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Resistance Trend, Antibiotic Utilization and Mortality in Patients with *E. coli* Bacteraemia

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Abstract

BACKGROUND: Incidence of bacteraemia and driving concerns about antibiotic resistance is increasing globally. Risk factors for developing antimicrobial resistance are antibiotic overuse, incorrect dosing and extended duration of administration.

AIM: This study was conducted to examine the prescription and susceptibility pattern of antibiotics in bacteraemia patients with ESBL producing and Non-ESBL-producing *E. coli* and their correlation with mortality.

METHODS: Data were collected from medical records of the patients aged 18 years and above, diagnosed with E. coli bacteremia from January 2013 through July 2017. Institutional ethics committee approval was obtained before the study (IEC 483/2017). Cumulative sensitivity/resistance pattern of isolated microorganisms and DDD/100 bed days of prescribed antibiotics were obtained.

RESULTS: 182 cases of *E. coli* bacteraemia were reviewed. 59.9% (n = 109) were male with an age range of 20-90 years. The mortality rate was 24.9% (n = 44). 55.5% (n = 101) of the isolated organisms were ESBL-producing. A high percentage of resistance to cephalosporins and fluoroquinolones were observed among the patients, and most of the identified isolates were sensitive to the aminoglycosides, carbapenems and β-lactam and β-lactamase inhibitor combinations (BLBLIs).

CONCLUSIONS: Frequent utilisation of the high-end antibiotics and increase in microorganism's resistance to different antibiotics can lead to a worrisome level. Local antibiotic resistance data and consumption policy are essential to prevent and slow down this process. We observed a descending resistance trend for amoxicillin-clavulanic acid combination in our setting to both the ESBL producing and non-producing.

Introduction

Antibiotic resistance can be considered as one of the most critical public health issues in the world [1]. There are different risk factors for developing antimicrobial resistance. Antibiotic overuse, incorrect dosing and extended duration of administration can be among the most important ones [1], [2], [3], [4]. We observe a more challenging situation in less developed countries. In several studies, the inappropriate antimicrobial prescription was observed among the primary care physicians [5], [6], [7], [8] and development of bacterial resistance increases the challenges faced by the physicians to treat the patients [9], [10], [11].

Pathogenic *Escherichia coli* (*E. coli*) can cause serious diseases, such as urinary tract infections(UTIs) and bacteraemia [12], [13], [14], and incidence of bacteraemia increasing globally [15]. Bacteria which can usually develop the more serious disease is ESBL (Extended-spectrum β-lactamases) producing *E. coli*. ESBLs are enzymes that can hydrolyse penicillins, aztreonam and cephalosporin's [16]. These ESBL producing bacteria showed lesser acceptable clinical outcome in comparison to susceptible (non-ESBL producing bacteria) bacteria [17], [18], [19], [21], which can be related to delay in appropriate antimicrobial treatment to some extent

[22], [23], [24]. The high rate of clinical successes was observed in existing literature with carbapenems administration for ESBL producing bacteria [25], [26], [27], [28]. On the other hand, the use of Cephalosporins [29] and β-lactam–β-lactamase inhibitor combinations [28], [30] have also been suggested recently with ESBL-positive isolates if MICs are below clinical breakpoints. Moderate to high in vitro activity of piperacillin-tazobactam (PTZ) against ESBLs is suggested by several studies [31], [32], [33]. Equivalence between PTZ and carbapenems in the treatment of ESBL infection was demonstrated in some studies [17].

This study was conducted to examine the prescription and susceptibility pattern of antibiotics in bacteraemia patients with ESBL producing and Non-ESBL-producing *E. coli* and their correlation with mortality. Based on the above background, this study focus on the resistance trend, antibiotic utilisation and mortality in patients with *E. coli* bacteraemia.

Material and Methods

In this cross-sectional study, we reviewed data obtained from 182 patients aged 18 years and above who had experienced bloodstream infection with *E. coli* during five years from Jan 2013 through Dec 2017. The Institutional Ethics Committee approval (IEC 483/2017) was obtained before the start of the study.

Bacteremia was defined as the presence of viable bacteria in the bloodstream [34]. Patients were excluded if the presence of *E. coli* was not confirmed by blood culture testing and through microbiology laboratory report. Antibiotic sensitivity results were obtained from the patient medical record [35].

The culture reports and antibiotic resistance pattern were extracted from online microbiology lab reports database and information on antibiotic prescription from the patient's records. The DDD/100 bed days was calculated for the antibiotics by using the AMC tools software.

The data was analysed by SPSS 20.0 software.

Results

Of the 182 patients who met the inclusion criteria, 59.9% (n = 109) of the patients were male, with age range from 20 to 90 years. The mortality rate was 24.9% (n = 44), and mortality rates trends over time are displayed in Figure 1.
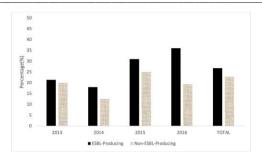

Figure 1: Mortality rate in patients with different types of E.coli isolates over time

The isolated organisms were 55.5% (n = 101) ESBL-producing *E. coli,* and the rest of the organisms were at least sensitive to 4th generation cephalosporins.

Antibiotic sensitivities among the total patient population, viz patients with ESBL producing *E. coli*, patients with non-ESBL producing *E. coli* represented in Table 1.

Table 1: Resistance pattern of different E. coli isolates

Antibiotic name	Non-ESBL producing *E. coli* resistance (%)	ESBL producing *E. coli* resistance (%)	All *E. coli* species resistance (%)
Amikacin	1.3	10.9	6.1
Ampicilin/amoxicillin	77.6	100	90.2
Cefotaxime/ceftriaxone	55.8	100	80.9
Cefuroxime	68.4	100	85.6
Cefazolin/cefadroxil	45.5	100	82.4
Cefpirome/cefepime	2.0	100	68
Ciprofloxacin	55.1	95	77.5
Amoxicillin-clavulanic-acid	24.7	93.1	55.6
Trimethoprim-sulphametoxazole	41.6	54.5	48.9
Gentamicin	21.8	50.5	38
Netilmicin	0.0	18.2	12.1
Imipenem	4.3	6.9	6.1
Piperacillin-tazobactam	8.5	29.7	23
Cefoperazone-sulbactam	2.1	22.8	16.2
Colistin	0	0	0

Among the patients with non-ESBL producing *E. coli*, 45 (55.8%) had an organism resistant to cefotaxime. Sensitivity to the colistin, imipenem, amikacin and netilmicin were observed in most of the ESBL enzyme producing as well as non-producing *E. coli* species. Utilisation pattern of antibiotics in terms of DDD/100 bed-days is depicted in Figure 2.
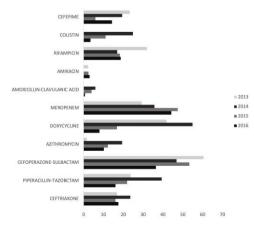

Figure 2: Antibiotic utilisation pattern of patients with E. coli bloodstream infections over time

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A group of 40.7% (n = 74) were treated with a cefoperazone-sulbactam combination, and 36.8% (n = 67) were treated with a piperacillin-tazobactam combination and were the most frequently administered antibiotics.

Sixty-two patients (34.1%) received ceftriaxone as empirical therapy. A group of 83.9% (n = 52) of these patients stopped receiving ceftriaxone before the full course of the antibiotic was completed and 35.5% (n = 22) of these patients received a single dose of ceftriaxone after their admission to the hospital. The trend in the change of antibiotic resistance is shown in Figure 3.
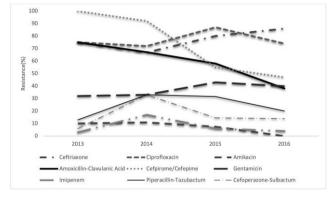

Figure 3: Resistant trends of E. coli isolates to different antibiotics over time

Discussion

ESBL enzyme producing species were dominant in this study, while a lower ratio was reported in other studies [36], [37]. Resistance among _E. coli_ species to a variety of antibiotics is increasing. A prior study suggested the use of Ceftriaxone as empirical therapy [29], while we observed an increasing trend of resistance to ceftriaxone among all the reviewed _E. coli_ isolates. More than one-third of the patients received ceftriaxone as antimicrobial therapy, and most of them received under-dose medication. This could have affected the increment of cephalosporin's resistance, revealing that added antimicrobial administration control policy may help to overcome antimicrobial resistance.

ESBL producing _E. coli_ species were 93.1% susceptible to carbapenems/imipenem which is supported by other studies [25], [26], [27], [28]. A group of 78.2% and 71.3 sensitivity was observed to the cefoperazone-sulbactam and piperacillin-tazobactam combinations respectively which is supported by other studies as well [28], [30]. Aminoglycosides were found to be effective against the entire reviewed _E. coli_ isolates. Netilmicin can be recommended as a superior antimicrobial over

gentamicin based on its similar activity and higher safety.

The most frequently prescribed antibiotics were cefoperazone-sulbactam, meropenem and piperacillin-tazobactam respectively. Comparison of the DDD/100 bed days results with the trend in resistance pattern of antibiotics over time revealed that a greater number of antibiotics administered in a specific year, more resistance was observed in the same or next year. The behaviour of the resistance pattern of organisms to antibiotics such as amoxicillin-clavulanic acid, cefepime-cefoperazone-sulbactam and piperacillin-tazobactam can support this claim.

The mortality rate of the patients with ESBL producing _E. coli_ bloodstream infection was higher in comparison with non-ESBL producing _E. coli_ infections, and it supports the prior studies [17], [18], [19], [20], [21]. The difference in the mortality rate of the ESBL producing and non-ESBL producing organisms has constantly been increasing from 2013, and this can reflect the increase in the ineffectiveness of antimicrobial therapy on resistant organism over time.

E. coli infection is the most prevalent bloodstream infection in our study population. Most of these patients received 3rd gen. cephalosporins empirical therapy and treatment usually continue with a β-lactam and β-lactamase inhibitor combination or carbapenems after releasing of culture sensitivity reports. Due to the high resistance of these isolates to cephalosporins, more appropriate empirical therapy can be selected. ESBL enzyme producing species are the most serious bacterial infection, and they should be treated according to evidence-based culture reports. The ability to identify patients at risk for resistant organisms has important implications. Therefore, an appropriate empirical therapy according to local resistance pattern database should be selected.

We observed a descending resistance trend for amoxicillin-clavulanic acid combination in our setting to both the ESBL producing and non-producing _E. coli_ isolates, and its use as empirical therapy for bloodstream infections by _E. coli_ organism. Despite high utilisation of cefoperazone-sulbactam, piperacillin-tazobactam and meropenem in our patients, the organisms still show a reliable sensitivity toward these antibiotics as shown in the figure3, and this can support the recommendation of other studies for their utilisation [28], [30].

After all, we should express that the pathogenic microorganisms are getting more susceptible to the older and rarely prescribed antibiotics. Local constantly updated microorganism's resistant data is essential in every hospital and must be prepared and used in antimicrobial treatment guidelines to improve the empirical therapies.

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