Pattern of Infections and Drug Resistance in Cirrhosis - A Study from Tertiary Care Centre in South Kerala, India

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ABSTRACT

BACKGROUND

Cirrhosis is an immunocompromised state that predisposes patients to spontaneous bacterial infections, hospital-acquired infections, and a variety of infections from uncommon pathogens. The incidence of antibiotic resistant pathogens has been increasingly detected, especially in healthcare-associated settings. In this era of highly effective antibiotics, infections are still found to be major cause for hospitalisation and mortality in patient with CLD (chronic liver disease). Viral infections and viral translocations in cirrhosis needs more data and research to comment at present. No recent data available about bacterial infections and resistance pattern in cirrhotic patients in our region including Kerala region (South India). There is a need to produce data regarding this, which can help to identify the burden and need for newer strategies.

METHODS

This is a retrospective study conducted in Department of Gastroenterology, Pushpagiri Medical College, Thiruvalla, from September 2018 to January 2019. A preliminary chart review of 30 patients showed that 46% had SBP. Sample size calculated was 95 for alpha error of 1.96 with an absolute precision of 10%. Consecutive 100 patients (approximated sample size) admitted with culture proven infections (except in skin and soft tissue infections) were evaluated between September 2018 to January 2019. Infections were classified according to source and drug resistance. Diagnosis based on culture positivity and standard diagnostic criteria. Skin and soft tissue infections diagnosed after meticulous clinical examinations, blood investigations, cultures and ruling out other possible mimics. In view of all the variables are nominal or ordinal, significance calculated as proportions and percentages.

RESULTS

In present study, common infections were SBP (40%), urinary tract infection (UTI) (28%), skin and soft tissue infections (SSTI) (18%) and lower respiratory infection (LRTI) (12%). Enterobacteriaceae (*E. coli* and klebsiella) was found to be commonest among all infections followed by enterococcus, streptococcus, staphylococcus and candida. *Pseudomonas aeruginosa* (second isolate) isolated from patient with SSTI and aeromonas species (second isolate) was isolated from one patient with SBP. Multidrug resistance (MDR) was reported in 44 cases out of 96 total culture positive cases. Approximately about 46% of the study sample reported as MDR.

CONCLUSIONS

Most common infection found to be SBP followed by UTI, SSTIs and LRTI. Most prevalent organisms were *E. coli* and klebsiella. Prevalence of SSTI was found to be higher compared to reported literature. Drug resistance especially in klebsiella infections found to be increased compared to available studies.

KEY WORDS

CLD: Chronic Liver Disease, SBP: Spontaneous Bacterial Peritonitis, UTI: Urinary Tract Infection, LRTI: Lower Respiratory Tract Infection, SSTI: Skin and Soft Tissue Infection, MDR: Multi Drug Resistance.

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BACKGROUND

In this era of highly effective antibiotics, infections are still found to be major cause for hospitalisation and mortality in patient with CLD (chronic liver disease). Since few decades there are several improvements seen in management of infections in these patients but it continues to be the major fraction of mortality among these patients.[1]

Cirrhosis is an immunocompromised state that predisposes patients to spontaneous bacterial infections, hospital-acquired infections, and a variety of infections from uncommon pathogens.[1]

Once infection develops, the excessive response of pro-inflammatory cytokines on a pre-existing hemodynamic derangement in cirrhosis further facilitate the development of severe complications such as septic shock, acute-on-chronic liver failure (ACLF), multiple organ failure, and death.[2]

The incidence of antibiotic resistant pathogens has been increasingly detected, especially in healthcare-associated settings. Preventive measures, early detection, and proper management are necessary to minimize morbidity and mortality. [2,3]

Mechanism of increased susceptibility and vulnerability to infection in patients with cirrhosis found to be multifactorial predominantly involves immune dysfunction, bacterial translocation (BT) and associated systemic response. [2,3] Immune dysfunction affected in many ways,

1. Natural barriers – Oedematous and thin skin, altered mucosal permeability, altered bacterial flora and GI mucosal ulcerations.
2. Hepatic RES activity- Decreased Kupfer cell number and activity
3. Defence mechanisms-decreased RES activation, decreased chemotaxis and phagocytic activity
4. Alteration in housekeeping serum factors-Decreased complement levels, opsonin activity, proteins, coagulation factors and anticoagulation factors
5. Treatment related-Increased invasive /therapeutic procedures, catheters, frequent hospitalisation, immunosuppressives, proton pump inhibitors, antibiotic usage
6. Nutritional- Protein energy malnutrition, sarcopenia, frailty.

Migration of viable native bacteria from gut lumen through systemic circulation *via* mesenteric lymph nodes (MLN) and portal vein is defined as the bacterial translocation in cirrhosis. This happens in healthy individuals too, but the intact immune system prevents the systemic effects of this process.[4-6] The diagnosis of BT relies on the isolation of viable bacteria in MLN, while the detection of bacterial DNA in serum or ascitic fluid can be considered as surrogated marker.[4-8]

BT is mostly associated with bacterial infections predominantly spontaneous bacterial peritonitis (SBP) than other infections.[4,5] The translocated bacterial or pathogenic products will stimulate the immune-inflammatory system which lead to circulatory dysfunction, end up with complications.[4] BT more seen in patients with decompensated stage but studies showed that it starts in early stages of disease. [4,6]

Epidemiology of Infections in Cirrhosis

Infections accounts for about 40%-50% death in patients with cirrhosis.[9,10,11] Infections present in 30%-34% of hospitalized patients with cirrhosis, which is 4-5 folds higher than hospitalized patients in general population.[9,10]

Spontaneous bacterial peritonitis (SBP) (25%-31%), urinary tract infection (UTI) (20%-25%), pneumonia (15%-21%), bacteraemia (12%), and soft tissue infection (11%)[3,12] are found to be common infections detected in cirrhotic patients. The major causative organisms are gram-negative bacteria, *e.g*., *E. coli*, klebsiella spp. and enterobacter spp., whereas gram positive bacteria, especially enterococci and *Staphylococcus aureus*, comprise about 20% and anaerobes only 3%.[3,12] Risk factors of infection by gram positive bacteria are recent or current hospitalization, receiving quinolones prophylaxis, and invasive procedures.[11-13]

Fungal infections are comparatively low but produce more severe infections and high mortality. Fungal infections include candidiasis (oral, skin, oesophageal), UTI and SBP are increasingly detected in hospitalised patients. Viral infections and viral translocations in cirrhosis needs more data and research to comment at present.

It is very difficult to differentiate infection from non-infectious inflammatory response in cirrhosis but which is the crucial point in managing the condition. There are several markers (ferritin, CRP, PCT) are studied but none of them found clinically useful. Because of most of the infections have subclinical presentation, clinical and available markers are not useful.[14]

The LPS or endotoxin is the main component of Gram-negative bacteria (section of the outer membrane) and is a marker when detected in the systemic circulation.[14,15] LBP is an acute-phase protein produced by hepatocytes in response to bacteraemia and endotoxemia. The LPS-LBP complex binds to CD14 in myeloid cells and promotes the systemic inflammatory response. [14-16] Circulating and peritoneal fluid fragments of bactDNA is also considered as newer marker of infection. Its detection by the polymerase chain reaction (PCR) is associated with a systemic inflammatory response and poor prognosis of liver disease.[7,15]

Bactericidal/permeability increasing protein (BPI) is a protein found in neutrophils that has endotoxin-binding and neutralization capacity and plasma BPI levels correlated with TNF-α. Anti-neutrophil cytoplasmic antibodies (ANCA) comprise a family of antibodies that recognize diverse components of neutrophil granulocytes are also under research as biomarker of infections in cirrhosis.[17,18] Newer markers are shown better results compared to older ones. Availability of these newer markers are issue in clinical setup where we are in short of time and financial burden.

Most important strategy of sepsis management in CLD is the use of antimicrobials. Newer antimicrobials are very potent compared to the older generation but still it's difficult to manage infections due to the acquired antimicrobial resistance. Multidrug resistance organisms (MDR) are defined by an acquired non susceptibility to at least one agent in three or more antimicrobial categories.[19] Extensively drug resistant (XDR) are defined by non-susceptibility to at least one agent in all but two or fewer antimicrobial categories and pan drug resistance (PDR) is defined by resistance to all drug categories.[19,20]

No recent data available about infections and resistance pattern in cirrhotic patients in our region including Kerala region (South India). There is a need to produce a data regarding this which can help to identify the burden and need for newer strategies.

Objectives

1. To determine pattern of infections by anatomical locations and microbes among in-patients admitted with liver cirrhosis
2. To describe drug resistance pattern of infections among in-patients admitted with liver cirrhosis.

METHODS

This retrospective study was conducted in the Department of Gastroenterology, Pushpagiri Medical College, Thiruvalla. Consecutive 100 patients admitted with culture proven infections (except in skin and soft tissue infections) were evaluated between September 2018 to January 2019. Infections were classified according to source and drug resistance. Diagnosis was based on culture positivity and standard diagnostic criteria. Skin and soft tissue infections diagnosed after meticulous clinical examinations, blood investigations, cultures and ruling out other possible mimics. Culture positive without any evidence of other infections classified as bacteraemia alone group. All patients included in study were decompensated /advanced chronic liver disease (CHILD B/C).

Statistical Analysis

All the variables are nominal or ordinal and were summarised as frequency and proportions. For the proportion of patients with infections in different anatomical locations, 95% confidence intervals were drawn.

RESULTS

In present study, common infections were SBP (40%), urinary tract infection (UTI) (28%), skin and soft tissue infections (SSTI) (18%) and lower respiratory infection (LRTI) (12%).

Infections	Proportion	95% CI	
		Lower	Upper
SBP	40%	30.4%	49.6%
UTI	28%	19.2%	36.8%
SSTI	18%	10.5%	25.5%
LRTI	12%	5.6%	18.4%
Bacteremia alone	2%	0%	4.7%

Table 1. Proportion of Patients with Infections in Different Anatomical Locations (N=100)

Enterobacteriaceae (*E. coli* and klebsiella) was found to be commonest among all infections followed by enterococcus, streptococcus, staphylococcus and candida. *Pseudomonas aeruginosa* (second isolate) isolated from patient with SSTI and aeromonas species (second isolate) was isolated from one patient with SBP. Common microbial agents and resistance pattern depicted in Fig 1.

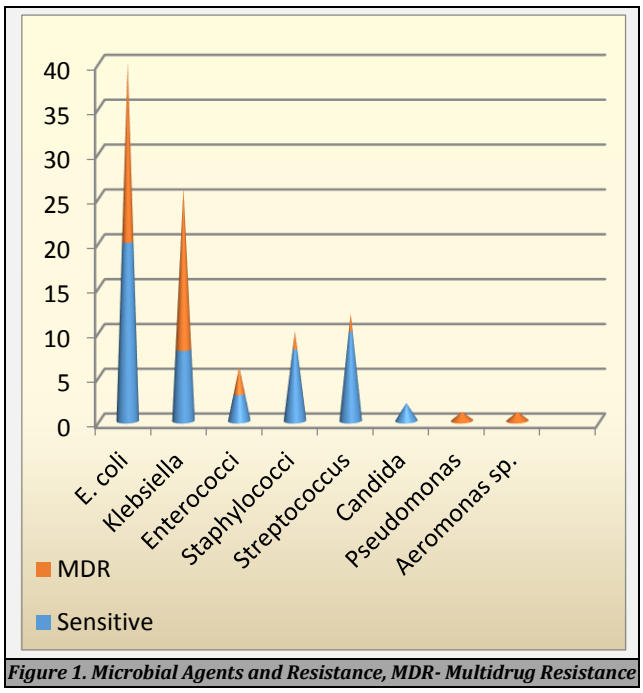

Figure 1. Microbial Agents and Resistance, MDR- Multidrug Resistance

Spontaneous bacterial peritonitis consists of 40 % of infections. *E. coli* isolated from 23 patients and klebsiella from 15 patients, are found to be the commonest among all. Microbial agents and its resistance pattern depicted in Fig 3.

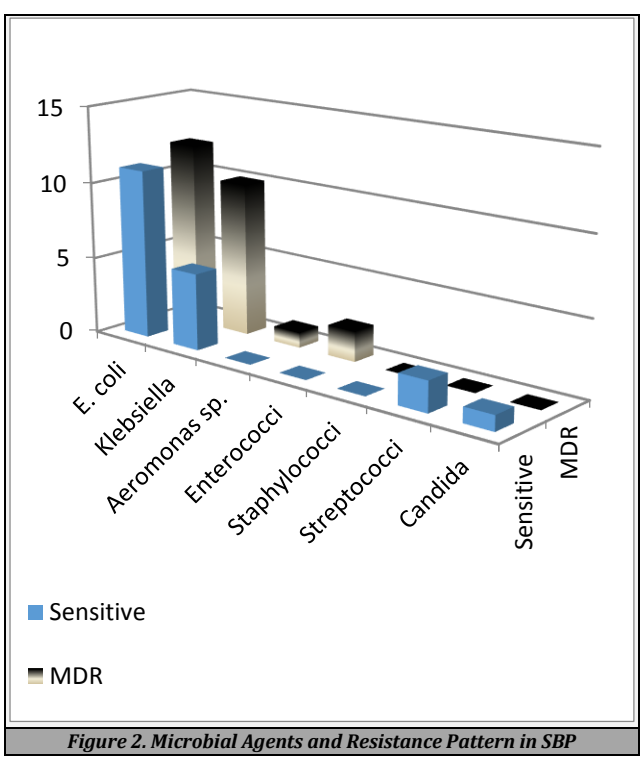

Figure 2. Microbial Agents and Resistance Pattern in SBP

MDR- Multidrug Resistance

UTIs found to be second commonest infection in our study, which consists of 28 % of all the infections. *E. coli* and klebsiella are detected in major portion of patients, 16 and 8 patients respectively.

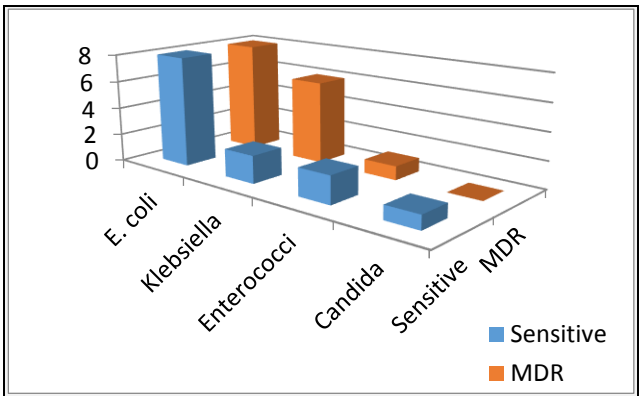

Figure 3. Microbial Agents and Resistance in Urinary Tract Infection

Skin and soft tissue infections diagnosed among 18 out of 100 patients. Most of the culture showed gram positive organisms (staphylococcus and streptococcus). 2 cultures showed gram negative organisms (*E. coli* and klebsiella, one each). SSTI diagnosed as per culture and clinical criteria, among 18 patients, 14 diagnosed with culture & sensitivity and 4 patients diagnosed purely on clinical criteria and expert opinion. Resistance among organisms less compared to other infections. Microbial agents and its resistance pattern in SSTI are given in Fig 4.

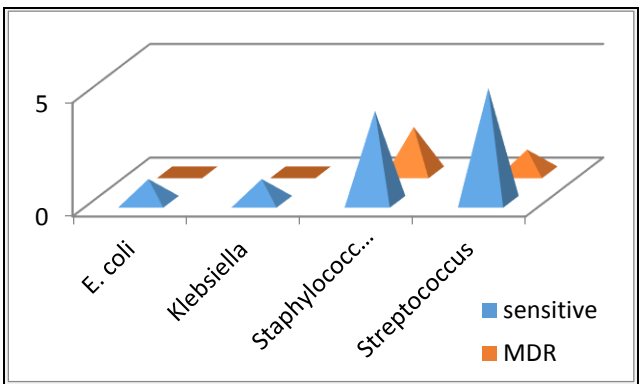

Figure 4. Microbial Agents and Resistance Pattern in SSTI

LRTIs is found to be fourth common infection among cirrhosis. 12 among 100 patients diagnosed as LRTI. In this study, upper respiratory infections, those who treated with antibiotics outside, viral infections and negative sputum culture patients are excluded. Predominantly cultured gram-positive organisms (6 among 10 patients). Microbial agents and resistance patterns in LRTI are depicted in Fig 5

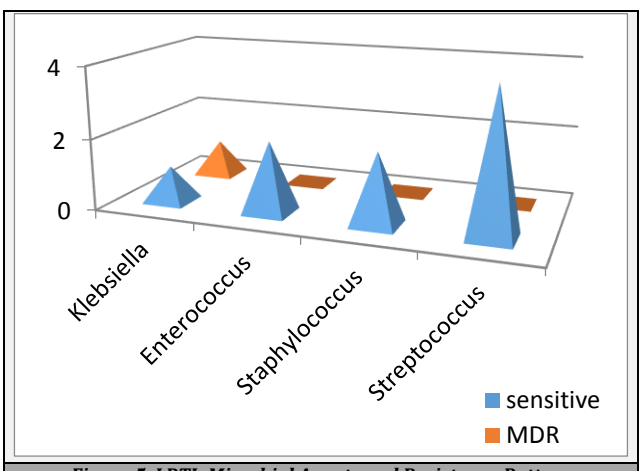

Figure 5. LRTI- Microbial Agents and Resistance Pattern

Multidrug resistance was reported in 44 cases out of 96 total culture positive cases. Approximately about 46% of the study sample reported as MDR.

Infection	SBP		UTI		SSTI		LRTI		Bacteremia			
Organism	s	m	s	m	s	m	s	m	s	m	Total	MDR
E. coli	11	12	8	8	1	0	0	0	0	0	40	20
Klebsiella	5	10	2	6	0	1	1	1	0	0	26	18
Enterococci	0	2	2	1	0	0	2	0	0	0	6	3
Staphylococci	0	0	0	0	4	2	2	0	2	0	10	2
Streptococci	2	0	0	0	5	1	4	0	0	0	12	1
Candida	1	0	1	0	0	0	0	0	0	0	2	0
Total	**40**		**28**		**14(14+4*=18)**		**12**		**2**		**96**	**44**

Table 2. Summary of Findings

(*4 patients are diagnosed without culture report)
s-sensitive; m-MDR

DISCUSSION

SBP (25%-31%), UTI (20%-25%), pneumonia (15%-21%), bacteraemia alone (12%), skin and soft tissue infection (11%) are found to be commonest infections as per previous studies. [3,12] In our study SBP (40%), UTI (28%), SSTI (18%) and LRTI (12%) showed as the commonest infections. In comparison with the available data, our study shows increased incidence of SSTIs and lower incidence of LRTI. As per available data, major causative organisms are gram-negative bacteria.[3] In the present study also gram-negative bacteria (*E. coli* and klebsiella) are found to be commonest. MDR infections found to be compared to available data,[20] consists about 46% over all infections. Among individual microbial agents klebsiella infections are more shown to be MDRs, approximately 69% followed by *E. coli* (50%) and enterococci (50%). In staphylococci, streptococci and fungal infections, proportion of MDRs were low. The results of the current study, which derive from a single-centre experience with a specific epidemiological pattern of multi-resistance, cannot be generalized to any hospital. Several reports and unpublished observations from other groups indicate that the increased rate of infections by multi-resistant bacteria becoming an emerging problem in cirrhosis. [20-21] The use of third-generation cephalosporins and long-term norfloxacin prophylaxis are probably important factors in its pathogenesis. Currently, we have no drugs to prevent bacterial translocation other than oral antibiotics. On the other hand, the diagnostic capacity of the current markers of bacterial infection in cirrhosis is low [22] and many noninfected patients receive antibiotics, thereby increasing antibiotic pressure over the endogenous flora and inducing the emergence of resistant strains.

CONCLUSIONS

Most common infection found to be SBP followed by UTI, SSTIs and LRTI. Most prevalent organisms were *E. coli* and klebsiella. Prevalence of SSTI was found to be higher compared to reported literatures. Drug resistance especially in klebsiella infections found to be increased.

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