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Ceftazidime-Avibactam for the Treatment of Carbapenem-Resistant *Klebsiella pneumoniae* Infections in Patients With Liver Cirrhosis

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Background: **Carbapenem-resistant *Klebsiella pneumoniae* (CRKP) infections in patients with cirrhosis represent a significant therapeutic challenge as they are associated with poor outcomes due to high rates of treatment failure, and frequently induce liver decompensation.** ***Aims:*** **To evaluate treatment failure and in-hospital mortality in two cohorts of patients with cirrhosis and with CRKP infections treated with antibiotic regimens including or excluding Ceftazidime-avibactam.** ***Methods:*** **Data from hospitalized patients with liver cirrhosis and CRKP infections were extracted and retrospectively analyzed.** ***Results:*** **During the study period, 39 cirrhotic patients with confirmed invasive CRKP infections were enrolled. Overall, the median age was 60 years with a median MELD score of 16 points. Urinary tract infections were diagnosed in 46%, followed by pneumonia in 23%, and primary bacteremia in 18% of patients. Treatment failure was reported in 10 patients (26%), while in-hospital mortality in 15 patients (38%). A monotherapy was used in 8 patients (20.5%), while a combination therapy was required in 31 patients (79.5%). Ceftazidime-avibactam therapy was associated with lower rates of treatment failure (7% vs. 38%, $P = 0.032$) independent of severity of liver disease (Child Class) and mono or combination antibiotic therapy. Acute kidney injury, hepatorenal syndrome, and acute-on-chronic liver failure were the consequences more frequently observed in patients with treatment failure. In-hospital mortality was associated with treatment failure, and Ceftazidime-avibactam therapy improved in-hospital survival (log rank test: $P = 0.035$) adjusted for Child class and mono or combination therapy.** ***Conclusion:*** **Treatment including ceftazidime-avibactam was associated with a lower rate of treatment failure in cirrhotic patients with CRKP infections. Considering the favorable efficacy and outcomes of ceftazidime-avibactam, this drug should be considered for the treatment of these severe infections in patients with liver cirrhosis, though further investigation is required. (J Clin Exp Hepatol xxxx;xxx:xxx)**

In recent years, infections caused by multidrug-resistant (MDR) pathogens have been increasingly observed in patients with liver cirrhosis. In particular, the emerging resistance to carbapenems, widely used for infections caused by MDR Gram-negative organisms such as *Enterobacterales* or *Pseudomonas aeruginosa,* is particularly challenging in these difficult-to-treat patients.[1,2]

As a matter of fact, cirrhosis is associated with many important dysfunctions: abnormalities of the immune system, leading to a general immunodeficiency[3]; susceptibility to translocation of bacteria from gut to bloodstream[4]; and frequent hospital admissions and invasive procedures, leading to an increased nosocomial exposure to MDR pathogens.[5,6] For all these reasons, these infections represent a significant therapeutic challenge in cirrhotic patients, resulting in the development of life-threatening complications and poor prognosis, in comparison to those caused by non-MDR organisms.[7,8]

Recently, data regarding the use of ceftazidime-avibactam (CAZ-AVI) prefer this new antibiotic over other antimicrobial regimens and indicate it as the first-line therapy for the treatment of carbapenem-resistant *Klebsiella*

Keywords: antibiotic therapy, bacterial infections, carbapenem-resistant strains, liver cirrhosis

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Abbreviations: ACLF: Acute-on-Chronic Liver Failure; AKI: Acute Kidney Injury; CAZ-AVI: Ceftazidime-Avibactam; COPD: Chronic Obstructive Pulmonary Disease; CRKP: Carbapenem-Resistant *Klebsiella Pneumoniae*; DCT: Double-Carbapenem Therapy; EASL-CLIF: European Association for the Study of the Liver- Chronic Liver Failure; Ecdc: European Centre for Disease Prevention and Control; EUCAST: EUropean Committee for Antimicrobial Susceptibility Testing; HCC: Hepatocellular Carcinoma; HRS: Hepatorenal Syndrome; MDR: Multi-Drug Resistant; MELD: Model for End-stage Liver Disease; MIC: Minimum Inhibitory Concentration; NASH: Non-Alcoholic Steatohepatitis; TIPS: Transjugular Intrahepatic Portosystemic Shunt

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pneumoniae (CRKP) infections.[9,10] However, there are no specific data regarding the use of CAZ-AVI for the treatment of these severe infections in cirrhotic patients.

The aim of this study was to explore factors associated with treatment failure or success, in a cohort of cirrhotic patients treated for CRKP infections during hospitalization with different antibiotic regimens.

MATERIALS AND METHODS

Study Population

This is a retrospective, single-center study, conducted at a large teaching 1200-bed hospital in Rome, Italy. During the study period, from January 2009 to June 2020, all hospitalized cirrhotic patients with a proven CRKP infection were enrolled and analyzed.

Inclusion criteria were the following: age ≥18 years; liver cirrhosis, based on liver biopsy and/or on clinical, biochemical, ultrasonographic and endoscopic features; and a documented CRKP infection. Exclusion criteria were a presence of end-stage neoplasia (including hepatocellular carcinoma) and a concomitant immunosuppressive therapy.

Data of patients were retrospectively extracted from medical records, computerized hospital databases, and/or clinical charts, using a standard form. Demographics, clinical radiological and laboratory findings, comorbidities (including Charlson Comorbidity Index), microbiological findings, previous invasive procedures, source of infection, duration of hospital stay, definitive antibiotic therapy, and in-hospital mortality were collected. Basal clinical and biochemical parameters were assessed to define the severity of liver disease, renal function, and electrolyte imbalance.

The severity of liver disease was assessed using either Child class or the model of end-stage liver disease score.[11] Acute kidney injury (AKI) and hepatorenal syndrome (HRS) were diagnosed according to international criteria.[12] Finally, acute-on-chronic liver failure (ACLF) was recorded in the setting of an acute deterioration of liver function or other system functions, according to the EASL-CLIF definition.[13]

Definitions

Infections were defined according to the standard definitions of the European Center for Disease Prevention and Control (eCDC);[14] *Length of hospital stay after CRKP infection* was defined as the number of days from diagnosis of the infection to discharge or death; *In-hospital mortality* was defined by death during the hospitalization; *Infection-related mortality* was defined by death attributed to CRKP infection when it was unresponsive to therapy and/or to death-related organ failures; *treatment failure* was defined by (1) persistence of clinical signs of infection as well as positive biomarkers of infection, including C-reactive protein and procalcitonin; (2) antibiotic resistance to the antimicrobial susceptibility test and/or persistence of culture positive after 72 h of antibiotic treatment.[15];

Infection relapse was defined as the onset of a second microbiologically documented CRKP infection during the index hospitalization, following the resolution of the original infection.

Microbiology

The etiology of the infection was determined using local laboratory techniques. The bacterial pellet from positive cultures was used for Matrix assisted laser desorption/ionization time of flight (MALDI-TOF) MS (Bruker Daltonics, Billerica, MA, USA) identification and for molecular analysis. The SensiTitre™ system (Thermo Fisher Scientific, Waltham, MA, USA) or the Vitek 2 automated system (bioMérieux, Marcy l'Etoile, France) were used for antimicrobial susceptibility testing. Minimum inhibitory concentrations were established according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint.[16]

Antimicrobial Treatment Evaluation

Empiric and definitive antibiotic regimens were selected according to clinical judgment by infectious disease specialists and were subsequently modified according to microbiological results. Depending on the number of drugs used (one or more than one), treatment regimens were classified either as monotherapy or combination therapy. Empiric antibiotic therapy (antimicrobial chemotherapy implemented within 24 h after the onset of infection) was assessed along with definitive antibiotic therapy (antimicrobial treatment based on in-vitro isolate susceptibility). Antibiotics analyzed in definitive therapy were administered for at least 50% of the total duration of therapy. The *time to initial definitive therapy* was the period between the diagnosis of infection and initial definitive therapy.[17]

Statistical Analysis

The primary endpoint was the analysis of factors associated with treatment failure. The secondary endpoint was the analysis of factors associated with in-hospital mortality.

Results were expressed as median and Interquartile Range (25th–75th) or mean and Standard Deviation (±SD) for continuous variables, or simple frequencies (n), proportion or percentages (%) for dichotomous variables. Mann–Whitney U test compared continuous variables since some continuous variables exhibited skewed distributions on visual inspection. Instead, the independent Student t-test was used to compare normally

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Table 1 Characteristics of Cirrhotic Patients According to Treatment, Including or Excluding CAZ-AVI, at the Time of Diagnosis of KPC Infection.

Variables	All treatments n = 39 (%)	Antibiotic regimens not including CAZ-AVI n = 24 (%)	Antibiotic regimens including CAZ-AVI n = 15 (%)	*P*-value
Demographics				
Male sex	37 (95)	23 (96)	14 (93)	0.753
Age, median (IQR)	60 (54–67)	58 (55–64)	64 (54–69)	0.452
Etiology of cirrhosis				
Viral	8 (21)	7 (29)	1 (7)	0.102
Alcohol	15 (38)	8 (33)	7 (47)	0.229
Nash	3 (8)	0	3 (20)	0.024
Viral + Alcohol	5 (13)	2 (8)	3 (20)	0.236
Cryptogenic	5 (13)	5 (21)	0	0.057
Other	3 (8)	2 (8)	1 (7)	0.910
Clinical characteristics				
Active alcohol abuse	8 (21)	5 (21)	3 (20)	0.952
HCC 'Milano in'	8 (21)	7 (29)	1 (7)	0.06
MELD score, median (IQR)	16 (12–20)	16 (12–20)	17 (11.5–19.5)	0.751
Ascites in history	35 (90)	21 (88)	14 (93)	0.547
Previous hepatic encephalopathy	23 (59)	15 (63)	8 (53)	0.588
Previous hepatorenal syndrome	13 (33)	11 (46)	2 (13)	0.024
Previous esophageal varices	29 (74)	19 (79)	10 (67)	0.418
Recent variceal bleeding	2 (5)	2 (8)	0	0.162
Comorbidities				
Diabetes	26 (67)	17 (71)	9 (60)	0.508
COPD	6 (15)	5 (21)	1 (7)	0.197
Cardiovascular disease	19 (49)	10 (42)	9 (60)	0.280
Neurological disease	3 (8)	1 (4)	2 (13)	0.37
Chronic kidney disease	7 (18)	3 (13)	4 (27)	0.311
Neutropenia	2 (5)	0	2 (13)	0.164
Charlson comorbidity index, mean (±SD)	6 ± 2	6 ± 1.9	5.8 ± 1.7	0.787
Healthcare interventions prior to infection onset				
Hospitalization (6 months prior to infection)	26 (67)	15 (63)	11 (73)	0.491
Antibiotic treatment (30 days prior to infection)	24 (62)	13 (54)	11 (73)	0.232
Invasive procedures (30 days prior to infection)	29 (74)	15 (63)	14 (93)	0.015
Dialysis (30 days prior to infection)	2 (5)	0	2 (13)	0.165
TIPS (in the medical history)	6 (15)	5 (21)	1 (7)	0.197
Recent TIPS (30 days prior to infection)	1 (3)	1 (4)	0	0.328
Urinary catheter (72 h prior to infection)	24 (62)	16 (67)	8 (53)	0.578
Endoscopy (72 h prior to infection)	3 (8)	0	3 (20)	0.082

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Table 1 (*Continued*)

Variables	All treatments n = 39 (%)	Antibiotic regimens not including CAZ-AVI n = 24 (%)	Antibiotic regimens including CAZ-AVI n = 15 (%)	*P*-value
Variceal ligation (72 h prior to infection)	4 (10)	2 (8)	2 (13)	0.603
Paracentesis (72 h prior to infection)	15 (38)	9 (38)	6 (40)	0.756
Site of primary infection				
Pneumonia	9 (23)	9 (38)	0	0.007
Urinary tract infection	18 (46)	10 (42)	8 (53)	0.51
Spontaneous bacterial peritonitis	3 (8)	2 (8)	1 (7)	0.91
Primary bacteremia	7 (18)	2 (8)	5 (33)	0.042
Skin and soft tissue infection	2 (5)	2 (8)	0	0.267
CRKP infection in >1 site	8 (21)	7 (29)	1 (7)	0.06
Polymicrobial infection	21 (54)	15 (63)	6 (40)	0.184

CAZ-AVI, Ceftazidime-Avibactam; NASH, Non-Alcoholic Steatohepatitis; HCC, Hepatocellular Carcinoma; MELD, Model for End-stage Liver Disease; COPD, Chronic Obstructive Pulmonary Disease; TIPS, Transjugular Intrahepatic Portosystemic Shunt; CRKP, Carbapenem-Resistant *Klebsiella pneumoniae*.

Table 2 Main Outcomes of CRKP Infections in Cirrhotic Patients.

Variables	All treatments n = 39 (%)	Other antibiotic regimens n = 24 (%)	CAZ-AVI n = 15 (%)	*P*-value
Duration of antibiotic therapy, median (IQR)	10 (8–19)	10 (7–15)	11 (8–17)	0.347
Duration of hospital stay after CRKP infection onset, median (IQR)	23 (14–35)	16 (10–25)	23 (15–44)	0.032
Duration from infection onset to initiation of targeted treatment, median (IQR)	3 (2–5)	3 (2–5)	3 (2–4.5)	0.721
Treatment failure	10 (26)	9 (38)	1 (7)	0.032
Acute kidney injury	14 (36)	9 (38)	5 (33)	0.755
Hepatorenal syndrome	11 (28)	7 (29)	4 (27)	0.894
Acute-on-chronic liver failure	18 (46)	13 (54)	5 (33)	0.206
In-hospital mortality	15 (38)	11 (46)	4 (27)	0.242
Death directly related to the infection	8 (21)	7 (29)	1 (7)	0.102
Infection relapse	2 (5)	0	2 (13)	0.074

CAZ-AVI, Ceftazidime-Avibactam; CRKP, Carbapenem-Resistant *Klebsiella pneumoniae*.

distributed variables. Dichotomous variables were evaluated by using the chi-square test or Fisher's exact test, as required. Univariate conditional logistic regression was used by comparing the two groups for each variable of interest, and Odds Ratio, 95% confidence intervals (95% CIs), and *P*-values were calculated. Multivariate logistic regression models were used to identify independent risk factors for treatment failure. Cox proportional hazard model was also used to identify parameters for treatment failure and in-hospital mortality. Kaplan–Meier survival curve (Log rank test) was also utilized for in-hospital mortality after considering confounding factors. When interpreting the results, a *P*-value of less than 0.05 was considered indicative of a significant difference. All computations were done with SPSS software (version 22; SPSS Inc. Chicago IL, USA).

RESULTS

During the study period, 57 cirrhotic patients with confirmed invasive CRKP infections were enrolled; of whom, 18 patients were excluded from final analysis (end-stage neoplasia and/or immunosuppressive therapy). In our epidemiological setting, all the CRKP infections were due to KPC-2 strains.

Characteristics of all 39 cirrhotic patients, according to treatment including or excluding CAZ-AVI, are reported in

Table 3 Variables Associated With Treatment Failure (Logistic Regression).

	B	S.E.	Wald	gl	Sign.	OR	95% C.I.
Treated with ceftazidime avibactam	−2.416	1.068	5.114	1	0.024	0.089	0.011—0.725
Child class (A, B, or C)	−0.549	0.659	0.693	1	0.405	0.578	0.159—2.103
Respiratory infection	0.556	0.802	0.481	1	0.488	1.744	0.362—8.398

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Table 4 Cox Regression Analysis for Factors Associated With Treatment Failure.

	B	S.E.	Wald	gl	Sign.	HR	95% C.I.
Treated with ceftazidime avibactam	−2.126	1.061	4.012	1	0.045	0.119	0.015—0.955
Child class (A, B, or C)	0.196	0.647	0.091	1	0.762	1.216	0.342—4.325
Monotherapy or polytherapy	0.263	0.810	0.106	1	0.745	1.301	0.266—6.364

Table 1. Overall, the median age was 60 years with a median model of end-stage liver disease score of 16 points and a Charlson Comorbidity Index of 6 points. Regarding the primary source of CRKP infection, urinary tract infection was diagnosed in 18 patients (46%), followed by pneumonia in 9 patients (23%), and primary bacteremia in 7 patients (18%). Main characteristics of the two cohorts at basal were comparable, although bacteremia was more frequent in patients treated with regimens including CAZ AVI and episodes of pneumonia were only reported, as the site of infection, in patients in the older cohort who were not treated with CAZ AVI. Polymicrobial infections were frequent and not significantly different in the two groups.

The main outcomes of CRKP infections are reported in Table 2. 10 patients (26%) experienced treatment failure. During hospitalization, 14 patients (36%) developed AKI, 11 patients (28%) developed HRS, and 18 patients (46%) developed ACLF. In-hospital mortality was observed in 15 patients (38%). Rates of treatment failure were lower in patients treated with regimens, including CAZ-AVI (7% vs 38%, $P = 0.032$).

Antibiotic regimen used for the treatment of CRKP infections was monotherapy in 8 patients (20.5%), and combination therapy in 31 patients (79.5%). The most frequently used combined antibiotic regimens were carbapenem + CAZ-AVI, double carbapenem therapy + tigecycline, and fosfomycin + CAZ-AVI (Supplementary Table 1).

Univariate analysis showed that age, gender, and comorbidities were not significantly associated with treatment failure. Pneumonia was associated with a higher rate of treatment failure. A logistic regression analysis of factors associated with treatment failure in cirrhotic patients is reported in Table 3. CAZ-AVI-containing regimens were associated with a lower rate of treatment failure independent of the severity of liver disease (Child class) or a diagnosis of pneumonia. A Cox regression analysis for treatment failure is reported in Table 4, in which we included among the variables, the use of mono or combination antibiotic regimens. CAZ-AVI-containing regimens were associated with a lower rate of treatment failure independent of the severity of liver disease (Child class) or the use of mono or combination antibiotic regimens (See Table 5).

As expected, AKI (70% vs 24%, $P = 0.01$), HRS (70% vs 14%, $P < 0.001$), and ACLF (90% vs 31%, $P = 0.001$) during the hospitalization, occurred more frequently in patients with treatment failure. Although in hospital mortality was not associated with treatment on univariate analysis, we examined this variable, which was related to treatment failure, by a Cox analysis. In-hospital survival was associated with CAZ-AVI containing regimens adjusted for the Child class and mono or combination antibiotic regimens.

As reported in Figure 1, the Kaplan–Meier curve depicts an improved in-hospital survival for cirrhotic patients treated with CAZ-AVI, after adjustments for Child class and the use of mono or combination antibiotic therapies ($P = 0.028$).

DISCUSSION

In recent years, the emergence of CRKP infections in cirrhotic patients has been reported worldwide, with studies examining their severe outcomes in this population.[1,18] In a recent small prospective study from Taiwan, liver cirrhosis was found to be a predictor for the presence of a CRKP infection.[19]

Many observational studies examined the outcomes of CRKP infections and their potential therapies in the general population. A recent meta analysis pooled the results from 51 studies, revealing an overall mortality rate of 37% and a clear survival benefit for the combination therapy compared to monotherapy (OR 1.45, 95% CI 1.18–1.78%).[20]

To the best of our knowledge, this is the first study evaluating the role of CAZ-AVI in infections caused by CRKP in cirrhotic patients. We reported, in our cohort, a lower rate of treatment failure in patients treated with antibiotic regimens containing CAZ-AVI. Additionally, we confirm

Table 5 Cox Regression Analysis for Factors Associated With in Hospital Survival.

	B	S.E.	Wald	gl	Sign.	HR	95% C.I.
Treated with ceftazidime avibactam	−1.313	0.662	3.927	1	0.048	0.269	0.073—0.986
Child class (A, B, or C)	0.401	0.562	0.509	1	0.475	1.493	0.497—4.490
Monotherapy or polytherapy	0.170	0.672	0.064	1	0.801	1.185	0.318—4.418

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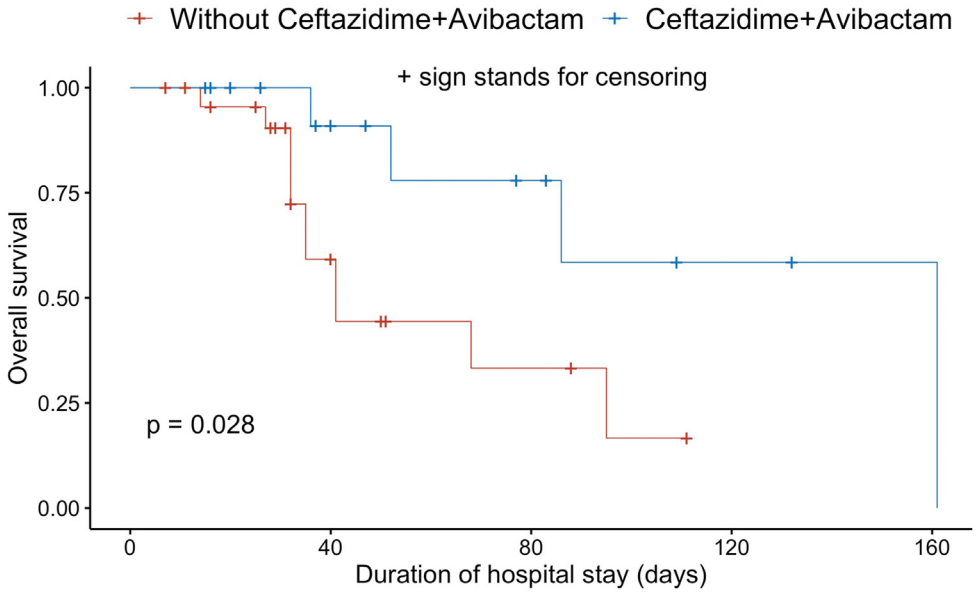

Figure 1 In hospital survival according to the presence of CAZ AVI in the antibiotic treatment of cirrhotic patients with CRKP infection. (CAZ-AVI, Ceftazidime-Avibactam).

that treatment failure is associated with the decompensation of cirrhosis and worse outcome (AKI, HRS, ACLF).

Studies and guidelines have clearly emphasized the importance of a timely administration of appropriate antimicrobial therapy after a diagnosis of bacterial infection in cirrhotic patients.[21,22] Our study adds some knowledge about the use of CAZ-AVI for the treatment of CRKP infections in patients with liver cirrhosis. The epidemiology of this infection has shown a steep increase in our hospital in the last years and treatment can be a challenge. Allaire *et al* demonstrated that the use of nephrotoxic drugs, such as aminoglycosides and colistin, in cirrhotic patients, increases the risk of renal failure, and subsequent mortality.[23] For this reason, even if these antibiotics are sometimes utilized in CRKP infections, their use in patients with liver cirrhosis is always to be considered with caution. CAZ-AVI has demonstrated a relatively safer profile that could potentially favor its use in cirrhotic patients.[24,25]

Recent studies have highlighted a statistically significant survival benefit for CAZ-AVI use over other antibiotic regimens in the general population, but no specific data about a cirrhotic cohort treated by CAZ-AVI are available.[26] In our study, we had the opportunity to examine a cohort of cirrhotic patients all with a microbiological diagnosis of CRKP treated with antibiotic regimens including or excluding CAZ-AVI. Unfortunately, all episodes of respiratory infections were reported in the older cohort, when CAZ-AVI was not yet available. This could represent a bias, as pneumonia are difficult-to-treat infections, considering the poor lung penetration of most antibiotics. Nevertheless, treatments including CAZ-AVI were associated with a lower rate of treatment failure even after adjusting for the presence of pneumonia.

Furthermore, the antibiotic regimens utilized in both cohorts of patients were less frequently monotherapies and more often combined therapies. This could raise the question whether the reduction of the rate of treatment failure was related to CAZ-AVI or more associated with the use of combined vs mono antibiotic therapy as suggested by a meta-analysis in the general population.[20] However, in our analysis treatment with CAZ-AVI was associated with a lower rate of treatment failure also when adjusted for mono or combined therapy.

Cirrhotic patients with CRKP infections are known to develop higher rates of complications than non-MDR infections.[27–29] In our analysis, complications like AKI, HRS, and ACLF were, as expected, consequences independently associated with treatment failure. This explains why the regimens including CAZ AVI in our study, through a lower rate of treatment failure, were also associated with a better in hospital survival when analyzed with the Cox regression analysis.

This study has important limitations. The retrospective design of the study and the relatively small sample size should be considered as an important bias limiting the strength of our results. Furthermore, CAZ-AVI was mostly utilized when combined with other antibiotics, which may prevent evaluating the specific effect of this antibiotic. Finally, Pneumonia, one of the most severe infections occurring in patients with cirrhosis, was only observed in patients not receiving CAZ-AVI, which could have had an impact on infection resolution and in-hospital mortality in the two groups.

Importantly, when considering the treatment for CRKP infections, an attention should be given to the type of Carbapenemases produced by the specific bacterial strains,

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conferring the resistance to Carbapenem, namely KPC (Klebsiella Pneumoniae Carbapenemase), OXA-48, and MBL (Metallo-Beta-Lactamase), in particular NDM (New Delhi Metallo-beta-lactamase). In fact, from an epidemiologic perspective, different areas in the world are characterized by prevalence of one of the above, rather than the other. In Italy, the location of this study, the prevalent strain is KPC-3.[7] Indeed, in previous studies, CAZ-AVI demonstrated in vitro activity against Carbapenem-resistant isolates that produce either KPC or OXA-48 carbapenemases but not for MBL.[30] Notably, in MBL strains, the addition of Aztreonam was found to be of advantage in the non-cirrhotic population in a recent study.[31] In this setting, it is possible that the clinical benefit of CAZ-AVI that was found in the present study might not be applicable in areas where MBL-producing strains are the prevalent CRKP Type.

In conclusion, this is the first study evaluating the role of CAZ-AVI regimens for the treatment of infections caused by CRKP in cirrhotic patients. Considering the lower rates of treatment failure and favorable in-hospital survival associated with the use of antibiotic regimens containing CAZ-AVI, this drug may be considered for the treatment of these severe infections in patients with cirrhosis. This study calls for future randomized trials with larger sample sizes to re-affirm our results and allow for the formulation of guidelines for the use of CAZ AVI treatment in cirrhotic patients.

AUTHOR CONTRIBUTIONS

Shani Feldman: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Writing - original draft, Writing - answering after review & editing. Alessandro Russo: Investigation, Methodology, Resources, Validation, Writing - original draft, Writing -. Giancarlo Ceccarelli: Conceptualization, Investigation, Methodology, Resources, Validation, Writing - review & editing. Cristian Borrazzo: Formal analysis, Software. Chiara Madge: Data curation. Mario Venditti: Investigation, Methodology, Supervision. Manuela Merli: Conceptualization, Investigation, Methodology, Resources, Supervision, Validation, Writing - answering after review & editing.

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None.

ETHICAL APPROVAL AND PATIENT CONSENT

All patients signed a consent at hospitalization, allowing the use of their data for scientific purposes, providing their identity is secured. Data were retrospectively obtained from medical records. The study protocol was approved by the local ethic committee as a retrospective analysis of data dealing with multidrug resistant infections (n. 4773) on October 12th, 2017.

CONFLICTS OF INTEREST

All authors have none to declare.

REFERENCES

1. Fernández J, Prado V, Trebicka J, 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. https://doi.org/10.1016/j.jhep.2018.10.027.
2. Jalan R, Fernandez J, Wiest R, et al. Bacterial infections in cirrhosis: a position statement based on the EASL Special Conference 2013. *J Hepatol*. 2014;60:1310–1324. https://doi.org/10.1016/j.jhep.2014.01.024.
3. Albillos A, Lario M, Álvarez-Mon M. Cirrhosis-associated immune dysfunction: distinctive features and clinical relevance. *J Hepatol*. 2014;61:1385–1396. https://doi.org/10.1016/j.jhep.2014.08.010.
4. Wiest R, Lawson M, Geuking M. Pathological bacterial translocation in liver cirrhosis. *J Hepatol*. 2014;60:197–209. https://doi.org/10.1016/j.jhep.2013.07.044.
5. Fernandez J, Arroyo V. Bacterial infections in cirrhosis: a growing problem with significant implications. *Clin Liver Dis*. 2013;2:102–105. https://doi.org/10.1002/cld.169.
6. Merli M, Lucidi C, Di Gregorio V, 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:e0127448. https://doi.org/10.1371/journal.pone.0127448.
7. Tzouvelekis LS, Markogiannakis A, Psichogiou M, Tassios PT, Daikos GL. Carbapenemases in Klebsiella pneumoniae and other Enterobacteriaceae: an evolving crisis of global dimensions. *Clin Microbiol Rev*. 2012;25:682–707. https://doi.org/10.1128/cmr.05035-11.
8. Cassotta A, Goldstein JD, Durini G, et al. Broadly reactive human CD4+ T cells against Enterobacteriaceae are found in the naöve repertoire and are clonally expanded in the memory repertoire. *Eur J Immunol*. 2021;51:648–661. https://doi.org/10.1002/eji.202048630.
9. Shields RK, Nguyen MH, Chen L, et al. Ceftazidime-avibactam is superior to other treatment regimens against carbapenem-resistant Klebsiella pneumoniae bacteremia. *Antimicrob Agents Chemother*. 2017;61:e00883-17. https://doi.org/10.1128/AAC.00883-17.
10. Tumbarello M, Trecarichi EM, Corona A, et al. Efficacy of ceftazidime-avibactam salvage therapy in patients with infections caused by Klebsiella pneumoniae carbapenemase-producing K. pneumoniae. *Clin Infect Dis*. 2019;68:355–364. https://doi.org/10.1093/cid/ciy492.
11. Kamath PS, Wiesner RH, Malinchoc M, et al. A model to predict survival in patients with end-stage liver disease. *Hepatology*. 2001;33:464–470. https://doi.org/10.1053/jhep.2001.22172.
12. Bucsics T, Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. *Gastroenterol Rep (Oxf)*. 2017;5:127–137. https://doi.org/10.1093/gastro/gox009.
13. Moreau R, Jalan R, Gines P, et al. Acute-on-chronic liver failure is a distinct syndrome that develops in patients with acute decompensation of cirrhosis. *Gastroenterology*. 2013;144:1426–1437. https://doi.org/10.1053/j.gastro.2013.02.042. e14379.
14. European Centre for Disease Prevention and Control. *Annual Epidemiological Report on Communicable Diseases in Europe, 2014*.

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Stockholm, Sweden: European Centre for Disease Prevention and Control; 2014 https://ecdc.europa.eu/sites/portal/files/media/en/publications/Publications/AER-VPD-IBD-2014.pdf.
15. Bassetti M, Montero JG, Paiva JA. When antibiotic treatment fails. *Intensive Care Med*. 2018 Jan;44:73–75. https://doi.org/10.1007/s00134-017-4962-2.
16. European Committee on Antimicrobial Susceptibility Testing. *EUCAST Guidelines for Detection of Resistance Mechanisms and Specific Resistances of Clinical And/or Epidemiological Importance*; July 2017 Version 2.0. https://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Resistance_mechanisms/EUCAST_detection_of_resistance_mechanisms_170711.pdfVersion 2.0.
17. Russo A, Giuliano S, Ceccarelli G, et al. Comparison of septic shock due to multidrug-resistant acinetobacter baumannii or Klebsiella pneumoniae carbapenemase-producing K. pneumoniae in intensive care unit patients. *Antimicrob Agents Chemother*. 2018;62e02562-17 https://doi.org/10.1128/AAC.02562-17.
18. Piano S, Singh V, Caraceni P, et al. Epidemiology and effects of bacterial infections in patients with cirrhosis worldwide. *Gastroenterology*. 2019;156:1368–1380. https://doi.org/10.1053/j.gastro.2018.12.005. e10.
19. Hsu JY, Chuang YC, Wang JT, Chen YC, Hsieh SM. Healthcare-associated carbapenem-resistant Klebsiella pneumoniae bloodstream infections: risk factors, mortality, and antimicrobial susceptibility, 2017-2019. *J Formos Med Assoc*. 2021;120:1994–2002. https://doi.org/10.1016/j.jfma.2021.04.014.
20. Agyeman AA, Bergen PJ, Rao GG, Nation RL, Landersdorfer CB. A systematic review and meta-analysis of treatment outcomes following antibiotic therapy among patients with carbapenem-resistant Klebsiella pneumoniae infections. *Int J Antimicrob Agents*. 2020;55:105833. https://doi.org/10.1016/j.ijantimicag.2019.10.014.
21. Merli M, Lucidi C, Di Gregorio V, et al. An empirical broad-spectrum antibiotic therapy in health-care-associated infections improves survival in patients with cirrhosis: a randomized trial. *Hepatology*. 2016;63:1632–1639. https://doi.org/10.1002/hep.28332.
22. Di Gregorio V, Lucidi C, Giannelli V, et al. Bacterial infections in cirrhotic patients: risk factors and rate of failure of the empirical antibiotic therapy. *J Hepatol*. 2014;60:S227. https://doi.org/10.1016/S0168-8278(14)60635-8.
23. Allaire M, Cadranel JF, Nguyen TTN, et al. Management of infections in patients with cirrhosis in the context of increasing therapeutic resistance: a systematic review. *Clin Res Hepatol Gastroenterol*. 2020;44:264–274. https://doi.org/10.1016/j.clinre.2019.10.003.
24. Bassetti M, Russo A, Carnelutti A, La Rosa A, Righi E. Antimicrobial resistance and treatment: an unmet clinical safety need. *Expet Opin Drug Saf*. 2018 Jul;17:669–680. https://doi.org/10.1080/14740338.2018.1488962.
25. Bassetti M, Righi E, Carnelutti A, Graziano E, Russo A. Multidrug-resistant Klebsiella pneumoniae: challenges for treatment, prevention and infection control. *Expert Rev Anti Infect Ther*. 2018;16:749–761. https://doi.org/10.1080/14787210.2018.1522249.
26. van Duin D, Lok JJ, Earley M, et al. Colistin versus ceftazidime-avibactam in the treatment of infections due to carbapenem-resistant enterobacteriaceae. *Clin Infect Dis*. 2018;66:163–171. https://doi.org/10.1093/cid/cix783.
27. Piano S, Romano A, Rosi S, Gatta A, Angeli P. Spontaneous bacterial peritonitis due to carbapenemase-producing Klebsiella pneumoniae: the last therapeutic challenge. *Eur J Gastroenterol Hepatol*. 2012;24:1234–1237. https://doi.org/10.1097/MEG.0b013e328355d8a2.
28. Salerno F, Borzio M, Pedicino C, et al. The impact of infection by multidrug-resistant agents in patients with cirrhosis. A multicenter prospective study. *Liver Int*. 2017;37:71–79. https://doi.org/10.1111/liv.13195.
29. European Association for the Study of the Liver. EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis. *J Hepatol*. 2018;69:406–460. https://doi.org/10.1016/j.jhep.2018.03.024.
30. Falcone M, Paterson D. Spotlight on ceftazidime/avibactam: a new option for MDR Gram-negative infections. *J Antimicrob Chemother*. 2016;71:2713–2722. https://doi.org/10.1093/jac/dkw239.
31. Falcone M, Daikos GL, Tiseo G, et al. Efficacy of ceftazidime-avibactam plus Aztreonam in patients with bloodstream infections caused by metallo-β-lactamase-producing Enterobacterales. *Clin Infect Dis*. 2021 Jun 1;72:1871–1878. https://doi.org/10.1093/cid/ciaa586.

APPENDIX A

SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2022.04.016.

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