Antimicrobial Resistance among Sputum Pathogens in Post Hepatitis C Cirrhotic Patients: a Cross-Sectional Study

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Background and study aim: Cirrhotic patients are more vulnerable to bacterial infection. Pneumonia is the fourth most common infection, particularly in advanced disease. Antimicrobial resistance (AMR) has great concern among cirrhotic. The aim of this study was to characterize the AMR, distribution of bacteria isolated from chronic hepatic patients with pulmonary infections, and evaluation the antimicrobial susceptibility of bacteria isolated from sputum.

Patients and Methods: This cross-sectional observational study was carried on 98 cirrhotic patients with healthcare-associated pneumonia. Antimicrobial susceptibility testing was conducted using the Kirby–Bauer disc diffusion process according to Clinical and Laboratory Standards Institute (CLSI) guidelines for various therapeutically applicable antibiotics. Data manipulation was done using Microsoft Excel® spreadsheet.

Results: The most common organisms isolated from sputum samples in the present study were *E coli* (19.39%), *Klebsiella* spp (15.31%), *Staph aureus* (14.29%) and *Pseudomonas* (9.18%) while no growth of organisms observed in 28.58%. The antimicrobial-susceptibility for *Enterobacteriaceae* species isolated from sputum showed higher sensitivity to Imipenem (88.2%), Piperacillin – tazobactam (73.5%), and Ampicillin (70.59%) while Ceftriaxone , Ceftazidime and Cefotaxime showed higher resistance respectively (64.71%, 58.82% and 55.89%). The antimicrobial-susceptibility results for *S.aureus* species isolated from sputum showed higher sensitivity to Vancomycin (100%) followed by Oxacillin (64.29%) while Penicillin G showed complete resistance 100%, followed by Tetracycline 92.86% ,and Co- trimoxazole 85.71%.

Conclusion: Gram-negative bacteria were the cause of bacterial infections in significant proportion of patients with increased sensitivity to B-lactam antibiotics and ampicillin. However third and fourth generation cephalosporin had the higher resistance values.

INTRODUCTION

Cirrhotic patients are more vulnerable to bacterial infection which is one of the most common causes of acute liver disease decompensation and deterioration of liver functions **[1].** Every year, twenty five to thirty five percent of patients with cirrhosis become infected during the stay in the hospital. The incidence is four to five times higher in comparison to the overall population **[2].**

Gut microbiota, intestinal permeability, bacterial translocation, and cellular and humoral immune deficiency in cirrhotic patients are the mechanisms underpinning the pathogenesis of bacterial infections **[3]**. In fifty to seventy percent of cases, infections are culture positive **[4]**.

Despite the fact that the incidence of gram-positive bacteria has been increasing over the last decade due to improvements in the management and advances of liver cirrhosis with increased use of invasive procedures and extended use of antibiotic therapy and prophylaxis (mainly norfloxacin), gram-negative bacteria was the cause of bacterial infections in a significant proportion of patients with cirrhosis **[3, 5].** They have been re-emerging as a source of bacterial infections in cirrhotic patients in recent years **[5].**

In patients with cirrhosis, pneumonia is the fourth most common infection worldwide, particularly in those with advanced disease **[6]**. It is responsible for 13 percent to 48 percent of all bacterial infections, with a mortality rate of forty one percent **[6-7]**. However, the mechanism was unexplained. **[22**], and innate immune response deficiency in cirrhotic patients often contributes to deficiency of lung bacteria elimination and unregulated pro-inflammatory cytokines synthesis **[23].** Systemic inflammation has also been related to critical conditions like hepatic encephalopathy, variceal bleeding, hepatorenal syndrome as well as acute-on-chronic liver cell failure **[24-26].**

Regarding the use of newer drugs in cirrhotic patients, enhanced patient supportive care, enhanced diagnosis, and multiple prevention measures, pulmonary infection is the leading cause of death and morbidity in intensive care units (ICUs). As a result, determining the severity of the disease and the likelihood of morbidity and death in these cases at an early stage is critical **[8]**.

From the pathophysiological point of view, cirrhosis and pneumonia have an impact on one another. On the one hand, cirrhosis was linked to and associated with impaired early and late neutrophil-mediated pulmonary immunity, making infection unmanageable **[9]**; on the other hand, excessive inflammatory cascade triggered by pneumonia also cause rapid worsening and deterioration of liver functions and directly diminish anti-bacterial immunity, leading to multi-organ damage **[10]**.

The emergence of bacterial multidrug resistance, an extensive drug resistance, and even pan drug bacterial resistance, have rendered bacterial resistance to antibiotics a severe global challenge **[11]**.

For the management of infections other than SBP, only EASL 2018 strongly recommended carbapenems alone or in combination with other antibiotics in healthcare-associated infections other than SBP if high bacterial resistance to antibiotics were detected **[33]**.

Antimicrobial resistance (AMR) has caused widespread concern among the population, as commonly available antibiotics may be ineffective in treating infections caused by these microorganisms **[12]**. AMR-related morbidity, death, and duration of hospital stay of patients are all on the rise **[13, 14].** Infections caused by resistant strains are expected to kill 300 million people prematurely by 2050 **[27].** AMR is a growing source of concern around the world, as it has a negative impact on the outcome of antibacterial treatment. This is especially concerning in cirrhotic patients, who have a compromised immune system and are more at risk to infection. Infection has been found to raise the mortality rate by four fold, exceeding approximately 38% after one month **[28]**. In the treatment of cirrhotic patients, as soon as possible early diagnosis and treatment of infection is critical **[29]**.

In cirrhotic patients, first-line standard antibiotics showed rising incidence of clinical failure and bad prognosis based on the microbiological activity **[15, 16],** so another therapeutic strategy (broad spectrum antibiotics) for patients with hospital-acquired infections has been proposed **[17-18]**. The aim and the goal of this research was to assess the antimicrobial resistance and distribution of bacteria isolated from post hepatitis C cirrhotic patients with pulmonary infections, as well as to determine the antimicrobial sensitivity of bacteria isolated from sputum of these patients.

PATIENTS AND METHODS

Study design: The study was a cross sectional study.

Study settings: Our research was carried out at Tanta University hospital in Tropical Medicine and Infectious Diseases Department. This study carried out between first March 2021 and 30 of October 2021.

Inclusion criteria: All patients aged from eighteen to seventy years; with post hepatitis C liver cirrhosis and acquired pneumonia within 48

hours of admission (healthcare-associated pneumonia) were allowed to join the study.

Healthcare-associated pneumonia (HAP) may be suspected if a patient develops new symptoms and signs consistent with respiratory tract infection (fever, abnormal chest examination, purulent sputum, tachypnea, impaired oxygenation) and laboratory results consistent with inflammation (raised white cell count and C-reactive protein). However, the diagnosis of HAP also requires radiological demonstration of a new or progressive lung infiltrate.

Healthcare-associated pneumonia can be defined as pneumonia in a patient with at least one of the following risk factors:

- hospitalization in an acute care hospital for two or more days in the last 90 days;
- residence in a nursing home or long-ter m care facility in the last 30 days
- receiving outpatient intravenous therapy (like antibiotics or chemotherapy) within the past 30 days
- receiving home wound care within the past 30 days
- attending a hospital clinic or dialysis center in the last 30 days
- having a family member with known multi-drug resistant pathogens

Exclusion criteria: Patients who meet the following conditions were not enrolled in the study: (1) pregnancy, (2) Intensive care unit stay of more than twenty four hours, (3) neoplastic, (4) organ transplantation, (5) acquired immune deficiency syndrome (AIDS), and (6) Sever diseases of other organ systems (excluding complications of liver cell failure and pneumonia).

Ninety eight patients with post hepatitis C liver cirrhosis and acquired pneumonia within 48 hours of admission were enrolled in our study from Tropical Medicine and Infectious Diseases Department. Early morning sputum samples were obtained. The samples were collected randomly by simple randomization technique. All samples were immediately transported to Medical Microbiology and Immunology Department to be subjected to microscopic examination by direct Gram stain.

Sample size

In our research, we used the free sample size calculator for cross-sectional study at (http://www. raosoft.com/samplesize.html) to calculate the sample size for this study. At test power of 0.8 and confidence interval of ninety five percent, sample size was considered to be seventy four patients in our study.

Data collection procedure:

Clinical findings of hepatic cell cirrhosis, presence of portal hypertension, ultrasonography finding or computed tomography result findings, were used to diagnose liver cirrhosis. Physical signs, clinical findings of infection, and a chest X-ray were used to detect pneumonia. Furthermore, the pathogen of pneumonia was identified using blood or sputum cultures.

Early morning sputum samples were obtained. Sputum was collected in clean, wide mouth, leak proof, tightly fitted lid and disposable containers. All samples were immediately transported to Medical Microbiology and Immunology Department to be subjected to microscopic examination by direct Gram stain [20].

Culture:

All specimens of sputum were inoculated on suitable agar media nutrient agar, McConkey agar media, blood agar media and Sabouraud dextrose agar media. The plates were incubated for 24-48 hours at 37°C. Then, the isolates in the primary plates were identified by colonial morphology, Gram stain, and appropriate biochemical tests.

Antibiotic susceptibility:

Test procedure:

On Muller Hinton agar, the antimicrobial susceptibility testing was assessed using the process of Kirby–Bauer disc diffusion according to Clinical and Laboratory Standards Institute (CLSI) guidelines for various therapeutically applicable antibiotics [20].

Results of antibiotic sensitivity tests were interpreted as stated by Clinical and Laboratory Standards Institute 2018 (CLSI recommendations) **[21]**.

Statistical analysis:

Data manipulation was done using Microsoft Excel® spreadsheet. They were described as

numbers (No.), Percentages (%), Means and Standard Deviation (SD).

RESULTS:

In this cross-sectional study ninety eight cirrhotic patients with healthcare-associated pneumonia were enrolled. There were sixty three men and thirty five women. The mean age of the participating patients was 53.45 ± 11.34 years. The characteristics base lines of the studied groups were summarized in **(table 1).**

The most common organisms isolated from sputum samples of cirrhotic patients in the present study were *E coli* (19.39%), *Klebsiella spp* (15.31%), *Staph aureus* (14.29%) and *Pseudomonas* (9.18%) while no growth of organisms occurred in28.58% **(table 2).** The gram negative bacteria isolated from positive cultures consisted of 61.4% (after exclusion of 28 samples that showed no growth).

The presence of antimicrobial sensitivity for *Enterobacteriaceae* species isolated from sputum showed higher sensitivity to Imipenem (88.2%), Piperacillin – tazobactam (73.5%), and Ampicillin (70.59%) while Ceftriaxone , Ceftazidime% and Cefotaxime showed higher resistance respectively(64.71%, 58.82% and 55.89%) **(table3**).

The presence of antimicrobial sensitivity results for *S.aureus* species isolated from sputum showed higher sensitivity to Vancomycin (100%) followed by Oxacillin (64.29%) while Penicillin G showed complete resistance 100%, followed by tetracycline 92.86%, and Co-trimoxazole 85.71% **(table 4).**

The antimicrobial-susceptibility results for *Pseudomonas* species isolated from sputum were higher sensitivity to Gentamycin 88.89%, Amikacin 66.67% while Cefepime showed 66.67% resistance. Azetroname, Ceftazidime and Piperacillin showed resistance in (55.56%) **(table 5).**

The antimicrobial-susceptibility results for *Acinetobacter* species isolated from sputum were moderate sensitivity to Ciprofloxacin 50% and totally resistant to Gentamycin and Piperacillin – tazobactam, Trimethoprim - sulfamethoxazole, Amikacin, and Tetracycline **(table 6).**

Table (1): The characteristics base lines of the studied groups.

Variable	No. (%)
Age (mean ± SD, range) years	53.45 ± 11.34
Gender: Males: Females:	 63 (64.28) 35 (35.72)
Smoking: Negative Positive Ex-smoker	 50 (51.02) 45 (45.92) 3 (3.06)
Diabetes mellitus (DM) Absent Present	 63 (64.28) 35 (35.72)
Hypertension (HTN) Absent Present	 68 (69.38) 30 (30.62)
Duration of hospitalization in days: mean (SD)	8.4(5.6)
Child Pugh classification Grade A Grade B Grade C	 2(2.04) 15(15.31) 81(82.65)

Table (2): Organisms isolated from sputum samples.

Caustive Organism			No.	%
Gram –ve	*Enterobacteriaceae*	*E coli*	19	19.39
		Klebsiella spp	15	15.31
	Pseudomonas		9	9.18
	Acinetobacter spp		4	4.08
	Stenotrophomonas maltophilia		2	2.04
Gram +ve	*S. aureus*		14	14.29
Fungus	*Candida*		6	6.12
	Aspergillus		1	1.02
No growth			28	28.58
Total			98	100

Table (3) : Antimicrobial resistance pattern of *Enterobacteriaceae* in all studied groups by modified Kirby-Bauer disc diffusion method.

Antibiotic	Sensitive		Resistant		Total	
	No	%	No	%	No	%
Ampicillin	24	70.59	10	29.41	34	100%
Chloramphenicol	23	67.64	11	32.36	34	100%
Amoxacillin – clavaulonic acid	22	64.71	12	35.29	34	100%
Piperacillin – tazobactam	25	73.5	9	26.47	34	100%
Ciprofloxacin	21	61.76	13	38.23	34	100%
Ceftriaxone	12	35.29	22	64.71	34	100%
Cefotaxime	15	44.11	19	55.89	34	100%
Cefoxitin	21	61.76	13	38.24	34	100%
Ceftazidime	14	41.18	20	58.82	34	100%
Imipenem	30	88.2	4	11.76	34	100%
Azetroname	16	47.05	18	52.95	34	100%

Table (4) : Antimicrobial resistance pattern of *S.aureus in* all studied groups by modified Kirby-Bauer disc diffusion method.

Antibiotic	Sensitive		Resistant		Total	
	No	%	No	%	No	%
Penicillin G	0	0	14	100	14	100
Erythromycin	8	57.14	6	42.86	14	100
Oxacillin	9	64.29	5	35.71	14	100
Cefoxitin	7	50	7	50	14	100
Ciprofloxacin	6	42.85	8	57.14	14	100
Ciftriaxone	7	50	7	50	14	100
Co- trimoxazole	2	14.29	12	85.71	14	100
Gentamycin	3	21.43	11	78.57	14	100
Tetracycline	1	7.14	13	92.86	14	100
Vancomycin	14	100	0	0	14	100

Table (5) : Antimicrobial resistance pattern of *Pseudomonas* in all studied groups by modified Kirby-Bauer disc diffusion method.

Antibiotic	Sensitive		Resistant		Total	
	No	%	No	%	No	%
Amikacin	6	66.67	3	33.33	9	100
Ciprofloxacin	5	55.56	4	44.44	9	100
Piperacillin	4	44.44	5	55.56	9	100
Piperacillin-tazobactam	5	55.56	4	44.44	9	100
Gentamycin	8	88.89	1	11.11	9	100
Cefepime	3	33.33	6	66.67	9	100
Ceftazidime	4	44.44	5	55.56	9	100
Imipenem	5	55.56	4	44.44	9	100
Azetroname	4	44.44	5	55.56	9	100

Table (6): Antimicrobial resistance pattern of *Acinetobacter* in all studied groups by modified Kirby-Bauer disc diffusion method.

Antibiotic	Sensitive		Resistant		Total	
	No	%	No	%	No	%
Gentamycin	0	0	4	100	4	100
Ceftazidime	1	25	3	75	4	100
Ciprofloxacin	2	50	2	50	4	100
Cefepime	1	25	3	75	4	100
Piperacillin – tazobactam	0	0	4	100	4	100
Trimethoprim - sulfamethoxazole	0	0	4	100	4	100
Amikacin	0	0	4	100	4	100
Tetracycline	0	0	4	100	4	100
Imipenem	1	25	3	75	4	100

DISCUSSION

In this cross- sectional study, the most common organisms isolated from sputum samples were gram negative bacteria in 61.4% (*Enterobacteriaceae* (*E coli* (19.39%), *Klebsiella spp* (15.31%., *Pseudomonas* (9.18%)), Followed by gram positive (*S aureus* 20%). No growth occurred in twenty eight samples, this may be attributable to the fact that, cirrhotic patients are given prophylactic antibiotics. Our results were in accordance to Baijal et al. 2014 and Jalan et al., 2014 who showed high prevalence of gram negative bacteria (54% and 82.5% respectively) in nosocomial infections [**30, 3**].Our results also supported by Ekpanyapong and Reddy 2019 who indicated that the most common pathogens for nosocomial chest infections were gram-negative bacilli and *staphylococci***[34]**.In accordance to our study, Hassan et al.,2021; *Klebsiella* species (32%), *Strept.pneumoniae* (12%), and *Staph aureus* (10%) were the most commonly identified organisms in their sputum culture results **[35]**.

Owing to the high mortality associated with this complication, determining an adequate empirical antibiotic therapy for bacterial infections in cirrhosis is necessary. It is a never ending challenge because of the progressive evolution of microorganisms and their antibiotic resistances. An increase in the prevalence of multi resistant pathogens has been reported in the past few decades in hospital-acquired (HA) and in HCA infections in many countries. It is an ongoing issue **[31, 32].** So we analyzed antibiotic sensitivity pattern for the *Enterobacteriaceae* and *Pseudomonas* and the higher sensitivity towards Imipenem (88.2%), Piperacillin – tazobactam (73.5%), Ampicillin (70.59%), Gentamycin 88.89%, Amikacin 66.67% was found, however third and fourth generation cephalosporirn had the higher resistance values.

Furthermore, third-generation cephalosporins cannot be used as first-line empirical treatment in cirrhotic patients. Despite the high susceptibility

to aminoglycosides, they are rarely used due to the risk of nephrotoxicity. B-lactam antibiotics and ampicillin were recommended to be used in cirrhotic patients. Our research has some drawbacks, such as being a single-center study with a limited number of patients.

CONCLUSION

Gram-negative bacteria were the cause of bacterial infections in a significant proportion of patients with increased sensitivity to B-lactam antibiotics and ampicillin. However third and fourth generation cephalosporin had the higher resistance values in cirrhotic patients.

Acknowledgement: Declared none.

Ethical consideration

Permission and official approval to carry out the study was obtained. The protocol of the research was accepted by the Tanta University Ethical Committee (protocol number of approval is .113 / 03/ 10) and clinical trial (NCT04915573) before taking part in the study, all of the participating patients signed a written informed permission form. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki

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Conflicts of interest: None.

HIGHLIGHTS

Despite the fact that the incidence of gram-positive bacteria has been increasing over the last decade due to improvements in the management and advances of liver cirrhosis with increased use of invasive procedures and extended use of antibiotic therapy and prophylaxis (mainly norfloxacin), gram-negative bacteria was the cause of bacterial infections in a significant proportion of patients with cirrhosis so, in our research:

- Gram-negative bacteria were the cause of bacterial infections in a significant proportion of patients
- Increased sensitivity to B-lactam antibiotics and ampicillin
- Third and fourth generation cephalosporin had the higher resistance values.

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