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Microbiological Spectrum, Antibiogram and Bacteraemia in Biliary Tract Infections- A Study from Tertiary Centre of North India

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Objectives: The present study was undertaken to understand the microbiological profile, clinical presentation, associated bacteraemia and present antibiogram pattern of various isolates from patients with biliary tract infection admitted in a tertiary care centre in India.
Methods: In this retrospective study, Bile samples were collected from adult patients admitted in our hospital and were processed as per standard protocol. The results were interpreted as per Clinical Laboratory Standards Institute (CLSI) 2020 guidelines. Bacterial isolates were categorised as MDR and PDR as per CDC.
Results: 326 bile samples were sent for aerobic culture and susceptibly testing. 197 (60.42%) of these samples were culture-positive, and the remaining 129 (39.57%) were sterile in nature. A total of 289 pathogens were isolated; *Escherichia coli* (37.37 % n=108) was predominant, followed by *Klebsiella pneumoniae* (25.60%, n=74). 170 (60.49%) isolates were resistant and the remaining 111 (39.50%) were susceptible to various drugs tested. 27 ESBL producing strains of *E.coli(n= 20)* and

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Klebsiella spp (n= 7) and 21 CRE producing strains of E coli (n= 12) and Klebsiella spp(n=9) were reported . 5 isolates of *Klebsiella* spp. and a single E.coli were PDR and susceptible to colistin (MIC =0.5 mcg/ml) by microbroth dilution test.

Conclusion: The soaring rates of infection mainly by gram-negative bacteria are a red flag with the emergence of multidrug resistant organisms and change in the anti-microbiological spectrum and pattern of biliary tract infections, there is an urgent need for the empirical and prophylactic antimicrobial therapy in every clinical setting.

Keywords: Biliary tract infections; cholecystitis; cholangitis; pan drug resistance; multi drug resistance; extended-spectrum beta-lactamase producing organism.

1. INTRODUCTION

The bile is a sterile sample, but stasis caused by obstruction of biliary tree increases the chances of cholangitis [1]. The bacterial colonization is mainly due to the presence of gallstones within either the gallbladder or biliary tract [2]. In certain clinical conditions, such as acalculous cholecystitis, previous biliary interventions and underlying conditions, such as biliary strictures, primary sclerosing cholangitis, cholangiopathy and presence of biliary parasites, are associated with high rates of bacteriobilia [2]. Extensive bacterial proliferation and an increase in ductal pressure may be the result of acute cholangitis and infection. In these cases, the clinical range of presentation is very diverse and can vary from a local biliary infection to an advanced disease, which leads to complications such as sepsis, multiple organ dysfunction syndrome, and death [3].

The most common pathogenic organisms associated with biliary tract infections are bacterial gram-negative organisms. Infectious etiologies caused by gram-positive and anaerobic organisms are uncommonly reported, and viral and fungal etiological agents are extremely rare [4]. The most common organisms isolated in bile are *Escherichia coli*, *Klebsiella* spp., *Enterococcus* spp., *Streptococcus* spp., *Enterobacter* spp., *Pseudomonas* spp., and *Candida* spp. [1,2,3,4]. Although the microbiological spectrum of cholangitis has not significantly changed in the past years, the treatment guidelines have seen a huge shift with the emergence of multidrug resistant organisms. The definitive management of cholangitis involves drainage of blocked biliary tract with antimicrobial coverage [5]. Thus, in the selection of effective empirical therapy in clinical setting, the resistance pattern of the organisms should be considered to prevent the unnecessary use of broad-spectrum antimicrobial drugs and to promote antimicrobial stewardship [3].

Therefore, the present study was conducted in the northern part of India to understand the microbiological pattern, clinical presentation, and antibiogram profile of biliary tract infection, as well as bacteremia associated with it, in patients admitted in a tertiary care center and to understand the changing etiological and antimicrobial patterns over time.

2. MATERIALS AND METHODS

This is a descriptive, hospital-based, retrospective study conducted from 1 April 2020 to 30 April 2021 at the department of clinical microbiology in a tertiary care center in New Delhi, India.

As part of the routine clinical procedure, bile samples were collected from admitted adult patients (aged > 18 years) with biliary tract infection; the bile samples were processed according to the standard protocol [6]. The samples were aseptically collected, transported, and processed within 1 h after the collection. The samples obtained directly were inoculated on 5% sheep blood agar and MacConkey agar & enrichment was done on Brain Heart Infusion Broth (BHIB) was inoculated as enrichment media. Subculture of BHIB was performed after overnight incubation (18–24 h) on 5% sheep blood agar and MacConkey agar. The inoculated plates were incubated at 37 °C for 18–24 h and observed for their growth and types of colonies. Grams smear was made from the colony and processed accordingly to identify their microbial etiology (bacteria and yeast), and their antimicrobial susceptibility testing was conducted using VITEK-AST systems (bioMerieux, USA). The antibiotics evaluated were as follows: for Enterobacteriaceae, the antibiotics were amikacin (30 µg), amoxicillin (30 µg), ampicillin (10 µg), cefoperazone/sulbactam (75/30 µg), cefotaxime (30 µg), cefuroxime (30 µg), ciprofloxacin (5 µg), co-trimoxazole (25 µg), gentamicin (10 µg), meropenem (10 µg), and

piperacillin/tazobactum (100/10 µg). For *Pseudomonas aeruginosa*, the antibiotics that were tested were amikacin (30 µg), aztreonam (30 µg), cefoperazone/sulbactam (75/30 µg), ceftazidime (30 µg), ciprofloxacin (5 µg), gentamicin (10 µg), meropenem (10 µg), and piperacillin/tazobactum (100/10 µg). For *Enterococcus* spp., ampicillin (10 µg), chloramphenicol (30 µg), ciprofloxacin (5 µg), erythromycin (15 µg), gentamicin (30 µg), linezolid (30 µg), piperacillin/tazobactum (100/10 µg), teicoplanin (30 µg), tetracycline (30 µg), ticarcillin/clavulanic acid (75/100 µg), and vancomycin (30 µg). The colistin susceptible isolates by VITEK-2 were confirmed for their minimum inhibitory concentrations (MIC) of colistin (Sigma-Aldrich) using the microbroth dilution method.

The results were interpreted as per Clinical & Laboratory Standards Institute guidelines [7]. The bacterial isolates were categorized as multidrug resistant (MDR) and pandrug resistant (PDR) according to the definitions specified by Centers for Disease Control and Prevention (CDC) : MDR was defined as being nonsusceptible to at least one agent in three or more antimicrobial categories, whereas PDR means being nonsusceptible to all agents in all antimicrobial categories [8].

3. RESULTS

In the study period, 326 bile samples were sent to the clinical microbiology laboratory for aerobic culture and susceptibly testing; 197 (60.42%) of these samples were culture-positive, and the remaining 129 (39.57%) were sterile in nature. The bile culture positivity was almost equal in both genders (48% in males and 53% in females). The culture positivity was highest in the age group of 41–50 years, and the highest preponderance was observed in the mean age of 43 years. A total of 289 pathogens were isolated; *E. coli* (37.37%, n = 108) was predominant, followed by *Klebsiella pneumoniae* (25.60%, n = 74). The microbiological spectrum of biliary tract infections is presented in Fig. 1. Other common organisms isolated were *Pseudomonas* (18.33%, n = 53), *Enterococcus* (10.38%, n = 30), *Citrobacter* (1.38%, n = 4), methicillin-resistant *Staphylococcus aureus* (MRSA) (2.07%, n = 6), and *Acinetobacter* (2.07%, n = 6) species. Among the isolated *Candida* species (2.76%, n = 8), an equal distribution of both *Candida albicans* (1.38%, n = 4) and non-*Candida albicans* (1.38%, n = 4) was observed.

The antimicrobial susceptibility pattern over the years (Fig. 2) shows overall resistance to various antibiotics. An increase in emerging PDR/MDR pathogens was noted very clearly. Among the 281 bacterial pathogens tested for their antimicrobial susceptibility, 170 (60.49%) isolates were resistant, and the remaining 111 (39.50%) were susceptible to various antimicrobials tested. A total of 27 extended-spectrum beta-lactamases (ESBLs) producing strains of *E. coli* (*n = 20*) and *Klebsiella* spp. (n = 7) and 21 carbapenemase-resistant enterobacteriaceae (CRE) producing strains of *E. coli* (n = 12) and Klebsiella spp. (n = 9) were also reported in this study, in which 5 isolates of *Klebsiella* spp. and 1 isolate of *E. coli* were PDR and susceptible to colistin (MIC = 0.5 mcg/mL) using the microbroth dilution test. Furthermore, all the MDR isolates were found to be susceptible to imipenem and tigecycline. The resistance pattern among the ESBL-positive *E. coli* and *K. pneumoniae* belonged to cephalosporins, penicillins, quinolones, monobactams, beta-lactam inhibitors, aminoglycosides, and trimethoprim/sulfamethoxazole. The antimicrobial drug susceptibility patterns of Enterobacteriaceae, *Pseudomonas aeruginosa*, and *Enterococcus* spp. are presented in Figs. 2, 3, and 4, respectively.

Clinical information of some the patients (n = 113/197) with biliary tract infections are presented in Table 1, whereas the correlation between biliary tract infection and blood culture positivity is presented in Table 2.

4. DISCUSSION

The microbial spectrum and antimicrobial susceptibility profile of bile samples are helpful in making treatment decisions. Infected bile is an important risk factor for sepsis, bacteremia, and surgical site infections [9]. Most common microorganisms causing biliary tract infections like various bacterial and candidal species have often exhibited increased drug resistance over the years [3]. Hence, the current retrospective study was conducted to evaluate the scope of microbial etiology and their antimicrobial resistance pattern using various biliary samples along with the underlying clinical etiology and corresponding blood culture correlation.

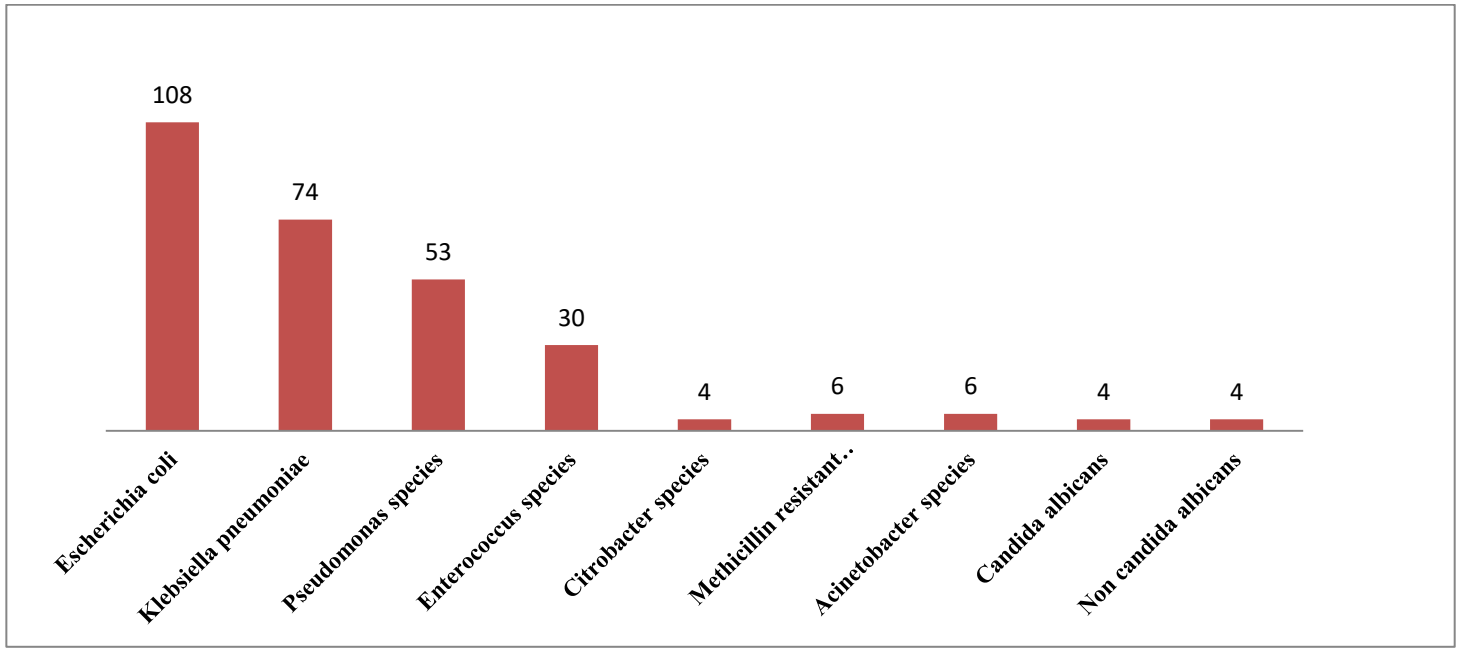

Fig. 1. Various microbiological etiologies of biliary tract infections (n = 289)

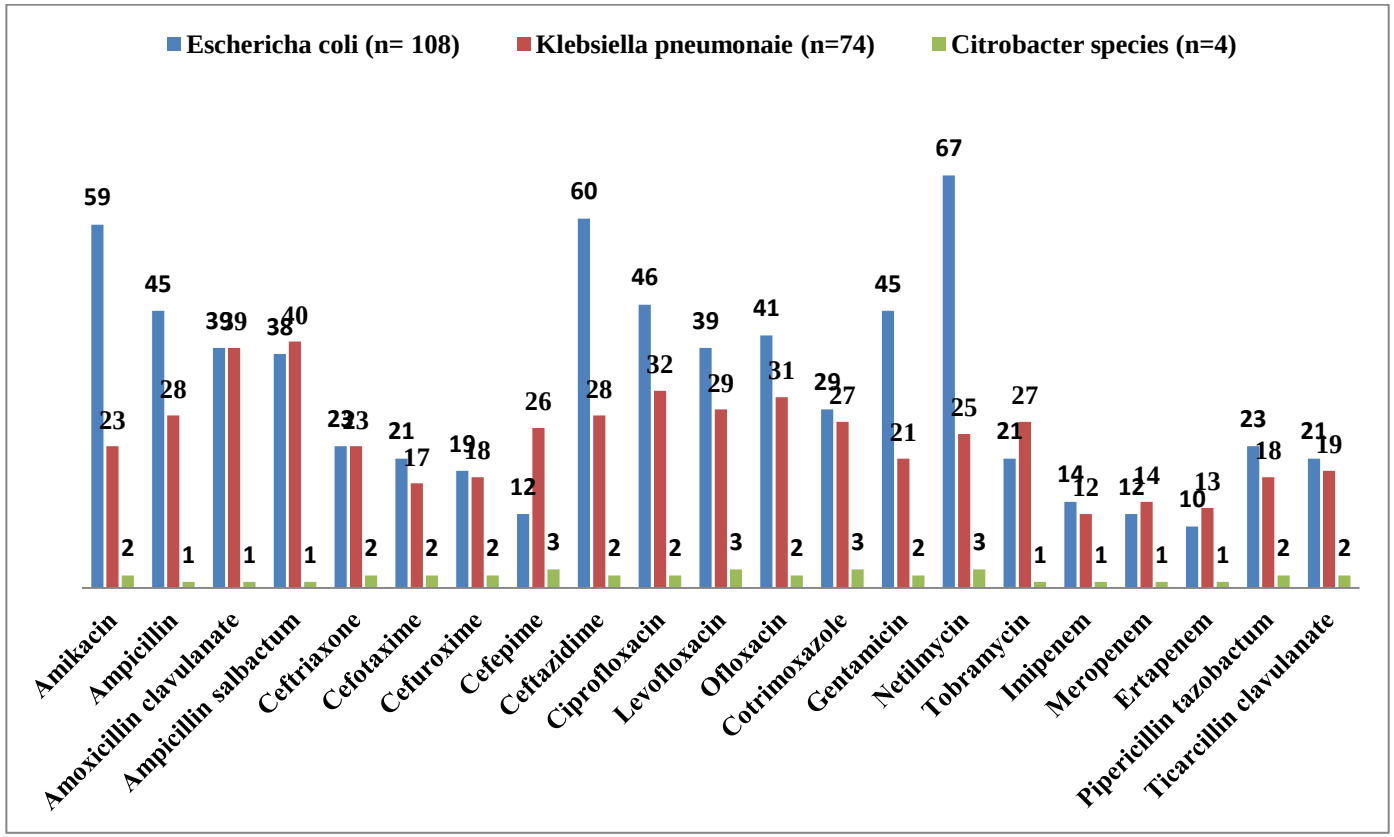

Fig. 2. Antimicrobial resistance pattern of Enterobacteriaceae

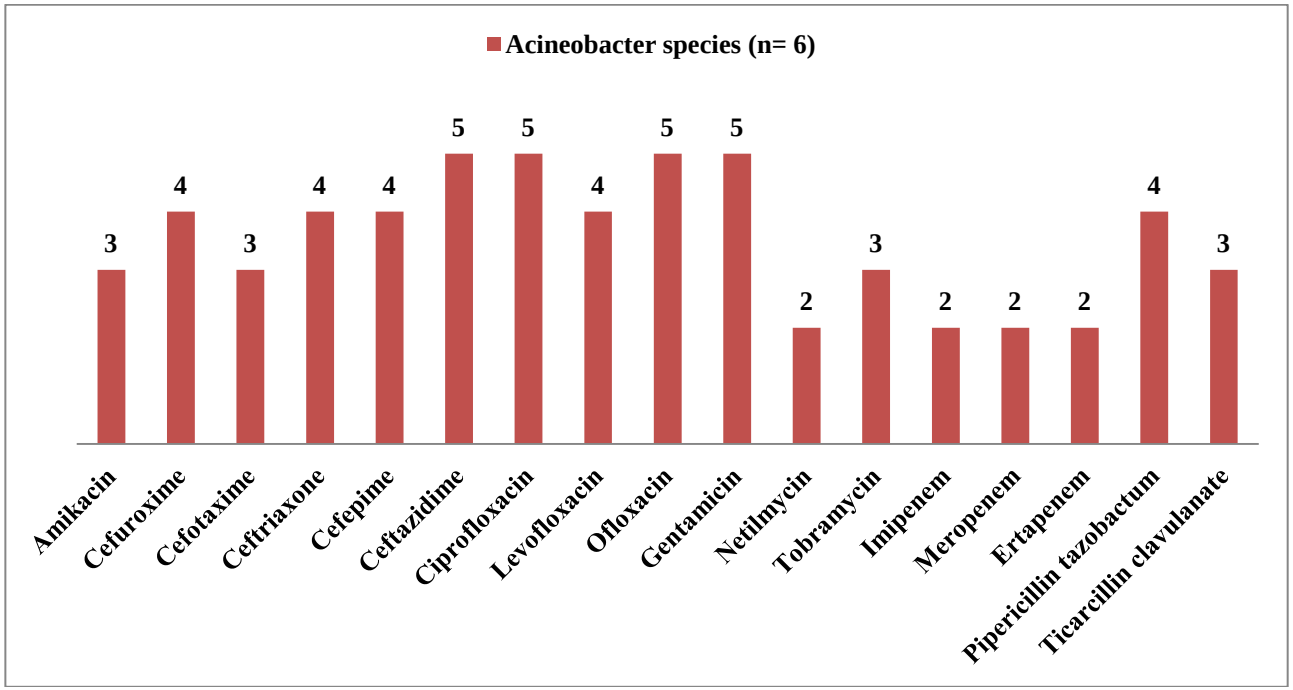

Fig. 3. Antimicrobial resistance pattern of non-fermenting organisms

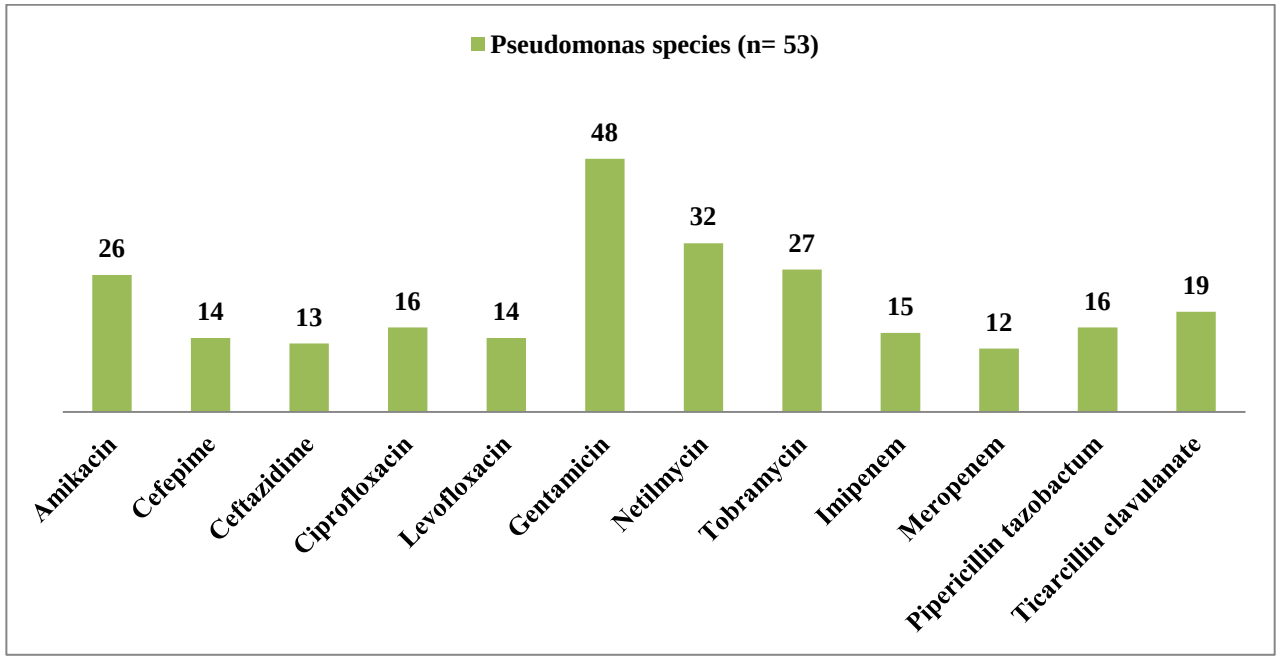

Fig. 4. Depicts antimicrobial resistance pattern in non-fermenting organisms

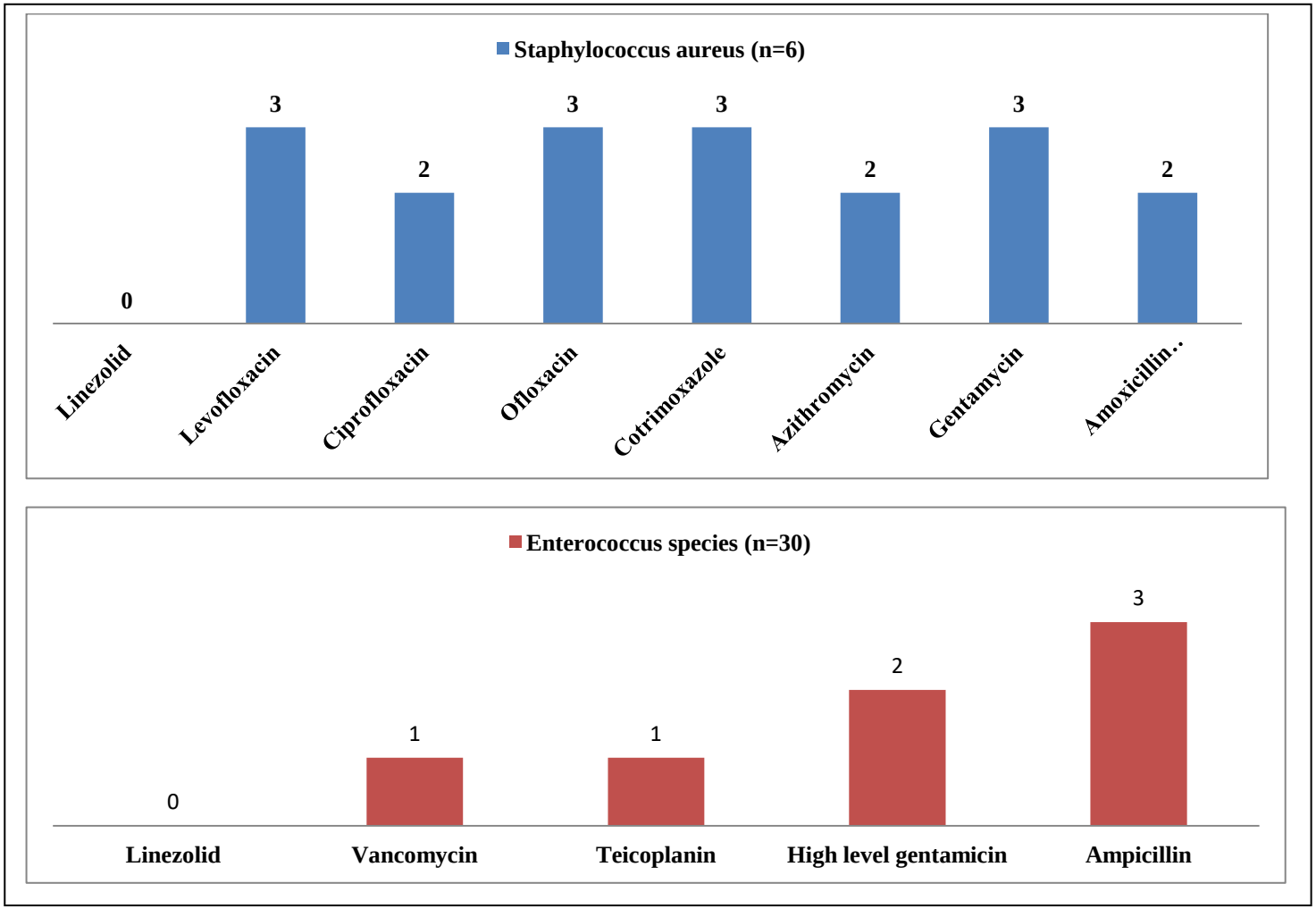

Fig. 5. Antimicrobial resistance pattern of gram-positive organisms

Table 1. Clinical diagnosis of biliary tract infections

Clinical Diagnosis of biliary tract infections	Number (n = 113)
Cholecystitis with CBD calculi	12
Cholangitis	3
Cholangiocarcinoma with cholangitis	1
Acute calculus cholecystitis	9
Cholangitis	3
Cholelithiasis	4
Choledochal cyst	2
CBD calculi with cholangitis	1
Carcinoma – head of pancreas	3
Choledocholithiasis with cholangitis	5
Obstructive jaundice	7
Acute cholecystitis	13
Obstructive jaundice	2
Malignant biliary obstruction with cholangitis	4
Cholecystitis	32
Chronic cholecystitis	12

Table 2. Blood culture profile of patients with bactobilia and fungobilia

	No. of isolates
Total blood culture and sensitivity requested	89/197 (45.17%)
No. of positive blood cultures (bacteremia)	25/89 (28.08%)
Distribution of isolates	
1. Escherichia coli	12/25 (48%)
2. Klebsiella pneumoniae	8/25 (32%)
3. Enterococcus species	3/25 (12%)
4. Pseudomonas species	2/25 (8%)

The bile positivity rate in our institute was 60.42%, which was higher compared with those of Kaur D et al. (44%) and Fan et al. (23%–46%); however, almost similar rates were observed by Ballal M et al. (60.91%) and Shenoy et al. (56%) [10,11,3,12]. In our study, the highest number of cases (38.07%, 75/197) was in the age group of 41–50 years, with a mean age of 43 years, whereas in the study conducted by Kaur D et al. (2015) [10], maximum age group involved was 51–60 years, while Capoor M et al. [2] median age of the patients studied was 41 years and the male/female ratio was 0.48, similar to our study. Similar findings were obtained in prior Indian studies [13] and Kaya et al. (53.7 ± 17.5 years) [14].

In our study (Fig. 1), the mono-microbial culture positivity was approximately 76.64%, with *E. coli* (37.37%) and *Klebsiella* species (25.60%) being the most prevalent pathogens. This finding is in agreement with those in the studies conducted by Ballal M et al. (80.7%), Kaur D et al. (86%), and Kaya et al. (95%) [3,10,14]. Mono-microbial organism infections pose a challenge in the selection of empirical and prophylactic antimicrobial drug therapy due to the preponderant coverage of either one of gram-negative or gram-positive organisms but generally not both [15].

In our study, the gram-negative enteric organisms accounted for 95.13% of the isolates (Fig. 1). *E. coli* (37.37%, 108/289) was the most common isolate, followed by *Klebsiella pneumoniae* (25.60%, 74/289) and *P. aeruginosa* (18.33%, 53/289). Similar results were obtained in a study conducted by Kumar P et al., with the highest prevalence seen in *E. coli* at 60.71% [16]; in the study by Wu et al. the highest prevalence was observed in *E. coli* at 33.5% [17]; in Suri et al. *E. coli* at 53.84% [18]; and in Bae et al. *E. coli* at 25% [19].

Gram-positive enteric organisms accounted for 12.42% of the isolates with *Enterococcus species* isolated in 10.38% (30/289) cases, followed by MRSA in only 2.07% (6/289) cases. On the other hand, Kumar P et al. [16] isolated *Enterococcus* species in 14.28% and *S. aureus* in 10.71%. Wu Zn et al. [17] isolated gram-positive organism in 26.1% of cases and were

Enterococcus species. Suri et al. [18] isolated *S. aureus* in 19.23%, and Bae et al. [19] isolated *Enterococcus* species in 13.4% and *coagulase-negative staphylococcus* (CONS) in 9.7% of cases.

The microbial profile was a little different in some of the authors. Vaishnavi et al. [13] isolated 5.8% of *Salmonella species* from the 445 bile samples obtained from patients with biliary disease requiring biliary drainage during their hospital stay. Kumar P et al. isolated *Salmonella species* in 7.14%, unlike in our study. *Aeromonas hydrophila* (n = 2) was isolated from bile as mono-microbial pathogen by Ballal M et al. [3]. Okumura K et al. [20] presented a rare case of *A. hydrophila* sepsis and acute suppurative cholangitis in an elderly patient with gallstones and rheumatoid arthritis to whom tocilizumab was administered. *Aeromonas* species infection in acute suppurative cholangitis (2.9%, 30/1445) was also observed by Chan FK et al. [21]. Bae et al. isolated CONS in 9.7% of cases [19]. *Stenotrophomonas maltophilia* (0.5%, 1/187), an unusual pathogen, was isolated along with *Pseudomonas aeruginosa by* Ballal M et al. [3]. Papakdikas et al. also reported *Stenotrophomonas maltophilia* as a causative organism in a case of cholangitis [22]

In our study, *Candida* species (2.76%, 8/289) were found to be predominant in polymicrobial infection along with commonly isolated bacterial organisms. Some of the major risk factors of the presence of *Candida* in bile are multiple surgical interventions, biliary stenting after malignant strictures, etc. [23]. Isolation of *Candida* species from biliary sample may be a colonizer or a contaminant, not a pathogen always. Hence, the clinical condition of the patient must be considered before starting the administration of antifungal agents to prevent cholangiosepsis [23]. A similar distribution of *Candida* species was also observed by Ballal M et al. (8.02%, 15/187) [3].

The increase in antimicrobial resistance (PDR/MDR) over time is a wake-up call for everyone. The empirical use of broad-spectrum antibiotics may be one of the major contributing factors for increasing antimicrobial resistence. Therefore, narrow-spectrum antimicrobials should be used to prevent the occurrence of added superinfection and treatment failure. Furthermore, it is necessary to know the common etiological agents of biliary tract infections as well as their antimicrobial susceptibility and resistance pattern to ensure appropriate and timely administration of empiric, prophylactic, and therapeutic antimicrobial therapy [23,15].

In the present study, 19.75% (48/243) of gram-negative isolates were MDR, whereas 2.44% (6/243) were PDR in nature. About 100% of the MDR strains were susceptible to tigecycline and imipenem. The strains exhibited higher susceptibility pattern to amikacin and carbapenems, whereas cephalosporins, fluoroquinolones, piperacillin/tazobactam, and cefoperazone/sulbactam demonstrated low susceptibility (Fig. 2, Fig. 3). Similar results were also obtained by Kaya et al. [14], with high sensitivity to amikacin (86%), carbapenems (83%), and piperacillin/tazobactam (61%) but low susceptibility to ampicillin (21%) and cefotaxime (14%). Even other Indian authors like Kaur D et al. and Ballal M et al. obtained similar results, which indicated that drug-resistant pathogens were susceptible to amikacin and meropenem [10,3,24]. All the gram-positive organisms were sensitive to linezolid, and one strain of vancomycin- and teicoplanin-resistant *Enterococcus* species was reported. Similar findings were observed in a study conducted by Bae EK et al. [19].

The screening and microbiological susceptibility analysis of various biliary tract infections, especially candidiasis, revealed to be most common in patients with underlying risk factors and diseases (Table 1) or in patients receiving long-term antimicrobial therapy or in immunocompromised patients as this factor may be significant in choosing the appropriate anti-mycotic therapy. Due to resource limitations, we could not perform antifungal susceptibility testing on all the strains; however, echinocandins demonstrated activity against most *Candida* species . A positive culture is more common in acute clinical conditions compared with chronic disease in patients with an obstructed cystic ducts with stones, strictures, etc. in approximately 75%–100% of cases [25,26].

The exact source of biliary tract infection may sometimes be difficult to trace. Ascending infections from the intestines and duodenum may be one of the reasons [26]. Gram-negative septicemia following biliary infection commonly occurs after surgical invasive procedures. In our study, only in 45.17% of cases (Table 2), parallel blood culture samples were sent for culture sensitivity along with bile samples. Among these

samples, 28.08% were culture-positive for *Escherichia coli* in 48% followed by *Klebsiella pneumoniae* in 32%. Underlying conditions, such as shock or sepsis, organ failure, and wound abscess, may be complicated by the presence of positive biliary infection [27].

One of the limitations of this study was that it was conducted in a single tertiary care hospital, and the study duration was only 1 year. Anaerobic culture sensitivity and antifungal susceptibility patterns could not be investigated due to the lack of resources in our setup.

5. CONCLUSION

In conclusion, in the present study, gram-negative bacteria were the most common isolates in bile. These bacteria exhibited high resistance to commonly used antimicrobials, such as fluoroquinolones, cephalosporins, and aminoglycosides. Early suspicion and routine culturing of bile samples obtained from patients with biliary tract infections of various etiologies are necessary. The increasing rates of infection mainly by gram-negative bacteria are considered a red flag. Therefore, initiation of antimicrobial therapy is important as soon as culture reports or the clinical condition of patient forewarns us. With the emergence of MDR organisms and change in the anti-microbiological spectrum and patterns of biliary tract infections, there is an urgent need for empirical and prophylactic antimicrobial therapy in every clinical setting.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

INFORMED CONSENT

Authors have obtained the informed consent from patients.

ETHICAL APPROVAL

Permission from the institutional ethics committee to use hospital data was obtained.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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