ORIGINAL ARTICLE

AG-2021-167
doi.org/10.1590/S0004-2803.202200001-18

Analysis of healthcare associated and hospital acquired infections in critically ill patients with cirrhosis

Ricardo Azevedo Cruz **D'OLIVEIRA**[1,2], Lívia Carolina Dourado **PEREIRA**[1], Liana **CODES**[1], Mário de Seixas **ROCHA**[2] and Paulo Lisboa **BITTENCOURT**[1,2]

Received: 23 August 2021
Accepted: 10 November 2021

ABSTRACT – Background – Bacterial infections occur in 43–59% of cirrhotic patients admitted to the intensive care unit with impact in morbidity and mortality. An increase in the frequency of multidrug-resistant (MDRO) and extensively drug-resistant (XDRO) organisms has been described in bacterial infections in cirrhotic patients with an adverse impact on survival. **Objective –** To characterize community-acquired (CA), healthcare-associated (HCA), and hospital-acquired (HA) infections in cirrhotic patients and their impact in the occurrence of adverse outcomes. **Methods –** This study included all cirrhotic patients admitted in an intensive care unit specialized in liver and gastrointestinal diseases in Brazil between January 2012 and June 2018. Frequency and topography of infections were retrospectively evaluated, as well as the frequency of MDRO and XDRO organisms, and their impact in occurrence of acute kidney injury, hepatorenal syndrome, acute-on-chronic liver failure, sepsis and mortality. **Results –** A total of 374 infections were observed and classified as CA (22%), HCA (34%) and hospital-acquired (44%). Eighty-nine (54%) episodes of hospital-acquired infections were second infections. Spontaneous bacterial peritonitis (32%) and urinary tract infection (23%) were the most common infections. Culture-proven infections were positive in 61% of the cases, mainly gram-negative bacteria (73%). Acute kidney injury, hepatorenal syndrome and sepsis were observed, respectively, in 48%, 15% and 53% of the cases. MDRO and XDRO were seen, respectively, in 35% and 16%, mainly in HCA (48% vs 26% in CA infections, P=0.02) and hospital-acquired (58% vs 26% in CA infections, P=0.0009). Adverse outcomes were more frequently observed in subjects with hospital-acquired infections when compared to HCA and CA infections. Hospital-acquired, HCA and second infections were independently associated with in-hospital mortality. **Conclusion –** Hospital-acquired, HCA and second infections are increasingly associated with either MDRO and/or XDRO and are independent predictors of in-hospital mortality. Their recognition and proper selection of appropriate empiric antibiotic regimens are important measures to reduce in-hospital mortality.

Keywords – Liver cirrhosis; bacterial infections; morbidity; mortality; intensive care unit.

INTRODUCTION

Bacterial infections occur in 43% to 59% of critically ill patients with cirrhosis[1,2] either with acute decompensation (AD) due to variceal hemorrhage (VH), hepatic encephalopathy (HE) and ascites, or with acute-on-chronic liver failure (ACLF). In fact, infections in patients with cirrhosis are considered to be the major trigger for the development of severe complications of cirrhosis, including ACLF, and to be associated with a four-fold increase in mortality mainly due to sepsis and multi-organ failure[3-5].

The epidemiology of bacterial infections in patients with cirrhosis has changed in recent years with the emergence of gram-positive[1,6,7] and multidrug (MDRO) and extended drug (XDRO) resistant organisms, particularly in those subjects with healthcare-associated (HCA) and hospital-acquired (HA) infections[8]. Not surprisingly, HCA infections are increasing in number since cirrhotic patients are frequently hospitalized and readmitted to the hospital in short time intervals[9,10]. Treating those patients with empiric antibiotic regimens recommended for community-acquired (CA) infections with inadequate coverage for MDRO and XDRO may lead to treatment failure with a detrimental effect on survival[11-13]. Several reports have highlighted that MDRO and XDRO are significantly associated with worse response to initial antibiotic therapy, higher progression to sepsis and septic shock, organ dysfunction development, and increased mortality[13-15].

The purpose of the study was to characterize the frequency of MDRO and XDRO in cirrhotic patients admitted to the intensive care unit (ICU) with CA, HCA, and HA infections and to assess their impact on clinical in-hospital outcomes.

METHODS

All admissions in the electronic database of the Unit of Gastroenterology and Hepatology of the Portuguese Hospital of Salvador, Brazil, from January 2012 to June 2018 were retrospectively reviewed in search of AD of cirrhosis or ACLF as the cause for hospitalization. This ICU is a reference unit for critically ill patients with cirrhosis.

Declared conflict of interest of all authors: none
Disclosure of funding: no funding received
[1] Hospital Português da Bahia, Unidade de Gastroenterologia e Hepatologia, Salvador, BA, Brasil. [2] Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brasil.
Corresponding author: Ricardo Azevedo Cruz D'Oliveira E-mail: gastroricardo@gmail.com

The diagnosis of cirrhosis was based on clinical, biochemical, and echographic findings, as well as on liver histology, whenever liver biopsy results were available. The etiology of cirrhosis and the reason for hospitalization were established in all patients. When there was more than one reason for admission, the main cause was reckoned based on the following hierarchy: VH, bacterial infections, HE, tense ascites and others. All cirrhotic patients admitted in the postoperative period of abdominal surgery, including liver transplantation, intra-arterial chemoembolization for hepatocellular carcinoma, and subjects with co-infection with HIV were excluded from the study. Fungal infections were also not taken into consideration.

Data at admission regarding demographics; clinical and laboratory parameters; prognostic variables such Child-Pugh (CPS), MELD, APACHE II, SOFA and CLIF-SOFA scores and the updated Charlson comorbidity index[16]; etiology of cirrhosis; the main cause of admission, either AD of cirrhosis or ACLF were collected in all subjects with clinical or microbiological evidence of bacterial infections.

The occurrence of CA, HCA, and HA infections was reckoned in every patient. Infections were classified as HA when acquired 48 hours after hospital admission and CA when diagnosed at admission or up to 48 hours of admission to the hospital. Community-acquired were considered as HCA infection in those subjects who fulfilled any one of the following criteria: 1) attendance in a dialysis facility in the last thirty days; 2) hospitalization for at least 48 hours, surgery or residence in a nursing home or assisted living facilities in the last 3 months. Second infections were categorized as a new nosocomial infection apart from one first infection, either CA, HCA or HA infection[10].

Bacterial infections were defined according to established international criteria. Briefly, spontaneous bacterial peritonitis (SBP) were considered in the presence of polymorphonuclear (PMN) cell count in the ascitic fluid of more than 250 cells/mm^3; spontaneous bacterial empyema if the fluid analysis showed a positive culture and more than 250 neutrophils/mm^3 or a negative culture and more than 500 neutrophils/mm^3, in the absence of lung infection; secondary bacterial peritonitis in the presence of PMN of more than 250 cells/mm^3 associated with evidence of imaging and/or surgical evidence for an intra-abdominal source of infection; urinary tract infection (UTI) as the occurrence of more than 10 leukocytes per field with positive urinary culture or numerous leukocytes per field along with fever or urinary symptoms and a negative urinary culture; pneumonia as clinical signs of infection associated with new pulmonary infiltrates on x-rays or chest CT scans; tracheobronchitis as clinical signs of infection without lung infiltrates with positive sputum cultures; skin and soft infections (SSTI) in the presence of clinical signs of infection associated with swollen, red and tender area in the affected skin; cholangitis in the presence of fever and/or right upper quadrant pain associated with jaundice or laboratory signs of cholestasis and radiological evidence of biliary obstruction; spontaneous bacteremia, characterized by positive blood cultures in the absence of an identified source of infection associated or not with invasive procedures whenever performed 24 hour prior to its diagnosis. The diagnosis of catheter-associated UTI, ventilator-associated pneumonia (VAP) or tracheobronchitis, or central line-associated bloodstream infections were considered according to Centers of Disease Control criteria. Infections were described as suspected whenever clinical and laboratory signs of infection elicited antibiotic therapy without any identified source or positive blood culture results.

Bacterial cultures and antimicrobial susceptibility testing were performed according to standard methods. Briefly, MDRO, XDRO and pan-drug resistant (PDRO) organisms were considered, respectively, in the presence of nonsusceptibility to at least one agent in at least three categories of antimicrobials, to at least one agent in all but less than two antimicrobial categories, and to all antimicrobial classes of drugs. As previously stated, well-known intrinsic resistance to a particular antimicrobial was not considered to establish antimicrobial resistance patterns[17].

Infections were treated using therapeutic regimens based on international guidelines[18,19].

The presence of AKI, HRS and ACLF, sepsis, septic shock and death was evaluated and compared to the occurrence of CA, HCA, HA and a second infection. Diagnosis of AKI, HRS and ACLF was established based on international criteria[20,21]. Sepsis and septic shock were considered based on current criteria according to physician's discretion[22,23]. Patients were followed until death or hospital discharge.

The study was approved by the Ethics Committee in Research of the Portuguese Hospital of Salvador, Bahia.

Statistical analysis

Categorical or nominal variables are presented in the text and tables as numbers and percentages and were compared using the chi-square test or Fisher's test, when appropriate. Continuous variables are reported as mean and standard deviation (SD) if the distribution was normal or median and interquartile range if not and, were compared using the Student *t*-test or the Mann-Whitney U test when appropriate. A *P*-value ≤0.05 was considered significant. Univariate analysis was performed to assess the influence of CA, HCA and HA infections and other well-recognized prognostic predictive variables on the development of in-hospital mortality. Variables associated with mortality at univariate analysis with a *P*-value of <0.10 were entered in multivariate logistic regression modeling using stepwise elimination. The software used for analysis was the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, EUA), version 14.0 for Windows.

RESULTS

From January 2012 to June 2018, 784 consecutive patients were admitted to the ICU due to AD of cirrhosis or ACLF. Bacterial infections were identified in 285 (36%) patients (147 males, mean age 67±11 years). Demographics and clinical features of those patients are depicted in TABLE 1. Most of the patients were male with Child-Pugh C cirrhosis with a high index of comorbidities. Acute kidney injury, HRS and ACLF were recorded on admission, respectively, in 48%, 15% and 45% of the patients. Sepsis and septic shock were observed in 152 (53%) and 120 (42%) patients at the time of hospitalization. The mean in-ICU and in-hospital length of stay (LOS) were 8 [3–12] and 8 [8–19] days. One hundred and twenty-five (44%) subjects died. The main causes of death were septic shock (n=95), ACLF (n=16), hypovolemic shock (n=8), acute respiratory distress syndrome (n=5) and acute kidney injury (n=1).

Three hundred and seventy-four episodes of infections were recorded. According to the site of acquisition, 81 (22%), 129 (34%) and 164 (44%) were classified as CA, HCA and HA infections. Eighty-nine (54%) episodes of HA infections were a second infection after CA (n=19), HCA (n=41) and HA (n=29) infections. Demographics, severity of liver disease assessed by CPS and MELD

TABLE 1. Demographics, clinical features and outcomes of cirrhotic patients with bacterial infections at admission in the intensive care unit.

Age (years)	67±11
Male sex	147 (72%)
Etiology of cirrhosis	
Alcohol liver disease	68 (33%)
Undefined	49 (24%)
Hepatitis C virus	39 (19%)
Non-alcoholic steatohepatitis	24 (12%)
Mixed	11 (6%)
Others	12 (6%)
Child-Pugh Score	11±2
CPS A	2 (1%)
CPS B	75 (26%)
CPS C	208 (73%)
MELD score	23±8
Apache II score	16±7
SOFA	5±3
Charlson Comorbidities Index	8±3
Concurrent hepatocellular carcinoma	63 (22%)
Main reason for ICU admission	
Bacterial Infection with sepsis or septic shock	108 (38%)
Hepatic encephalopathy	91 (32%)
Ascitis	54 (19%)
Variceal hemorrhage	28 (10%)
Other causes	4 (1%)
Outcomes	
Acute Kidney Injury	138 (48%)
Hepatorenal syndrome	42 (15%)
Dialysis during hospitalization	46 (16%)
ACLF	128 (45%)
Sepsis	152 (53%)
Septic shock	120 (42%)
ICU length of stay	8 (3–12)
Hospital length of stay (days)	8 (8–19)
Mortality	125 (44%)

ACLF: acute-on-chronic liver failure; APACHE II: *acute* physiology; CPS: Child Pugh Score; ICU: intensive care unit; MELD: Model for End – Stage Liver Disease; SOFA: Sequential Organ Failure Assessment.

scores and CCI were similar in those subjects with CA, HCA and HA infections, but patients with HA infections had higher APACHE II scores when compared to their counterparts with CA infections (17±7 vs 14±5 in CA infections, *P*=0.01) (TABLE 2).

The most frequent bacterial infections were SBP (32%), UTI (23%), pneumonia (14%) and SSTI (7%) (FIGURE 1). Spontaneous bacterial peritonitis was more frequently observed in HCA infections when compared to HA infections, pneumonia in HA infections when compared to CA infections and SSTI in CA

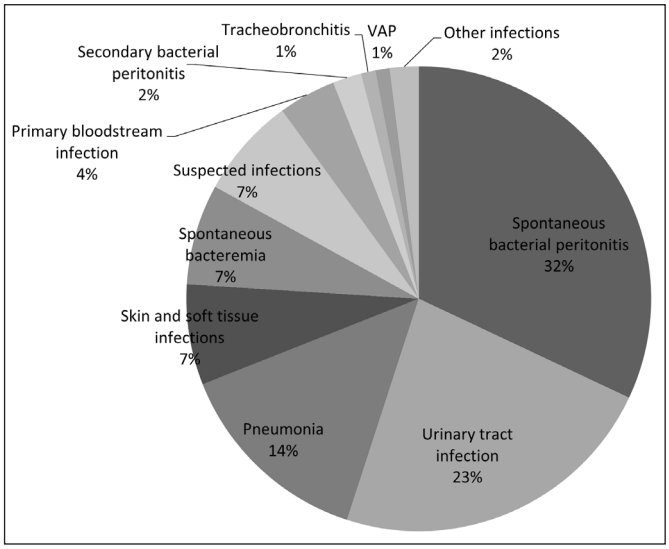

FIGURE 1. Characterization of bacterial infections in cirrhotic patients admitted to the intensive care unit (n=374).
VAP: ventilator associated pneumonia.

infections when compared either with HCA or HA infections (TABLE 2). Two hundred and thirty (61%) patients with clinically suspected bacterial infections had positive cultures, much more frequently in HA infections when compared to CA and HCA infections (TABLE 2). Gram-negative bacteria (GNB) were the most common microorganisms (73%), mainly *Klebsiella pneumoniae* and *Escherichia coli* (TABLE 3), irrespective of the site of acquisition of infection (TABLE 2). Gram-positive bacteria (GPB) were observed in 27% of the isolates, mainly *Enterococcus faecalis*, *coagulase-negative Staphylococcus* and *Staphylococcus aureus* (TABLE 3). The frequencies of MDRO and XDRO in CA, HCA and HA infections were 20% and 6%, 31% and 19%, 41% and 17%, respectively. The frequencies of MDRO and/or XDRO were similar in HCA infections when compared to HA infections (TABLE 2). Both types of organisms were observed more often in HCA (48% vs 26% in CA infections, *P*=0.02) and HA infections (58% vs 26% in CA infections, *P*=0.0009) when compared to CA infections. However, considering only MDRO, the difference remained significant only when HA infections were compared to CA infections (41% vs 20% in CA infections, *P*=0.03). Most MDRO were extended-spectrum beta-lactamase (ESBL) producing-*Klebsiella pneumoniae* and ESBL producing-*Escherichia coli*, whereas all XDRO gram-negative bacteria were carbapenemase-producing *Enterobacteriaceae* (TABLE 3).

Regarding outcomes, patients with HA-infections compared to their counterparts with CA and HCA infections, had a respectively higher frequency of HRS (15% vs 6% in CA infections, *P*=0.03) and a higher need for dialysis (16% vs 9% in HCA infections, *P*=0.04), but the occurrence of AKI and ACLF at the time of infection was similar in all groups of patients. On the contrary, sepsis, septic shock, in-ICU and in-hospital LOS and mortality were significantly higher in those subjects with HA infections when compared to their counterparts with CA and HCA infections (TABLE 4). Those adverse outcomes were even more overrepresented in those patients with a second infection. When compared to their counterparts with a single HA infection, patients with a second infection had more AKI (71% vs 49% in single HA infection, *P*=0.006), more sepsis

TABLE 2. Demographics, clinical and microbiological features of patients with bacterial infections according to site of acquisition.

	CA infections (n=81)	HCA infections (n=129)	HA infections (n=164)	*P*
Age (years)	68±11	68±12	69±10	0.50
Child-Pugh Score				
A	2 (3%)	0 (0%)	0 (0%)	–
B	27 (33%)	32 (25%)	41 (25%)	0.30
C	52 (64%)	97 (75%)	123 (75%)	0.15
MELD	23±7	23±8	23±8	0.80
APACHE II	14±5	16±8	17±7	0.01[b]
Charlson Comorbidities Index	8±3	8±3	8±2	0.08
SOFA	5±3	5±2	5±3	0.60
Types of infections				
Spontaneous bacterial peritonitis	27 (33%)	51 (40%)	40 (24%)	0.02[c]
Urinary tract infection	19 (23%)	33 (26%)	34 (21%)	0.60
Pneumonia	6 (7%)	16 (12%)	31 (19%)	0.04[b]
Skin and soft tissue infection	14 (17%)	9 (7%)	5 (3%)	<0.001[a,b]
Infection with undefined site	6 (7%)	10 (8%)	9 (5%)	0.70
Spontaneous bacteremia	2 (2%)	7 (5%)	17 (10%)	0.05 [b]
Primary bloodstream infection	0 (0%)	0 (0%)	16 (10%)	–
Secondary bacterial peritonitis	2 (2%)	1 (1%)	6 (4%)	0.20
Tracheobronchitis	0 (0%)	0 (0%)	4 (2%)	–
Ventilator-associated pneumonia	0 (0%)	0 (0%)	2 (1%)	–
Other infections	5 (6%)	2 (2%)	0 (0%)	–
Microbiological results				
Positive cultures (n=230)	35 (43%)	70 (54%)	125 (76%)	<0.001[b,c]
Bacterial profile				
Gram-negative	25 (71%)	48 (69%)	95 (76%)	0.50
Gram-positive	10 (29%)	22 (31%)	30 (24%)	0.50
Multidrug-or extensively drug resistant organisms	9 (26%)	34 (48%)	72 (58%)	0.003[a,b]
Multidrug-resistant organisms	7 (20%)	22 (31%)	51 (41%)	0.03[b]
Extensively drug-resistant organisms	2 (6%)	13 (19%)	21 (17%)	0.20

CA: community-acquired; HCA: healthcare-associated; HA: hospital acquired. [a]$P<0.05$ when comparing CA vs HCA infections; [b]$P<0.05$ when comparing CA vs HA infections and [c]$P<0.05$ when comparing HCA vs HA infections.

TABLE 3. Frequency of Gram-negative bacteria and Gram-positive cocci according to patterns of microbiological resistance.

	All (n=230)	CA infections (n=35)	HCA infections (n=70)	HA infections (n=125)
Gram-negative bacteria	169 (73%)	26 (74%)	48 (69%)	95 (76%)
Klebsiella pneumoniae	13 (6%)	3 (9%)	3 (4%)	7 (6%)
Escherichia coli	29 (13%)	10 (29%)	10 (14%)	9 (7%)
Aeromonas hydrophila	3 (1%)	2 (6%)	–	1 (1%)
Enterobacter cloacae	5 (2%)	–	2 (3%)	3 (2%)
Pseudomonas aeruginosa	8 (3%)	–	2 (3%)	6 (5%)
Burkholderia cepacia	4 (2%)	1 (3%)	–	3 (2%)
Stenotrophomonas maltophilia	3 (1%)	–	–	3 (2%)
Proteus mirabilis	2 (1%)	–	–	2 (2%)
Others	9 (4%)	2 (6%)	1 (1%)	6 (5%)
Acinetobacter Baumanni	2 (1%)	–	–	2 (2%)
MDR Gram-negative bacteria	60 (26%)	6 (17%)	19 (27%)	35 (28%)
ESBL-producing *Klebsiella pneumoniae*	34 (15%)	6 (17%)	10 (14%)	18 (14%)
ESBL-producing *Escherichia coli*	16 (7%)	–	8 (11%)	8 (6%)
Enterobacter cloacae	3 (15)	–	–	3 (2%)
Brevundimonas diminuta	2 (1%)	–	–	2 (2%)
Proteus mirabilis	3 (1%)	–	–	3 (2%)
Others	2 (1%)	–	1 (1%)	1 (1%)
XDR Gram-negative bacteria	31 (13%)	2 (6%)	11 (16%)	18 (14%)
Carbapanemase-producing *Klebsiella pneumoniae*	25 (11%)	2 (6%)	10 (1%)	13 (10%)
Carbapanemase-producing *Escherichia coli*	3 (1%)	–	–	3 (2%)
Others	3 (1%)	–	1 (1%)	2 (2%)
Gram-positive cocci	61 (27%)	9 (26%)	22 (31%)	30 (24%)
Streptococcus pneumoniae	10 (4%)	4(12%)	6 (9%)	–
Staphylococcus aureus	8 (3%)	2 (6%)	4 (6%)	2 (2%)
Coagulase negative *Staphylococcus*	9 (4%)	–	4 (6%)	5 (4%)
Enterococcus faecalis	9 (4%)	2 (6%)	3 (4%)	4 (3%)
MDR Gram-positive cocci	20 (9%)	1 (3%)	4 (6%)	15 (12%)
Methicilin-resistant *Staphylococcus aureus*	4 (2%)	–	2 (3%)	2 (2%)
Coagulase negative *Staphylococcus*	11 (5%)	–	1 (1%)	10 (8%)
Enterococcus faecalis	5 (2%)	1 (3%)	1 (1%)	3 (2%)
XDR Gram-positive cocci	5 (2%)	–	1 (1%)	4 (3%)
Coagulase negative *Staphylococcus*	1 (0%)	–	–	1 (1%)
Enterococcus faecalis	4 (2%)	–	1 (1%)	3 (2%)

CA: community-acquired; HCA: healthcare-associated; HA: hospital acquired; MDR: multidrug-resistant; XDR: extensively drug-resistant.

TABLE 4. Outcomes of patients with bacterial infections according to site of acquisition.

Outcomes	Community-acquired infections (n=81)	Healthcare-associated infections (n=129)	Hospital-acquired infections (n=164)	*P*
ICA-AKI	36 (44%)	65 (50%)	75 (46%)	0.70
Hepatorenal syndrome	5 (6%)	12 (9%)	25 (15%)	0.07[b]
Dialysis requirement	8 (10%)	11 (9%)	27 (16%)	0.09 [c]
ACLF	28 (35%)	64 (50%)	75 (46%)	0.09[a]
Sepsis	22 (27%)	41 (32%)	89 (54%)	<0.01[b,c]
Septic shock	13 (16%)	31 (24%)	76 (46%)	<0.01[b,c]
Hospital length of stay (days)	11 (7–15)	11 (8–17)	17 (11–28)	<0.001[b,c]
ICU length of stay (days)	5 (3–11)	6 (3–10)	10 (4–15)	<0.001[b,c]
Mortality	15 (19%)	32 (25%)	78 (48%)	<0.001[b,c]

ICA-AKI: International Club of Ascitis Acute Kidney Injury criteria; ACLF: acute on chronic liver failure. [a]$P<0.05$ when comparing community-acquired vs healthcare-associated infections; [b]$P<0.05$ when comparing community-acquired vs hospital acquired infections and [c]$P<0.05$ when comparing healthcare-associated vs hospital acquired infections.

(72% vs 45% in single HA infection, *P*<0.001), septic shock (62% vs 39% in single HA infection, *P*=0.004), higher mortality (64% vs 39% in single HA infection) and a longer stay at the hospital (24 [13–27] vs 16 [10–29] days in single HA infection, *P*<0.001) and in ICU LOS (14 [6–17] vs 9 [3–14] days in single HA infection, *P*<0.001). In addition, subjects with a second infection, when compared to those with single HA-infection, also had higher CCI (10±3 vs 7±2 in single HA infection, *P*=0.01), higher frequency of primary bloodstream infection (15% vs 4% in single HA infection, *P*=0.02), culture-positive infection (98% vs 51% in single HA infection, *P*<0.001) and MDRO (49% vs 21% in single HA infection, *P*=0.002).

TABLE 5 discloses the variables associated with mortality in multivariate analysis. The parameters associated with mortality in univariate analysis were female sex, in-ICU and in-hospital LOS, baseline leukocyte count, baseline MELD, APACHE II and SOFA scores, HCA and HA infections, second infections, HE and VH at admission, dialysis during hospitalization, SBP, pneumonia, secondary bacterial peritonitis and infections by XDRO. However, on multivariate analysis, only female gender (odds ratio [OR] 2.24, confidence interval [CI] 95%CI 1.05–4.77 *P*=0.04), MELD (OR 1.15, 95%CI 1.09–1.21, *P*<0.001), APACHE II (OR 1.12, 95%CI 1.06–1.19, *P*<0.001), HCA (OR 2.30, 95%CI 1.00–5.29, *P*=0.04), HA infection (OR 3.64; 95%CI: 1.46–9.11; *P*=0.006), pneumonia (OR 2.71; 95%CI: 1.11–6.61, *P*=0.03), SBP (OR 0.24; 95%CI: 0.12–0.52, *P*<0.001), second infection (OR 2.47, 95%CI 1.11–5.47, *P*=0.03) and in-ICU LOS (OR 1.13, 95%CI 1.06–1.20, *P*<0.001) were independently associated with mortality.

TABLE 5. Logistic regression model for the prediction of in-hospital mortality in critically ill patients with cirrhosis.

	OR	95%CI		*P*
Healthcare-associated infections	2.30	1.00	5.29	0.04
Pneumonia	2.71	1.11	6.61	0.03
Second infections	2.47	1.11	5.47	0.03
Hospital-acquired infections	3.64	1.46	9.11	0.006
Female sex	2.24	1.05	4.77	0.04
MELD	1.15	1.09	1.21	<0.001
In-ICU length of stay	1.13	1.06	1.20	<0.001
APACHE II	1.12	1.06	1.19	<0.001
Spontaneous bacterial peritonitis	0.24	0.12	0.52	<0.001

APACHE II: *acute* physiology, age, chronic health evaluation II; MELD: Model for End – Stage Liver Disease; ICU: intensive care unit.

DISCUSSION

Bacterial infections are life-threatening events in patients with cirrhosis. They can worse the clinical course of the disease, triggering the development of organ failure and ACLF. In this study, infections were observed in one-third of the patients with cirrhosis admitted to a single-center ICU in Brazil. In agreement with other reports, most of those infections were SBP, UTI and pneumonia[5,8,10,24-26]. Nosocomial infections were observed in almost half of the patients, but two-thirds of the remaining infection episodes contracted before hospital admission were considered HCA infections due to prior exposure to healthcare facilities in the previous three months. This is in consonance with previous data showing that HCA infections, whenever adequately investigated, are increasing in prevalence in hospitalized subjects with cirrhosis due to frequent admissions and readmissions of those patients to the hospital[6,7,9,27]. When compared to other studies[5,8,10,13], more patients in the present cohort developed a second infection, probably due to advanced age and a higher presence of comorbidities leading to prolonged in-hospital LOS. As previously described, pneumonia was more commonly observed in HA-infections, particularly in subjects admitted to the ICU[1,2] or with a second infection[10]. As expected, primary bloodstream infections, SBP and SSTI were more frequently seen in patients with a second infection, HCA and CA infection, respectively. In accordance with the literature, culture-proven infections were observed in 60% of the cases[7,8,28,29], with a higher frequency observed in those subjects with HA infection[5,25], particularly a second infection.

Regarding the site of acquisition, no difference in the frequency of GNB or GPC was disclosed. In contrast to other studies which reported a higher frequency of GPC[1,6,10,29] or *Escherichia coli* as the main isolated microorganism[14,15,27,30], most of the isolates in the present investigation were GNB, particularly MDR and XDR *Klebsiella pneumoniae.* In this study, MDRO and XDRO were responsible for 35% and 16% of the bacterial infections, respectively. However, their frequency was shown to vary sharply when subjects with either HCA or HA infections when compared to their counterparts with CA infections. This is in accordance with recent studies showing a sharp increase in the frequency of MDRO in the last 2 decades[24,26]. One recent global multicenter study also disclosed a frequency of MDRO and XDRO in 35% and 8% of those hospitalized with cirrhosis, with higher frequencies observed in countries from South America and Asia, particularly India[7]. Besides geographical location, other independent predictors of infections by MDRO disclosed by those authors were UTI, pneumonia, cellulitis, previous use of antibiotics, occurrence of HCA and HA infection. They also observed an adverse impact on survival associated with the presence of MDRO, probably due to the use of ineffective empiric antibiotic regimens[8]. Not surprisingly, the frequencies of MDRO and XDRO in the current study were similar in subjects with HCA and HA infections, mainly due to ESBL-producing and cabarpamenase producing *Klebsiella pneumoniae.*

Bacterial infections are well-recognized triggers for AKI, HRS and ACLF in cirrhosis[8,25]. In those studies, sepsis and septic shock were reported to occur in 22%–26% and 13%–15% of the patients, respectively. When compared to other studies, our patients had similar rates of in-hospital AKI and ACLF[25,29,31,32], a lower rate of HRS[9,10,26], but a higher frequency of sepsis and septic shock[8,25,32], which may be due to the employment of distinct criteria for sepsis assessment in those different studies over the years, as well as enrollment of sicker critically-ill patients with cirrhosis in the present study. There was no difference in severity of liver disease evaluated by CPS or MELD in those patients with CA, HCA and HA infections, but patients with HA and HCA infections tended to have more AKI and ACLF when compared to their counterparts with CA infections. On the other hand, sepsis and septic shock development were significantly higher in those with HA infections than those with CA or HCA infections. It is also worth mentioning that those adverse outcomes were even more pronounced in those with a second infection. These findings may be ascribed to the increase in MDRO infections observed in those with HA infection, as pointed out by others[24,32], but also due to the prescription of ineffective empiric antibiotic regimens, which were not evaluated in our study[14].

Approximately half of our patients died due to septic shock or ACLF. Lower mortality rates were observed in other reports involving mainly hospitalized cirrhotic patients with infections outside the ICU[5,10,14,15], but similar death rates were described in critically-ill cirrhotic subjects[2,33]. Mortality[26,27] and in-hospital LOS[29] were significantly higher in those subjects with HA infection when compared to those patients either with CA or HCA infection. Patients with a second infection also had higher mortality when compared to their counterparts with HA infection[10].

Independent predictors of in-hospital mortality disclosed in the present study were MELD and APACHE II scores reflecting disease severity, HCA and HA infection and occurrence of pneumonia and a second infection[8,27]. Unlike previous reports, infections with either MDRO or XDRO, which were more common in HCA, HA and a second infection, were not shown to be independent predictors of mortality. Those discrepancies could be ascribed to a recent shift favoring the use of broad-spectrum antibiotics with adequate coverage against ESBL-producing GNB, particularly in HCA infections, according to updated international guidelines. As previously reported, SBP was associated with a lower risk[10], while pneumonia and a second infection to a higher risk for mortality[7,10].

This study, being retrospective, has some limitations. We were unable to assess previous hospitalizations either due to AD of cirrhosis or bacterial infections. None of the patients were on rifaximin because the drug was not marketed in Brazil, but some could be using norfloxacin for SBP prophylaxis. The antibiotic regimens used in these individuals for both prophylaxis and treatment have not been evaluated. The study also did not assess the use of intravenous albumin during hospitalization, which could impact the clinical outcomes of cirrhotic patients with infection.

In summary, HA and HCA-related infections are increasingly associated with either MDRO or XDRO, with an adverse impact on survival. Recognition of HCA infections and proper selection of appropriate empiric antibiotic regimens tailored to local antibiotic resistance patterns are of utmost importance since those bacterial infections are associated with an increased risk for mortality.

Authors' contribution

D'Oliveira RAC: conceptualization, formal analysis, investigation, methodology project administration, supervision, writing-original draft, writing-review and editing. Pereira LCD: investigation. Codes L: formal analysis, writing review and editing. Rocha MS: conceptualization. Bittencourt PL: conceptualization, methodology, project administration, writing review and editing.

Orcid

Ricardo Azevedo Cruz D'Oliveira: 0000-0002-4037-7545.
Lívia Carolina Dourado Pereira: 0000-0001-5550-0676.
Liana Codes: 0000-0001-5178-8705.
Mário de Seixas Rocha: 0000-0002-3990-7158.
Paulo Lisboa Bittencourt: 0000-0003-0883-4870.

D'Oliveira RAC, Pereira LCD, Codes L, Rocha MS, Bittencourt PL. Análise das infecções relacionadas aos cuidados de saúde e hospitalares nos pacientes cirróticos críticos. Arq Gastroenterol. 2022;59(1):102-9.

RESUMO – **Contexto –** As infecções bacterianas ocorrem em 43–59% dos pacientes cirróticos internados em unidade de terapia intensiva com impacto na morbimortalidade. Um aumento na frequência de bactérias multirresistentes e com resistência estendida foi descrito em infecções bacterianas em pacientes cirróticos, com um impacto adverso na sobrevida. **Objetivo –** Caracterizar as infecções adquiridas na comunidade, relacionadas aos cuidados de saúde (RCS) e hospitalares em pacientes cirróticos e seu impacto na ocorrência de desfechos adversos. **Métodos –** Este estudo incluiu todos os pacientes cirróticos internados em uma unidade de terapia intensiva especializada em doenças hepáticas e gastrointestinais no Brasil entre janeiro de 2012 e junho de 2018. A frequência e topografia das infecções foram avaliadas retrospectivamente, bem como a frequência de bactérias multirresistentes e resistência estendida, e seu impacto na ocorrência de lesão renal aguda, síndrome hepatorrenal, insuficiência hepática crônica agudizada, sepse e mortalidade. **Resultados –** Um total de 374 infecções foram observadas e classificadas como infecções adquiridas na comunidade (22%), RCS (34%) e infecções hospitalares (44%). Oitenta e nove (54%) episódios de infecções hospitalares foram identificadas como segunda infecção. Peritonite bacteriana espontânea (32%) e infecção do trato urinário (23%) foram as infecções mais comuns. As infecções comprovadas por cultura foram positivas em 61% dos casos, principalmente ocasionadas por bactérias gram-negativas (73%). Lesão renal aguda, síndrome hepatorrenal e sepse foram observados respectivamente, em 48%, 15% e 53% dos casos. Bactérias multirresistentes e resistência estendida foram observadas respectivamente, em 35% e 16%, principalmente nos RCS (48% vs 26% em infecções adquiridas na comunidade, *P*=0,02) e infecções hospitalares (58% vs 26% em infecções adquiridas na comunidade, *P*=0,0009). Os resultados adversos foram observados com mais frequência em indivíduos com infecções nosocomiais em comparação com infecções relacionadas aos cuidados de saúde e comunitárias. Infecções hospitalares, RCS e ocorrência de uma segunda infecção foram independentemente associadas à mortalidade intra-hospitalar. **Conclusão –** Infecções hospitalares, relacionadas aos cuidados de saúde e reinfecções estão cada vez mais associadas a bactérias multirresistentes e/ou resistência estendida e são preditores independentes de mortalidade intra-hospitalar. Seu reconhecimento e seleção adequada de regimes antibióticos empíricos apropriados são medidas importantes para reduzir a mortalidade intra-hospitalar.

Palavras-chave – Cirrose hepática; infecções bacterianas; morbidade; mortalidade; unidade de terapia intensivo.

REFERENCES

1. Gustot T, Felleiter P, Pickkers P, Sakr Y, Rello J, Velissaris D, et al. Impact of infection on the prognosis of critically ill cirrhotic patients: Results from a large worldwide study. Liver Int. 2014;34:1496-503. doi:10.1111/liv.12520.
2. Skurzak S, Carrara G, Rossi C, Nattino G, Crespi D, Giardino M, et al. Cirrhotic patients admitted to the ICU for medical reasons: Analysis of 5506 patients admitted to 286 ICUs in 8 years. J Crit Care. 2018;45:220-8. doi:10.1016/j.jcrc.2018.03.018.
3. Arvaniti V, D'Amico G, Fede G, Manousou P, Tsochatzis E, Pleguezuelo M, et al. Infections in patients with cirrhosis increase mortality four-fold and should be used in determining prognosis. Gastroenterology. 2010;139:1246-56.e5. doi:10.1053/j.gastro.2010.06.019.
4. Fernández J, Acevedo J, Wiest R, Gustot T, Amoros A, Deulofeu C, et al. Bacterial and fungal infections in acute-on-chronic liver failure: Prevalence, characteristics and impact on prognosis. Gut. 2017;67:1870-80. doi:10.1136/gutjnl-2017-314240.
5. Fernández J, Acevedo J, Prado V, Mercado M, Castro M, Pavesi M, et al. Clinical course and short-term mortality of cirrhotic patients with infections other than spontaneous bacterial peritonitis. Liver Int. 2017;37:385-95. doi:10.1111/liv.13239.
6. Alexopoulou A, Papadopoulos N, Eliopoulos DG, Alexaki A, Tsiriga A, Toutouza M, et al. Increasing frequency of gram-positive cocci and gram-negative multidrug-resistant bacteria in spontaneous bacterial peritonitis. Liver Int. 2013;33:975-81. doi:10.1111/liv.12152.
7. Lutz P, Nischalke HD, Krämer B, Goeser F, Kaczmarek DJ, Schlabe S, et al. Antibiotic resistance in healthcare-related and nosocomial spontaneous bacterial peritonitis. Eur J Clin Invest. 2017;47:44-52. doi:10.1111/eci.12701.
8. Piano S, Singh V, Caraceni P, Maiwall R, Alessandria C, Fernandez J, et al. Epidemiology and Effects of Bacterial Infections in Patients With Cirrhosis Worldwide. Gastroenterology. 2019;156:1368-80.e10. doi:10.1053/j.gastro.2018.12.005.
9. Merli M, Lucidi C, Giannelli V, Giusto M, Riggio O, Falcone M, et al. Cirrhotic patients are at risk for health care-associated bacterial infections. Clin Gastroenterol Hepatol. 2010;8:979-85.e1. doi:10.1016/j.cgh.2010.06.024.
10. Bajaj JS, O'Leary JG, K Reddy R, Wong F, Olson JC, Subramanian RM, et al. Second Infections Independently Increase Mortality in Hospitalized Cirrhotic Patients: The NACSELD Experience. Hepatology. 2012;56:2328-35. doi:10.1002/hep.25947.
11. Bartoletti M, Giannella M, Caraceni P, Domenicali M, Ambretti S, Tedeschi S, et al. Epidemiology and outcomes of bloodstream infection in patients with cirrhosis. J Hepatol. 2014;61:51-8. doi:10.1016/j.jhep.2014.03.021.
12. Bartoletti M, Giannella M, Lewis R, Caraceni P, Tedeschi S, Paul M, et al. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. Clin Microbiol Infect. 2018;24:546.e1-546.e8. doi:10.1016/j.cmi.2017.08.001.
13. Merli M, Lucidi C, Di Gregorio V, Lattanzi B, Giannelli V, Giusto M, et al. An empirical broad spectrum antibiotic therapy in health-care-associated infections improves survival in patients with cirrhosis: A randomized trial. Hepatology. 2016;63:1632-9. doi:10.1002/hep.28332.
14. Merli M, Lucidi C, Gregorio V Di, Falcone M, Giannelli V, Lattanzi B, et al. The spread of multi drug resistant infections is leading to an increase in the empirical antibiotic treatment failure in cirrhosis: A prospective survey. PLoS One. 2015;10:1-10. doi:10.1371/journal.pone.0127448.
15. Klímová K, Padilla C, Ávila JC, Clemente G, Ochoa A. Epidemiology of bacterial infections in patients with liver cirrhosis. Experience in a Spanish tertiary health center. Biomédica. 2016;36:121-32. doi:10.7705/biomedica.v36i1.2600.
16. Quan H, Li B, Couris CM, Fushimi K, Graham P, Hider P, et al. Updating and validating the charlson comorbidity index and score for risk adjustment in hospital discharge abstracts using data from 6 countries. Am J Epidemiol. 2011;173:676-82. doi:10.1093/aje/kwq433.
17. Magiorakos A-P, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18:268-81. doi:10.1111/j.1469-0691.2011.03570.x.
18. Angeli P, Bernardi M, Villanueva C. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. J Hepatol. 2018;69:406-60. doi:10.1016/j.jhep.2018.03.024.
19. Jalan R, Fernandez J, Wiest R, Schnabl B, Moreau R, Angeli P, et al. Position Paper Bacterial infections in cirrhosis : A position statement based on the EASL Special Conference 2013. J Hepatol. 2014;60:1310-1324. doi:10.1016/j.jhep.2014.01.024
20. Angeli P, Gines P, Wong F, Bernardi M, Boyer TD, Gerbes A, et al. Diagnosis and management of acute kidney injury in patients with cirrhosis: Revised consensus recommendations of the International Club of Ascites. Gut. 2015;64:531-7. doi:10.1136/gutjnl-2014-308874.
21. Moreau R, Jalan R, Gines P, Pavesi M, Angeli P, Cordoba J, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. Gastroenterology. 2013;144:1426-37.e9. doi:10.1053/j.gastro.2013.02.042.
22. Levy MM, Fink MP, Marshall JC, Abraham E, Angus D, Cook D, et al. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. Intensive Care Med. 2003;29:530-8. doi:10.1007/s00134-003-1662-x.
23. Singer M, Deutschman CS, Seymour C, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (sepsis-3). JAMA. 2016;315:801-10. doi:10.1001/jama.2016.0287.
24. Fernández J, Acevedo J, Castro M, Garcia O, de Lope CR, Roca D, et al. Prevalence and risk factors of infections by multiresistant bacteria in cirrhosis: A prospective study. Hepatology. 2012;55:1551-61. doi:10.1002/hep.25532.
25. Fernández J, Prado V, Trebicka J, Amoros A, Gustot T, Wiest R, et al. Multidrug-resistant bacterial infections in patients with decompensated cirrhosis and with acute-on-chronic liver failure in Europe. J Hepatol. 2019;70:398-411. doi:10.1016/j.jhep.2018.10.027.
26. Fernández J, Navasa M, Gómez J, Colmenero J, Vila J, Arroyo V, et al. Bacterial infections in cirrhosis: Epidemiological changes with invasive procedures and norfloxacin prophylaxis. Hepatology. 2002;35:140-8. doi:10.1053/jhep.2002.30082.
27. Ariza X, Castellote J, Lora-Tamayo J, Girbau A, Salord S, Rota R, et al. Risk factors for resistance to ceftriaxone and its impact on mortality in community, healthcare and nosocomial spontaneous bacterial peritonitis. J Hepatol. 2012;56:825-32. doi:10.1016/j.jhep.2011.11.010.
28. Bajaj JS, Reddy KR, Tandon P, Wong F, Kamath PS, Biggins SW, et al. Prediction of Fungal Infection Development and Their Impact on Survival Using the NACSELD Cohort. Am J Gastroenterol. 2018;113:556-63. doi:10.1038/ajg.2017.471.
29. Sargenti K, Prytz H, Strand A, Nilsson E, Kalaitzakis E. Healthcare-associated and nosocomial bacterial infections in cirrhosis: Predictors and impact on outcome. Liver Int. 2015;35:391-400. doi:10.1111/liv.12625.
30. Kim WR, Biggins SW, Kremers WK, Wiesner RH, Kamath PS, Benson JT, et al. Hyponatremia and Mortality among Patients on the Liver-Transplant Waiting List. N Engl J Med. 2008;359:1018-26. doi:10.1056/nejmoa0801209.
31. Kim J, Kang C-I, Gwak G-Y, Chung DR, Peck KR, Song J-H. Clinical impact of healthcare-associated acquisition in cirrhotic patients with community-onset spontaneous bacterial peritonitis. Korean J Intern Med. 2020;35:215-21. doi:10.3904/kjim.2017.231.
32. Bartoletti M, Giannella M, Lewis RE, Caraceni P, Tedeschi S, Paul M, et al. Extended Infusion of β-Lactams for Bloodstream Infection in Patients With Liver Cirrhosis: An Observational Multicenter Study. Clin Infect Dis. 2019;69:1731-9. doi:10.1093/cid/ciz032.
33. Weil D, Levesque E, McPhail M, Cavallazzi R, Theocharidou E, Cholongitas E, et al. Prognosis of cirrhotic patients admitted to intensive care unit: a meta-analysis. Ann Intensive Care. 2017;7:33. doi:10.1186/s13613-017-0249-6.