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

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Research Article
Cirrhosis

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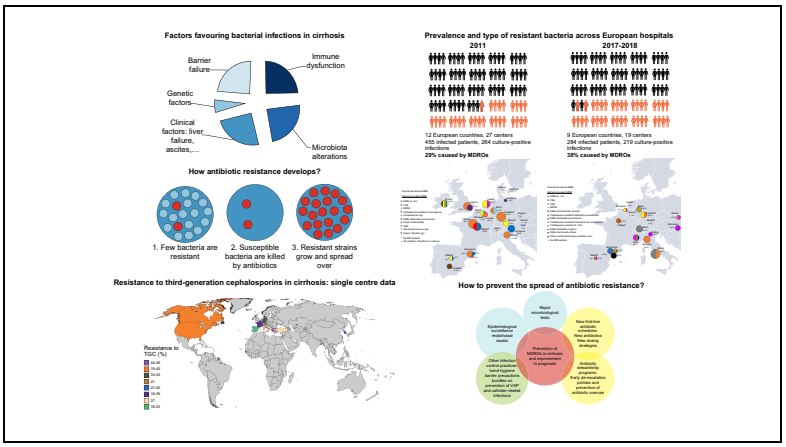
Graphical abstract



Highlights

- MDR bacterial infections are a prevalent, growing and complex healthcare problem in decompensated cirrhosis and ACLF.
- Prevalence increased from 29% to 38% in culture-positive infections from 2011 to 2017-2018.
- Antibiotic resistance negatively impacts prognosis and is associated with higher mortality rates.
- Nosocomial infection, ICU admission and recent hospitalization are independent risk factors of MDR infection.
- Strategies aimed at preventing the spread of antibiotic resistance in cirrhosis should be urgently evaluated.

Authors

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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 resolve less frequently and often cause the death of the patient. The type of resistant bacteria varies markedly among different hospitals.

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

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Background & Aims: Antibiotic resistance has been increasingly reported in patients with decompensated cirrhosis in single-center studies. Prospective investigations reporting broad epidemiological data are scarce. We aimed to analyze epidemiological changes in bacterial infections in patients with decompensated cirrhosis.

Methods: This was a prospective evaluation of 2 series of patients hospitalized with decompensated cirrhosis. The Canonic series included 1,146 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 between 2017–2018.

Results: A total of 455 patients developed 520 infections (39.7%) in the first series, with spontaneous bacterial peritonitis, urinary tract infections and pneumonia the most frequent infections. Nosocomial episodes predominated in this series. Nearly half of the infections were culture-positive, of which 29.2% were caused by multidrug-resistant organisms (MDROs). MDR strains were more frequently isolated in Northern and Western Europe. Extended-spectrum beta-lactamase-producing *Enterobacteriaceae* were the most frequent MDROs isolated in this series, although prevalence and type differed markedly among countries and centers. Antibiotic resistance was associated with poor prognosis and failure of antibiotic strategies, based on third-generation cephalosporins or quinolones. Nosocomial infection (odds ratio [OR] 2.74; $p < 0.001$), intensive care unit admission (OR 2.09; $p = 0.02$), and recent hospitalization (OR 1.93; $p = 0.04$) were identified as independent predictors of MDR infection. The 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 patients with decompensated cirrhosis and acute-on-chronic liver failure across Europe, negatively impacting on 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 resolve less frequently and often cause the death of the patient. The type of resistant bacteria varies markedly among different hospitals.

Keywords: Epidemiology; Prevalence; Prognosis; Antibiotic resistance; Antibiotic strategies.
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Introduction

Bacterial infections constitute a frequent complication in patients with decompensated cirrhosis and are the most frequent trigger of acute-on-chronic liver failure (ACLF) in Western countries.[1–5] Patients with cirrhosis and acute decompensation (AD) are prone to developing spontaneous and secondary bacterial infections, a risk that is magnified in patients with ACLF.[1,5,6] Bacterial infection has a critical relevance in the clinical course of decompensated cirrhosis, increasing the rate of short-term mortality by 2–4 fold.[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, the epidemiology of bacterial infections is now 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 because of 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 derives from single-center studies[2,4,10–13,15–20] or from multicenter studies performed in specific countries[21] or assessing specific infections.[22] However, at present no study has explored the epidemiology of MDROs in large geographical, multinational regions in patients with cirrhosis and all types of infection. 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 potential epidemiological changes.

Patients and methods

Study population and aims of the study

In the current investigation, 2 prospective series were evaluated. The first considered all patients included in the Canonic series (February to September 2011). Fifty-three individuals with and 150 without infection with incomplete data at inclusion or during follow-up were excluded. Therefore, 1,146 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 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-week follow-up were included (883 patients out of 1,295).

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. Firstly, infections developing in the whole region and in the different European regions as defined by the United Nations Geoscheme for Europe were compared. In the 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 the Czech Republic were not considered in this analysis (n = 3; Eastern Europe). The second series included infections developed in Western (Belgium, France, Germany, the Netherlands and Switzerland), Southern (Italy and Spain) and Eastern Europe (Hungary, Slovakia). Secondly, 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 24 h 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/mm^3 (250/mm^3 if positive culture); secondary peritonitis: PMN count in ascitic fluid ≥250/mm^3 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 (≥38 °C) 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 (CA) when they were present at admission or developed within the first 48 h 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 3 or more antimicrobial categories. Extensively-drug resistant (XDR) was defined as non-susceptibility to at least one agent in all but 2 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 Amp-C beta-lactamase-producing *Enterobacteriaceae* (*Enterobacter or Citrobacter spp*), carbapenem-resistant *Klebsiella pneumoniae,* carbapenem-resistant *Escherichia coli*, 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 the diagnosis of infection was defined according to the EF-Clif consortium criteria.[5] Patients were considered to have systemic inflammatory response syndrome (SIRS) if they fulfilled at least 2 of the following criteria: (a) core temperature >38 °C or <36 °C; (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 <4,000/mm^3, or differential count showing ≥10% immature PMN neutrophils. Severe sepsis was defined by the presence of SIRS and at least 1 acute organ failure. Septic shock was diagnosed by the presence of data compatible with SIRS and the need for 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/mm^3 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 a 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 stepwise 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

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 are provided (Table 1). 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 intensive care unit (ICU; 81.8%). Regular wards were 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 proven 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 unproven 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; $p < 0.001$). The 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, $p < 0.001$).

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)	

ACLF, acute-on-chronic liver failure; HCA, healthcare-associated; ICU, intensive care unit; SBP, spontaneous bacterial peritonitis; UTI, urinary tract infections.
Data are shown as number of infections and percentage. Chi-square test was used for comparisons applying Fisher exact test when required. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.
* Three infections occurring in 3 patients in Czech Republic (Eastern Europe) were not considered in the comparative analysis among European regions.

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%). The 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, HCA and 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.

All bacteria isolated in the whole series are shown (Table S1), 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 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%]; $p < 0.001$). The prevalence of MDROs also differed significantly among countries ranging from 0% in Switzerland, the Czech Republic and Denmark, 7% in Spain, 19.6% in Italy, 21% in the UK, 25% in Ireland and 34% in France ($p < 0.001$) (Table 2).

The type of isolated MDROs also differed between countries (Table 2) and European regions (Table 2, Fig. S1). ESBL and Amp-C producing *Enterobacteriaceae* were more frequent in France (18%), followed by Italy (13%), the UK and the 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%), the 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 the 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 were reported.

The MDR bacteria isolated in the different centers in the Canonic series are shown (Table S2 and Fig. 1). 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-*Escherichia coli* predominated in Clichy, Frankfurt, Barcelona (St. Pau), Padua, London (King's College) and Leuven and ESBL-*Klebsiella pneumoniae* in London (UC) and Hamburg. The prevalence of ESBL/Amp-C beta-lactamase-producing *Enterobacteriaceae* (Fig. 2A) and of MRSA (Fig. 2B) observed in the different centers

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)

Results are presented as frequencies and percentages. Chi-square test was used for comparisons applying Fisher exact test when required. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.

* 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.

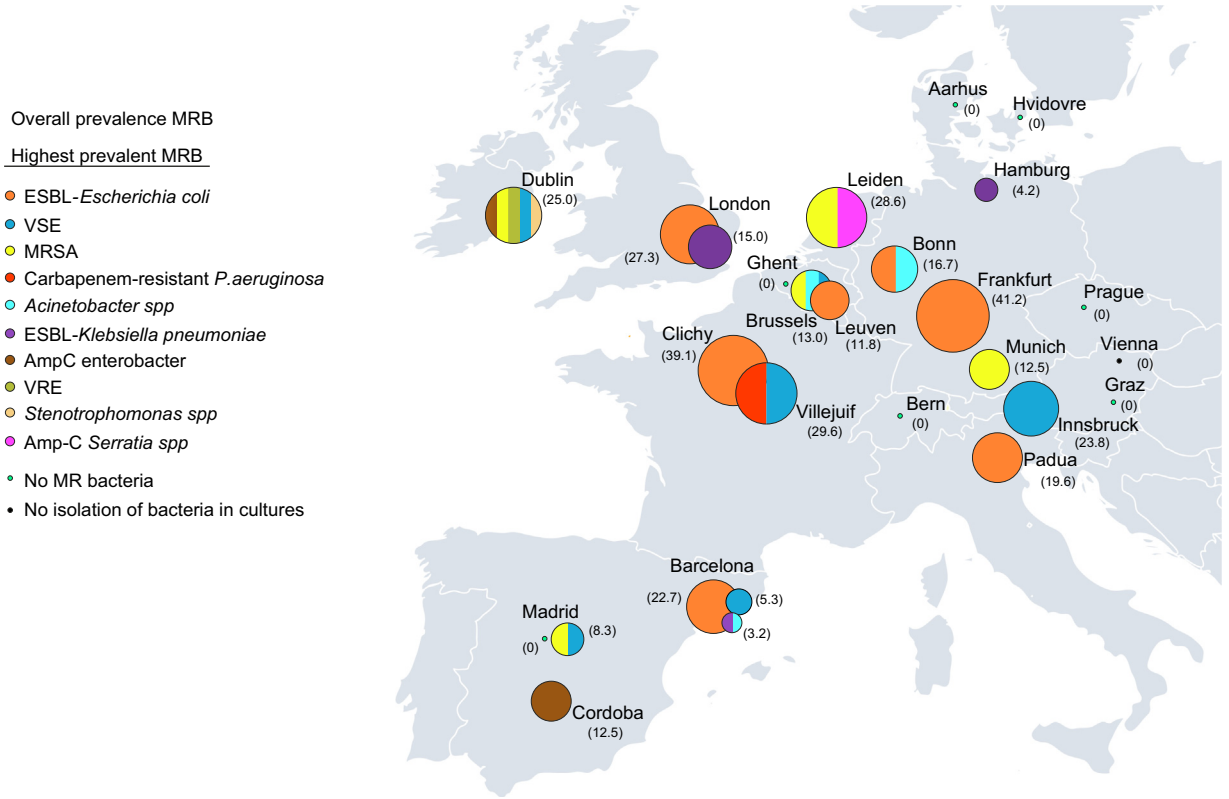

Fig. 1. Type and overall rate of MDROs isolation in the different European centers participating in the Canonic study. Different colors represent different MDR bacteria. The color of the circle is determined by the most prevalent MDROs in each center and its size correlates with the overall prevalence of MDROs at this center, also shown in brackets. Marked differences in the type and prevalence of MDROs were observed among centers. MDROs, multidrug-resistant organisms; MRB, multiresistant bacteria. (This figure appears in colour on the web.)

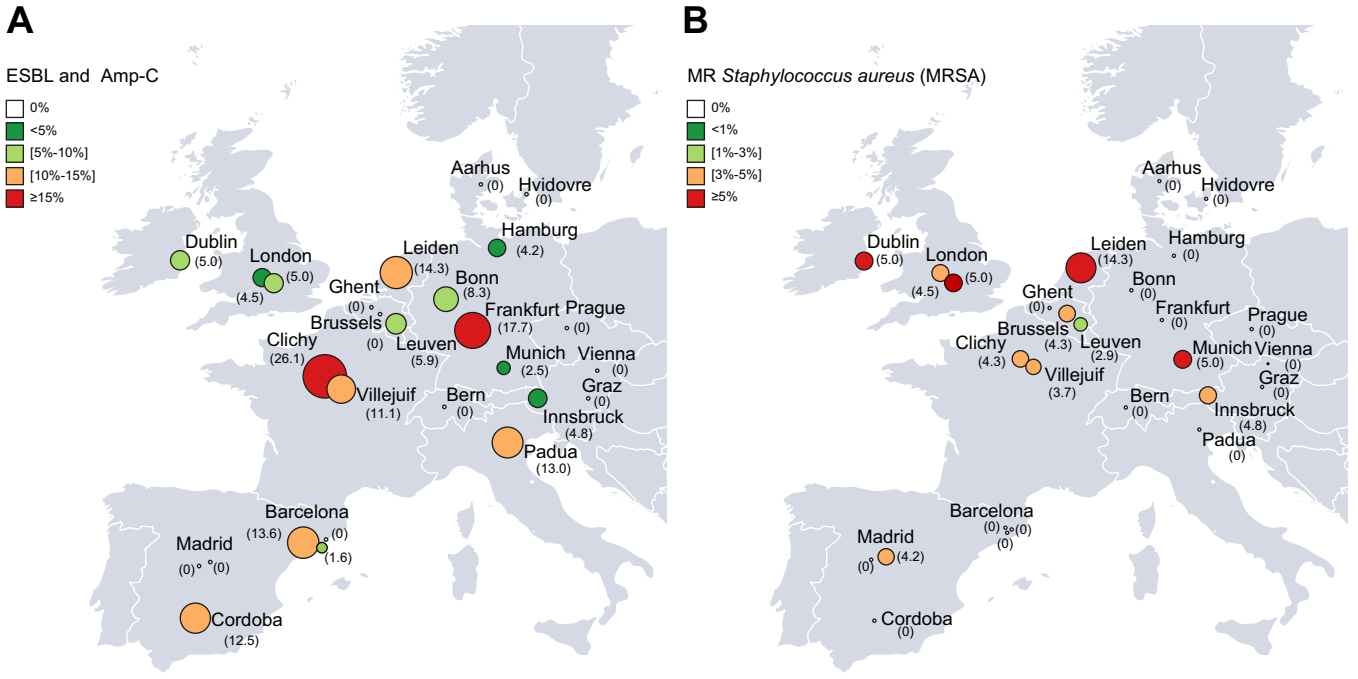

Fig. 2. Rate of infections caused by ESBL and Amp-C producing *Enterobacteriaceae* and MRSA across the different European centers participating in the Canonic study. Marked differences were observed among centers. ESBL, extended-spectrum beta-lactamase; MRSA, methicillin-resistant *Staphylococcus aureus.* (This figure appears in colour on the web.)

participating in the Canonic Study is shown. A heterogeneous distribution of MDROs was observed among different centers, even in those located in the same geographical region and city.

Infections caused by MDROs

The prevalence, type, clinical and epidemiological characteristics of bacterial infections caused by MDROs in the whole series and in the different European regions is shown (Table 3). The prevalence of MDR bacterial infections was 14.8% if considering all infections (13.4% if restricting the analysis to only one infection per patient) and 29.2% in culture-positive episodes. The 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 between specific infections in the different European regions. MDR bacteria were also more frequently isolated in the 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 (Table S3). 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 Northern Europe (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 more frequently received 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 Northern Europe (93.3%) and classical strategies in Southern Europe (72%).

The efficacy of classical and MDR empirical antibiotic strategies is shown (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

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

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

Data are shown as number of infections and percentage. Chi-square test was used for comparisons applying Fisher exact test when required. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.

[*] Data on severity of infection were not available in 54 episodes.

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 acquisition (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

CA, community-acquired; HCA, healthcare-associated.
Data are shown as number of infections and percentage. Chi-square test was used for comparisons. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.
[*] Resolution of infection without further escalation/bacterial susceptibility to initial antibiotics in culture positive infections.
[**] Data were not available in 76 infections.
[***] One to third generation cephalosporins, amoxicillin-clavulanic acid, quinolones.
[#] Piperacillin-tazobactam or carbapenem±glycopeptide/linezolid/daptomycin.

strategies increased 28-day mortality in both AD (33.3% *vs.* 7.7%; $p < 0.001$) and ACLF patients (50% *vs.* 25.8%, $p = 0.002$) (Table S4, Fig. 3).

Table S5 shows the type of empirical antibiotic strategies prescribed in the centers, showing a high prevalence of MDR bacterial infections (>15%). Initial schemes and resolution rates differed markedly between centers.

Impact of antibiotic resistance on clinical outcome

The clinical outcomes of patients infected with MDROs were compared to the outcomes in patients with infections caused by susceptible bacteria or with no microbiological isolation, in the whole series and across European regions (Table 5). The resolution rate of infections was significantly lower in episodes caused by MDROs (71.4% *vs.* 87.6%, $p < 0.001$). Infections caused by MDR strains led to a 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-day mortality (35.1% *vs.* 18.1%, $p < 0.001$). The negative impact of antibiotic resistance on clinical outcomes was confirmed across the different European regions, although we only observed significant differences in short-term mortality in Northern and Western Europe, probably as a result of the higher baseline severity of infections in these regions.

The clinical impact of antibiotic resistance was also evaluated based on the adequacy of initial antibiotic strategies (Table 5). The 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-day 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 rates (82.2% *vs.* 58.1%; $p = 0.02$) and a trend towards lower 28-day mortality (26.7% *vs.* 45.2%, $p = 0.09$) in infections caused by MDROs.

Risk factors for MDR bacterial infection

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 are shown (Table 6 and Table S6). Nosocomial infection (odds ratio [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. The prevalence of infection was significantly higher in Eastern (45.4%) and Southern Europe (39.4%) than in Western Europe (18.5%; $p < 0.0001$; Table S7). UTI (n = 104), SBP (n = 50), pneumonia (n = 43), bacteremia (n = 38) and SSTI (n = 24) were the most frequent proven infections in this series. CA infections predominated in the whole population (n = 189; 53%) and in the different European regions. The severity of infection at diagnosis was similar among the different European regions. The prevalence of MDR bacterial infections was 23.3% if

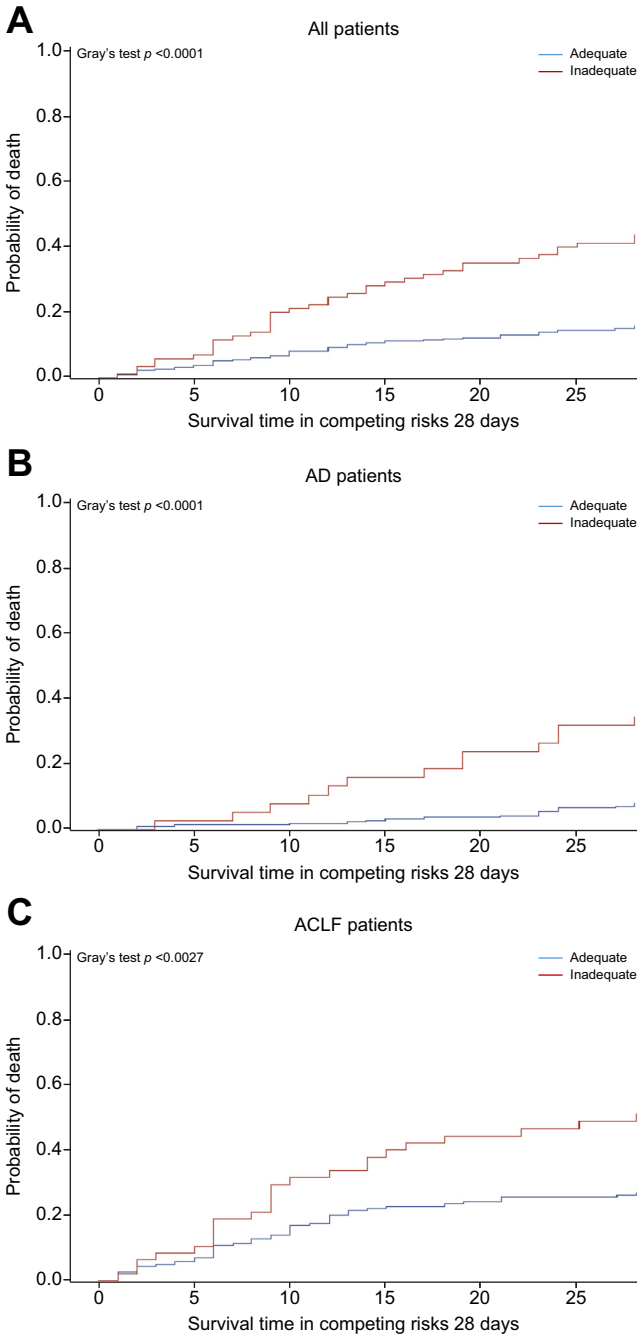

Fig. 3. Probability of death at day 28 in infected patients receiving adequate or inadequate empirical antibiotic strategies. (A) In the whole series, (B) in patients with AD and (C) in patients with ACLF in the Canonic study. Inadequacy of empirical strategies significantly increased the probability of death in the 3 populations. ACLF, acute-on-chronic liver failure; AD, acute decompensation. (This figure appears in colour on the web.)

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 (Table S7).

The types of MDROs isolated in the second series are shown (Table S8). 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 were reported. The prevalence and type of MDR bacteria isolated in the different centers are shown (Fig. 4). Fifteen centers (79%) from 8 countries (89%) reported infections caused by MDROs. Remarkable differences were observed in the prevalence and type of MDR strains between 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 2 series and includes 739 patients with bacterial infection enrolled in 32 centers from 16 countries. From a geographical 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 2 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 to date 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. The isolation rate of MDROs varied from 0% in Switzerland, the Czech Republic and Denmark and 7% in Spain to 20% in Italy, 21% in the UK, 25% in Ireland and 34% in France. Belgium, Germany, the Netherlands and Austria showed intermediate rates of MDROs. The prevalence of MDR bacterial infections increased to 38% in culture-positive episodes in the second series, with 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 2 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

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
Northern Europe (n)	**72**	**59**	**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
Southern Europe (n)	**207**	**189**	**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)	**238**	**192**	**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

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 N = 520	No isolation/ susceptible bacteria				MR bacteria			
			Initial antibiotic therapy				Initial antibiotic therapy		
		Total n = 443	Inadequacy n = 56	Adequacy* n = 335	*p*	Total n = 77	Inadequacy n = 31	Adequacy* n = 45	*p*
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.
Data are shown as number of infections and percentage. Chi-square test was used for comparisons. SAS (version 9.4; SAS Institute Inc.; Cary, NC) statistical package.
* Resolution of infection without further escalation/bacterial susceptibility to initial antibiotics in culture positive infections.

the highest prevalence of MDROs, while 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. Meanwhile, both series were analysed over a short time period (7 and 11 months), which 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 2 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 most 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, the UK and the Netherlands; VSE predominated in France and Austria and MRSA in infections occurring in the Netherlands, the UK and Ireland. ESBL-producing *Enterobacteriaceae* continued to be the most frequent MDRO reported in the 2017–2018 series, but marked differences were observed in the type of resistant bacteria among regions and centers. This finding underlines the importance of having surveillance programs aimed at investigating the prevalence and epidemiological pattern of MDROs at each hospital. Global epidemiological data are informative but are not applicable to specific centers.[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 either series. Therefore, our results suggest that although XDR bacteria constitute a growing

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**	**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	–	–

ACLF, acute-on-chronic liver failure; ICU, intensive care unit; MELD, model for end-stage liver disease.
Data are presented as mean ± SD or number of infections and percentage. Chi-square test was used for categorical variables and Student's t-test for continuous variables. Logistic regression models were used in the multivariate analysis. Variables showing a *p* value <0.1 were introduced in the model
* Within the previous 3 months.

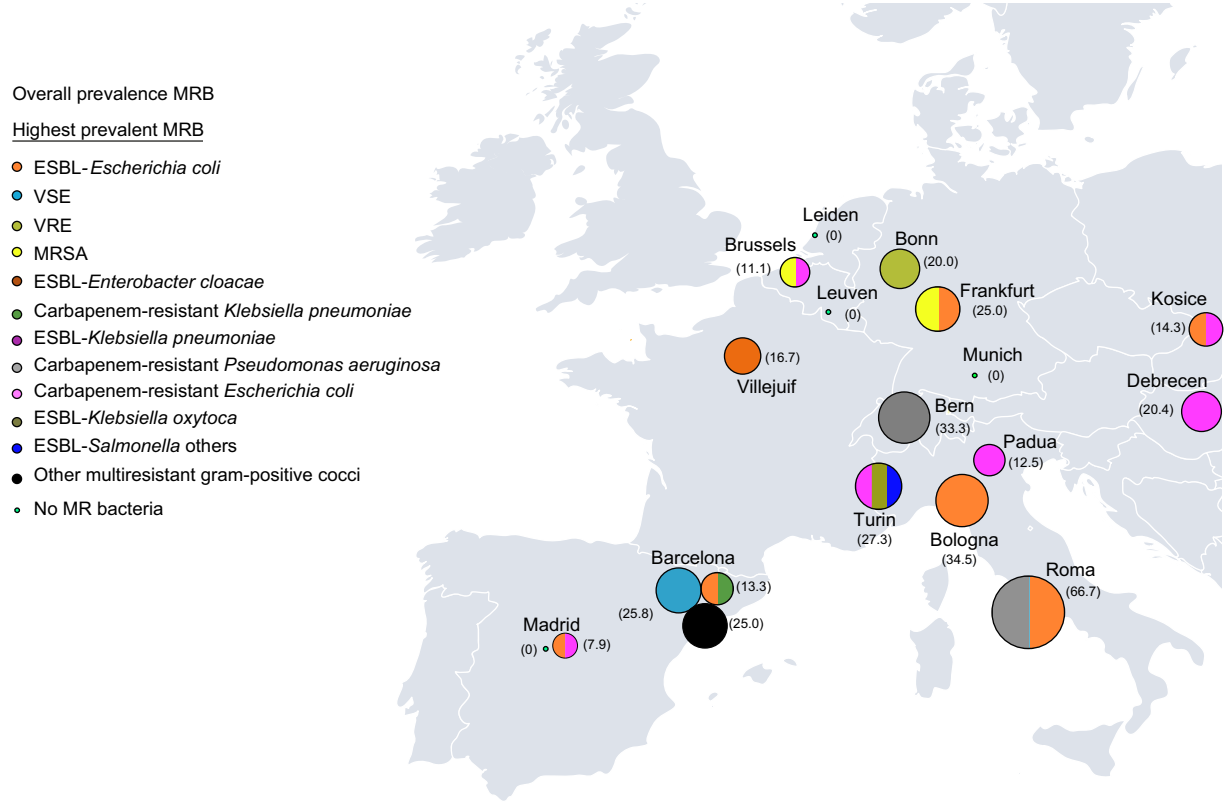

Fig. 4. Type and overall rate of MDROs isolation in the different European centers participating in the second study (2017–2018). Different colors represent different MDR bacteria. The color of the circle is determined by the most prevalent MDROs in each center and its size correlates with the overall prevalence of MDROs at this center, also shown in brackets. Marked differences in the type and prevalence of MDROs were observed among centers. MDRO, multidrug-resistant organisms; MRB, multiresistant bacteria. (This figure appears in colour on the web.)

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 days, especially if treated with inadequate empirical antibiotic strategies. Our results, therefore, confirm previous studies in decompensated cirrhosis showing that antibiotic resistance is associated with 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]

A 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, a 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 a risk factor of MDR in the current series. The low number of patients on long-term quinolone prophylaxis in our study (n = 7) prevented us from adequately evaluating this potential risk factor. The 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, a feature probably related to differences in the epidemiological characteristics between countries and centers. Mechanical ventilation, a parameter reflecting both organ support and a 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 48 h 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 patients with AD and ACLF, a feature also observed when the analysis was restricted to MDR bacterial infections. Therefore, our findings support 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, which is 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. Based on this observation, the urgent evaluation of new strategies aimed at preventing the spread of antibiotic resistance in the cirrhotic population is warranted. 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 to 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 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 with poor prognosis and failure of first-line antibiotic strategies based on third-generation cephalosporins or quinolones.

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Conflicts of interest

Javier Fernández 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

Authors' 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.

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.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2018.10.027.

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Author names in bold designate shared co-first authorship

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