

# Epidemiology and risk factors for multidrug-resistant bacteria in critically ill patients with liver disease

## ABSTRACT

**Background and Aims:** The critically ill patients with liver disease are vulnerable to infections in both community and hospital settings. The nosocomial infections are often caused by multidrug-resistant (MDR) bacteria. The present observational study was conducted to describe the epidemiology, course, and outcome of MDR bacterial infection and identify the risk factors of such infection in critically ill patients with liver disease.

**Materials and Methods:** A retrospective observational study was conducted on 106 consecutive critically patients with liver disease admitted in the Intensive Care Unit between March 2015 and February 2017. The MDR and non-MDR (non-MDR) groups were compared and the risk factors identified by multivariate analysis.

**Results:** Out of the 106 patients enrolled in the study, 23 patients had infections caused by MDR bacteria. The MDR-infected patients had severe liver disease (Child–Pugh score  $11 \pm 2.3$  vs.  $7 \pm 3.9$ ;  $P = 0.04$ ), longer duration of antibiotic usage ( $6 \pm 2.7$  days vs.  $2 \pm 1.5$  days;  $P = 0.04$ ), greater use of total parenteral nutrition (TPN) (73.9% vs. 62.6%;  $P = 0.04$ ), and more concurrent antifungal administration (60.8% vs. 38.5%;  $P = 0.04$ ). The mortality was higher in MDR group (hazard ratio = 1.86;  $P < 0.05$ ). The independent predictors of MDR bacterial infection were Child–Pugh score  $>10$ , prior carbapenem use, antibiotic use for more than 10 days, TPN use, and concurrent antifungal administration.

**Conclusion:** The study demonstrated a high prevalence of MDR bacterial infection in critically ill patients with a higher mortality over non-MDR bacterial infection and also identified the independent predictors of such infections.

**Key words:** Critically ill; liver disease; multidrug-resistant bacteria

## Introduction

The growing resistance to antibacterials is a serious problem in all parts of the world and is now acknowledged as a major public health crisis.<sup>[1]</sup> The emergent multidrug-resistant (MDR) bacteria are more relevant in the Intensive Care Units (ICUs) because of the high mortality consequent upon narrowed therapeutic options in the face of increased severity of infection. Moreover, high antibiotic

selection pressure and overuse in the non-ICU areas also manifest their deleterious effects in the ICU.<sup>[2]</sup> Many studies have shown the high prevalence of MDR infections in patients with liver disease, particularly cirrhotics awaiting liver transplant.<sup>[3-5]</sup> However, the risk factors for acquisition and the magnitude of their effects on the vulnerability are poorly understood and inadequately described in most studies.

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Therefore, the present study was conducted to understand the epidemiological and clinical characteristics of MDR infections in critically ill patients with liver disease and to identify the risk factors for acquisition of the same.

## Materials and Methods

An observational, retrospective study was conducted in a cohort of 106 consecutively admitted critically ill patients with liver disease in the seven-bedded mixed medical-surgical ICU of a 750 bedded tertiary care superspeciality institute affiliated to the University of Delhi between March 2015 and February 2017. Data were extracted from the hospital ICU database maintained for the administrative and clinical purpose. Approval was sought from the Institution Ethics Committee for waiver of informed consent.

The primary objective was comparison of the epidemiology, clinical characteristics, and outcome of the MDR and non-MDR group of critically ill patients in the ICU with liver disease.

The secondary objectives were identification of the risk factors for acquisition of MDR infections in these patients.

The following definitions were used for the purpose of the study.

MDR infection – it was considered on the basis of the existing knowledge during the study period which included the following pathogens with given antibiotic resistance characteristics: extended-spectrum  $\beta$ -lactamase-producing Gram-negative *Enterobacteriaceae*, such as *Klebsiella* spp., *Escherichia coli*, and *Proteus* spp.; *Pseudomonas aeruginosa* resistant to ceftazidime or carbapenems; other pan-resistant *Enterobacteriaceae* bacteria or those sensitive only to carbapenems; *Acinetobacter* spp. resistant to ampicillin, ampicillin/sulbactam, or carbapenems; methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp. Other organisms were considered MDR if they were found to be resistant to at least three of the following antibiotic classes: Antipseudomonal cephalosporins/penicillins, macrolides, carbapenems, fluoroquinolones, aminoglycosides, colistin, and tigecycline.

Non-MDR infection – all infections other than those included as MDR infection.

The presence or absence of infection was suspected by the ICU physician on clinical basis and confirmed from the microbiology reports.

Any one or more of the following body fluids were chosen for sample collection for microbiological examination depending on the patient's illness – blood, urine, endotracheal aspirate, drains, pleural fluid, ascitic fluid, and cerebrospinal fluid. The isolates with colony-forming unit count more than  $10^5$ /cu mm<sup>3</sup> were only considered as infection.

The patients with clinical diagnosis of infection but negative microbiology reports and those without clinical infection but positive microbiology reports were not included in the study.

The following variables were chosen for comparison between the MDR and non-MDR groups: age, sex, type of liver disease, severity of liver disease (Child–Pugh score), need for mechanical ventilation and invasive monitoring, need for total parenteral nutrition (TPN), usage of antibiotics before ICU admission, duration of antibiotic use, antifungal use, type of body fluid with microbiological isolates, length of ICU stay, and outcome (death or survival).

Categorical variables were presented as absolute and relative frequencies and compared in the univariate analysis using Pearson's Chi-square test or Fisher's exact test, as appropriate. For those analyses, two-tailed tests and  $P \leq 0.05$  were considered statistically significant. Logistic regression analysis was used to determine the relationship between the risk factors and infection with MDR organism in the multivariate analysis. Variables with  $P \leq 0.15$  were considered significant and were entered into the multivariate model. In the multivariate model, variables with  $P \leq 0.05$  were considered significant. Continuous variables were presented as means and standard deviations. For the comparison of continuous variables, Mann–Whitney U-test and Student's *t*-test were used depending on distribution. The cumulative survival and cumulative hazard (or death) between the groups were compared using the Kaplan–Meier curve. All tests were performed using statistical software SPSS version 21.0 (SPSS, Inc., Chicago, IL, USA).

## Results

Out of 106 patients enrolled in the study, 23 patients had infection due to MDR bacteria and 83 due to non-MDR bacteria. The predominant bacteria identified in both the groups combined were *Klebsiella* followed by *Acinetobacter* and *E. coli* [Figure 1].

There was no difference between the MDR and non-MDR groups with respect to age, sex, diagnosis, and cause of ICU admission, need for mechanical ventilation and/or invasive monitoring, and the length of ICU stay [Table 1]. The

patients in MDR group had greater severity of disease (higher Child–Pugh score), more usage of TPN, antibiotics before ICU admission, and concurrent antifungal treatment [Table 1]. The ICU mortality was higher in the MDR group [Table 1].

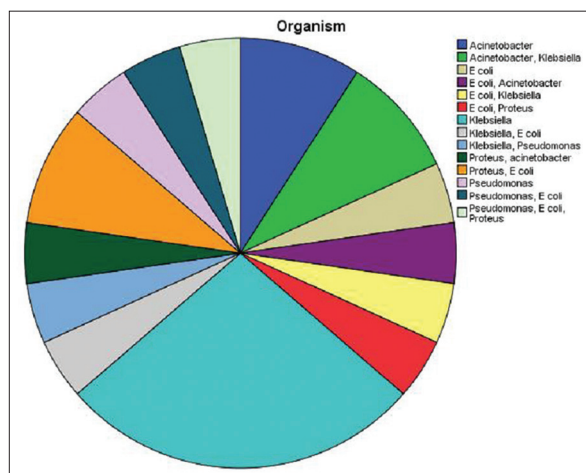


Figure 1: The distribution of bacteria in the isolates of multidrug-resistant and nonmultidrug-resistant group

The multivariate analysis model correctly classified 78.7% of the patients so far as MDR infection was concerned. It identified the following independent risk factors for MDR infections: Child–Pugh score > 10, TPN use, prior carbapenem use, total duration of antibiotic for more than 7 days, and concurrent antifungal usage [Table 2].

The ICU survival was similar in both the groups till day 5 and thereafter better in the non-MDR group [Figure 2]. The greatest number and proportion of terminal events (death) occurred within the first 10 days in MDR group and within 15 days in non-MDR group and were statistically different across the group (Wilcoxon statistic 1.867, degree of freedom = 1, P = 0.04) [Figure 3].

### Discussion

In the present single-center study, there was a high prevalence of MDR infections in critically ill patients with liver disease. The severity of liver disease (Child–Pugh score > 10), prior

Table 1: Comparison of the demography and clinical profile of multidrug-resistant and nonmultidrug-resistant groups

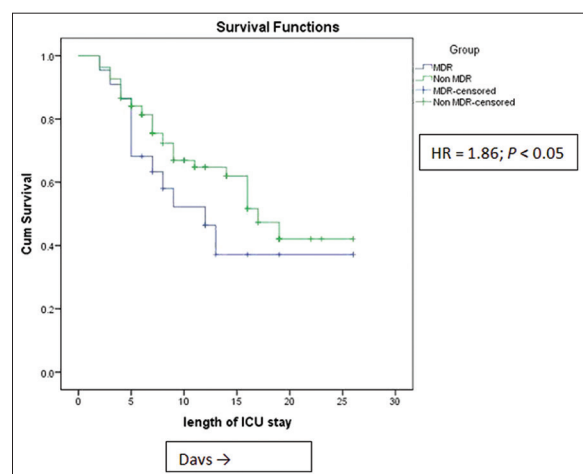
	MDR (n=23)	Non-MDR (n=83)	P
Age (years) (mean±SD)	56±12.3	52±7.5	0.16
Sex (male/female)	16/7	52/31	0.22
Primary diagnosis, n (%)			
Alcoholic liver disease	9 (39.1)	43 (51.8)	0.07
NASH	4 (17.3)	11 (13.2)	0.12
Hepatitis	B-3 (13.0)	B-9 (10.8)	0.07
Hepatitis	C-4 (17.3)	C-7 (8.4)	0.06
Others	3 (13.0)	13 (15.6)	0.08
Cause of ICU admission, n (%)			
Hepatic encephalopathy	11 (47.8)	38 (45.7)	0.07
ARDS	2 (8.6)	17 (20.4)	0.06
Pneumonia	7 (30.4)	19 (22.8)	0.14
SBP	2 (8.6)	6 (7.2)	0.06
HRS	2 (8.6)	9 (10.8)	0.09
Sepsis	14 (60.8)	37 (44.5)	0.06
Others	1 (4.3)	4 (4.8)	0.08
Child-Pugh score	11±2.3	7±3.9	0.04*
Need for mechanical ventilation, n (%)	21 (91.3)	80 (96.3)	0.11
Need for invasive monitoring, n (%)	22 (95.6)	81 (97.5)	0.14
TPN, n (%)	17 (73.9)	52 (62.6)	0.04*
Prior antibiotic usage, n (%)			
Carbapenems	12 (52.1)	14 (16.8)	0.03*
Beta-lactams	9 (39.1)	20 (24.0)	0.03*
Others	16 (69.5)	27 (32.5)	0.04*
Duration of antibiotic usage (days) (mean±SD)	6±2.7	2±1.5	0.04*
Concurrent antifungal use, n (%)	14 (60.8)	32 (38.5)	0.04*
Positive microbiology isolates in more than one body fluid, n (%)	9 (39.1)	22 (26.5)	0.06
Length of ICU stay (days) (mean±SD)	15±3.2	11±6.2	0.06
Death, n (%)	14 (60.8)	36 (43.3)	0.04*

\*P<0.05 is considered significant. MDR: Multidrug-resistant organisms; NASH: Nonalcoholic steatohepatitis; ARDS: Acute respiratory distress syndrome; SBP: Spontaneous bacterial peritonitis; HRS: Hepatorenal syndrome; ICU: Intensive Care Unit; SD: Standard deviation

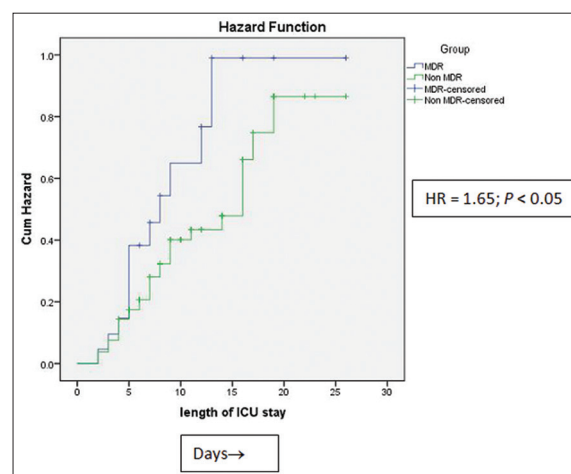
**Table 2: Multivariate analysis to identify the predictors of multidrug-resistant infection in critically ill patients with liver disease**

Variables	Factors	MDR ( <i>n</i> =23) (%)	Non-MDR ( <i>n</i> =83) (%)	OR (95% CI)	
				Unadjusted	Adjusted
Age (year)	>60	11 (47.8)	46 (55.4)	0.89 (0.32-4.27)	0.98 (0.56-2.27)
	<60	12 (52.2)	37 (44.6)	0.96 (0.43-4.21)	0.91 (0.69-3.27)
Sex	Male	16 (69.5)	52 (62.6)	1.01 (0.47-2.45)	0.95 (0.48-1.56)
	Female	7 (30.5)	31 (37.4)	1.03 (0.82-1.79)	1.06 (0.98-1.27)
Child-Pugh score	>10	15 (65.2)	46 (55.4)	2.39 (1.06-2.83)	2.29 (1.02-3.61)*
	<10	8 (34.6)	37 (44.6)	1.48 (1.07-1.95)	1.31 (1.07-1.83)
TPN	Yes	17 (73.9)	52 (62.6)	1.84 (0.45-3.49)	1.67 (1.25-2.59)*
	No	6 (26.1)	31 (37.4)	2.50 (0.80-4.84)	2.15 (1.69-2.38)*
Prior antibiotic usage	β-lactam	9 (39.1)	20 (24.0)	1.15 (1.08-1.22)	1.07 (1.14-1.36)
	Carbapenem	12 (52.1)	14 (16.8)	1.86 (1.37-2.45)	1.57 (1.45-2.06)*
	Others	16 (69.5)	27 (32.5)	1.23 (0.64-3.26)	1.33 (1.12-3.26)
Duration of antibiotic usage (days)	>7	13 (56.5)	26 (31.3)	2.37 (0.48-4.46)	2.11 (1.23-3.18)*
	<7	10 (43.5)	57 (68.7)	2.17 (1.23-5.46)	1.91 (0.96-4.12)*
Concurrent antifungal usage	Yes	14 (60.8)	32 (38.5)	3.12 (1.35-5.27)	3.26 (2.12-5.19)*
	No	9 (39.1)	41 (61.5)	2.79 (1.84-6.45)	2.14 (2.27-3.69)*

\**P*<0.05 was considered significant. TPN: Total parenteral nutrition; OR: Odds ratio; CI: Confidence interval



**Figure 2: Comparing the Intensive Care Unit survival among multidrug-resistant and nonmultidrug-resistant group. Cum survival: Cumulative survival; HR: Hazard ratio**



**Figure 3: Comparing the Intensive Care Unit death (or hazard) between multidrug-resistant and nonmultidrug-resistant group. Cum hazard: Cumulative hazard (death); HR: Hazard ratio**

use of carbapenem antibiotics, more than 7 days of antibiotic usage, TPN use, and concurrent antifungal administration were identified as independent risk factors for MDR infections in such patients. Most of the findings correlate with our existing knowledge and available evidences about MDR infections prevailing in the literature with some additional findings pertinent to those with liver disease.

The prevalence of MDR infection in our study was to be 21.6% which is comparable to the prevalence published elsewhere in the world. Fernández *et al.* reported rising prevalence of MDR bacterial infections from 10% to 23% during the period 1998–2011 in single Spanish center.<sup>[4]</sup> The prevalence was 35%–39% in the nosocomial setting and only 0%–4% in the community setting. Our study did not have the scope to estimate the prevalence in community setting.

The patients with advanced liver disease are frequently exposed to the hospital environment for treatment of various complications, and this makes them vulnerable to nosocomial infections. It has been reported in a study of 41 patients with decompensated cirrhosis and ascites who required 127 hospital admissions, 1164 occupied bed days, and 733 medical imaging sessions.<sup>[6]</sup> In another study, the frequency of unplanned hospital admissions were reportedly 24.2% within 30 days and 35.9% within 90 days among patients with three or more complications of liver cirrhosis.<sup>[7]</sup> Since the nosocomial infections have strong correlation with MDR bacteria, the patients with liver disease with a higher likelihood of nosocomial infections also have a greater preponderance to MDR infections. It is also acknowledged that patients with advanced liver disease have decreased reticuloendothelial system (RES) function

besides impairment of several components of humoral and cell-mediated immunity.<sup>[8]</sup> The preservation of a minimum volume of functioning liver is essential for RES phagocytosis to prevent the spread of microorganisms and their products into the systemic circulation. The increasing Child–Pugh score depicts a decreasing volume of functioning liver with disease severity and can be recognized as a major hindrance in the body's defense against infection.<sup>[9,10]</sup>

The increased use of carbapenem antibiotics has been associated with growing resistance to many organisms particularly *Acinetobacter*.<sup>[11]</sup> It has been reported that in comparison to other antibiotics, carbapenems increase the colonization of MDR *Acinetobacter*, MDR *P. aeruginosa*, carbapenemase-positive *Klebsiella*, and *Clostridium difficile* through collateral damage.<sup>[11]</sup> Our study found the high prevalence of all these bacterial infections and therefore can well explain the association of carbapenem usage and MDR bacterial infection. Kalpoe *et al.* found that survival rate after carbapenemase-resistant *Klebsiella pneumoniae* (CRKP) infection is significantly lower than non-CRKP infections (29% vs. 86%, log-rank  $P < 0.001$ ) in patients following liver transplant.<sup>[12]</sup> The lower survival of MDR group in our study can be explained on a similar basis.

Our study has found antibiotic usage for more than 7 days as a predictor of MDR infection. This can be explained on the basis of our understanding of horizontal genome transfer which enhances the transmissibility of plasmid-mediated antibiotic resistance.<sup>[13,14]</sup> It is recognized that such a transfer is facilitated by the prolonged duration of antibiotic use.

The most common bacteria isolated in our patients were *Klebsiella* spp. It is reported that *Klebsiella* strains have more accumulated plasmids to carry virulence and resistance genes to resist the main antibiotics such as cephalosporins, carbapenems, penicillins, aminoglycosides, or fluoroquinolones.<sup>[15-17]</sup> It is also clear that plasmids are not just carriers of antibiotic resistance genes but also genes or groups of genes that specify properties essential to the virulence of the host bacteria.<sup>[18,19]</sup>

The risk of catheter-associated bloodstream infection (CLABSI) is high after TPN, and the patients with liver disease are also no exceptions.<sup>[20,21]</sup> However, the presence of liver diseases poses extra threat due to CLABSI because of the underlying immune dysfunction, portal hypertension-related changes, poor nutrition, and gastrointestinal bleeding.<sup>[22]</sup> This explains the higher prevalence of MDR bacterial infection observed in patients with TPN usage observed in our study.

The complex interaction between antifungals and liver disease has been highlighted in many studies following a surge in the antifungal use since the past decade.<sup>[23-25]</sup> Although no studies have found any causal association between antifungal use and antibiotic resistance, some studies have observed an incidental overlapping of antibiotic and antifungal reservoirs in nonpathogenic, commensal, and environmental organisms.<sup>[26]</sup> Functional metagenomic selections have identified the existence of previously unrecognizable genes that can serve as bifunctional resistance to bacteria and fungi.<sup>[27]</sup> Still, the observations are rudimentary considering the future scope of research on this subject.

However, our study had several limitations. First, it did not identify the species types and subtypes of the bacteria. The same could have provided more vital informations pertaining to the bacteria. Second, it did not microbiologically confirm the presence or absence of fungal infection which could have improved our understanding of the concurrent antifungal infections. Third, the liver diseases had considerable heterogeneity among themselves all of which were not encompassable by the mere assessment of disease severity on the basis of Child–Pugh score. Some limitations could not be nullified. Fourth, the discontinuation of antibiotics did not follow any predictable pattern. This was not based purely on the microbiological confirmation of the absence or presence of infection but also on clinical grounds. This variable pattern of discontinuation can introduce several biases affecting study results. Finally, all methodological constraints inherent in a retrospective study can exist naturally in our study.

## Conclusion

Our study found a high prevalence of MDR infections in critically ill patients with liver disease and identified severity of liver disease, prior carbapenem use, antibiotic usage for more than 10 days, TPN use, and concurrent antifungal administration as independent predictors of MDR bacterial infections. However, larger prospective studies are required for better understanding of these factors and their implications in clinical practice.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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