ORIGINAL ARTICLE

ANTIBIOTIC SENSITIVITY SPECTRUM OF ACUTE BACTERIAL CHOLANGITIS: TRENDS FROM A TERTIARY REFERRAL CENTER IN PAKISTAN

Muhammad Abdurrahman Butt[1], Maahin Manzoor Khan[1], Myyra Omar[1], Muslim Atiq[2], Maaz Bin Badshah[2], Mohammad Salih[2], Mehwish Rafique[2], Muhammad Usman[2], Syed Murtaza Kazmi[2]

[1]Shifa College of Medicine, Islamabad-Pakistan
[2]Shifa International Hospital, Islamabad-Pakistan

Background: Significant morbidity can arise from acute bacterial cholangitis. Key to improving outcomes is the implementation of aggressive antibiotic therapy and prompt biliary decompression through either endoscopic or percutaneous means. However, the challenge in treating these infections is amplified by the evolving patterns of antimicrobial resistance, particularly when determining the appropriate empiric therapy. **Methods:** The present study was conducted at Shifa International Hospital in Islamabad. The patients with the diagnosis of Acute bacterial cholangitis between July 2016 and June 2022 were included. Data was analyzed using SPSS-26.0 to identify any significant associations or correlations among the study variables. **Results:** A total of 144 patients with a diagnosis of acute bacterial cholangitis were included in the study. 51 of these patients had a positive blood culture. The most commonly identified organism was *E. coli,* followed by *Klebsiella pneumonia, Pseudomonas aeruginosa, Proteus, Enterococcus spp* and others. Antibiotic sensitivity pattern revealed resistance to Ceftazidime in 87%, Piperacillin-Tazobactam in 63.7%, Ertapenem in 34.4%, Meropenem in 26.1%, Imipenem in 25.0% and Colistin in 16.1%. **Conclusion:** A high resistance pattern for antibiotics was observed in our study. This might, in turn, represent the prior judicious use of antibiotics in our community hospitals before these patients are referred to a tertiary referral center.

Keywords: Antibiotic Resistance; Acute Cholangitis; Bacterial Cholangitis; Antibiotic Stewardship

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INTRODUCTION

Acute cholangitis represents an infectious process involving the biliary tree, extending from the extrahepatic bile ducts to the common hepatic duct and the common bile duct (CBD). The pathophysiology of the disease involves duct obstruction, resulting in bile stasis. Stagnant bile allows intestinal microorganisms to ascend from the duodenum, causing local inflammation. This leads to increased biliary tract pressure and damage to the biliary epithelium, allowing bacterial invasion into the systemic circulation and triggering a systemic inflammatory response.[1]

Clinical signs and symptoms of acute cholangitis vary depending on the severity of the disease. Patients typically present with Charcot's triad, characterised by high fever lasting more than 24 hours, right upper quadrant pain, and jaundice. As the disease progresses, patients may exhibit Reynolds pentad, which includes hypotension and altered mental status in addition to Charcot's triad.[2]

Diagnosis of acute cholangitis is made using the Tokyo Guidelines TG18 scoring system, which is highly sensitive and specific.[3] Blood cultures and bile cultures are important diagnostic tools in acute cholangitis to identify the causative organism and initiate appropriate antibiotic therapy. Definitive treatment involves relieving the cause of bile stasis. However, empirical antibiotic therapy is crucial to limit disease spread and complications. Antibiotics may be adjusted based on the results of blood and bile cultures if necessary.[4,5]

In blood cultures, the causative organism of acute cholangitis is typically a single organism, whereas bile cultures often report polymicrobial infections. This should be considered when selecting appropriate empirical antibiotic therapy.[6] Studies have consistently shown that gram-negative enterobacteria are the most common causative agents in bile cultures, followed by gram-positive organisms. Gram-negative organisms are highly sensitive to imipenem, amikacin, and gentamicin, while resistance is observed against cefepime, ceftriaxone, and cefixime. Gram-positive organisms have shown sensitivity to imipenem, vancomycin, clindamycin, and rifampin, but resistance to fluoroquinolones and penicillin.[7]

Several studies have repeatedly identified three organisms as the most common causes of acute cholangitis: *E. coli*, *Klebsiella spp*., and *Enterococcus spp*. The risk of infection with resistant strains depends on individual patient factors and region-specific resistance patterns. Carbapenems are the safest choice against resistant gram-negative rods. Considering these factors, the Tokyo guidelines recommend empirical treatment with third-generation cephalosporins, piperacillin/tazobactam, or carbapenems.[1]

MATERIAL AND METHODS

We conducted a retrospective, single-centre study at a Tertiary care hospital in Pakistan to investigate patients diagnosed with Acute Bacterial Cholangitis. Our primary objective was to assess the spectrum of antibiotic sensitivity and regional trends in this patient population.

The dataset for this study comprised patient data spanning from July 2016 to June 2022 and was extracted from electronic medical records. To retrieve data on patients with acute cholangitis, we utilised the ICD-10 coding system. Based on the data obtained using the following coding system, our initial sample consisted of 384 patients diagnosed with acute bacterial cholangitis. In our analysis, we included patients who satisfied the diagnostic criteria specified in the Tokyo Guidelines 2018 for acute cholangitis. Additionally, we included patients who had positive blood cultures and/or bile cultures obtained via endoscopic or percutaneous sampling. Exclusion criteria for our study involved cases with diagnoses other than cholangitis, inconsistent clinical and laboratory records, as well as patients below the age of 18 years. Patients whose sensitivity analysis of blood and bile culture were not available were also excluded.

Data collection in our study was facilitated through the utilization of a standardized questionnaire. Our data collected encompassed various factors, including age, sex, comorbidity, laboratory data (including microorganism evaluation, sensitivity, and resistance pattern of the identified microorganism), severity and causes of cholangitis, history of prior and current biliary drainage and interventions, duration of hospitalization, and previous antibiotic use. To assess the spectrum of antibiotic sensitivity, we performed susceptibility testing using the Disk Diffusion Method & Minimal Inhibitory Concentration (MIC) through VITEK 2, Agar Dilution and Novel Screening Agar method. The sensitivity and resistance of individual microorganisms to antibiotics were assessed based on the institute's established antibiogram (Figure 1), which served as a reference for determining their susceptibility to different antibiotics. To assess the sensitivity and resistance of microorganisms according to the antibiogram study Clinical & Laboratory Standards Institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) criteria were both considered.

The statistical analysis was conducted with the support of a designated research centre at a tertiary care hospital. The analysis utilised SPSS version 26, and key associations relevant to the study were identified through the utilization of the Pearson Chi-squared test. Associations with a significance level of $p<0.05$ were considered statistically significant. This study was approved by the Ethical Committee at Shifa International Hospital.

RESULTS

A total of 144 patients met the inclusion criteria of this study. Among them, 83 (57.6%) were male and 61 (42.4%) were female. The mean age of the patient population was 60.2±18.6 years (17–97). The mean length of hospital stays for patients admitted with Acute Bacterial Cholangitis was 5.31 days±3.96 (1–22) days. Out of the 144 patients, 7 (4.9%) died during their hospital stay.

Blood cultures were performed on 108 patients. Of those, 51(47.2%) blood cultures yielded growth. Out of the positive blood cultures, 12 samples (23.5%) were polymicrobial. *E. coli* was the most commonly identified organism with 30 samples (58.8%) showing growth of this organism. Among these 30 samples, 6 (20%) were identified as Multi-Drug Resistant (MDR) strains, while 16 (53.3%) were identified as Extended Spectrum Beta-Lactamase (ESBL) strains. *Pseudomonas aeruginosa* was found in 7 (13.7%) blood samples, and among those 7 samples, 1 (14.3%) was identified as an MDR strain of Pseudomonas. Klebsiella was identified in 6 samples (11.8%), of which 3 (50%) were MDR strains and 3 (50%) were ESBL strains. *Proteus spp*. were identified in 3 (5.9%) of the positive samples, while Enterococcus spp. were identified in 1 (2.0%) of the positive blood cultures. Additionally, 15 (29.4%) of the positive blood cultures yielded other organisms, including Group D Streptococcus, *Staphylococcus epidermidis*, *Streptococcus anginosa*, *Citrobacter freundii*, *Streptococcus pneumoniae*, *Morganella morgani*, *Citrobacter koseri*, *Bacteroides spp*., and *Ralstonia*.

Out of the positive blood cultures, 10 samples (19.6%) were of MDR species, while 19 samples (37.3%) included ESBL species.

Bile cultures were performed on 12 patients, and 9 samples showed the growth of organisms. Among these, *Klebsiella pneumoniae* was the most prevalent;

and identified in 4 samples (30.8%). All 4 of these samples were identified as MDR strains. Three (25%) of the bile samples yielded growth of *E. coli*, and among them, 1 (8.3%) was identified as an ESBL variant. One (8.3%) sample each yielded growth of *Pseudomonas aeruginosa* and *Enterococcus spp*. Other organisms found in bile cultures included Enterobacter, methicillin-sensitive *Staphylococcus aureus*, and an MDR strain of Acinetobacter.

Antibiotic sensitivity spectra were analysed for positive blood cultures, revealing antibiotic resistance trends in the organisms. Antibiotic resistance was identified for Ceftazidime, Piperacillin-Tazobactam, Ertapenem, Meropenem, Imipenem, and Colistin in 87%, 63.7%, 34.4%, 26.1%, 25.0% and 15.6% of these samples respectively (Figure 2). Individuals who had prior biliary intervention were more likely to be infected with MDR strains of *E. coli* (p=0.026), Proteus species (p=0.033), and polymicrobial strains (p=0.040).

Table-1: Organisms Identified on Blood Cultures*

Organism	Isolated (%)	MDR strain (%)	ESBL strain (%)
E.Coli	30 (58.8)	6 (20%)	16 (53.3%
Klebsiella Spp.	6 (11.8)	3 (50%)	3 (50%)
Pseudomonas Aeruginosa	7 (13.7)	1 (14.3%)	0 (0)
Enterococcus	1 (2.0)	0 (0)	0 (0)
Proteus	3 (5.9)	0 (0)	0 (0)
Others	15 (29.4)	N/A	N/A
*The figures in these tables take into account polymicrobial cultures			

Table 2: Antibiogram

Antibiotic	Sensitive (%)	Resistant (%)	Intermediate (%)
Piperacillin-Tazobactam	13 (29.5)	28 (63.7)	3 (6.8)
Colistin	19 (59.4)	5 (15.6)	8 (25.0)
Ertapenem	5 (15.6)	11 (34.4)	16 (50.0
Meropenem	33 (71.7)	12 (26.1)	1 (2.2)
Imipenem	35 (72.9)	12 (25.0)	1 (2.1)
Ceftazidime	5 (10.9)	40 (87.0)	1 (2.1)

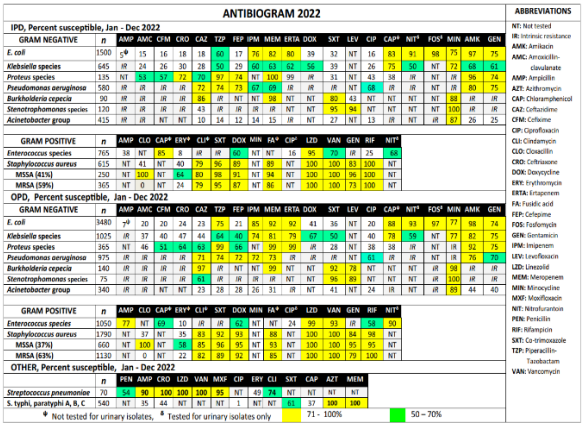

Figure-1: Institutional Antibiogram

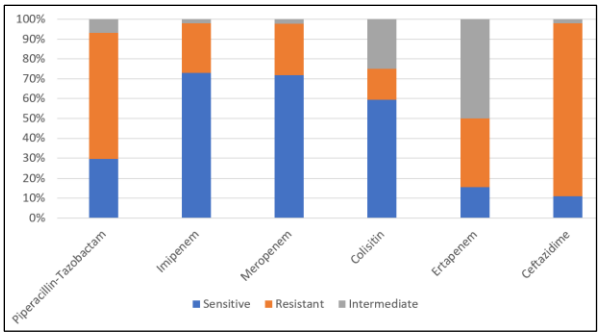

Figure-2: Antibiotic Sensitivity Spectrum

DISCUSSION

In light of current literature and guidelines, empirical treatment of Acute Bacterial Cholangitis consists of Antipseudomonal Penicillins, Carbapenems, and 3rd generation cephalosporins.[1] These antibiotics have proven to be effective treatments for this condition. However, as antimicrobial resistance is an ever-evolving challenge, the results of our study indicate that the common causative organisms of this condition are developing resistance to these first-line drugs.

In our study, the most commonly isolated organisms on blood cultures were gram-negative rods; including *E.Coli*, which constituted more than half of the identified organisms, followed by Klebsiella Species. Other species that were identified included but were not limited to, *Pseudomonas aeruginosa*, *Proteus Spp*, and *Enterococcus*. Around one-fifth of E.Coli were Multi-Drug Resistant (MDR) strains, whereas approximately half of the identified *Klebsiella Spp* were MDR. The isolation of Extended Spectrum Beta Lactamase (ESBL) Strains was also quite notable with almost half of the identified species of *E.Coli* and Klebsiella identified as ESBL (Table 1). Similar trends were seen in another study which also reported *E. Coli* and Klebsiella species as the most common organisms for acute bacterial cholangitis.[7]

Quite interestingly, and yet alarmingly, we noted a higher trend in antibiotic resistance patterns in patients with bacterial cholangitis (Figure 1) when compared with institutional antibiogram, collaborating data from all infections (Figure 2). The reason behind the unsynchronous pattern is not entirely clear at this point.

Biliary obstruction usually sets the stage for bacterial growth into the bile fluid. Frequently, biliary obstruction results from choledocholithiasis, benign biliary stenosis, anastomotic strictures and malignancy.[8]

One of the more daunting findings in this study was the finding of high resistance to agents like Piperacillin-Tazobactam and Ceftazidime. More than three-fifths of organisms reported resistance to Piperacillin-Tazobactam, whereas approximately more than four-fifths reported resistance to Ceftazidime (Table 2). Compared to previous studies, our study documents a high antimicrobial resistance in all those antibiotics that

have previously shown remarkably low rates of resistance, particularly the Carbapenems and the 3rd generation cephalosporins such as Ceftazidime.[1,5,6] This could partly be attributed to the general lack of regulation on antibiotic use. However, in our specific setting, this could be related to the fact that a substantial number of patients are being transferred from other health facilities; and have already been administered antibiotics.

One of the more significant findings of our study was that there was a statistically significant association between infections with certain organisms and patients who had undergone prior biliary intervention. Patients who had undergone previous biliary intervention were more likely to have experienced acute bacterial cholangitis with MDR strains of *E.Coli*, Proteus, and Polymicrobial organisms. A study in China determined that *Enterococcus faecium* was the most common organism responsible for acute bacterial cholangitis in patients who underwent ERCP.[9] The Biliary Tree is traditionally considered sterile.[10] Prior biliary interventional procedures, particularly Endoscopic Retrograde Cholangiopancreatography (ERCP) with biliary stenting, can introduce bacteria into the biliary tree. With these findings at hand, we must encourage the judicious use of antibiotics, according to international guidelines' especially since antibiotic resistance is becoming rampant both at the national and international levels. Effective antibiotics of today, which provide excellent broad-spectrum coverage, will be rendered ineffective if they are not used properly. In light of our findings, consideration should be made to treat patients with acute bacterial cholangitis and a prior biliary intervention with a broader spectrum of activity to tackle the increased risk of infection with resistant organisms or polymicrobial infections.

One of the major limitations of our study was insufficient follow-up data for patients who were discharged in critically ill conditions due to various reasons like socioeconomic conditions, refusal of treatment or request for a transfer to other centres.

CONCLUSION

Antibiotic resistance is a global threat, as first-line antibiotics used to treat Acute Bacterial Cholangitis, are experiencing significantly decreased effectiveness. Moreover, our study found that patients who had undergone previous biliary intervention were more likely to have MDR strains of E. coli, Proteus spp, and polymicrobial infections.

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AUTHORS' CONTRIBUTION

MAB: Contributed to study design, data collection, analysis and manuscript writing. MMK: Contributed to study design, data collection and manuscript writing. MA: Supervisor and principal investigator- contributed extensively to the study design and writing of the manuscript. MO: Contributed to study design, data collection and manuscript writing. MR: Contributed to study design and data analysis. MBB: Contributed to writing and editing of the manuscript. MS: Contributed to writing and editing of the manuscript. MU: Contributed to study design, writing and editing of the manuscript. MK: Contributed to writing and editing of the manuscript.

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Address for Correspondence:
Dr Muslim Atiq, Professor of Gastroenterology, Shifa International Hospital, Islamabad-Pakistan
Cell: +92 300 856 9030
Email: atiqsm@gmail.com