Infection and Drug Resistance

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ORIGINAL RESEARCH

Treatment of Hospital-Acquired Infections in Patients with Cirrhosis – New Challenges

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Background: Hospital acquired infections (HAI) in the cirrhotic patients contribute to hepatic decompensation. With emergence of bacterial drug resistance, designing the treatment protocol of HA infection has become the foremost challenge.

Purpose: To analyze the resistance pattern of organisms isolated from hospital-acquired (HA) infections and determine appropriate antibiotics treatment protocols for these infections.

Study Design: A prospective hospital based observational study was undertaken.

Patients and Methods: The present study was conducted over 18 months at Kasturba Medical College, Mangalore, Karnataka, India. Patients with suspected HA infections were subjected to clinical, hematological and microbiological evaluation. Antibiotic sensitivity evaluation was undertaken for the bacteria isolated from these patients.

Results: During the study period, 398 patients with cirrhosis were 472 times admitted to the hospital for treatment. Out of these patients, 40 patients were diagnosed with 50 HA infections. Fifty five different organisms were isolated from these infections. It was found that these 55 bacteria isolates comprised 30 (54.54%) gram-negative (GN) and 25 (45.45%) gram-positive (GP) bacteria. Quite seriously, extended-spectrum beta-lactamase (ESBL) producers and methicillin-resistant *Staphylococcus aureus* (MRSA) were detected in 40% and 58% of GN and GP infections respectively. A total of 36 (65.4%) and (14.5%) 8 out of 55 isolated organisms exhibited multi–drug resistance (MDR) and extensive drug resistance (XDR) behavior, respectively.

Conclusion: Cirrhosis patients with HA infection possess higher prevalence of MDR and XDR infections. In such sick patients, cephalosporin and quinolones are not the appropriate empirical antibiotics. Herein, we propose a tigecycline with carbapenem like meropenem and vancomycin based empirical antibiotics protocol to be prescribed for such patients. De-escalation is advised after the culture sensitivity report is obtained.

Keywords: drug resistance, antibiotic sensitivity, nosocomial infections, tigecycline

Introduction

The severe scarring of liver also known as cirrhosis represents an immune-compromised condition where patients are predisposed to numerous infections ascribable to alterations in defense mechanisms and movement of gut flora.[1,2] Consequently, higher bacterial infections rate of 32–34% is observed in hospitals admitting cirrhotic patients as compared to 5–7% observed in general population hospitals.[3,4] Additionally, bacterial infections in patients with cirrhosis may predispose to development of hepatic decompensation.[5]

A study involving only cirrhotic patients reported that 28.3%, 40%, and 50% of MDR isolates were obtained from the emergency department, ICU and hospital ward, respectively in a hospital.[6] It has also been observed that an almost 100% increase in the rate of infections caused by MDR bacteria occurred due to the infections ascribable to ESBL-producing *Enterobacteriaceae* (ESBLE) and *Enterococcus faecium (E. faecium)*.[3]

MDR bacteria including the ESBL-E, non-fermentable GN bacteria such as *Pseudomonas aeruginosa* (*P. aeruginosa*) and MRSA are difficult to treat. The extensively drug-resistant bacteria (XDR) like the carbapenemase-producing

Received: 22 November 2021
Accepted: 2 March 2022
Published: 15 March 2022

Klebsiella pneumoniae (*K. pneumoniae*) and the vancomycin resistant *enterococci* (VRE) have recently been diagnosed among cirrhotic patients.[7]

The success of commonly used empirical antibiotic therapy has been reported to be poor in HA infections (40%), compared to community-acquired (CA) infections.[3] Treatment protocols for HA infections are difficult to design due to increased MDR infections, poor response to present therapy leading to higher septic shock and mortality rate.

In this context, the present study analyzes the patterns of resistance of organisms isolated from HA infections in cirrhotic patients and design an appropriate antibiotic treatment protocol for such infections.

Patients and Methods

The present study was undertaken at Kasturba Medical College Hospital, Mangalore, a tertiary care centre for over 18 months from 1st October 2015 to 31st March 2017. Patients above 18 years of age having chronic liver disease/cirrhosis of liver and culture-positive HA bacterial infections were included in the study.

Hospital-acquired (HA) infections, are typically developed in a patient after 48 hours of hospital admission, 3 days of discharge or 30 days after a surgical intervention at a hospital.[8] Informed consent was obtained from all the patients. The diagnosis of chronic liver disease was established by clinical profile, biochemical investigations and imaging studies. Patients who did not patient, patients with CA infections, HIV positive patients, patients on immunosuppressive therapy, other infections eg fungal, viral, parasitic infections and patients with underlying malignancy were excluded from this study.

The detailed clinical history and allied examinations were carried out for all the patients involved in the study. They were also examined in terms of routine hematological, biochemical, and microbiological work-up. On admission, ascitic fluid leukocyte count was measured in all patients having ascites and the bacterial culture was performed in a semi-automated BacTAlert (Biomerieux, France). Whenever felt appropriate and needed, blood, urine, sputum, pus, stool and bile samples from patients examined microscopic, culture and sensitivity testing. All necessary cultures were examined before administration of antibiotics to the patients. The grown organisms were identified and their sensitivity performance was studied by Vitek 2 Compact System.

Accordingly, MDR is defined as acquired non-susceptibility to at least one agent in three or more antimicrobial categories, XDR is referred to as non-susceptibility to at least one agent in all but two or fewer antimicrobial categories (ie bacterial isolates remain susceptible to only one or two categories) and pan drug resistance (PDR) is termed as non-susceptibility to all agents in all antimicrobial categories.[9]

Initially, the patients were provided supportive care and empirical broad-spectrum antibiotics were administered according to the source of infection, probable type of infection, and patient's overall status as per the antibiotic policy of the hospital. Subsequently, empirical antibiotics were replaced by sensitive antibiotics according to the culture sensitivity report.

Results

During the study period, 398 patients with cirrhosis having clinical features of infection were involved. These patients underwent 472 admissions. Of these, culture positive HA infections were detected among 40 patients. These 40 patients (36 male and 4 female) were included in our study. These 40 patients had 45 hospital admissions and 50 culture-positive bacterial HA infections were reported among them. Fifty-five organisms were isolated from these 50 infections.

Twenty five (62.5%) patients belonged to the age group of 40 to 60 years. Eleven (27.5%) patients were older than 60 years (Table 1). Jaundice and coagulopathy with prolonged INR and decreased serum albumin was observed in majority of the patients. Almost all the patients had a model for end stage liver disease (MELD) score of more than 10 and more than 80% had MELD score in excess of 15. Three fourth patients were in Child class C (74.46%) and remaining were in Child class B (25.53%) (Table 1).

Table 1 Baseline Characteristics of the Patients

Laboratory Parameter	Attribute	No. of Patients	%
Age in years (n^a =40)	≤30	1	2.5
	>30–40	3	7.5
	>40–50	9	22.5
	>50–60	16	40.0
	>60	11	27.5
Sex (n^a=40)	M	36	90
	F	4	10
Haemoglobin (g/dl) (N^b=45)	>12	5	11.1
	10–12	14	31.1
	8-<10	11	24.4
	< 8	15	33.3
Total white blood cell count (cells/mm^3) (N^b =45)	< 4000	3	6.67
	4000–11,000	17	37.8
	>11,000	25	55.5
Serum creatinine (mg/dl) (N^b =45)	<1.0	5	11.1
	>1.0–1.5	15	33.3
	>1.5	25	55.5
Serum sodium (mmol/l) (N^b =45)	>135	2	4.44
	130–135	6	13.3
	125-<130	10	22.2
	120-<125	23	51.1
	<120	4	8.9
Total serum bilirubin (mg/dl) (N^b =45)	<2	5	11.1
	2–3	10	22.2
	>3	30	66.7
International Normalised Ratio (INR) (N^b =45)	< 1.7	9	20
	1.7–2.3	11	24.4
	>2.3	25	55.5
Serum albumin (g/dl) (N^b =45)	<2.8	23	51.1
	2.8–3.5	18	40.0
	>3.5	4	8.9

(*Continued*)

Table 1 (Continued).

Laboratory Parameter	Attribute	No. of Patients	%
Model for End stage Liver Disease (MELD) score (N^b =45)	≤10	1	2.2
	>10-15	3	6.67
	>15.1	41	91.1
Child Turcotte Pugh (CTP) class (N^b =45)	Class A (<7)	0	0
	Class B (7–9)	9	20.0
	Class C (>9)	36	80.0

Notes: (N^a =40) = No. of patients, (N^b =45)= No. of hospital admissions.

Types of Infections

Among the 50 HA infections in the patients, the most common diagnosed infection (n=20/50) was urinary tract infection (UTI) followed by ascitic fluid infection (AFI) (n=9) and respiratory tract infection (RTI) (n=9). Spontaneous bacteremia (SB) and cellulitis were reported in 5 and 6 patients, respectively. One patient was even diagnosed with pyometra (Table 2).

Types of Organisms

In patients with HA infections, the 55 bacterial species which were isolated comprised 30 (54.54%) GN and 25 (45.45%) GP organisms. *Enterococcus* (n=13) was the most common organism isolated, closely followed by *Staphylococcus aureus (S. aureus)* (n=12). Common isolated GN bacteria were *K. pneumoniae* (n=11) and *E. coli* (n=10). *P. aeruginosa* and *Acinetobacter* each were isolated from 4 infections. Only 1 infection was caused by *Citrobacter*.

Among 30 GN bacterial infections, 40% (n=12) were found out to be ESBL producers. Quite interestingly, 90% *E. coli* (n=9/10) and 27% *K. pneumoniae* (n=3/11) were found to be ESBL producers. ESBL producers were isolated more commonly from AFI (n=6), followed by UTI (n=3). One case of ESBL producer was isolated from sepsis, cellulitis and pyometra each (Table 3).

MRSA was isolated in 58.33% (n=7/12) of GP infections. Two cases of AFI, SB and RTI were caused by MRSA.

Drug Resistance

In this study, a significant 36 of the 55 isolated organisms exhibited MDR whereas 8 displayed extensive XDR behaviour. All (100%) of isolated *E. coli, K. pneumoniae, Acinetobacter*, and *Citrobacter* belonged to MDR species. Ninety percent

Table 2 Types of Infections Observed Among Patients

Type of Infection	No. of Patients
UTI	20
Cellulitis	6
Spontaneous bacteraemia (SB)	5
Respiratory tract infections (RTI)	9
Ascitic fluid infections (AFI)	13
Tuberculosis	0
Other	2
Total	55

Table 3 ESBL Infections Observed Among Patients

Infections	Bacteria Species		Total
	E. coli	*K. pneumoniae*	
UTI	1	2	3
Sepsis	1	0	1
AFI	6	0	6
Cellulitis	1	0	1
Respiratory	0	0	0
Pyometra	0	1	1
Total	9/10(90%)	3/11(27.27%)	12/30(40%)

(n=27/30) of GN bacteria were found to have developed MDR. Seven *S. aureus* and eight *Enterococcus* based infections belonged to MDR category (Table 4).

Antibiotic Sensitivity

In HA infections, antibiotics such as cephalosporin (GN n= 28/30, GP n=9/12), quinolones (GN n= 26/30, GP n=25/25), carbapenem (GN n= 14/30, GP n=11/13), piperacillin - tazobactum (GN n= 18/30, GP n=10/13), and aminoglycoside (GN n= 21/30, GP n=21/25) exhibited significant resistance in both GN and GP infections (Tables 5 and 6). Tigecycline (GN n= 0/25, GP n=0/25) and colistin (GN n= 2/29) were observed to be the only two antibiotics which displayed significant sensitivity against HA infections. Tigecycline had 100% sensitivity whereas colistin had 94%. Although, most commonly administered initial antibiotics were carbapenem and piperacillin – tazobactum, significant resistance was noted for them for both GN and GP organisms in the present study. Antibiotics such as Teicoplanin (n=0/25), vancomycin (n==0/25) and linezolid (n=0/13) were tested mostly against GP infections and no resistance was noted. The following pattern of bacterial infections in different types of sepsis was found out:

Ascitic Fluid Infection (AFI)

10 patients had developed the symptoms of AFI, seven were caused due to GN while 3 were ascribable to GP bacteria. The only GN organism grown in the cultures of patients suffering from AFI was *E. coli*. Two of the patients suffering from AFI caused by GP bacteria had *S. aureus* and the remaining one had *Enterococci* infection. Six of the 7 GN

Table 4 Frequency of Drug Resistance in Isolated Organisms

Bacteria	n	MDR	XDR	PDR	Total
E coli	10	10	0	0	10
K. pneumoniae	11	6	5	0	11
Pseudomonas aeruginosa	4	1	1	0	2
Acinetobacter	4	3	1	0	4
Citrobactor	1	1	0	0	1
Staphylococcus aureus	12	7	0	0	7
Enterococcus	13	8	1	0	8
Total	55	36	8	0	44

Table 5 Drug Resistance Patterns in Isolated Gram Negative Organisms

Bacteria	n	Frequency of Resistance to Antibiotics						
		Cep	Que	PT	Car.	Amg	TG	Col
E coli	10	10/10	10/10	5/10	2/10	5/10	0/10	0/10
K. pneumoniae	11	11/11	10/11	9/11	6/11	10/11	0/11	1/11
Pseudomonas aeruginosa	4	2/4	2/4	1/4	2/4	2/4	NT	0/4
Acinetobacter	4	4/4	3/4	3/4	4/4	3/4	0/4	1/4
Citrobactor	1	1/1	1/1	0/1	0/1	1/1	NT	NT
Total	30	28/30	26/30	18/30	14/30	21/30	0/25	2/29
		93.33%	86.66%	60%	46.66%	70%	0%	6.89%

Abbreviations: Cep, cephalosporin; Que, quinolones; PT, piperacillin-tazobactum; Car, carbapenem; Amg, aminoglycoside; Tg, tigecycline; TCol, colistin; NT, not tested.

Table 6 Drug Resistance Patterns in Isolated Gram Positive Organisms

Bacteria	n	Frequency of Resistance to Antibiotics									
		Cep	Que	PT	Car.	Amg	TG	T	V	L	Col
Staphylococcus aureus	12	9/12	12/12	NT	NT	8/12	0/12	0/12	0/12	0/12	NT
Enterococcus	13	NT	13/13	10/13	11/13	13/13	0/13	0/13	0/13	NT	NT
Total	25	9/12	25/25	10/13	11/13	21/25	0/25	0/25	0/25	0/12	NT
		75%	100%	80%	84.6%	84%	0%	0%	0%	0%	–

Abbreviations: Cep, cephalosporin; Que, quinolones; PT, piperacillin-tazobactum; Car, carbapenem; Amg, aminoglycoside; Tg, tigecycline; T, teicoplanin; V, vancomycin; L, linezolid; Col, colistin; NT, not tested.

bacterial infections were seen to be ESBL producers and 2 of the 3 GP infections were attributable to MRSA. Eight of the 10 infections had developed MDR and none exhibited symptoms due to XDR.

Urinary Tract Infection (UTI)

20 patients were diagnosed with UTI. GN bacterial infection was noted in 9 of them and 11 had infections caused due to GP bacteria. The predominant GN organism grown was *K. pneumoniae* (7/9) and *Enterococcus* (10/11) was seen to be responsible for causing the most number of infections attributable to GP microorganisms. In 11 of the 20 patients, the microorganisms causing the UTI had developed MDR while, 6 developed XDR.

Respiratory Tract Infection (RTI)

Overall, ten cases of RTI were seen. Six and four of the ten infections were caused due to GN and GP bacteria, respectively. The GN organisms grown from the samples of the patients suffering from RTI were *K. pneumonia* (2 nos), and *Acinetobacter* (2 nos) and *P. aeruginosa* (1 no) and Citrobacter (1 no). *S. aureus* was the only bacterial specie causing all GP organisms associated RTI. Five of the RTI patients were infected with the microorganism exhibiting MDR and 2 displayed the symptoms of XDR.

Spontaneous Bacteremia (SB)

Five patients suffering from SB were examined, 2 were infected by GN and other 3 were infected by GP bacteria. SB infection causing GN bacteria included one each of *E. coli* and *Acinetobacter* and infection causing GP bacterium in all 3 patients was *S. aureus* only. In four of five SB cases, MDR was observed in infection causing microorganisms, however, XDR was not observed in any one of them.

Cellulitis

There were 9 cases of cellulitis; five and four of these infections were caused due to GP and GN bacteria respectively. Infection triggering GN bacteria included *E. coli* (2 cases) and one each of *K. pneumoniae, P. aeruginosa* and *Acinetobacter*. Cellulitis infection causing GP bacteria were found out to be *S. aureus* and *Enterococcus* in 2 each of four patients. In seven out of nine cellulitis cases, though the isolated microorganisms developed MDR, did not show XDR behavior.

Course in the Hospital

Twenty five of the 45 admitted patients recovered well, nine recovered partially and were discharged upon prescribing oral antibiotics. Overall 11 patients died (mortality rate of 24.5%).

Discussion

Nosocomial bacterial infections in the cirrhotic patients may contribute to decompensating events.[10] In such events, administration of adequate empirical antibiotics becomes an imperative factor. Over the last few decades, 3 major epidemiological changes of bacterial infections in patients with cirrhosis have occurred. The first change involved the development of quinolone-resistant bacteria as evinced from the faecal flora of cirrhotic patients who had received long term oral norfloxacin prophylaxis.[11,12] A relatively higher rate of infection caused by GP bacteria due to increasing use of invasive procedures and treatment in the intensive care units constituted the second change.[13] Finally, the third change was marked with the increased prevalence of MDR infections in HA infections and was seen in up to 39% of the cases.[3] This has been attributed to the emergence of infections caused by ESBL – E and *E. faecium*. The prevalence of infection caused by ESBL – E was reported to be increased from 1.2 to 7.5 to 8.7% and that by *E. faecium* from 1% to 3.7%.[3]

In our study, a remarkably high prevalence of MDR and XDR infections (80%) in patients with HA infections was found out which is 2 times higher than earlier reported study conducted during 2010 to 2012.[3] This could be ascribable to the indiscriminate use of higher antibiotics in our population and lack of adherence to antibiotic policy/guidelines. Moreover, most of the patients in this region do not undergo liver transplantation. Their health issues are managed conservatively via repeated admissions to hospitals. They may often be exposed to broad spectrum antibiotics during such hospitalizations and are prescribed first line antibiotics as chemoprophylaxis to prevent infections.[14] Consequently, their normal gut flora may have changed. The endogenous gut flora may itself contain multidrug resistant bacteria. Endogenous MDR bacteria and exogenous bacteria from the hospital environment may be the cause of higher infections in cirrhotic patients. Occurrence of such infections from MDR bacteria pose serious therapeutic challenges.

Much higher prevalence (40%) of ESBL producers in GN infections was also noticed in our studies as compared to 16% and 20% reported in earlier studies.[3,7] Third generation cephalosporin which is usually used as initial empirical antibiotic may not be very effective in such MDR resistant bacterial infections. Thus, MDR infections are associated with the increased failure of empirical antibiotic therapy. It is established from the current investigation that MDR infections in all varieties of infections, be it ascitic fluid infection, UTI, RTI etc. from various sites and sources of infection, the failure of empirical antibiotic therapy is more likely. It is recommended that empirical antibiotic therapy should be started as early as possible for bacterial infections in patients with cirrhosis.[15,16] A delay in initiating appropriate antibiotic treatment in suspected infections can subsequently culminate into increased mortality and septic shock.[17] Studies have shown that appropriate empirical antibiotic therapy is the strongest predictor of short term mortality in bacterial infections of cirrhosis.[18,19] Therefore, herein we propose a new treatment protocol based on combination of various antibiotics.

The empirical antibiotic therapy should include judicious combination of antibiotics having efficacy against both GN and GP microorganisms based infections considering the fact that in our study as many as 45% of infections were caused by GP bacteria. For example, in patients suffering from cellulitis, mere use of antibiotics with GP coverage was not adequate as up to 55% of patients with cellulitis had developed GN bacterial infections. In order to overcome this increasing failure of empirical antibiotic therapy, new guidelines have been promulgated by European association for study of liver (EASL).[20] For HA infections, a combination of antibiotics like piperacillin – tazobactum or meropenem

have been recommended with or without a glycopeptide. In areas of low prevalence infections due to MDR bacteria, piperacillin – tazobactum was recommended and carbapenem was advised only when the coverage of ESBL producing bacteria is required. Vancomycin and teicoplanin were recommended only if high prevalence of MRSA and vancomycin - susceptible *enterococci* is observed in patients. Linezolid or daptomycin was advised for patients identified with infection of high prevalence of vancomycin resistant *enterococci*. Though the guidelines published by EASL recommended carbapenems with or without glycopeptides, our study has established that carbapenems exhibited significant resistance. In our study, the two antibiotics which had very good sensitivity, namely, tigecycline and colistin having negligible resistance of 0% and 6.8%, respectively, was established. Tigecycline, a glycylcycline, has been found to be efficient against carbapenemase producing *Enterobacteriaceae*. It is also found to be effective in the treatment of other MDR pathogens including the MRSA, vancomycin sensitive *enterococci* (VSE), VRE and ESBL-producing *Enterobacteriaceae*. A combination of tigecycline (high doses) with carbapenem has also been reported to be effective in continuous infusion against XDR strains.[21,22]

Since tigecycline and colistin have exhibited low efficacy when used alone, we recommend addition of carbapenem or piperacillin-tazobactum along with these antibiotics. For GP bacteria infection coverage, all three antibiotics namely, vancomycin, teicoplanin and linezolid are effective. As 45% of our HA infections are GP, these antibiotics should be added to the initial empirical antibiotic therapy. After the availability of the report of culture and sensitivity, de-escalation of antibiotic should be carried out. HA infections are very much common in the end stage liver disease and in one large study they were reported to be responsible for 15% of infections.[23] However, in the present study, the prevalence of HA infections was 10%. The patterns of these HA infections were similar to the review article presented by Piano et al.[24] These infections are associated with poor outcomes in the form of greater AKI, extra-hepatic organ failure, ACLF and poorer survival.[20] The risk factor accounting for the development of these HA infections includes a MELD value of more than 20 with SIRS criteria and use of proton-pump inhibitors (PPI), lactulose and rifaximin. These medications apart from PPI are used when liver disease is at severe stage.[25] In these patients, a combination of inflammation, liver disease and potential alteration of gut flora is observed which predisposes to HA and ACLF.[26,27]

Conclusion

In nutshell, HA infections is a major challenge in our patients suffering from end stage cirrhosis. Empirical antibiotic therapy with third generation cephalosporin and then escalating the antibiotic later is not a good option in these very sick patients. Therefore we have designed and proposed a new antibiotic combination treatment protocol consisting of tigecycline, colistin and allied drugs. Patients should be managed aggressively at admission with higher antibiotics and de-escalation should be done when culture reports are available.

Abbreviations

NI, nosocomial infections; HA infections, hospital-acquired infections; GN, Gram negative; GP, Gram positive; ESBL, extended-spectrum beta-lactamase; ESBLE, ESBL-producing *Enterobacteriaceae*; MRSA, methicillin-resistant *Staphylococcus aureus*; MDR, multi–drug resistance; XDR, extensive drug resistance; PDR, pan drug resistance; VRE, vancomycin resistant *enterococci*; VSE, vancomycin sensitive *enterococci*; CA infections, community-acquired infections; PPI, proton-pump inhibitors; MELD, model for end stage liver disease; INR, international normalized ratio; AFI, ascitic fluid infections; RTI, respiratory tract infection; UTI, urinary tract infection; SB, spontaneous bacteremia; EASL, European association for study of liver; AKI, acute kidney injury; SIRS, systemic inflammatory response syndrome; ACLF, acute-on-chronic liver failure; CTP, Child Turcotte Pugh.

Ethics Statement

The study was approved by the institutional ethics committee (KmcMG/ETHICS/01/2017) at Kasturba Medical College Hospital, Mangalore. The study was conducted in accordance to the Declaration of Helsinki.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors declare no conflicts of interest in this work.

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