus	14 (8)
Enterococcus faecium	15 (9)
Acinetobacter baumannii	10 (6)
Pseudomonas aeruginosa	8 (5)
Different strain isolated, n (%)[a]	100 (85)
MDR bacteria, n (%)[c]	88 (50)
XDR bacteria, n (%)[d]	30 (17)

[a]Secondary bacteremia (n = 18), *Clostridium difficile* infection (n = 16), signs of sepsis without focus (n = 4), cholangitis (n = 5), endocarditis (n = 3), bone or joint infection (n = 3), pleural empyema (n = 3), secondary bacterial peritonitis (n = 2), upper respiratory infection (n = 2), and other (n = 7).
[b]Of 118 bacteria isolated in patients with positive cultures from the first and second infections (n = 107).
[c]In 81 patients (51%).
[d]In 27 patients (17%).

Supplementary Table 9. Clinical Outcomes of Infections due to MDR Bacteria and Impact of Appropriate Empirical Antibiotic Treatment

	Overall positive cultures			MDR bacterial infections		
Variable	No MDR (n = 487)	MDR (n = 253)	*P* value	Susceptible to empirical antibiotic treatment (n = 98)	Nonsusceptible to empirical antibiotic treatment (n = 155)	*P* value
Clinical efficacy of empirical antibiotic treatment, n (%)	331 (68)	100 (40)	<.001	65 (66)	35 (23)	<.001
Escalation of antibiotic treatment, n (%)	124 (26)	148 (59)	<.001	31 (32)	117 (76)	<.001
Duration of antibiotic treatment (*d*), median (IQR)	10 (7–15)	12 (7–18)	.013	10 (7–15)	14 (8–20)	.006
Resolution of infection, n (%)	398 (82)	182 (72)	.003	84 (86)	98 (63)	<.001
Development of new infections, n (%)	101 (21)	53 (21)	1.000	21 (21)	32 (21)	1.000
Transfer to ICU, n (%)[a]	94 (23)	72 (36)	.001	26 (33)	46 (37)	.725
Development of ACLF during hospitalization, n (%)[b]	92 (28)	59 (36)	.118	19 (30)	40 (39)	.279
Development of septic shock during hospitalization, n (%)[c]	62 (13)	57 (27)	<.001	20 (25)	37 (28)	.684
Administration of mechanical ventilation, n (%)[d]	53 (12)	48 (20)	.003	11 (12)	37 (26)	.019
Administration of renal replacement therapy, n (%)	34 (7)	42 (17)	<.001	16 (16)	26 (17)	1.000
Length of hospital stay (d), median (IQR)	15 (9–26)	18 (10–30)	.032	20 (10–33)	17 (10–27)	.277
In-hospital mortality, n (%)[e]	97 (21)	75 (31)	.004	21 (23)	54 (35)	.040
28-d mortality, n (%)[f]	99 (22)	72 (34)	.002	19 (24)	53 (39)	.029

IQR, interquartile range.
[a]Patients with indication to ICU admission at inclusion (n = 121) were excluded from this analysis.
[b]Patients with ACLF at inclusion (n = 248) have been excluded from this analysis.
[c]Patients with septic shock at inclusion (n = 105) were excluded from this analysis.
[d]Patients on mechanical ventilation at inclusion were excluded from this analysis (n = 47).
[e]Patients who received a transplant during hospitalization (n = 25) were excluded from this analysis.
[f]Patients who received a transplant or were lost to follow-up (n = 73) were excluded from this analysis.

Supplementary Table 10. Demographic, Clinical, and Laboratory Characteristics of Survivors vs Nonsurvivors[a]

Variables	Survivors (n = 974)	Nonsurvivors (n = 293)	*P* value
Age (*y*), mean (SD)	56 (13)	57 (13)	.575
Men, n (%)	657 (68)	217 (74)	.037
Etiology of cirrhosis (alcohol), n (%)	516 (53)	169 (58)	.161
Type of infections, n (%)			<.001
Urinary tract infection	230 (24)	51 (17)	
Spontaneous bacterial peritonitis	253 (26)	90 (31)	
Pneumonia	157 (16)	80 (27)	
Spontaneous bacteremia	76 (8)	20 (7)	
Skin and soft tissue infection	83 (9)	18 (6)	
Other	175 (18)	34 (12)	
Treatment with β-blockers, n (%)	651 (67)	207 (71)	.227
Ascites, n (%)	725 (74)	245 (84)	.001
Hepatic encephalopathy, n (%)	307 (32)	174 (59)	<.001
Respiratory rate (*breaths/min*)– mean (SD)	18 (16–20)	20 (18–22)	<.001
Body temperature (°*C*), median (IQR)	36.9 (36.4–37.6)	37.0 (36.4–37.4)	.461
MAP (*mm Hg*), mean (SD)	83 (12)	80 (15)	.008
Heart rate (*bpm*), mean (SD)	87 (17)	91 (17)	.001
INR, median (IQR)	1.5 (1.3–2.0)	1.9 (1.5–2.4)	<.001
Bilirubin (*mg/dL*), median (IQR)	3.2 (1.6–6.8)	5.6 (2.5–13.8)	<.001
Albumin (*g/dL*), mean (SD)	2.6 (2.3–3.10)	2.5 (2.1–2.9)	<.001
SCr (*mg/dL*), median (IQR)	1.0 (0.8–1.7)	1.6 (1.0–2.5)	<.001
Serum sodium (*mmol/L*), media (DS)	133 (7)	131 (8)	<.001
CRP (*mg/L*), median (IQR)	31 (12–68)	52 (24–97)	<.001
Leukocytes ($\times 10^9$/L), median (IQR)	8.0 (5.0–12.2)	10.4 (6.9–14.5)	<.001
MELD-Na score, mean (SD)	23 (7)	28 (7)	<.001
Child-Pugh score, mean (SD)	9.6 (2.2)	11.1 (2.0)	<.001
ACLF at inclusion, n (%)	270 (28)	176 (60)	<.001
SIRS, n (%)	273 (33)	123 (48)	<.001
Positive qSOFA score, n (%)	147 (18)	100 (39)	<.001
Septic shock	93 (10)	72 (25)	<.001
Nosocomial infections, n (%)	220 (23)	101 (35)	<.001
MDR bacteria, n (%)	170 (18)	75 (26)	.003
XDR bacteria, n (%)	35 (4)	26 (9)	.001
In vitro susceptibility to empirical antibiotic treatment, n (%)			<.001
Nonsusceptible	143 (15)	72 (25)	
Susceptible	400 (41)	100 (34)	
Negative culture	431 (44)	121 (41)	
Antibiotic changes, n (%)			<.001
No changes	616 (63)	80 (27)	
De-escalation	86 (9)	13 (4)	
Escalation	272 (28)	200 (68)	
Second infections, n (%)	150 (15)	110 (38)	<.001
Resolution of infection, n (%)	921 (95)	87 (30)	<.001

CRP, C-reactive protein; INR, international normalized ratio; MAP, mean arterial pressure; SCr, serum creatinine; SD, standard deviation; SIRS, systemic inflammatory response syndrome.

[a]Patients who received a transplant (n = 35) were not included in this table.

Supplementary Table 11. Independent Predictors of In-Hospital and 28-Day Mortality Using Clinical Efficacy Rather Than Microbiologically Efficacy of Empirical Antibiotic Treatment

Variables	sHR	95% CI	*P* value
In-hospital mortality			
Age	1.02	1.01–1.03	.002
MELD-Na score	1.58	1.05–1.10	<.001
ACLF	1.61	1.14–2.18	.006
Positive qSOFA	1.33	0.99–1.78	.058
Leukocytes ($\times 10^3$)°	1.52	1.15–2.01	.004
C-reactive protein (mg/l)°	1.18	1.03–1.35	.015
Clinical efficacy of empirical treatment[a]	0.22	0.16–0.30	<.001
28-d mortality			
Age	1.02	1.01–1.03	.001
MELD-Na score	1.07	1.05–1.10	<.001
ACLF	1.65	1.17–2.34	.005
Positive qSOFA	1.42	1.05–1.91	.024
C-reactive protein (*mg/L*)[b]	1.21	1.06–1.37	.001
Clinical efficacy of empirical treatment[a]	0.20	0.14–0.27	<.001

CI, confidence interval.
[a]Ineffective treatment was used as the reference group.
[b]Variables were log-transformed.

Supplementary Table 12. Adherence to the EASL Empirical Antibiotic Treatment Recommendations Among Geographic Areas

	Adherent	Weaker	Broader	*P* value
Geographic area, n (%)				<.001
India	132 (53)	72 (29)	46 (18)	
Other Asian centers	95 (57)	51 (31)	20 (12)	
North Europe	82 (60)	43 (31)	12 (9)	
South Europe	279 (65)	88 (21)	60 (14)	
North America	31 (46)	16 (31)	21 (24)	
South America	177 (70)	55 (8)	20 (22)	