World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i15.4049

World J Gastroenterol 2016 April 21; 22(15): 4049-4056
ISSN 1007-9327 (print) ISSN 2219-2840 (online)
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ORIGINAL ARTICLE

Prospective Study

Extensively drug-resistant bacteria are an independent predictive factor of mortality in 130 patients with spontaneous bacterial peritonitis or spontaneous bacteremia

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Institutional review board statement: The study was reviewed and approved by the Hippokration Hospital Review Board.

Informed consent statement: All study participants or their legal guardians provided written consent prior to study enrollment.

Conflict-of-interest statement: The authors disclose no conflicts.

Data sharing statement: No additional data are available.

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Received: December 10, 2015
Peer-review started: December 11, 2015
First decision: January 13, 2015
Revised: January 18, 2015
Accepted: February 20, 2016
Article in press: February 22, 2016
Published online: April 21, 2016

Abstract

AIM: To evaluate the epidemiology and outcomes of culture-positive spontaneous bacterial peritonitis (SBP) and spontaneous bacteremia (SB) in decompensated cirrhosis.

METHODS: We prospectively collected clinical, laboratory characteristics, type of administered antibiotic, susceptibility and resistance of bacteria to antibiotics in one hundred thirty cases (68.5% males) with positive ascitic fluid and/or blood cultures during the period from January 1, 2012 to May 30, 2014. All patients with SBP had polymorphonuclear cell count in ascitic fluid > 250/mm^3. In patients with SB a thorough study did not reveal any other cause of bacteremia. The patients were followed-up for a 30-d period

following diagnosis of the infection. The final outcome of the patients was recorded in the end of follow-up and comparison among 3 groups of patients according to the pattern of drug resistance was performed.

RESULTS: Gram-positive-cocci (GPC) were found in half of the cases. The most prevalent organisms in a descending order were *Escherichia coli* (33), *Enterococcus spp* (30), *Streptococcus spp* (25), *Klebsiella pneumonia* (16), *S. aureus* (8), *Pseudomanas aeruginosa* (5), other Gram-negative-bacteria (GNB) (11) and anaerobes (2). Overall, 20.8% of isolates were multidrug-resistant (MDR) and 10% extensively drug-resistant (XDR). Health-care-associated (HCA) and/or nosocomial infections were present in 100% of MDR/XDR and in 65.5% of non-DR cases. Meropenem was the empirically prescribed antibiotic in HCA/nosocomial infections showing a drug-resistance rate of 30.7% while third generation cephalosporins of 43.8%. Meropenem was ineffective on both XDR bacteria and *Enterococcus faecium* (*E. faecium*). All but one XDR were susceptible to colistin while all GPC (including *E. faecium*) and the 86% of GNB to tigecycline. Overall 30-d mortality was 37.7% (69.2% for XDR and 34.2% for the rest of the patients) (log rank, P = 0.015). In multivariate analysis, factors adversely affecting outcome included XDR infection (HR = 2.263, 95%CI: 1.005-5.095, P = 0.049), creatinine (HR = 1.125, 95%CI: 1.024-1.236, P = 0.015) and INR (HR =1.553, 95%CI: 1.106-2.180, P = 0.011).

CONCLUSION: XDR bacteria are an independent life-threatening factor in SBP/SB. Strategies aiming at restricting antibiotic overuse and rapid identification of the responsible bacteria could help improve survival.

Key words: Spontaneous bacterial peritonitis; Spontaneous bacteremia; Multidrug-resistant bacteria; Extensively drug-resistant bacteria; Susceptibility to antibiotics

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Core tip: This is a prospective, observational, single Center study seeking to evaluate the epidemiology and outcomes of 130 patients with decompensated cirrhosis and culture-positive spontaneous bacterial peritonitis or spontaneous bacteremia. Both multidrug-resistant (MDR) and extensively drug-resistant (XDR) bacteria were isolated in about one third of the cases. Patients with XDR demonstrated high mortality compared to the rest of the patients. All MDR/XDR associated infections were health-care associated and/or nosocomial. Independent factors adversely affected survival included XDR infection, renal dysfunction and coagulation disorder.

Alexopoulou A, Vasilieva L, Agiasotelli D, Siranidi K, Pouriki S, Tsiriga A, Toutouza M, Dourakis SP. 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(15): 4049-4056 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i15/4049.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i15.4049

INTRODUCTION

Infections are the most common precipitating event in acute-on-chronic liver failure[1] and are associated with high mortality in patients with decompensated cirrhosis[2]. Pathological bacterial translocation (BT) in cirrhosis involves alterations in gut microbiota, deficiency in intestinal barrier and an impaired immune response by the gut associated lymphatic tissue[3,4]. The most typical clinical expressions of pathological BT are spontaneous bacterial peritonitis (SBP) and spontaneous bacteremia (SB) (positive blood culture with no cause of bacteremia)[5]. Prompt and appropriate treatment is important in patients with bacterial infections and decompensated cirrhosis, to cover the most commonly isolated bacteria and maximize the patient's chance of survival[6]. In recent years, a change in epidemiology of bacterial infections in cirrhosis has been observed worldwide characterized by an increasing rate of multi-drug resistant (MDR) bacteria and a decreased efficacy of antibiotics[7-12]. Risk factors associated with resistance to antibiotics are nosocomial or health care-associated acquisition, long-term norfloxacin prophylaxis, recent use of b-lactams and recent infection with MDR[5,7,12-14]. A position statement based on the EASL Special Conference 2013 recommended as empirical treatment for community-acquired infections either cefotaxime (or ceftriaxone) or amoxicillin/clavulanate and for nosocomial either piperacillin/tazobactam or meropenem ± glycopeptide[5].

MDR are difficult to treat bacteria including extended-spectrum beta-lactamases (ESBL)-producing *Enterobacteriaceae*, nonfermentable Gram-negative bacteria (GNB) *Pseudomanas aeruginosa* (*P. aeruginosa*) and methicillin-resistant *Staphylococcus aureus* (*S. aureus*) (MRSA). Recently, extensively drug-resistant bacteria (XDR) such as Carbapenemase-producing (KPC) *Klebsiella pneumonia* (*K. pneumoniae*) and vancomycin-resistant enterococci (VRE) emerged in patients with cirrhosis[12,14,15]. We recently reported an increased prevalence in MDR in SBP cases in the period 2008-2011[14].

In this study we aimed at assessing the possible changes in microbial etiology of culture-positive SBP

and SB, the risk factors of acquisition of microorganisms resistant to third generation cephalosporins and quinolones and the difference in survival between patients with different patterns of drug-resistance and those with no drug-resistance.

MATERIALS AND METHODS

Study design

This prospective, observational study was conducted in the 2nd Department of Internal Medicine of our hospital from January 1, 2012 to May 30, 2014. We prospectively collected data on patients with decompensated cirrhosis and either spontaneous bacteremia without SBP or (ascitic fluid and/or blood) culture-positive SBP. Patients with human immunodeficiency virus infection, previous transplantation or any other type of immunodeficiency, multi-microbial infections, in peritoneal dialysis or those with secondary bacterial peritonitis were excluded. The study protocol was approved by the Hospital Ethical Committee. All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

The diagnosis of SBP was based on neutrophil count in ascitic fluid of > 250/mm^3 as determined by microscopy[6]. After SBP or SB diagnosis and in patients with clinical suspicion of infection, empirical treatment was administered intravenously and was maintained or replaced subsequently following a second paracentesis in two days or the *in vitro* susceptibility of isolated organisms from ascitic fluid or blood. In patients with SB thorough investigation did not reveal any specific cause of bacteremia. Infections were classified as HCA in patients with a hospitalization for at least 2 d in the previous 180 d or as nosocomial those which developed in more than 48 h after admission[16]. We did not include any patients with a previous hospitalization in intensive care unit (ICU). The remaining infections were considered community-acquired (CA) when they were present on admission or developed within the first 48 h after admission[16]. Clinical doctors and infectious diseases specialists decided about the empirical antibiotic regimens and assessed the clinical course and the resolution of the infection. The empirical antibiotic regimen according to local policies and recent guidelines[5] was ceftriaxone IV for the community-acquired and meropenem for HCA and/or nosocomial infections. SBP and SB considered as cured if polymorphonuclear cell count was < 250/mm^3 and negative blood cultures were obtained after antibiotic treatment, respectively. Only fifteen patients (11.5%) had been receiving prophylactic quinolone treatment as secondary prevention for SBP.

Bacterial cultures technique and multi-drug resistant bacteria definition

On admission, diagnostic paracentesis and inoculation of ascitic fluid into two blood culture bottles for aerobic and anaerobic bacteria was routinely performed at bedside. Separate and simultaneous blood cultures were collected. Aerobic, anaerobic and broth cultures were initiated in BACTEC 9240 (Becton, Dickinson). All the isolated organisms were identified by the VITEK2 system (Biomerieux, Marcy l'Etoile, France). Antibiotic susceptibility testing was performed by the Kirby-Bauer method according to Clinical and Laboratory Standards Institute guidelines. The minimum inhibitory concentrations were determined by the E-test system (AB Biodisk, Solna, Sweden) and by the VITEK2 system. Double disc synergy (DDST), ESBL E-test (AB) and VITEK2 ESBL card (Biomerieux) were used to detect ESBL frequency. The detection of KPC carbapenemase was based on a phenotypic screen for carbapenem resistance followed by the modified Hodge test as a confirmatory test. DDST and E-test-MBL were used to detect MBL carbapenemase frequency. Only monomicrobial infections were included. All patients with simultaneous fungi-positive culture were excluded from the study. When the same strain was isolated twice or more from the same patient, it was counted only once. Multi-drug resistant (MDR) bacteria are strains non susceptible to $\geqslant$ 1 agent in $\geqslant$ 3 antimicrobial categories[17]. Extensively drug-resistant bacteria (XDR) defined as non-susceptible to $\geqslant$ 1 agent in all but $\leqslant$ 2 antimicrobial categories[17]. *Enterococcus faecium* (*E. faecium*) was considered an MDR organism and was classified as such.

Collection of the data

Clinical and laboratory data were collected at the time of admission including age, gender, cause of admission, etiology of cirrhosis, full blood count, international normalized ratio of prothrombin time (INR), renal and hepatic function biochemical tests and ascitic fluid evaluation. Severity of liver disease was assessed by Model for End-Stage Liver Disease (MELD) score for each patient. Days of hospitalization within 6 months before infection were also recorded.

Statistical analysis

All data were analysed using the statistical package SPSS (version 21.0 SPSS Inc., Chicago, IL, United States). The characteristics of the patients were assessed using median (interquartile range) for continuous variables and count (percentage) for categorical variables. In order to test for differences in the univariate analysis among the different categories of patients with MDR, XDR and non-DR bacteria, we used Mann-Whitney test for continuous variables and chi-squared test for categorical variables. Survival rates were evaluated using the Kaplan-Meier estimator and were compared between groups by the log-rank test. The Cox proportional-hazards model was used to estimate the risk of death due to MDR or XDR. Factors associated with mortality with a *P* value of < 0.10 in the univariate analysis were entered in the multivariate

Table 1 Demographic characteristics of patients with bacterial infections classified according to the drug resistance of the organism

	Total	Non-DR	MDR	XDR	*P* vaule[1]	*P* vaule[2]
	n = 130	*n* = 90	*n* = 27	*n* = 13		
Age (yr)	62 (55-73)	62 (54-63)	62.5 (54.7-73.2)	62 (59-79)	0.928	0.379
Gender (Males)	89 (68.5)	57 (63.3)	23 (85.2)	9 (69.2)	0.768	0.035
Etiology of liver cirrhosis						
Alcoholic	54 (41.5)	35 (38.9)	13 (48.1)	6 (46.2)	0.476	0.718
Viral	47 (36.1)	32 (35.6)	10 (37)	5 (38.5)		
Other	29 (22.3)	23 (25.6)	4 (14.8)	2 (15.4)		
MELD	20 (15-25)	20 (15-25)	19.5 (16-23)	25 (18-36)	0.947	0.044
Hospitalization days over the preceding 6 mo	10 (5-19)	9 (4-16)	15 (6.75-28)	11 (7.5-22)	0.014	0.249
Nosocomial infections, *n* (%)	47 (36.1)	23 (25.5)	16 (59.2)	8 (61.5)	0.001	0.008
HCA infections, *n* (%)	75 (57.6)	48 (53.3)	18 (66.6)	9 (69.2)	0.220	0.281
HCA and/or nosocomial infections, *n* (%)	99 (76.1)	59 (65.5)	27 (100)	13 (100)	< 0.001	0.011

[1]Comparison between MDR and non-DR; [2]Comparison between XDR and Non-DR, values are expressed in median (interquartile range). HCA: Health care associated infections; MDR: Multi-drug resistant; XDR: Extensively drug resistant.

Table 2 Laboratory characteristics of patients with bacterial infections classified according to the drug resistance of the organism

	Total	Non-DR	MDR	XDR	*P* vaule[1]	*P* vaule[2]
	n = 130	*n* =90	*n* = 27	*n* = 13		
Leucocyte count × 10^9/L	7.38 (4.6-11.3)	7.34 (4.85-11.27)	7.2 (4.18-11.73)	7.51 (4.39-11.61)	0.797	0.967
Neutrophil/leucocyte%	81 (71-88)	79 (70-87)	84 (72-88)	83 (76-90)	0.608	0.163
Total Bilirubin (mg/dL)	3.8 (1.9-8.7)	4.2 (1.9-9.2)	2.6 (1.6-6.1)	4.2 (1.7-19.7)	0.305	0.792
Creatinine (mg/dL)	1.1 (0.8-1.7)	1.1 (0.8-1.5)	1.2 (0.8-1.7)	2 (0.8-5.0)	0.269	0.093
INR	1.6 (1.4-2.1)	1.6 (1.3-2.2)	1,5 (1.4-1.9)	2 (1.3-2.2)	0.958	0.423
AST (IU/L)	53 (30-105)	55 (30-121)	45 (32-74)	23 (18-78)	0.423	0.057
C-reactive protein (mg/L)	59 (23-108)	52 (22-102)	68 (30-138)	101 (18-120)	0.318	0.302
Fibrinogen (mg/dL)	239 (134-496)	344 (130-516)	170 (156-273)	247 (119-460)	0.393	0.628

[1]Comparison between MDR and Non-DR; [2]Comparison between XDR and non-DR; values are expressed in median (interquartile range). MDR: Multi-drug resistant; XDR: Extensively drug resistant.

model and non-significant factors were removed by a backward selection process. A two-tailed *P* value less than 0.05 was considered to be statistically significant.

RESULTS

Clinical and laboratory characteristics in overall

We prospectively recorded 130 cases (68.5% males, median age 62 years) with culture positive-SBP (70 cases) or spontaneous bacteremia without SBP (60 cases) in patients with decompensated cirrhosis. In total, 58 (44.6%) cases had positive ascitic fluid culture, 64 (49.2%) positive blood culture and 8 (6.2%) both. Patients were classified into 3 groups according to the drug-resistance pattern: ninety (69.2%) patients had infections with non-DR, 27 (20.8%) with MDR and 13 (10%) with XDR bacteria. Etiology of cirrhosis was chronic viral hepatitis in 47 (36.1%), alcohol in 54 (41.5%) and other causes in 29 (22.3%). The median MELD score was 20 (15-25). Ninety nine patients (76.1%) had been hospitalized within the last six months (HCA) and/or developed nosocomial infections (23 were both HCA-associated and nosocomial) (Table 1). Only 31 (23.8%) infections were community-acquired. The laboratory characteristics of patients on admission are demonstrated in Table 2.

Comparison of 3 groups of patients according to different patterns of drug resistance

No difference in age, gender and etiology of cirrhosis was observed between patients with XDR or MDR and those with non-DR bacteria. More severe liver disease was observed in patients with XDR than in those with non-DR bacteria [median MELD score 25 (interquartile range 18-36) *vs* 20 (15-25), respectively *P* = 0.044] (Table 1). Nosocomial infections were more frequent in the XDR or MDR groups compared to the non-DR one. Community-acquired infections were evident only in the non-DR group (Table 1). No difference in laboratory characteristics was shown among the groups (Table 2).

Type of bacteria and drug resistance

Gram-positive cocci (GPC) were found in half of the cases (48.5%). The most prevalent organisms in a descending order were *Escherichia coli* (*E. coli*) (33), *Enterococcus spp* (30, including 17 *E. faecium*), *Streptococcus spp* (25), *K. pneumonia* (16), *S. aureus* (8), *P. aeruginosa* (5), other *GNB* (11) and anaerobes (2). Twenty seven (20.8%) of the isolated bacteria were MDR, including ESBL - GNB (9), *P. aeruginosa* (3) and *E. faecium* (15). Thirteen (10%) of the bacteria were XDR including KPC *K. pneumonia* (5), colistin-resistant KPC-producing *K. pneumonia* (1), *P.*

Table 3 Isolated bacteria and antibiotic susceptibility tests

Antibiotic	OX	AMC	MEM	CTX	FEP	TGC	VA	CT	CIP	SXT
Gram-positive bacteria (63)										
Resistance	34/63	22/63	25/63	27/63	26/63	0/63	2/63	51/63	38/63	24/63
S. aureus (8)	0/8	5/8	8/8	8/8	8/8	0/8	0/8	8/8	2/8	0/8
Streptococcus spp. (23)	3/22	0/23	0/23	0/23	0/23	0/23	0/23	11/23	11/23	0/23
S. pneumonia (2)	2/2	0/2	0/2	0/2	0/2	0/2	0/2	2/2	2/2	0/2
E. faecalis (13)	12/13	0/13	0/8	2/13	1/13	0/13	0/13	13/13	6/13	7/13
E. faecium (15)	15/15	15/15	15/15	15/15	15/15	0/15	0/15	15/15	15/15	15/15
E. faecium VRE (2)	2/2	2/2	2/2	2/2	2/2	0/2	2/2	2/2	2/2	2/2
Gram-negative bacteria (65)										
Resistance	65/65	34/65	15/65	28/65	20/65	9/65	65/65	1/65	24/65	33/65
E. coli (25)	25/25	3/25	0/25	1/25	0/25	0/25	25/25	0/25	5/25	5/25
ESBL-*E. coli* (7)	7/7	7/7	0/7	7/7	6/7	0/7	7/7	0/7	7/7	6/7
MBL-*E. coli* (1)	1/1	1/1	1/1	1/1	1/1	0/1	1/1	0/1	1/1	1/1
K. pneumonia (9)	9/9	1/9	0/9	0/9	0/9	0/9	9/9	0/9	1/9	7/9
KPC-*K. pneumonia* (5)	5/5	5/5	5/5	5/5	5/5	2/5	5/5	0/5	4/5	1/1
ESBL-*K. pneumonia* (1)	1/1	1/1	0/1	1/1	0/1	0/1	1/1	0/1	0/1	1/1
K. pneumonia KPC+, col-R (1)	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1	1/1
P. aeruginosa (5)	5/5	5/5	2/5	5/5	3/5	5/5	5/5	0/5	2/5	5/5
S. marcescens (2)	2/2	2/2	0/2	0/2	0/2	0/2	2/2	0/2	0/2	0/2
S. maltophilia (3)	3/3	2/3	3/3	3/3	1/3	0/3	3/3	0/3	0/3	0/3
A. baumannii (2)	2/2	2/2	2/2	2/2	2/2	1/2	2/2	0/2	2/2	2/2
ESBL P. mirabilis- (1)	1/1	1/1	0/1	1/1	1/1	0/1	1/1	0/1	1/1	1/1
E. cloacae (2)	2/2	2/2	1/2	0/2	0/2	0/2	2/2	0/2	0/2	2/2
E. aerogenes (1)	1/1	1/1	0/1	1/1	0/1	0/1	1/1	0/1	0/1	1/1
Anaerobes (2)										
Resistance	2/2	1/2	0/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2
Bacteroides spp (2)	2/2	1/2	0/2	2/2	2/2	2/2	2/2	2/2	2/2	2/2

OX: Oxacillin; AMC: Amoxicillin/Clavulanic acid; MEM: Meropenem; CTX: Cefotaxime; FEP: Cefepime; TGC: Tigecycline; VA: Vancomycin; CT: Colistin; CIP: Ciprofloxacin; SXT: Cotrimoxazole; ESBL: Extended-spectrum-beta-lactamase-producing; KPC+, col-R: Carbapenemase-producing colistin-resistant *K. pneumonia*; MBL: Metallo-β-lactamase-producing; VRE: Vancomycin-resistant *E. Faecium*. *S. aureus*: *Staphylococcus aureus*; *S. pneumonia*: *Streptococcus pneumoniae*; *E. faecalis*: *Enterococcus faecalis*; *E. faecium*: *Enterococcus faecium*; *E. coli*: *Escherichia coli*; *K. pneumonia*: *Klebsiella pneumonia*; *P. aeruginosa*: *Pseudomanas aeruginosa*; *S. marcescens*: *Serratia marcescens*; *S. maltophilia*: *Stenotrophomonas maltophilia*; *A. baumannii*: *Acinetobacter baumannii*; *P. mirabilis*: *Proteus mirabilis*; *E. cloacae*: *Enterobacter cloacae*; *E. aerogenes*: *Enterobacter aerogenes*.

aeruginosa (2), *A. baumannii* (2), VRE *E. faecium* (2) and metallo-β-lactamase-producing (MBL) - *E. coli* (1).

Resistance to antimicrobial agents

Fifty seven (43.8%) of the isolated bacteria were third-generation cephalosporin-resistant. Resistance to quinolones was observed in sixty four (49.2%) microorganisms. Amoxycilline-clavulanate resistance was demonstrated in 57 (43.8%) cases (Table 3). The 50/57 (88%) third-generation cephalosporine-resistant bacteria showed cross-resistance to amoxicillin/clavulanate and the 42/57 (73.7%) were also resistant to quinolones (Table 3). Meropenem, the most frequent empirically prescribed antibiotic for HCA/nosocomial infections, showed a drug resistance rate of 30.7%. Meropenem was ineffective on both XDR bacteria and *E. faecium*. Ten out of 13 (77%) XDR were susceptible to colistin while all GPC including *E. faecium* and the 86% of GNB to tigecycline. Only 54% of the XDR were susceptible to tigecycline. All but one XDR bacteria were susceptible to a possible combination of colistin and tigecycline.

Survival analysis according to drug resistance pattern

Kaplan-Meier analysis showed that patients with XDR bacteria had a worse 30-d survival compared to those with MDR or non-DR bacteria (log rank, $P = 0.015$) (Figure 1). The outcome of patients with XDR was worse compared to MDR- and non-DR-infected patients separately (log rank $P = 0.012$ and $P = 0.008$, respectively). Consequently, patients with MDR had similar 30-d-survival rate to those with non-DR bacteria (log rank $P = 0.604$). In overall, 30-d-mortality was 37.7%. In particular, 30 d-mortality rate for patients with XDR *vs* the rest of the patients were 69.2% *vs* 34.2%, respectively.

In Cox univariate analysis, variables that had at least a trend ($P < 0.10$) for association with 30-d survival included age ($P = 0.089$), neutrophil-to-leucocyte ratio ($P = 0.072$), INR ($P = 0.001$), creatinine ($P = 0.036$), total bilirubin ($P = 0.001$) and XDR infection ($P = 0.007$). In multivariate Cox regression analysis, factors adversely affecting outcome were XDR infection (HR = 2.263, 95%CI: 1.005-5.095, $P = 0.049$), creatinine (HR = 1.125, 95%CI: 1.024-1.236, $P = 0.015$) and INR (HR = 1.553, 95%CI: 1.106-2.180, $P = 0.011$) (Table 4).

DISCUSSION

A worrisome increase in infections caused by MDR pathogens in decompensated cirrhosis has been

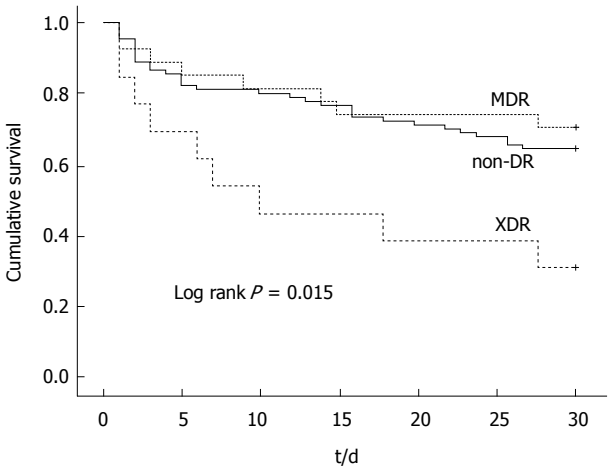

Figure 1 Comparison of survival among patients infected with extensively drug-resistant, multi-drug-resistant and non-drug-resistant bacteria. Non-DR: Non-drug-resistant bacteria; MDR: Multi-drug resistant; XDR: Extensively drug-resistant.

Table 4 Univariate and multivariate Cox regression analysis of factors predicting 30-d mortality in 130 patients with bacterial infections

	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Age (per 1 yr)	1.017 (0.997-1.037)	0.089		
Gender	1.134 (0.833-1.542)	0.425		
Neutrophil-to-Leucocyte ratio	1.026 (0.998-1.055)	0.072		
C-reactive protein	1.004 (0.999-1.008)	0.129		
XDR infections	2.7 (1.310-5.565)	0.007	2.263 (1.005-5.095)	0.049
Total bilirubin	1.051 (1.020-1.082)	0.001		
Creatinine	1.097 (1.006-1.197)	0.036	1.125 (1.024-1.236)	0.015
INR	1.746 (1.271-2.399)	0.001	1.553 (1.106-2.180)	0.011
AST	1.000 (0.999-1.001)	0.442		

XDR: Extensively drug-resistant; INR: International normalized ratio.

emerged in many countries[7-12]. An increasing frequency in MDR in 47 cases with culture-positive-SBP was described in a previous study from our Center (2008-2011)[14]. The current collection of data from culture-positive infections of both blood stream and ascitic fluid over the period 2012-2014, showed similar rates of Gram-positive cocci, MDR pathogens and *E. faecium*, with those reported previously.

However, an increasing variety in XDR was currently recorded. MBL-producing *E. coli*, VR-*enterococci* and colistin-resistant KPC-producing *K. pneumonia* were isolated for the first time, while ESBL-producing *Enterobacteriaceae,* KPC-producing *K. pneumonia*, A. baumanni and multi-drug resistant *P. aeruginosa* were also observed in the previous cohort. Notably, the MDR/XDR pathogens were coming from regular hospital wards and not from the ICU. In addition, no previous hospitalizations in ICU were recorded. MDR/XDR bacteria were exclusively associated with HCA/nosocomial infections. On the other hand, non-DR bacteria were encountered only in patients with community-acquired infections. It is remarkable that community-acquired infections prevalence is reduced in current cohort compared to that reported in the literature[12].

E. faecium is a common pathogen in the current cohort comprising the 57% of the total *Enterococci*. *E. faecium* is considered by previous investigators as a multiresistant organism[5,18] because of resistance to ampicillin, third generation cephalosporins and quinolones[17]. Hence, we decided to include susceptible to vancomycin *E. faecium* in the MDR group. Eventually, we observed that all the *E. faecium*-associated infections were health-care-associated and/or nosocomial and patients with *E. faecium* had prolonged previous hospitalizations comparable to those recorded in MDR/XDR bacteria. The above findings advocated that this pathogen belongs to MDR bacteria.

Regarding microbial resistance, no major changes were recorded in amoxicillin-clavulanate, third generation cephalosporins and quinolone compared to the previous study. As reported before in the local nosocomial setting, the above antibiotics were ineffective to treat health care-associated and/or nosocomial infections[14]. In addition, a relatively high prevalence of ESBL-producing *Enterobacteriaceae* was previously described[14]. For all reasons reported above, clinical doctors and infection specialists decided to administer ceftriaxone to the community-acquired and meropenem to the health care-associated (HCA) and/or nosocomial infections during the whole period of current study. The widespread administration of carbapenems in the majority of the patients with HCA/nosocomial infections may have resulted in the emergence of new XDR strains and warns against the expanded use of these antibiotics. KPC-producing *K. pneumonia*, colistin-resistant or not, MBL-producing bacteria and multi-resistant *P. aeruginosa* may be the consequences of the aforementioned clinical approach which allows few available therapeutic options. As the clinicians usually approve the early antibiotic administration in cirrhotics, many non-infected patients may receive antibiotics, increasing the rate of colonization of enteric flora with resistant bacteria which eventually may become virulent.

The study illustrates two major changes in clinical practice with important clinical implications. Firstly, only few patients were receiving quinolone prophylaxis and as a result MDR/XDR infection development was not associated with the use of prophylaxis against SBP. The high prevalence of Gram positive cocci observed worldwide[12,19-22] was also confirmed in both 2008-2011[14] and 1998-2002[23] studies in culture-positive SBP cases from our Department. In addition, a remarkable number of MDR/XDR-associated infections were demonstrated

in 2008-2011 study. More specifically, GPC accounted for the half and MDR/XDR for the one third of the cases. Besides quinolone resistance accounted for almost half of the cases rendering quinolones ineffective for secondary prophylaxis. Similar high rates of quinolone resistance in isolated bacteria were reported in previous investigations[12,24-26]. The low rate of quinolone prophylaxis in the current cohort prevented us from considering quinolone as a risk factor for the development of multiresistant bacteria. Second, similar 30-d-survival rates were found between patients infected with non-DR and those with MDR pathogens. On the contrary, patients with XDR had significantly lower survival rate compared to both MDR and non-DR groups. This finding is not surprising since the impact of MDR on survival is blunted by the extended use of carbapenems, producing bacteriological clearance and achieving the best outcomes in the most MDR Enterobacteriaceae-associated infections. However, carbapenems are inefficient at treating both XDR bacteria and *E. faecium*. Colistin seemed to be the optimal choice for the former and glycopeptides for the later except for vancomycin-resistant strains where tigecycline is highly effective. As empirical treatment administered contained neither colistin nor glycopeptides, antibiotic failure is the cause of poor survival in patients infected with XDR bacteria. It is a routine in our Center to take both blood and ascitic fluid culture on admission and perform a second paracentesis after 48 h of start of treatment to check the effect of empirical antibiotic therapy. In case of XDR bacteria, first choice antibiotic treatment failure was frequent. Thus, the delay of *in vitro* susceptibility test, may also delay the modification of antibiotic treatment and have deleterious effects on outcome. XDR bacteria were a strong predictive factor of death in current study even in multivariate analysis. Hence, empirical antibiotic treatment requires the use of broad spectrum antibiotics adapted to the local epidemiological pattern. A recent investigation recommended a broad spectrum antibiotic combination including meropenem plus daptomycin as first line treatment of nosocomial SBP with favorable effect on survival compared to ceftazidime alone[27].

In conclusion, extensively drug-resistant bacteria are an independent life-threatening factor of outcome in cirrhotic patients with spontaneous bacterial peritonitis and spontaneous bacteremia. Even if our results could not be extrapolated to other institutions, it is useful to know local bacterial epidemiology of infections in cirrhosis in order to restrict overuse and make a more rational use of antibiotics. In addition, new microbiological methods aiming at rapid identification of the responsible bacteria could help improve survival. As monotherapy seems to be ineffective in a significant proportion of patients, a more complex approach including broad spectrum antibiotic combinations should be considered for empirical therapy of HCA/nosocomial infections.

COMMENTS

Background

Spontaneous bacterial peritonitis (SBP) and spontaneous bacteremia (SB) (positive blood culture with no cause of bacteremia) are the most typical infections in patients with decompensated cirrhosis related to bacterial translocation. Early administration of the appropriate empirical antibiotics is important in order to cover the most commonly isolated bacteria and maximize the patient's chance of survival.

Research frontiers

Recently, a change in epidemiology of bacterial infections in cirrhosis has been observed worldwide characterized by an increasing prevalence of multi-drug resistant (MDR) bacteria and a decreased efficacy of antibiotics. In this study, there is an increased rate of MDR and extensively drug-resistant (XDR) bacteria even in the absence of quinolone prophylaxis particularly in health-care associated and/or nosocomial infections.

Innovations and breakthroughs

The literature suggests a high mortality of patients infected with MDR bacteria. The current study showed a similar mortality in patients with MDR and non-DR bacteria probably because of the wide use of meropenem in health-care associated and/or nosocomial infections in local area. However, a high mortality of XDR was observed.

Applications

This study highlights the relatively high prevalence of XDR pathogens in SBP and SB in decompensated cirrhosis in the local setting and the importance to modify regional epidemiological factors in order to improve outcome. In addition, rapid identification of the causative organism and empirical treatment with a combination of broad-spectrum antibiotics may help improving survival.

Terminology

Multidrug resistant bacteria: strains non susceptible to $\geqslant$ 1 agent in $\geqslant$ 3 antimicrobial categories. Extensively drug-resistant bacteria: strains non-susceptible to $\geqslant$ 1 agent in all but $\leqslant$ 2 antimicrobial categories.

Peer-review

This is a nicely written paper about an important and interesting area. In this paper, Alexopoulou *et al* evaluated the epidemiology and outcomes of culture-positive SBP and SB in decompensated cirrhosis patients and revealed the factors adversely affecting outcome included XDR infection, elevated creatinine and INR. The drug resistance of isolated bacteria to antibiotics also were investigated and authors provided the explanations of drug-resistance and the measures of preventing antibiotic-resistance. These findings are useful for clinicians to restrict overuse, make a more rational use of antibiotics, and eventually improve the survival of these patients.

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P- Reviewer: January R, Velliyagounder K, Wan QQ **S- Editor**: Qi Y
L- Editor: A **E- Editor**: Liu XM

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