Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe

Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe

Javier Fernández [1,2,3], Verónica Prado[1], Jonel Trebicka[2,4], Alex Amoros[2], Thierry Gustot[5], Reiner Wiest[6], Carme Deulofeu[2], Elisabet Garcia[2], Juan Acevedo[7], Valentin Fuhrmann[8], François Durand[9], Cristina Sánchez[2], Maria Papp[10], Paolo Caraceni[11], Victor Vargas[3,12], Rafael Bañares[3,13], Salvatore Piano[14], Martin Janicko[15], Agustin Albillos[16], Carlo Alessandria[17], German Soriano[3,18], Tania M. Welzel[19], Wim Laleman[20], Alexander Gerbes[21], Andrea De Gottardi[6], Manuela Merli[22], Minneke Coenraad[23], Faouzi Saliba[24], Marco Pavesi[2], Rajiv Jalan[25], Pere Ginès[1,3], Paolo Angeli[14], Vicente Arroyo[2] and the European Foundation for the Study of Chronic Liver Failure (EF Clif)

[1]Liver ICU, Liver Unit, Hospital Clinic, University of Barcelona, Barcelona, Spain,

[2]European Foundation of Chronic Liver Failure (EF-Clif), Barcelona, Spain

[3]Centro de Investigación Biomédica en Red de Enfermedades Hepáticas y Digestivas (CIBEREHED), ISCIII

[4]University of Bonn, Germany

[5]Liver Transplant Unit, Erasme Hospital, Brussels, Belgium,

[6]Department of Medicine and Surgery, Inselspital, University of Bern, Bern, Switzerland

[7]South West Liver Unit, Derriford Hospital, UK

[8]University Medical Center Hamburg-Eppendorf, Germany

[9]Hopital Beaujon, Paris, France

[10]Department of Internal Medicine, Division of Gastroenterology, Faculty of Medicine, University of Debrecen, Hungary

[11]University of Bologna, Italy

[12]Hospital Vall d'Hebron, Barcelona, Spain

[13]Hospital Gregorio Marañon, Madrid, Spain

[14]University of Padova, Padova, Italy

[15]Pavol Jozef Safarik University in Kosice, Slovakia

[16]Hospital Universitario Ramon y Cajal, Madrid, Spain

[17]San Giovanni Battista Hospital, Turin, Italy

[18]Hospital of Santa Creu i Sant Pau, Barcelona, Spain

[19]University Hospital of Frankfurt, Germany

[20]University UZ Leuven, Belgium

[21]Department of Medicine II, Liver Centre Munich, University Hospital, LMU Munich, Germany

[22]Sapienza University of Rome, Italy

[23]Leiden University Medical Centre, Netherlands

[24]Centre Hepato-Biliare, Hòpital Paul Brousse, Paris, France

[25]ILDH, Division of Medicine, University College London Medical School, London, United Kingdom

Address for correspondence: J. Fernández, MD, PhD. Liver Unit, Hospital Clínic, Villarroel 170, 08036, Barcelona. Spain. Phone: 34-93-2275400 3329; Fax: 34-93-4515522; E-mail: Jfdez@clinic.ub.es.

Word count: 6736 with references

Number of figures and tables: 4 figures; 6 tables, 8 Supplementary tables, 1 Supplementary figure

Keywords: epidemiology; prevalence; prognosis; antibiotic resistance; antibiotic strategies

List of Abbreviations: ACLF: acute-on-chronic liver failure; AD: acute decompensation; CANONIC: chronic liver failure (CLIF) Acute-on-Chronic Failure in Cirrhosis; SBP: spontaneous bacterial peritonitis; UTI: urinary tract infection; SSTI: skin and soft tissue infections; MDROs: multidrug-resistant organisms; PMN: polymorphonuclear; SBE: spontaneous bacterial empyema;

XDR: extensively-drug resistance; PDR: pandrug resistance; ESBL: extended-spectrum beta-lactamase; MRSA: methicillin-resistant *Staphylococcus aureus*; VSE: vancomycin-susceptible *Enterococcus*; VRE: vancomycin-resistant *Enterococcus;* CDI: *Clostridium difficile* infection; SIRS: systemic inflammatory response syndrome; ICU: intensive care unit; HCA: healthcare-associated; CA: community-acquired.

Financial support: The study was supported by the European Foundation for the Study of Chronic Liver Failure (EF-Clif). EF-Clif received unrestricted donations from Grifols and Cellex Foundations and is partner or contributor in several projects of the EU Horizon 2020 research program. Maria Papp was supported by the Janos Bolyai Research Scholarship of the Hungarian Academy of Science (BO/00232/17/5) and the New National Excellence Program of the Ministry of Human Capacities (ÚNKP-18-4 Bolyai Plus). Pere Ginès is a recipient of the ICREA ACADEMIA AWARD (2015-2020).

Disclosures

The EASL-CLIF Consortium is a network of 101 European University hospitals supported by the EF-Clif. EF-Clif is a private non-profit organization aimed at improving clinical and translational research in cirrhosis. The scientific agenda of the EASL-CLIF Consortium and the specific research protocols are made exclusively by the Steering Committee members without any participation of pharmaceutical companies.

Conflicts of interest

Javier Fernandez has received grant and research support from Grifols, speaker honorarium from MSD and educational grant from Pfizer. François Durand has received research funding and grant from Astellas and Gilead and served scientific advisory board for Novartis and Gilead.

Agustin Albillos has served as advisor/lecturer for Abbvie, Gilead, Gore, Grifols, Intercept Pharmaceuticals, Pfizer and Merck & Co and received research/educational grants from Gilead. Tania M. Welzel received consultant honorariums from Abbvie, Gilead and BMS. Manuela Merli has received speaker honorarium from Kedrion. Pere Ginès has received speaker honorarium and research funding from Grifols, served on the scientific advisory board for Ferring and Sequena and received research funding from Sequena. Vicente Arroyo has received grant and research support from Grifols. All other authors declare that they have no conflict of interest

Author contributions: JF, VP, JA, AA, CD, EG, CS, MP and VA participated in data analysis and interpretation. JF, TG, RW, VF, JT, FD, RJ, MP, PC, VV, RB, SP, MJ, AA, CA, GS, TN, WL, AG, AdG, MM, MC, PG, PA and VA participated in the writing group. VA was responsible for obtaining funding and overall project collaboration.

Abstract

Background: Antibiotic resistance has been increasingly reported in decompensated cirrhosis in single-center studies. Prospective investigations reporting broad epidemiological data are scarce.

Aims and Methods: Prospective evaluation in 2 series of patients hospitalized with decompensated cirrhosis. The Canonic series included 1146 patients from Northern, Southern and Western Europe in 2011. Data on epidemiology, clinical characteristics of bacterial infections, microbiology and empirical antibiotic schedules were assessed. A second series of 883 patients from Eastern, Southern and Western Europe was investigated to evaluate potential epidemiological changes (2017-2018).

Results: 455 patients developed 520 infections (39.7%) in the first series. Spontaneous bacterial peritonitis, urinary tract infections and pneumonia were the most frequent infections. Nosocomial episodes predominated in this series. Nearly half of the infections were culture-positive; 29.2% of them were caused by multidrug-resistant organisms (MDROs). MDR strains were more frequently isolated in Northern and Western Europe. ESBL-producing *Enterobacteriaceae* were the most frequent MDROs isolated in this series although prevalence and type of MDROs differed markedly among countries and centers. Antibiotic resistance was associated to poor prognosis and to failure of antibiotic strategies based on third-generation cephalosporins or quinolones. Nosocomial infection (OR: 2.74; p<0.001**),** ICU admission (OR: 2.09; p=0.02), and recent hospitalization (OR: 1.93; p=0.04**)** were identified as independent predictors of MDR infection. Prevalence of MDROs in the second series (392 infections/284 patients) was 23%; 38% in culture-positive infections. A mild increase in the rate of carbapenem-resistant *Enterobacteriaceae* was observed in this series.

Conclusions: MDR bacterial infections constitute a prevalent, growing and complex healthcare problem in decompensated cirrhosis and ACLF across all Europe and negatively impact

prognosis. Strategies aimed at preventing the spread of antibiotic resistance in cirrhosis should be urgently evaluated.

LAY SUMMARY

Infections caused by bacteria resistant to the main antibiotic families are prevalent in patients with cirrhosis. This study demonstrates that this healthcare problem is increasing and extends through all European regions. Infections caused by these difficult to treat bacteria solve less frequently and often cause the death of the patient. Type of resistant bacteria varies markedly among different hospitals.

INTRODUCTION

Bacterial infections constitute a frequent complication of patients with decompensated cirrhosis and the most frequent trigger of ACLF in Western countries.[1 5] Patients with cirrhosis and acute decompensation (AD) are prone to develop spontaneous and secondary bacterial infections, risk that magnifies at short-term in patients with ACLF.[1,5,6] Bacterial infection has a critical relevance in the clinical course of decompensated cirrhosis, increasing 2-4 fold short-term mortality.[7,8] Recent data also show that bacterial infections are severe and associated with intense systemic inflammation, poor clinical course and high mortality in patients with ACLF.[6]

Early diagnosis and adequate empirical antibiotic therapy of bacterial infections is key in the management of cirrhotic patients.[1,9] However, epidemiology of bacterial infections is nowadays much more complex than in the past.[9] The efficacy of classical empirical antibiotic strategies based on the administration of third-generation cephalosporins has markedly decreased in the last decade due to the emergence of multidrug-resistant (MDR) bacteria.[9 13] Resistance to antibiotics in pathogenic bacteria is currently a major global public health problem,[14] and is particularly serious in patients with decompensated cirrhosis. These patients frequently accumulate several risk factors for MDR organisms (MDROs) including recurrent hospitalizations, invasive procedures and repeated exposures to prophylactic or therapeutic antibiotics.[9] Antibiotic overuse and failure of control measures to prevent the spread of MDROs in the healthcare setting have magnified antimicrobial resistance in cirrhosis. Therefore, the characterization of these

epidemiological changes and the identification of the MDROs that infect our cirrhotic patients are of major clinical relevance. The great majority of the epidemiological data on antibiotic resistance in cirrhosis derive from single-centre studies[2,4,10 13,15 20] or from multicentre studies performed in specific countries[21] or assessing specific infections.[22] However, at present no study has been reported in patients with cirrhosis and all type of infections, exploring the epidemiology of MDROs in large geographical, multinational regions. These studies are essential to understand the global impact of antibiotic resistance.

Therefore, the current study was designed to assess the prevalence of MDR bacterial infections in cirrhosis across Europe, potential epidemiological differences among regions and centers, the characteristics of these infections, their impact on prognosis, risk factors for MDR and type and efficacy of empirical antibiotic treatment using information carefully collected on bacterial infection from the Canonic Study database.[5] Additionally we analyzed a more recent series to detect new potential epidemiological changes.

PATIENTS AND METHODS

Study population and aims of the study

In the current investigation two prospective series were evaluated. The first one considered all patients included in the Canonic series (February to September 2011). Fifty-three subjects with and 150 without infection with incomplete data at inclusion or during follow-up were excluded. Therefore, 1146 patients were analyzed, 375 with ACLF (269 diagnosed at enrolment and 106 during hospitalization) and 771 with AD. Data on epidemiology, clinical characteristics of infections, microbiology and empirical and final antibiotic schedules were prospectively recorded. A more recent series was also evaluated to assess new potential epidemiological changes (April 2017 to February 2018). It was extracted from a currently ongoing prospective study on the natural history of decompensated cirrhosis. Patients who completed the 12 weeks follow-up were included (883 patients out of 1295).

The aim of the study was to assess the epidemiology of bacterial infections across Europe and potential differences in the prevalence and type of MDROs among geographical areas, countries and centers. Three different strategies for the analysis of the data were used. First, infections developing in the whole region and in the different European regions as defined by the United Nations Geoscheme for Europe were compared. In Canonic series the regions and countries included were the following: Northern Europe (Denmark, Ireland, UK), Western Europe (Austria, Belgium, France, Germany, Netherlands and Switzerland) and Southern Europe (Italy and Spain). Infections occurring in Czech Republic were not considered in this analysis (n=3; Eastern Europe). The second series included infections developed in Western (Belgium, France, Germany, Netherlands and Switzerland), Southern (Italy and Spain) and Eastern Europe (Hungary, Slovakia). Second, comparisons were performed among countries (11 in the first series and 9 in the second) and centers (27 in the Canonic series and 19 in the second series). Finally, the third objective was to perform a comprehensive assessment of the impact and risk factors of

MDR bacterial infections and to evaluate the type and efficacy of empirical antibiotic strategies used in the whole region. This last objective was only evaluated in the Canonic series.

Definitions on bacterial infection and ACLF

Diagnostic criteria of bacterial infections were the following: spontaneous bacterial peritonitis (SBP): polymorphonuclear (PMN) cell count in ascitic fluid ≥250/mm^3; urinary tract infection (UTI): abnormal urinary sediment (>10 leukocytes/field) and positive urinary culture or uncountable leukocytes per field if negative cultures; spontaneous bacteremia: positive blood cultures and no cause of bacteremia; secondary bacteremia: a) catheter-related infection (positive blood and catheter cultures), b) bacteremia occurring within 24h after an invasive procedure; pneumonia: clinical signs of infection and new infiltrates on chest x-ray; bronchitis: clinical features of infection, no radiographic infiltrates and positive sputum culture; skin and soft tissue infections (SSTI): clinical signs of infection associated with swelling, erythema, heat and tenderness in the skin; cholangitis: cholestasis, right upper quadrant pain and/or jaundice and radiological data of biliary obstruction; spontaneous bacterial empyema (SBE): PMN count in pleural fluid ≥500/mm³ (250/mm³ if positive culture) ; secondary peritonitis: PMN count in ascitic fluid ≥250/mm³ and evidence (abdominal CT/ surgery) of an intraabdominal source of infection; *Clostridium difficile* infection (CDI): positive stool toxin in a patient with diarrhea; unproved bacterial infection: presence of fever (≥ 38ºC) and leukocytosis (white blood cell count ≥ 12.000 /mm^3) requiring antibiotic therapy without any identifiable source. Infections diagnosed at admission or within 2 days after admission were classified as healthcare-associated (HCA) in patients with a prior contact with the healthcare environment (hospitalization or short term-admission for at least 2 days in the previous 90 days, residence in a nursing home or a long-term care facility or chronic hemodialysis). The remaining infections were considered community-

acquired when they were present at admission or developed within the first 48 hours after hospitalization and nosocomial when the diagnosis was made thereafter.[6,10]

MDR was defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories. Extensively-drug resistance (XDR) was defined as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and pandrug-resistant (PDR) as non-susceptibility to all currently available agents.[23] The following bacteria were considered MDR in the current study: extended-spectrum beta-lactamase (ESBL, mainly *Escherichia coli* and *Klebsiella pneumoniae)* or desrepressed chromosomic AmpC ß-lactamase-producing *Enterobacteriaceae* (*Enterobacter or Citrobacter spp),* carbapenem-resistant *Klebsiella pneumoniae,* carbapenem-resistant *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia,* carbapenem-resistant *Acinetobacter baumanii*, *Burkholderia cepacia*, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-susceptible and vancomycin-resistant *Enterococcus faecium* (VSE, VRE).

ACLF at infection diagnosis was defined according to the CLIF consortium criteria.[5] Patients were considered to have SIRS (sepsis) if they fulfilled at least two of the following criteria: (a) core temperature > 38ºC or < 36ºC; (b) heart rate > 90 beats/minute; (c) respiratory rate > 20 breaths/minute in the absence of hepatic encephalopathy; and (d) white blood cell count > 12.000 or < 4000 /mm^3, or differential count showing ≥ 10% immature PMN neutrophils. Severe sepsis was defined by the presence of SIRS and at least one acute organ failure. Septic shock was diagnosed by the presence of data compatible with SIRS and need of vasopressor drugs in the setting of hypotension.[24] Recently defined sepsis criteria were not applied in the current study as they were proposed after the end of the Canonic Study.[25]

Infections were considered cured when all clinical signs of infection disappeared and on the presence of: a) urinary infections: normal urine sediment and negative urine culture; b) spontaneous or secondary bacteremia: negative control cultures after antibiotic treatment; c)

pneumonia: normal chest X-ray and negative control cultures if positive at diagnosis; d) bronchitis: negative bronchial aspirate/sputum culture; e) cellulitis: normal physical exam of the skin and negative control cultures if positive at diagnosis; f) cholangitis: improvement of cholestasis, resolution of clinical symptoms and negative control cultures if positive at diagnosis; g) SBP and SBE: PMN cell count in ascitic/pleural fluid < 250/mm³ and negative control cultures if positive at diagnosis. Resolution of the rest of infections was based on conventional clinical criteria.

Definitions on antibiotic therapy in the Canonic series

Two types of empirical antibiotic strategies were considered: 1) "Classical" strategies: those including first to third-generation cephalosporins, amoxicillin clavulanic-acid/cloxacillin or quinolones and 2) MDR strategies: regimens using piperacillin-tazobactam, carbapenems or ceftazidime/cefepime± glycopeptides (or linezolid/daptomycin).

The criteria used to consider an initial antibiotic therapy appropriate were the following: 1) Culture positive infections: if an antibiotic with an in vitro activity appropriate for the isolated pathogen or pathogens was administered at diagnosis of infection; 2) Culture-negative infections: when the antibiotic strategies administered at the time of infection diagnosis solved the infection without need for further escalation. Otherwise, the initial therapy was considered inappropriate.[6] Fulfillment of international guidelines[1] was not used as criterion because there were no broadly accepted norms for empiric management of bacterial infections in cirrhosis at the time of performing the study. Time to antibiotic therapy administration after diagnosis of infection was not recorded.

Statistical analysis

Results are presented as frequencies and percentages for categorical variables, means and SDs for normally distributed continuous variables and median and interquartile range for not normally

distributed continuous variables. In univariate analyses, Chi-square test was used for categorical variables, Student's t-test or ANOVA for normal continuous variables and Mann-Whitney or Kruskal Wallis test for not normally distributed continuous variables. To identify predictors of infection caused by MDROs, logistic regression models were carried out. Factors showing a clinically and statistically significant association to the outcome in univariate analyses ($p<0.1$) were selected for the initial model. The final models were fitted by using a step-wise forward method based on Likelihood Ratios with the same significance level ($p<0.05$) for entering and dropping variables. Binary logistic regression models were used to identify independent predictors of MDROs. In all statistical analyses, significance was set at $p<0.05$. Analyses were done with SPSS (version 23.0; SPSS, Inc. Chicago, IL) and SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical packages.

RESULTS

CANONIC SERIES

Overall bacterial infections

Table 1 shows the prevalence, type, clinical and epidemiological characteristics of bacterial infections diagnosed in the whole Canonic series and in patients from Northern, Southern and Western Europe. A total of 455 patients (39.7%) developed 520 bacterial infections during the study period with no differences in the prevalence of infection between European regions. Fifty-eight patients developed 2 or more infections. The majority of infections were diagnosed outside the ICU (81.8%). Regular ward was the most frequent site of hospitalization at infection diagnosis in Northern and Western Europe (49% and 42.5%, respectively) and emergency department (64%) in Southern Europe ($p<0.001$). SBP (n=130) and UTI (n=111) were the most frequent proved infections in the whole series and in patients from Southern and Western Europe. Pneumonia was the most prevalent infection in Northern Europe. Pseudomembranous colitis was mainly observed in Northern Europe ($p=0.002$) while unproved infections were less prevalent in the West ($p=0.03$). No other differences in the type of infections were observed between groups. Nosocomial infections predominated in the whole series (n=273; 52.5%), being more frequent in Western and Northern Europe (64% and 56% vs. 38% in the South; $p<0.001$). Severity of infection at diagnosis was also significantly higher in Northern and Western Europe with a higher prevalence of severe sepsis/shock (22% and 19% vs. 9% in the South, $p<0.001$) and ACLF (56% and 57% vs. 38% in the South, $p<0.001$).

Bacteria isolated in the whole series, across European regions, per country and per center

A total of 284 bacteria were isolated in 264 culture-positive infections (50.8%). Isolation rate was significantly higher in Northern and Western Europe (56% each vs. 43.5% in the South; $p<0.001$, Table 1). Bacterial isolation was similar in nosocomial, healthcare-associated (HCA)

and community-acquired (CA) infections (53% vs. 47% vs. 49%; p=0.519). The rate of positive cultures was 75% in UTI, 52% in SBP, 45% in SSTI and 43% in pneumonia.

Supplementary Table 1 shows all bacteria isolated in the whole series, in Northern, Southern and Western Europe and per country. *Escherichia coli* was the most frequently isolated organism (35%), followed by *Staphylococcus aureus* (10.5%), *Enterococcus faecalis* (10%), *Klebsiella pneumoniae* (7%) and *Streptococcus viridans and Enterococcus faecium* (5% each).

Eighty out of the 284 organisms isolated in the study (28.1%) were MDROs. They were isolated in 77 infections (14.8% of all infections, 29.2% of culture-positive infections) from 61 patients (13.4%). As a whole, ESBL-producing *Escherichia coli* was the most frequent MDRO reported (n=19), followed by VSE (n=15), MRSA (n=12) and ESBL-producing *Klebsiella pneumoniae* (n=9) (Table 2). The total number of isolated MDROs was significantly higher in infections occurring in Northern and Western Europe [14 (19%) and 46 (19%) vs. 20 (9.7%); p<0.001]. Prevalence of MDROs also differed significantly among countries ranging from 0% in Switzerland, Czech Republic and Denmark, 7% in Spain, 19.6% in Italy, 21% in UK, 25% in Ireland and 34% in France (p <0.001) [Table 2].

Type of isolated MDROs also differed among countries (Table 2) and European regions (Table 2, Suppl Figure 1). ESBL and Amp-C producing *Enterobacteriaceae* were more frequent in France (18%), followed by Italy (13%), UK and Netherlands (12% each), Austria (3.8%), Belgium (3.4%) and Spain (3%). VSE predominated in France and Austria (8% each) and MRSA in infections occurring in The Netherlands (6%), UK and Ireland (5% each). Infections by XDR bacteria were infrequent and heterogeneously distributed. Carbapenem-resistant *Klebsiella pneumoniae* was reported in 2 patients (<1%), 1 from UK and 1 from Germany while carbapenem-resistant *Pseudomonas aeruginosa* was reported in 4 cases, 2 in Southern Europe (0.8%; 1 in Italy, 1 in Spain) and 2 in Western Europe (0.8%; France). VRE was also infrequent (n=3) and diagnosed in Northern (2.8%; 1 in UK and 1 in Ireland) and Western Europe (0.4%; 1 in Germany). No

statistically significant differences were observed when comparing the type of MDROs isolated in the different European regions. No PDR bacteria was reported.

Suppl Table 2 and Figure 1 show the MDR bacteria isolated in the different centers in the Canonic series. Nineteen centers (70%) reported infections caused by MDROs. Remarkable differences were observed in the prevalence and type of MDR strains among hospitals. Frankfurt (41%), Clichy (39%), Villejuif (30%) and London (King's College, 27%) showed the highest prevalence of MDROs while no resistant strains were reported in Aarhus, Hvidovre, Bern, Graz, Ghent, Madrid (Ramon y Cajal) and Prague. No culture-positive infections were reported in Vienna. ESBL-*E. coli* predominated in Clichy, Frankfurt, Barcelona (St. Pau), Padua, London (King's College) and Leuven and ESBL-*Klebsiella pneumoniae* in London (UC) and Hamburg. Prevalence of ESBL/Amp-C ß-lactamase-producing *Enterobacteriaceae* (panel A) and of MRSA (panel B) observed in the different centres participating in the Canonic Study is shown in Figure 2. A heterogeneous distribution of MDROs was observed among different centres, even in those located in the same geographical region and city.

Infections caused by MDROs

Table 3 shows the prevalence, type, clinical and epidemiological characteristics of bacterial infections caused by MDROs in the whole series and in the different European regions. Prevalence of MDR bacterial infections was 14.8% if all infections are considered (13.4% if analysis is restricted to only one infection per patient) and 29.2% in culture-positive episodes. Prevalence of MDROs was significantly higher in Northern and Western Europe (all infections: 18.1% and 19.3%; culture-positive infections: 32.5% and 34.6%) than in Southern Europe (8.7% and 20%, respectively). MDROs were more frequently isolated in bacteremia (28.6%), pneumonia (23.5%), and UTI (20.7%) in the whole series, although differences were not statistically significant. The rate of isolation of MDROs was not significantly different among specific

infections in the different European regions. MDR bacteria were also more frequently isolated in ICU (23.8% vs. 12.2%; p=0.005) and in nosocomial infections (21.3% vs. 8.3% and 6.6% in CA and HCA infections, respectively; p<0.001). Finally, MDROs were more prevalent in infections causing severe sepsis/shock (30.3% vs. 12.2%, p<0.001) or ACLF (20.5% vs. 9.4%, p<0.001).

Type and efficacy of first line antibiotic strategies

Two main factors influenced first line antibiotic schemes: the site of acquisition of infection and severity (Suppl. Table 3). Classical antibiotic strategies were used frequently in CA infections as first line therapy in Western (80.5%) and Southern Europe (74.6%) but not in the North (33.3). In contrast, nosocomial episodes were mainly treated with strategies covering MDROs in the 3 European regions analyzed (71.1%, 63.6% and 60%, in Northern, Southern and Western Europe, respectively). Both strategies were similarly used for the empirical treatment of HCA infections, except for Northern Europe, where MDR covering strategies were again predominantly used. Remarkably, patients with severe sepsis/shock received more frequently broad-spectrum antibiotics covering MDROs in the whole series and in Northern, Southern and Western Europe (73.3%, 62.5%, and 67.5%, respectively). However, antibiotic prescription differed among European regions in patients with sepsis. MDR covering strategies were used more frequently in septic patients in the North (93.3%) and classical strategies in the South (72%).

The efficacy of classical and MDR empirical antibiotic strategies is shown in Table 4. In the whole series, empirical MDR covering strategies were more effective (higher infection resolution rate or higher adequacy to the microbiological susceptibility) than empiric classical schemes in nosocomial infections (81.7% vs. 68%, respectively, p=0.01). A trend towards statistical significance was also observed in severe sepsis/shock (81.3% vs. 60.9%, p=0.06) and in infectious episodes with or without sepsis (84.7% vs. 76.7%, p=0.06). This higher efficacy of MDR covering strategies was observed in nosocomial episodes reported in the 3 European

regions, although differences were only statistically significant in Western Europe. Inadequacy of first line antibiotic strategies increased 28-d mortality in both AD (33.3% vs. 7.7%; p<0.001) and ACLF patients (50% vs. 25.8%, p=0.002)(Suppl. Table 4, Figure 3).

Suppl. Table 5 shows the type of empirical antibiotic strategies prescribed in the centers showing a high prevalence of MDR bacterial infections (>15%). Initial schemes differed markedly among centers as well as resolution rate.

Impact of antibiotic resistance on clinical outcome

Table 5a shows the clinical outcome of infections caused by MDROs in comparison to that observed in infections caused by susceptible bacteria or with no microbiological isolation in the whole series and across European regions. Resolution of infection was significantly lower in episodes caused by MDROs (71.4% vs. 87.6%, p<0.001). Infections caused by MDR strains showed higher prevalence of severe sepsis/shock (31.9% vs. 12.2%, p<0.001), ACLF (67.5% vs. 45.6%, p<0.001) and 28-d mortality (35.1% vs. 18.1%, p= p<0.001). The negative impact on clinical outcome of antibiotic resistance was confirmed across the different European regions, although we only observed significant differences on short-term mortality in Northern and Western Europe, probably as result of the higher baseline severity of infections in these regions.

Clinical impact of antibiotic resistance was also evaluated considering the adequacy of initial antibiotic strategies (Table 5b). Resolution rate of infections with no isolation or caused by susceptible bacteria was significantly higher (90.8% vs. 71.4%; p<0.001) and 28-d mortality significantly lower (14.9% vs. 41.1%; p<0.001) if initial antibiotic strategies were adequate. Adequacy of empirical antibiotic strategies was also associated with higher resolution rate (82.2% vs. 58.1%; p=0.02) and a trend towards lower 28-d mortality (26.7% vs. 45.2%, p=0.09) in infections caused by MDROs.

Risk factors for MDR bacterial infection

Table 6 and Suppl. Table 6 show the risk factors associated with the development of infections caused by MDROs in the univariate and multivariate analysis in the whole series and in culture-positive infections. Nosocomial infection (OR: 2.74; 95% CI: 1.45-5.19; p=0.002**)**, ICU admission (OR: 2.09; 95% CI: 1.11-3.96; p=0.02**)** and recent hospitalization (OR: 1.93; 95% CI: 1.04-3.58; p=0.038**)** were identified as independent predictors of MDR infection in the whole series. Mechanical ventilation (OR: 2.90; 95% CI: 1.35-6.23; p=0.006**)** was the only factor independently associated with MDR infection in nosocomial episodes. No independent predictors of MDR infection were identified for CA and HCA infections. Similar results were obtained when the analysis was restricted to culture-positive infections.

SECOND SERIES

Clinical characteristics and epidemiology of bacterial infections

A total of 284 patients (32.2%) developed 392 bacterial infections. Prevalence of infection was significantly higher in Eastern (45.4%) and Southern Europe (39.4%) than in the West (18.5%; p<0.0001; Suppl. Table 7). UTI (n=104), SBP (n=50), pneumonia (n=43), bacteremia (n= 38) and SSTI (n=24) were the most frequent proved infections in this series. CA infections predominated in the whole population (n=189; 53%) and in the different European regions. Severity of infection at diagnosis was similar among the different European regions. Prevalence of MDR bacterial infections was 23.3% if all infections are considered and 37.9% in culture-positive episodes. No significant differences in the prevalence of MDR bacterial infections were observed among European regions when all infections were considered. In contrast, MDR strains were more

frequently isolated in culture-positive infections developed in Eastern and Southern Europe (Suppl. Table 7).

Suppl. Table 8 shows the type of MDROs isolated in the second series. Ninety-six MDR strains were isolated in 83 MDR bacterial infections. As a whole, ESBL-producing *Escherichia coli* continued to be the most frequent MDRO reported (n=25), followed by VSE (n=15), ESBL-producing *Klebsiella pneumoniae* (n=14), carbapenem-resistant *Enterobacteriaceae* (n=8), and MRSA and VRE (n=5 each). When comparing the type of MDROs isolated in the different European regions only ESBL-producing *Klebsiella pneumoniae* was significantly more frequent in Eastern Europe (11.8% vs. 2.3% and 1.2% in Southern and Western Europe; p=0.002). No PDR bacteria was reported. Figure 4 shows the prevalence and type of MDR bacteria isolated in the different centers. Fifteen centers (79%) from 8 countries (89%) reported infections caused by MDROs. Remarkable differences were observed in the prevalence and type of MDR strains among hospitals.

DISCUSSION

The current investigation reports for the first time the epidemiology of MDR bacterial infections in decompensated cirrhosis and ACLF across Europe. The study analyzes information prospectively recorded in two series and includes 739 patients with bacterial infection enrolled in 32 centers from 16 countries. From a geographically point of view, the study constitutes the broadest epidemiological assessment of bacterial infections ever performed in cirrhosis. Our investigation confirms that MDR bacterial infections constitute a global and growing healthcare problem in hepatology. MDR were reported in 70% of the liver units and in 9 of the 12 countries participating in the Canonic study, figures that increased to almost 80% of hospitals and 8 out of 9 countries in the more recent series. Prevalence of MDR bacterial infections varied markedly among European regions being higher in Northern and Western Europe in the Canonic series and in Eastern and Southern Europe in the second series. This discrepancy is probably related to differences in the epidemiological characteristics of infections between series. The pattern of antibiotic resistance was highly heterogeneous, with marked differences in the type of MDROs among countries and centers in the two series analyzed.

The overall prevalence of MDR bacterial infections in the whole Canonic cohort of culture-positive infections was 29.2% (14.8% if all infections are considered). This figure is similar to that reported in some single-center investigations performed in European countries. Studies published so far report a prevalence of MDROs in culture-positive infections ranging from 8% in Turkey, 19-21% in Greece, 14-24% in Sweden-Germany and 21-31% in Spain to 31% in France and 27-46% in Italy.[6,12,13,15,20,26 31] It is important to remark that there were marked differences in the prevalence of MDROs among countries in the first series. MDROs isolation rate varied from 0% in Switzerland, Czech Republic and Denmark and 7% in Spain to 20% in Italy, 21% in UK, 25% in Ireland and 34% in France. Belgium, Germany, The Netherlands and Austria showed intermediate rates of MDROs. Prevalence of MDR bacterial infections increased to 38% in

culture-positive episodes in the second series, with also important differences among regions. This increase in the rate of MDR bacterial infections, almost 10% in less than 8 years, underlines the growing clinical relevance of antibiotic resistance in decompensated cirrhosis and ACLF.

Differences in the prevalence of MDROs were also observed among the participant centers in the two series, even among those located in the same geographical region or city. Frankfurt, Clichy, Villejuif and King's College of London in the Canonic series and Roma, Bologna, Bern and Turin in the second series showed the highest prevalence of MDROs meanwhile other centers reported no resistant strains or intermediate MDR rates. The low number of infections recorded in centers reporting no MDROs in the first and second series (44 and 37 infections in total, respectively) probably explain the absence of MDROs isolation. On the other hand, both series extended for a short time period (7 and 11 months), feature that could have limited our capacity to precisely evaluate the real prevalence of MDROs in the different countries and centers. Both factors could also explain the discrepancies observed in the prevalence of MDROs in the same center between the two series (Bern, Leiden, Munich) and between our study and other investigations (i.e. Spain and Italy).[6,12,21]

In the Canonic series, ESBL-producing *Enterobacteriaceae* was the MDRO more frequently isolated in the study followed by VSE and MRSA. However, the type of resistant strain significantly differed across countries and centers. ESBL and Amp-C producing *Enterobacteriaceae* were more frequently isolated in France, Italy, UK and The Netherlands; VSE predominated in France and Austria and MRSA in infections occurring in The Netherlands, UK and Ireland. ESBL-producing *Enterobacteriaceae* continued to be the most frequent MDRO reported in the 2017-2018 series, but marked differences were newly observed in the type of resistant bacteria among regions and centers. This finding underlines the importance of having surveillance programs at a local level aimed to investigate the prevalence and epidemiological

pattern of MDROs at each hospital. Global epidemiological data are informative but are not applicable to specific centres.[32]

Infections by XDR bacteria were infrequent and heterogeneously distributed in the Canonic series. Carbapenem-resistant *Klebsiella pneumoniae,* carbapenem-resistant *Pseudomonas aeruginosa* and VRE were reported sporadically in different European regions in this first series. Infections by these difficult to treat bacteria continued to be infrequent in the more recent series but we observed the emergence of carbapenem-resistant *Eschericha coli* as XDR bacteria and a small increase in the rate of infections caused by VRE. No PDR bacteria were reported in both series. Our results suggest therefore that although XDR bacteria constitute a growing and extremely dangerous problem in cirrhosis, global infection rates are far from those reported in single center studies (from 3% to 14%).[12 , 32].

MDR bacteria were more frequently isolated in the ICU and in nosocomial episodes. MDR bacterial infections were more severe (higher rate of severe sepsis/shock and/or ACLF at diagnosis) and associated to lower resolution rate and higher mortality at 28-d, especially if treated with inadequate empirical antibiotic strategies. Our results, therefore, confirm previous studies in decompensated cirrhosis showing that antibiotic resistance is associated to poor prognosis and high short-term mortality.[10,13,17,20 22] This poor prognosis of infections caused by MDROs has also been reported in patients with solid or hematological malignancies and in critical care in the general population.[33 35]

Nosocomial origin of infection, ICU admission and recent hospitalization within the previous 3 months were the only independent risk factors for MDR bacterial infections identified in the whole Canonic cohort, finding that underlines the key relevance of hospitalization in determining the epidemiological risk of antibiotic resistance in the cirrhotic population. Instrumentation, exposure to broad-spectrum antibiotics and possibly in-hospital colonization by MDR bacteria could account for this finding. In contrast to previous studies, long-term norfloxacin prophylaxis[10] was

not identified as risk factors of MDR in the current series. The low number of patients on long-term quinolone prophylaxis in our study (n=7) prevented us from evaluating adequately this potential risk factor. Rate of antibiotic resistance was low in HCA infections in the Canonic series but similar to that observed in nosocomial episodes in the more recent series, feature probably related to differences in the epidemiological characteristics between countries and centers. Mechanical ventilation, a parameter reflecting both organ support and high degree of instrumentation, was the only factor independently associated with MDR infection in nosocomial episodes. Regretfully, we were unable to identify risk factors for MDR infections developing within the first 48h of hospitalization.

The current study also describes for the first time the type and efficacy of empirical antibiotic strategies used across Europe. Classical antibiotics, those based on third-generation cephalosporins and quinolones, were mainly used in CA infections while schemes covering MDROs were prescribed more frequently in nosocomial episodes and in severe sepsis/shock. As a whole, MDR covering strategies were more effective than classical schemes, especially in nosocomial infections. Importantly, inadequacy of first line antibiotic strategies had a negative impact on short-term survival, both in AD and in ACLF patients, feature also observed when the analysis was restricted to MDR bacterial infections. Our findings support therefore the current recommendations on empirical antibiotic strategies in decompensated cirrhosis. Broad schemes covering all potential pathogens should be empirically used in the nosocomial setting and in severe sepsis/shock and should be followed by rapid de-escalation strategies to avoid a further spread of antibiotic resistance.[1,9,36,37] First line antibiotic strategies should be decided locally together with the infectious disease specialists and should consider the specific epidemiological pattern of antibiotic resistance, feature highly heterogeneous according to the results of the current investigation. Two recent studies demonstrate the efficacy of adapting the empirical antibiotic strategies to the local pattern of resistance.[38,39]

Our investigation confirms the increasing prevalence and negative impact of MDR bacterial infections in cirrhosis in the majority of the European centers participating in the study. This observation demands the urgent evaluation of new strategies aimed at preventing the spread of antibiotic resistance in the cirrhotic population. Clinical impact and cost/effectiveness of measures such as epidemiological surveillance (regular assessment of potential carriers of MDROs through rectal and nasal swabs during hospitalization)[40,41], rapid microbiological tests (micro-arrays or multiplex PCR techniques capable of detecting gene targets specific of MDROs and MALDI-TOF MS),[42,43] and antibiotic stewardship programs deserve further evaluation. [9,44,45]

In conclusion, our study demonstrates that MDR bacterial infections constitute a global and growing healthcare problem in decompensated cirrhosis and ACLF across all Europe. The pattern of antibiotic resistance was highly heterogeneous, with marked differences in the type of MDROs among countries and centers. Antibiotic resistance was associated to poor prognosis and to failure of first line antibiotic strategies based on third-generation cephalosporins or quinolones.

FIGURE LEGENDS

Figure 1

Type and overall rate of MDROs isolation in the different European centres participating in the Canonic study. Different colours represent different MDR bacteria. The colour of the circle is determined by the most prevalent MDROs in each centre and its size correlates with the overall prevalence of MDROs at this centre, also shown in brackets. Marked differences in the type and prevalence of MDROs were observed among centres.

Figure 2

Rate of infections caused by ESBL and Amp-C producing *Enterobacteriaceae* (Panel A) and MRSA (Panel B) across the different European centres participating in the Canonic study. Marked differences were observed among centres.

Figure 3

Probability of death at day 28 in infected patients receiving adequate or inadequate empirical antibiotic strategies in the whole series (Panel A), in patients with acute decompensation (AD; Panel B) and in ACLF patients (Panel C) in the Canonic study. Inadequacy of empirical strategies significantly increased the probability of death in the three populations.

Figure 4

Type and overall rate of MDROs isolation in the different European centres participating in the second study (2017-2018). Different colours represent different MDR bacteria. The colour of the circle is determined by the most prevalent MDROs in each centre and its size correlates with the

overall prevalence of MDROs at this centre, also shown in brackets. Marked differences in the type and prevalence of MDROs were observed among centres.

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: 1310-1324.
2. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, *et al*. Bacterial infections in cirrhosis: epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology 2002; 35: 140-148.
3. Bajaj JS, O'Leary JG, Reddy KR, Wong F, Olson JC, Subramanian RM, *et al*. Second infections independently increase mortality in hospitalized cirrhotic patients: the NACSELD experience. Hepatology 2012; 56: 2328-2335.
4. Merli M, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, *et al*. Cirrhotic patients are at risk for health care-associated bacterial infections. Clin Gastroenterol Hepatol 2010;8:979-85.
5. Moreau R, Jalan R, Ginès P, Pavesi M, Angeli P, Cordoba J, *et al*. Acute-on-chronic liver failure is a distinct syndrome developing in patients with acute decompensation of cirrhosis. Gastroenterology 2013;144:1426-37.
6. Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, *et al*. Bacterial and fungal infections in acute-on-chronic liver failure: prevalence, characteristics and impact on prognosis. Gut. 2017 [Epub ahead of print].
7. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, *et al.* Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology 2010; 139: 1246-1256.
8. Gustot T, Felleiter P, Pickkers P, Sakr Y, Rello J, Velissaris D, *et al*. Impact of infection on the prognosis of critically ill cirrhotic patients: results from a large worldwide study. Liver Int 2014;34:1496-503.
9. Fernández J, Bert F, Nicolas-Chanoine MH. The challenges of multi-drug-resistance in hepatology. J Hepatol 2016;65:1043-1054.
10. Fernández J, Acevedo J, Castro M, Garcia O, Rodríguez de Lope C, Roca D, *et al*. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: a prospective study. Hepatology 2012; 55: 1551-1561.

11. Di Gregorio V, Lucidi C, Giannelli V, Lattanzi B, Giusto M, Iacovone G, *et al*. Bacterial infections in cirrhotic patients: risk factors and rate of failure of the empirical antibiotic therapy. J Hepatol 2014; 60: S227.
12. Merli M, Lucidi C, Di Gregorio V, Falcone M, Giannelli V, Lattanzi B, *et al*. The spread of multi drug resistant infections is leading to an increase in the empirical antibiotic treatment failure in cirrhosis: a prospective survey. PLoS One. 2015; 10(5): e0127448.
13. Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, *et al*. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. J Hepatol 2012; 56: 825-832.
14. Carlet J, Pulcini C, Piddock LJV. Antibiotic resistance: a geopolitical issue. Clin Microbiol Infect 2014; 20: 949-953.
15. Cheong HS, Kang CI, Lee JA, Moon SY, Joung MK, Chung DR, *et al*. Clinical significance and outcome of nosocomial acquisition of spontaneous bacterial peritonitis in patients with liver cirrhosis. Clin Infect Dis 2009; 48: 1230-1236.
16. Chaulk J, Charbonneau M, Qamar H, Keough A, Chang HJ, Ma M, *et al*. Third-generation cephalosporin-resistant spontaneous bacterial peritonitis: a single-center experience and summary of existing studies. Can J Gastroenterol Hepatol 2014; 28: 83-88.
17. Campillo B, Richardet JP, Kheo T, Dupeyron C. Nosocomial spontaneous bacterial peritonitis and bacteremia in cirrhotic patients: impact of isolate type on prognosis and characteristics of patients. Clin Infect Dis 2002; 35: 1-10.
18. Tandon P, Delisle A, Topal JE, Garcia-Tsao G. High prevalence of antibiotic-resistant bacterial infections among patients with cirrhosis at a US liver center. Clin Gastroenterol Hepatol 2012; 10: 1291-1298.
19. Song KH, Jeon JH, Park WB, Park SW, Kim HB, Oh MD, et al. Clinical outcomes of spontaneous bacterial peritonitis due to extended-spectrum beta-lactamase-producing *Escherichia coli* and *Klebsiella* species: A retrospective matched case-control study. BMC Infect Dis 2009; 9:41-46.
20. Bartoletti M, Giannella M, Caraceni P, Domenicali M, Ambretti S, Tedeschi S, *et al*. Epidemiology and outcomes of bloodstream infection in patients with cirrosis. J Hepatol 2014;61:51-8.
21. Salerno F, Borzio M, Pedicino C, Simonetti R, Rossini A, Boccia S, *et al*. The impact of infection by multidrug-resistant agents in patients with cirrhosis. A multicenter prospective study. Liver Int. 2017;37:71-79.

22. Bartoletti M, Giannella M, Lewis R, Caraceni P, Tedeschi S, Paul M, *et al*. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. Clin Microbiol Infect 2017 [Epub ahead of print].
23. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, *et al*. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect 2012; 18: 268-281.
24. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 1992;20:864-874.
25. 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;315:801-810.
26. Piroth L, Pechinot A, Minello A, Jaulhac B, Patry I, Hadou T, *et al*. Bacterial epidemiology and antimicrobial resistance in ascetic fluid: a 2-year retrospective study. Scand J Infect Dis 2009;37:2-8.
27. Novovic S, Semb S, Olsen H, Moser C, Knudsen JD, Homann C. First-line treatment with cephalosporins in spontaneous bacterial peritonitis provides poor antibiotic coverage. Scand J Gastroenterol 2012;47:212-6.
28. Umgelter A, Reindl W, Miedaner M, Schmid RM, Huber W. Failure of current antibiotic first-line regimens and mortality in hospitalized patients with spontaneous bacterial peritonitis. Infection 2009;37:2-8.
29. Alexopoulou A, Vasilieva L, Agiasotelli D, Siranidi K, Pouriki S, *et al*. Extensively drug-resistant bacteria are an independent predictive factor of mortality in 130 patients with spontaneous bacterial peritonitis or spontaneous bacteremia. World J Gastroenterol 2016 ;22:4049-5.
30. Sargenti K, Prytz H, Strand A, Nilsson E, Kalaitzakis E. Healthcare-associated and nosocomial bacterial infections in cirrhosis: predictors and impact on outcome. Liver Int 2015;35:391-400.
31. Nahon P, Lescat M, Layese R, Bourcier V, Talmat N, Allam S, *et al*. Bacterial infection in compensated viral cirrhosis impairs 5-year survival (ANRS CO12 CirVir prospective cohort). Gut 2017 66:330-341.
32. European Center for Disease Prevention and Control. Antimicrobial resistance surveillance in Europe 2013.

http://ecdc.europa.eu/en/publications/Publications/antimicrobial-resistance-europe-2013.pdf.

33. Nazer LH, Kharabsheh A, Rimawi D, Mubarak S, Hawari F. Characteristics and Outcomes of Acinetobacter baumannii Infections in Critically Ill Patients with Cancer: A Matched Case-Control Study. Microb Drug Resist.2015;21:556-61
34. Bastug A, Kayaaslan B, Kazancioglu S, But A, Aslaner H, Akinci E, *et al*. Emergence of multidrug resistant isolates and mortality predictors in patients with solid tumors or hematological malignancies. J Infect Dev Ctries 2015;9:1100-7.
35. Gudiol C, Tubau F, Calatayud L, Garcia-Vidal C, Cisnal M, Sánchez-Ortega I, *et al.* Bacteraemia due to multidrug-resistant Gram-negative bacilli in cancer patients: risk factors, antibiotic therapy and outcomes. J Antimicrob Chemother 2011;66:657-63
36. Fernández J, Tandon P, Mensa J, Garcia-Tsao G. Antibiotic prophylaxis in cirrhosis: good and bad. Hepatology 2016;63:2019-31
37. Bassetti M, Merelli M, Temperoni C, Astilean A. New antibiotics for bad bugs: where are we? Ann Clin Microbiol Antimicrob 2013; 12:22 doi: 10.1186/1476-0711-12-22.
38. Piano S, Fasolato S, Salinas F, Romano A, Tonon M, Morando F, *et al*. The empirical antibiotic treatment of nosocomial spontaneous bacterial peritonitis: Results of a randomized, controlled clinical trial. Hepatology 2016;63:1299-309.
39. 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.
40. Bert F, Larroque B, Dondero F, Durand F, Paugam-Burtz C, Belghiti J, *et al*. Risk factors associated with preoperative fecal carriage of extended-spectrum β-lactamase-producing *Enterobacteriaceae* in liver transplant recipients. Transpl Infect Dis 2014; 16: 84-89.
41. Crum-Cianflone NF, Sullivan E, Ballon-Landa G. Fecal microbiota transplantation and successful resolution of multidrug-resistant-organism colonization. J Clin Microbiol 2015;53: 1986-1989.
42. Naas T, Cuzon G, Truong H, Bernabeu S, Nordmann P. Evaluation of a DNA microarray, the Check-Points ESBL/KPC array, for rapid detection of TEM, SHV, and CTX-M extended-spectrum β-lactamases and KPC carbapenemases. Antimicrob Agents Chemother 2010; 54: 3086-3092.
43. Mancini N, Infurnari L, Ghidoli N, Valzano G, Clementi N, Burioni R, *et al*. Potential impact of a microarray-based nucleic acid assay for rapid detection of Gram-negative

bacteria and resistance markers in positive blood cultures. J Clin Microbiol 2014; 52: 1242-1245.

44. Perez KK, Olsen RJ, Musick WL, Cernoch PL, Davis JR, Peterson LE, *et al*. Integrating rapid diagnostics and antimicrobial stewardship improves outcomes in patients with antibiotic-resistant Gram-negative bacteremia. J Infect 2014; 69: 216-225.
45. Kaki R, Elligsen M, Walker S, Simor A, Palmay L, Daneman N. Impact of antimicrobial stewardship in critical care: a systematic review. J Antimicrob Chemother 2011;66:1223-30.

Table 1. Prevalence, type, epidemiological characteristics and baseline severity of bacterial infections across Europe (Canonic series)

	Total	Northern Europe	Southern Europe	Western Europe	p
Prevalence (infected patients/%)	455(39.7)*	66(39.1)	178(40.6)	208(38.9)	0.846
Overall infections (number of infections/%)	520*	72(13.9)	207(40.0)	238(46.1)	
Overall culture-positive infections (number of infections/%)	264(50.8)*	40(55.6)	90(43.5)	133(55.9)	<0.001
Type of infection (n /%)					
SBP	130(25.0)	13(18.1)	52(25.1)	62(26.1)	0.375
UTI	111(21.4)	10(13.9)	51(24.6)	50(21.0)	0.156
Skin and soft tissue infections	44(8.5)	10(13.9)	15(7.3)	19(8.0)	0.203
Pneumonia	85(16.4)	16(22.2)	23(11.1)	46(19.3)	0.024
Unproved infections	67(12.9)	11(15.3)	35(16.9)	21(8.8)	0.033
Secondary bacterial peritonitis	21(4.0)	6(8.3)	8(3.9)	7(2.9)	0.125
Spontaneous or secondary bacteremia	28(5.4)	2(2.8)	12(5.8)	14(5.9)	0.566
Pseudomembranous colitis	4(0.8)	3(4.2)	1(0.5)	0(0.0)	0.002
Other	30(5.8)	1(1.4)	10(4.8)	19(8.0)	0.082
Site of admission at infection dx (n /%)					<0.001
Emergency department	189(43.1)	16(24.6)	105(64.0)	68(32.9)	
Ward	170(38.7)	32(49.2)	47(28.7)	88(42.5)	
ICU	80(18.2)	17(26.2)	12(7.3)	51(24.6)	
Site of acquisition (n /%)					<0.001
Community-acquired	156(30.0)	20(27.8)	90(43.5)	45(18.9)	
HCA	91(17.5)	12(16.7)	38(18.4)	40(16.8)	
Nosocomial	273(52.5)	40(55.6)	79(38.2)	153(64.3)	

Severity at infection diagnosis (n/%)					<0.001
No sepsis	295(62.4)	36(53.7)	140(73.3)	116(54.7)	
Sepsis	106(22.4)	16(23.9)	34(17.8)	56(26.4)	
Severe sepsis or septic shock	72(15.2)	15(22.4)	17(8.9)	40(18.9)	
ACLF at infection diagnosis (n /%)					<0.001
No	266(51.1)	32(44.4)	129(62.3)	103(43.3)	
Yes	254(48.9)	40(55.6)	78(37.7)	135(56.7)	

SBP: spontaneous bacterial peritonitis; UTI: urinary tract infections; ICU: intensive care unit; HCA: healthcare-associated; ACLF: acute on chronic liver failure.

*Three infections occurring in 3 patients in Czech Republic (Eastern Europe) were not considered in the comparative analysis among European regions

Data are shown as number of infections and percentage. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.

Table 2. Rate and type of MDROs isolated in the whole series, in Northern, Southern and Western Europe and by country (Canonic series)

	Northern Europe N=72	Southern Europe N=207	Western Europe N=238	P	Austria N=26	Belgium N=58	Germany N=93	Ireland N=20	UK N=42	The Netherlands N=7	Italy N=46	Spain N=161	France N=50	All infections* N=520
Total isolated MDR (n/%)	14(19.4)	20(9.7)	46(19.3)	0.012	5(19.1)	7(12.1)	15(16.3)	5(25.0)	9(21.4)	2(11.8)	9(19.6)	11(6.8)	17(34.0)	80(15.4)
Total isolated MDR in culture-positive infections (n/%)	14(35.0)	20(22.2)	46(34.6)	0.302	5(31.3)	7(21.9)	15(34.1)	5(55.6)	9(36.0)	2(28.6)	9(52.9)	11(15.1)	17(50.0)	80(30.3)
Total isolated MDR GNB (n/%)	8(11.1)	14(6.8)	28(11.8)	0.186	2(7.6)	3(5.2)	11(12.0)	2(10.0)	6(14.3)	1(5.9)	7(15.2)	7(4.3)	11(22.0)	50(9.6)
ESBL-producing *Escherichia coli*	2(2.8)	6(2.9)	11(4.6)	0.571	1(3.8)	2(3.4)	3(3.2)	-	2(4.8)	-	4(8.7)	2(1.2)	5(10.0)	19(3.7)
ESBL-producing *Klebsiella pneumonia*	3(4.2)	4(1.9)	2(0.8)	0.161	-	-	1(1.1)	-	3(7.1)	-	2(4.3)	2(1.2)	1(2.0)	9(1.7)
ESBL-producing *Klebsiella oxytoca*	-	-	1(0.4)	1.000	-	-	1(1.1)	-	-	-	-	-	-	1(0.2)
Amp-C producing *Enterobacter spp.*	1(1.4)	1(0.5)	4(1.7)	0.491	-	-	1(1.1)	1(5.0)	-	-	-	1(0.6)	3(6.0)	6(1.2)
ESBL-producing *Serratia spp*	-	-	1(0.4)	1.000	-	-	-	-	-	1(5.9)	-	-	-	1(0.2)
Carbapenem-resistant Klebsiella pneumonia	1(1.4)	-	1(0.4)	0.411	-	-	1(1.1)	-	1(2.4)	-	-	-	-	2(0.4)
Carbapenem-resistant Pseudomonas aeruginosa	-	2(1.0)	2(0.8)	1.000	-	-	-	-	-	-	1(2.2)	1(0.6)	2(4.0)	4(0.8)
Stenotrophomonas maltophilia	1(1.4)	-	2(0.8)	0.548	1(3.8)	-	1(1.1)	1(5.0)	-	-	-	-	-	3(0.6)
Burkholderia cepacia.	-	-	1(0.4)	1.000	-	-	1(1.1)	-	-	-	-	-	-	1(0.2)
Acinetobacter baumanii	-	1(0.5)	3(1.3)	0.348	-	1(1.7)	2(2.2)	-	-	-	-	1(0.6)	-	4(0.8)

Total isolated multiresistant GPC (n/%)	6(8.3)	6(2.9)	18(7.6)	0.068	3(11.5)	4(6.9)	4(4.3)	3(15.0)	3(7.1)	1(5.9)	2(4.3)	4(2.5)	6(12.0)	30(5.8)
MR Staphylococcus aureus (MRSA)	3(4.2)	1(0.5)	8(3.4)	0.071	1(3.8)	2(3.4)	2(2.2)	1(5.0)	2(4.8)	1(5.9)	-	1(0.6)	2(4.0)	12(2.3)
Vancomycin-susceptible *Enterococcus faecium (VSE)*	1(1.4)	5(2.4)	9(3.8)	0.493	2(7.7)	2(3.4)	1(1.1)	1(5.0)	-	-	2(4.3)	3(1.9)	4(8.0)	15(2.9)
Vancomycin-resistant enterococci (VRE)	2(2.8)	-	1(0.4)	0.136	-	-	1(1.1)	1(5.0)	1(2.4)	-	-	-	-	3(0.6)

* Seventeen infections reported in Switzerland (n=4), Czech Republic (n=3) and Denmark (n=10) had no isolation of MDR bacteria. Data are presented as number of bacteria and percentage

Table 3 Prevalence, type, epidemiological characteristics and severity of bacterial infections caused by MDROs in the whole series and in Northern, Southern and Western Europe* (Canonic series)

	Total	Northern Europe	Southern Europe	Western Europe	P
Prevalence	61/455(13.4)	12/66(18.2)	12/178(6.7)	37/208(17.8)	0.005
Overall infections (n MDRi*/total infections/%)	77/520(14.8)	13/72(18.1)	18/207(8.7)	46/238(19.3)	0.005
Culture-positive infections (n MDRi*/total infections/%)	77/264(29.2)	13/40(32.5)	18/90(20.0)	46/133(34.6)	0.056
Type of infection (n MDRi*/total infections/%)					
Spontaneous bacterial peritonitis	18/130(13.9)	4/13(30.8)	4/52(7.7)	10/62(16.1)	0.084
Urinary tract infection	23/111(20.7)	1/10(10.0)	9/51(17.7)	13/50(26.0)	0.398
Skin and soft tissue infections	5/44(11.4)	2/10(20.0)	1/15(6.7)	2/19(10.5)	0.582
Pneumonia	20/85(23.5)	4/16(25.0)	2/23(8.7)	14/46(30.4)	0.132
Secondary bacterial peritonitis	3/21(14.3)	1/6(16.7)	0/8(0.0)	2/7(28.6)	0.283
Spontaneous or secondary bacteremia	8/28(28.6)	1/2(50.0)	2/12(16.7)	5/14(35.7)	0.442
Other	0/30(0.0)	0/1(0.0)	0/10(0.0)	0/19(0.0)	-
Site of admission at dx (n MDRi*/total infections/%)					
Emergency department	20/189(10.6)	2/16(12.5)	7/105(6.7)	11/68(16.2)	0.135
Ward	22/170(12.9)	6/32(18.8)	3/47(6.4)	13/88(14.8)	0.228
ICU	19/80(23.8)	4/17(23.5)	2/12(16.7)	13/51(25.5)	0.811
Site of acquisition (n MDRi*/total infections/%)					
Community-acquired	13/156(8.3)	3/20(15.0)	5/90(5.6)	5/45(11.1)	0.284
HCA	6/91(6.6)	0/12(0.0)	1/38(2.6)	5/40(12.5)	0.133
Nosocomial	58/273(21.3)	10/40(25.0)	12/79(15.2)	36/153(23.5)	0.281
Severity at infection diagnosis (n MDRi*/total infections/%)**					
No sepsis	37/295(12.5)	6/36(16.7)	10/140(7.1)	21/116(18.1)	0.024
Sepsis	12/106(11.3)	0/16(0.0)	3/34(8.8)	9/56(16.1)	0.173
Severe sepsis or septic shock	23/72(30.3)	6/15(40.0)	4/17(23.5)	13/40(32.5)	0.604
ACLF at infection diagnosis (n MDRi*/total infections/%)					
No	25/266(9.4)	2/32(6.3)	9/129(7.0)	14/103(13.6)	0.186
Yes	52/254(20.5)	11/40(27.5)	9/78(11.5)	32/135(23.7)	0.053

SBP: spontaneous bacterial peritonitis; UTI: urinary tract infections; ICU: intensive care unit; HCA: healthcare-associated; MDRi: MDR infections; ACLF: acute on chronic liver failure

*Data on severity of infection were not available in 54 episodes. Data are presented as number of infections and percentage. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.

Table 4. Efficacy of first line antibiotic strategies in the whole series and among European regions (Canonic series)##

	Whole series			Northern Europe			Southern Europe			Western Europe		
	Classical*	MDR coverage**	P	Classical*	MDR coverage**	P	Classical*	MDR coverage**	P	Classical*	MDR coverage**	P
Total	165/218(75.7)	201/237(54.9)	0.014	15/21(71.4)	38/46(82.6)	0.296	73/88(83.0)	66/77(85.7)	0.627	76/108(70.4)	95/112(84.8)	0.010
Site of acquision (n/%)												
CA or HCA* **	99/121(81.8)	67/73(91.8)	0.056	8/10(80.0)	18/19(94.7)	0.216	53/60(88.3)	24/28(85.7)	0.729	37/50(74.0)	24/25(96.0)	0.021
Nosocomial	66/97(68.0)	134/164(81.7)	0.012	7/11(63.6)	20/27(74.1)	0.520	20/28(71.4)	42/49(85.7)	0.128	39/58(67.2)	71/87(81.6)	0.048
Severity of infection (n/%)												
No sepsis / sepsis only	138/180(76.7)	144/170(84.7)	0.057	11/15(73.3)	26/33(78.8)	0.677	66/79(83.5)	53/60(88.3)	0.426	60/85(70.6)	63/75(84.0)	0.045
Severe sepsis or shock	14/23(60.9)	39/48(81.3)	0.065	2/4(50.0)	10/11(90.9)	0.080	4/6(66.7)	7/10(70.0)	0.889	8/13(61.5)	22/27(81.5)	0.173

#Resolution of infection without further escalation/bacterial susceptibility to initial antibiotics in culture positive infections

Data were not available in 76 infections. Data are presented as number of infections and percentage. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.

* One to third generation cephalosporins, amoxicillin-clavulanic acid, quinolones

** Piperacillin-tazobactam or carbapenem±glycopeptide/linezolid/daptomycin

***CA: community-acquired; HCA: healthcare-associated

Table 5a. Clinical outcome of infections according to the antibiotic resistant profile of the responsible bacteria (Canonic series)

	Total N=520	No isolation/ susceptible bacteria N=443	Multiresistant bacteria* N=77	p-value
Overall Infections (n)				
Resolution (n/%)	445(85.6)	390(87.6)	55(71.4)	<0.001
ACLF	254(48.9)	202(45.6)	52(67.5)	<0.001
Severe sepsis or septic shock	72(15.2)	49(12.2)	23(31.9)	<0.001
Mortality at 28 days	107(20.6)	80(18.1)	27(35.1)	<0.001
Mortality Tx-free at 28 days	107(21.8)	80(19.2)	27(37.0)	<0.001
North Europe (n)	**N=72**	**N=59**	**N=13**	
Resolution (n/%)	59(81.9)	52(88.1)	7(53.9)	0.004
ACLF	40(55.6)	29(49.2)	11(84.6)	0.020
Severe sepsis or septic shock	15(22.4)	9(16.4)	6(50.0)	0.014
Mortality at 28 days	21(29.2)	13(22.0)	8(61.5)	0.005
Mortality Tx-free at 28 days	21(31.8)	13(24.1)	8(66.7)	0.004
South Europe (n)	**N=207**	**N=189**	**N=18**	
Resolution (n/%)	184(88.9)	171(90.5)	13(72.2)	0.019
ACLF	78(37.7)	69(36.5)	9(50.0)	0.259
Severe sepsis or septic shock	17(8.9)	13(7.5)	4(23.5)	0.081
Mortality at 28 days	34(16.4)	30(15.9)	4(22.2)	0.487
Mortality Tx-free at 28 days	34(17.2)	30(16.6)	4(23.5)	0.467
Western Europe (n)	**N=238**	**N=192**	**N=46**	

Resolution (n/%)	199(83.6)	164(85.4)	35(76.1)	0.125
ACLF	135(56.7)	103(53.7)	32(69.6)	0.050
Severe sepsis or septic shock	40(18.9)	27(16.0)	13(30.2)	0.098
Mortality at 28 days	52(21.9)	37(19.3)	15(32.6)	0.049
Mortality Tx-free at 28 days	52(23.4)	37(20.8)	15(34.1)	0.062

Data are presented as number of infections and percentage. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.

Table 5b. Clinical outcome of infections according to the antibiotic resistant profile of the responsible bacteria and the adequacy of empirical antibiotic therapy (Canonic series)

	Total	**No isolation/ susceptible bacteria**				**MR bacteria***			
			Initial antibiotic therapy				**Initial antibiotic therapy**		
		Total	**Inadequacy**	**Adequacy**	**p-value**	**Total**	**Inadequacy**	**Adequacy**	**p-value**
	N=520	**N=443**	**N=56**	**N=335**		**N=77**	**N=31**	**N=45**	
Overall Infections (n)									
Resolution (n/%)	445(85.6)	390(87.6)	40(71.4)	304(90.8)	<0.001	55(71.4)	18(58.1)	37(82.2)	0.021
ACLF	254(48.9)	202(45.6)	34(60.7)	158(47.2)	0.061	52(67.5)	24(77.4)	27(60.0)	0.112
Severe sepsis or septic shock	72(15.2)	49(12.2)	9(16.7)	39(12.8)	0.637	23(31.9)	14(46.7)	20(48.8)	0.984
Mortality at 28 days	107(20.6)	80(18.1)	23(41.1)	50(14.9)	<0.001	27(35.1)	14(45.2)	12(26.7)	0.095
Mortality Tx-free at 28 days	107(21.8)	80(19.2)	23(42.6)	50(16.2)	<0.001	27(37.0)	14(46.7)	12(28.6)	0.102

ACLF: acute on chronic liver failure

#Resolution of infection without further escalation/bacterial susceptibility to initial antibiotics in culture positive infections.
Data are presented as number of infections and percentage. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.

Table 6. Risk factors for the development of infections by multiresistant bacteria in the univariate and multivariate analysis (Canonic series)

	No multiresistant isolation (n=443)	**Multiresistant bacteria (n=77)**	**p**	**No MR/MR OR (CI 95%)****	**p**
Whole infections					
Nosocomial infection (%)	215(48.5)	58(75.3)	<0.001	2.74(1.45-5.19)	0.002
Health-care associated infection (%)	85(19.2)	6(7.8)	<0.001	-	-
Recent hospitalization* (%)	198(45.3)	48(63.2)	0.004	1.93(1.04-3.58)	0.038
Recent use of β-lactams* (%)	173(42.6)	32(47.1)	0.493	-	-
Long-term norfloxacin prophylaxis (%)	5(1.6)	2(3.0)	0.427	-	-

ICU admission (%)	61(15.6)	21(27.3)	0.003	2.09(1.11-3.96)	0.023
Mechanical ventilation (%)	96(31.1)	34(54.0)	<0.001	-	-
Hepatic encephalopathy at inclusion (%)	199(45.0)	29(37.7)	0.230	-	-
MELD score (%)	21 ± 8	23 ± 8	0.063	-	-
ACLF	202(45.6)	52(67.5)	<0.001	-	-
Second infection	42(9.5)	16(20.8)	0.003	-	-
Diabetes mellitus (%)	87(20.0)	23(31.5)	0.027	-	-
Culture-positive infections	**(n=187)**	**(n=77)**			
Nosocomial infection (%)	87(46.5)	58(75.3)	<0.001	3.04(1.52-6.10)	0.002
Health-care associated infection (%)	37(19.8)	6(7.8)	<0.001	-	-
Recent hospitalization* (%)	79(42.7)	48(63.2)	0.002	2.12(1.07-4.20)	0.032
Recent use of β-lactams* (%)	84(47.2)	32(47.1)	0.985	-	-
Long-term norfloxacin prophylaxis (%)	3(2.1)	2(3.0)	0.682	-	-
ICU admission (%)	21(12.9)	21(27.3)	0.015	2.56(1.20-5.49)	0.016
Mechanical ventilation (%)	41(29.3)	34(54.0)	<0.001	-	-
Hepatic encephalopathy at inclusion (%)	88(47.1)	29(37.7)	0.162	-	-
MELD score (%)	22 ± 8	23 ± 8	0.167	-	-
ACLF	84(44.9)	52(67.5)	<0.001	-	-
Second infection	20(10.7)	16(20.8)	0.030	-	-
Diabetes mellitus (%)	36(19.7)	23(31.5)	0.042	-	-

ICU: intensive care unit; MELD: model for end stage liver disease; ACLF: acute on chronic liver failure.

Data are presented as mean±SD or number of infections and percentage. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.
*: within the previous 3 months.

**Variables showing a p value <0.1 were introduced in the model

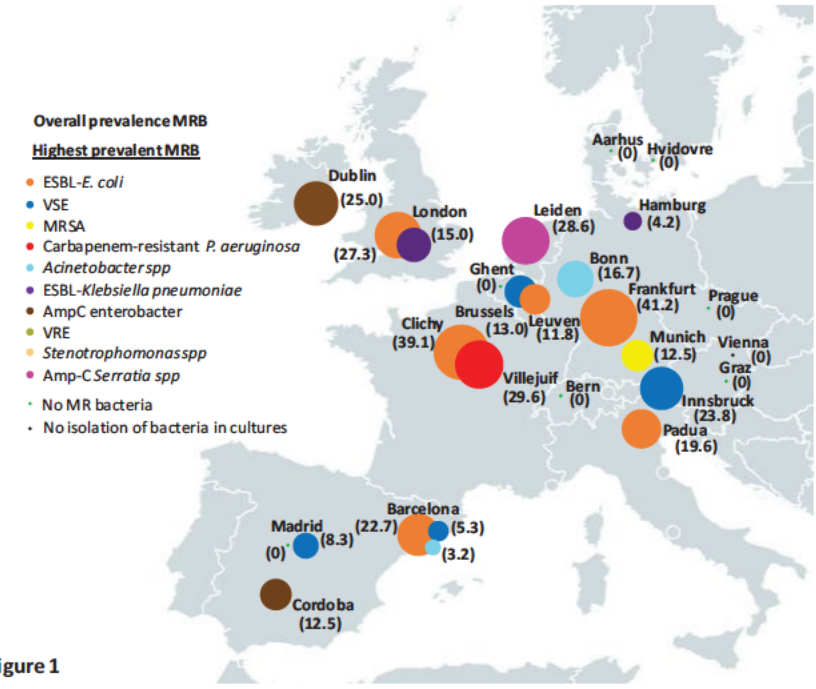

Overall prevalence MRB
Highest prevalent MRB
ESBL-E. coli
VSE
MRSA
Carbapenem-resistant P. aeruginosa
Acinetobacter spp
ESBL-Klebsiella pneumoniae
AmpC enterobacter
VRE
Stenotrophomonas spp
Amp-C Serratia spp
No MR bacteria
No isolation of bacteria in cultures
Dublin (25.0)
London (15.0) (27.3)
Aarhus (0)
Hvidovre (0)
Leiden (28.6)
Hamburg (4.2)
Ghent (0)
Bonn (16.7)
Frankfurt (41.2)
Prague (0)
Brussels (13.0)
Leuven (11.8)
Clichy (39.1)
Munich (12.5)
Vienna (0)
Graz (0)
Villejuif (29.6)
Bern (0)
Innsbruck (23.8)
Padua (19.6)
Barcelona (22.7) (5.3) (3.2)
Madrid (0) (8.3)
Cordoba (12.5)

Figure 1

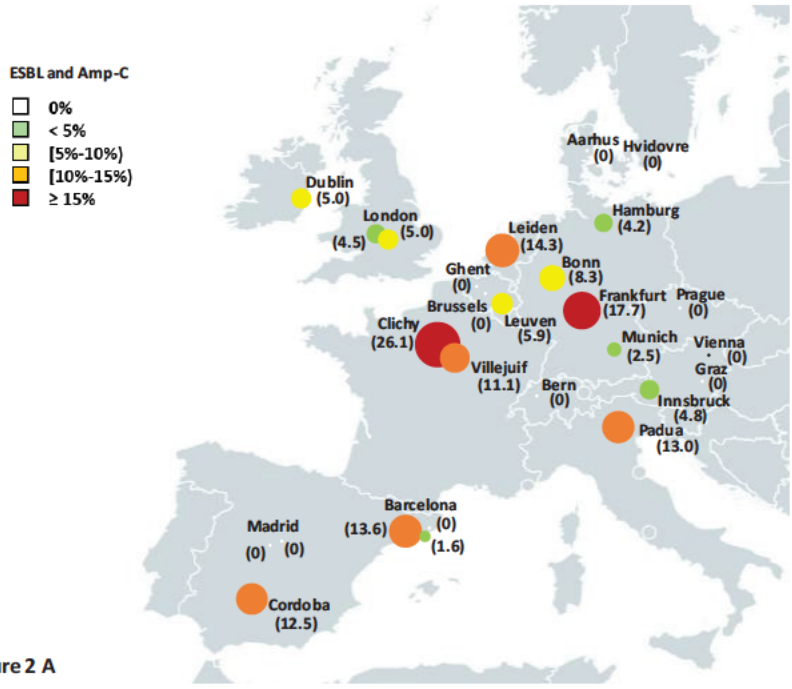

ESBL and Amp-C
0%
< 5%
[5%-10%)
[10%-15%)
≥ 15%
Aarhus (0)
Hvidovre (0)
Dublin (5.0)
London (4.5)
(5.0)
Hamburg (4.2)
Leiden (14.3)
Ghent (0)
Bonn (8.3)
Frankfurt (17.7)
Prague (0)
Brussels (0)
Leuven (5.9)
Clichy (26.1)
Munich (2.5)
Vienna (0)
Graz (0)
Villejuif (11.1)
Bern (0)
Innsbruck (4.8)
Padua (13.0)
Barcelona (13.6)
(0)
(1.6)
Madrid (0) (0)
Cordoba (12.5)

Figure 2 A

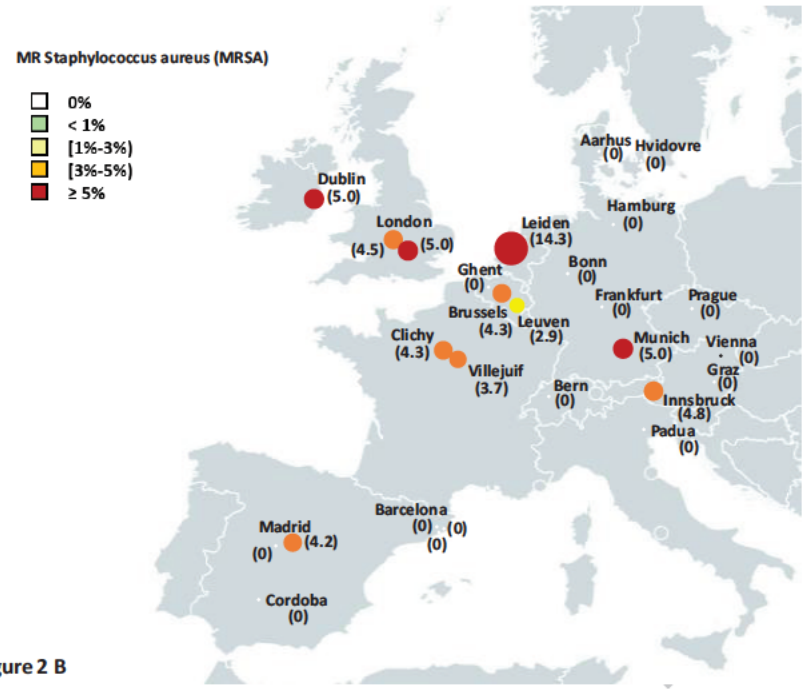

MR Staphylococcus aureus (MRSA)
0%
< 1%
[1%-3%)
[3%-5%)
≥ 5%
Aarhus (0)
Hvidovre (0)
Dublin (5.0)
Hamburg (0)
London (4.5)
(5.0)
Leiden (14.3)
Bonn (0)
Ghent (0)
Frankfurt (0)
Prague (0)
Brussels (4.3)
Leuven (2.9)
Clichy (4.3)
Munich (5.0)
Vienna (0)
Graz (0)
Villejuif (3.7)
Bern (0)
Innsbruck (4.8)
Padua (0)
Barcelona (0)
(0)
(0)
Madrid (0)
(4.2)
Cordoba (0)

Figure 2 B

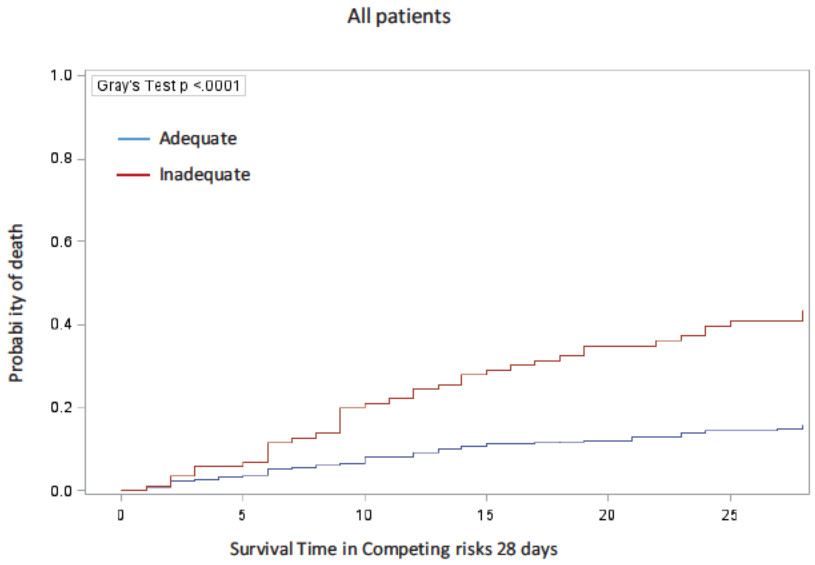

All patients
Gray's Test p <.0001
Adequate
Inadequate
Probabi ity of death
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
Survival Time in Competing risks 28 days

Figure 3 A

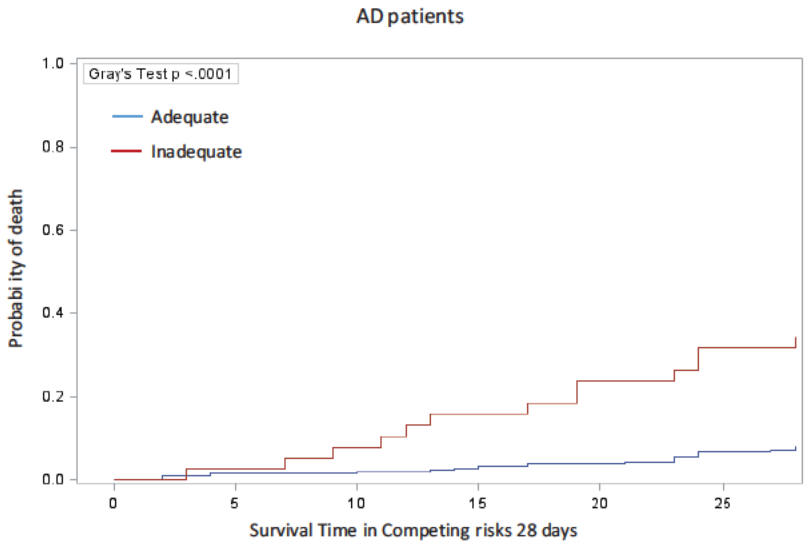

AD patients
Gray's Test p <.0001
Adequate
Inadequate
Probabi ity of death
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
Survival Time in Competing risks 28 days

Figure 3 B

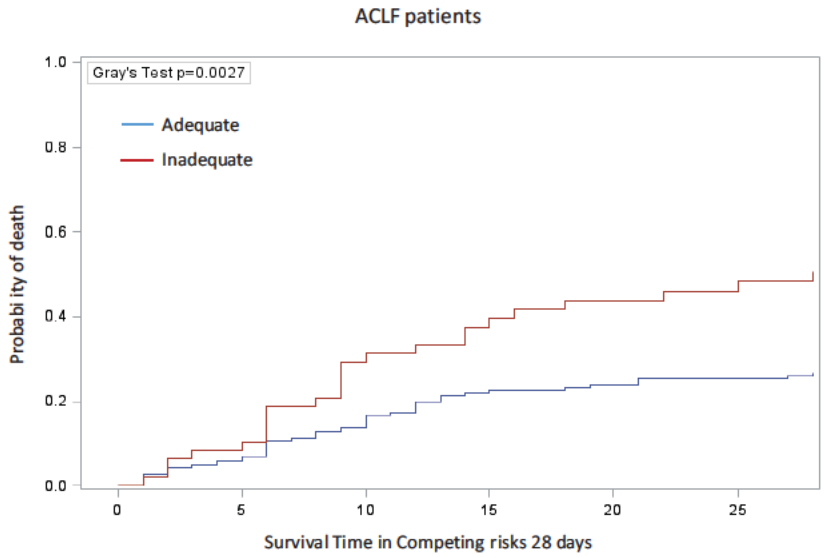

ACLF patients
Gray's Test p=0.0027
Adequate
Inadequate
Probabi ity of death
1.0
0.8
0.6
0.4
0.2
0.0
0
5
10
15
20
25
Survival Time in Competing risks 28 days

Figure 3 C

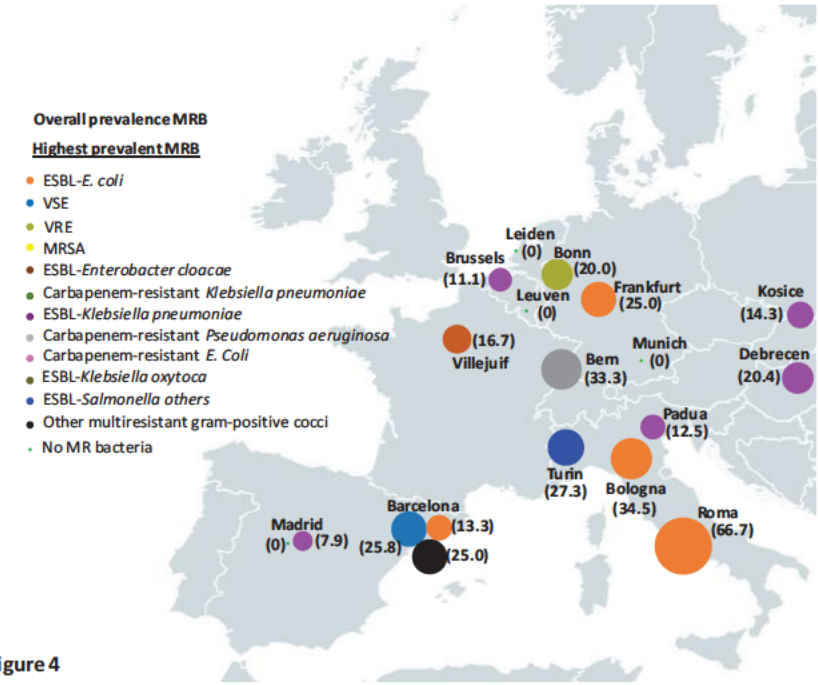
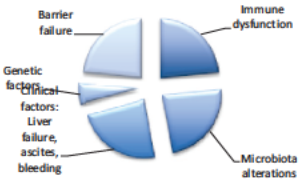


Figure 4

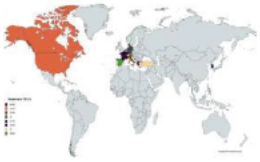
Factors favouring bacterial infections in cirrhosis



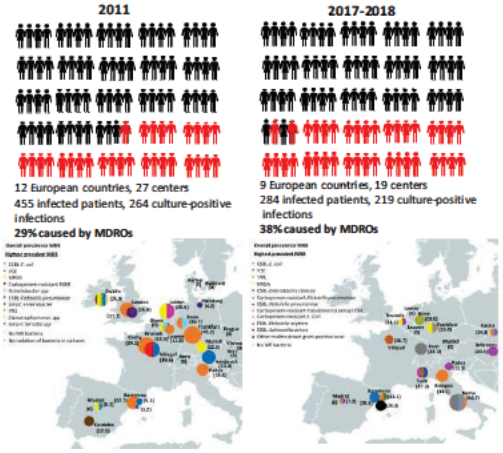
How antibiotic resistance develops?

1. Few bacteria are resistant
2. Susceptible bacteria are killed by antibiotics
3. Resistant strains grow and spread over

Resistance to third-generation cephalosporins in cirrhosis: single centre data



Prevalence and type of resistant bacteria across European hospitals



How to prevent the spread of antibiotic resistance?

HIGHLIGHTS

1. MDR bacterial infections constitute a prevalent, growing and complex healthcare problem in decompensated cirrhosis and ACLF across all European regions. Prevalence increased from 29% to 38% in culture-positive infections from 2011 to 2017-2018.
2. Prevalence and type of resistant organisms differ markedly among centers.
3. Antibiotic resistance negatively impact prognosis. It is associated to lower resolution rate of infections, higher incidence of septic shock and ACLF and higher mortality and to failure of antibiotic strategies based on third-generation cephalosporins or quinolones.
4. Nosocomial infection, ICU admission and recent hospitalization are independent risk factors of MDR infection.
5. Strategies aimed at preventing the spread of antibiotic resistance in cirrhosis should be urgently evaluated.