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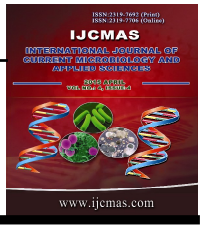


Original Research Article

Outcome of Cephalosporins Treatment in Patients with Extended Spectrum β-Lactamase (ESBL) Producing Bacterial Infections

Mohamudha Parveen Rahamathulla[1,2]* and Belgode Narasimha Harish[2]

[1]Department of Medical Lab Sciences, College of Applied Medical Sciences, Prince Sattam bin Abdul Aziz University, Wadi Al Dawaser, Kingdom of Saudi Arabia
[2]Department of Microbiology, Jawaharlal Institute of Postgraduate Medical Education and Research (JIPMER), Puducherry, India
**Corresponding author*

Keywords

Extended Spectrum β-Lactamase, Third generation cephalosporins, Antimicrobial resistance, Empirical Treatment, Patient outcome

A B S T R A C T

This was a prospective observational study carried out in a large teaching hospital in South India over a period of 24 months (February 2008- January 2010). Consecutive patients admitted in various wards and intensive care units (ICUs), who had blood stream infections caused by Extended Spectrum β-Lactamase (ESBL) producing *Klebsiella pneumoniae* and *Escherichia coli* were included. Antimicrobial susceptibility pattern of the ESBL producing isolates were recorded. Each patient was followed up after diagnosis of bacteremia to assess the clinical outcome. The patient's details were obtained from their case records. Patient's demographic data were recorded. An inappropriate therapy defined as, if the patient was prescribed a third generation cephalosporins (3GCs) for an infection with ESBL producing *K. pneumoniae* or *E. coli.* An appropriate therapy was defined as use of non-3GCs for an infection with ESBL producing *K. pneumoniae* or *E. coli*, to which the bacterial isolate was susceptible in-vitro. The effectiveness of 3GCs administration was monitored thrice a week. One hundred and sixty two in-patients were followed up during the study period. Of the 162 patients, 114 (70.3%) had blood culture positive for ESBL producing *K. pneumoniae*. Eighty three (51.2%) patients were in intensive care units, and 79 (48.7%) in other wards. Among the 162 patients infected with ESBL producing bacteria, 98 (60.4%) received appropriate empirical therapy, and 64 (39.5%) received inappropriate therapy. Of the 98 patients in the appropriate antimicrobial prescribed group, early improvement was seen in 64 (65.3%), early failure in 28 (28.5%) patients. Similarly, among the 64 patients in the inappropriate antimicrobial prescribed group, early improvement was noted in 37 (57.8%), early failure in 22 (34.3%) patients. The mortality was higher, 17.1% in inappropriate group than the 4% in appropriate group. The overall mortality in both the group is 9.2%. The empirical therapy with cephalosporins might not be sufficient in our setting because high rate of resistant to cephalosporins in the organisms with multiple β-lactamases producers exists. In view of their excellent in-vitro activity, carbapenems should be the initial empiric choice for serious life threatening infections caused by ESBL producing Enterobacteriaceae, with prompt de-escalation when culture and susceptibility results become available.

Introduction

Infections caused by Gram-negative bacilli are common in hospitalized patients and result in serious infections such as bacteremia and the majority of cases of nosocomial pneumonia. These infections are also associated with high rates of mortality. Blood-stream infections represent the most life-threatening infectious condition affecting critically ill patients. Sepsis is one of the most common causes of death (Kang *et al.*, 2004).

Beta-lactam antimicrobials are more often prescribed than any other antimicrobial agent, and the production of β-lactamases is the most prevalent cause of resistance against this important class of antibiotics (Holten and Onusko, 2000). The cephalosporins had been developed in response to the increased prevalence of β-lactamases such as TEM-1 and SHV-1 in organisms like *Escherichia coli* and *Klebsiella pneumoniae* and the spread of these β-lactamases into new hosts such as *Haemophilus influenzae* and *Neisseria gonorrhoeae* (Paterson and Bonomo, 2005). The introduction of the third generation cephalosporins (3GCs) into clinical practice in the early 1980s was heralded as a major breakthrough in the fight against β-lactamase mediated bacterial resistance to antibiotics. Not only were the 3GCs effective against most β-lactamase-producing organisms but, they had the major advantage of limited nephrotoxic effects compared to aminoglycosides and polymyxins. This causes the extensive usage and which have selected for the β-lactamases with increased resistance to 3GCs. This is exemplified in Gram-negative organisms producing ESBLs as well as the widespread stable derepression of AmpC β-lactamases (Paterson and Bonomo, 2005).

E. coli and *K. pneumoniae* are the most common Gram-negative pathogens that infect hospitalized patients. The management of these infections has become complicated because of the bacteria producing a variety of β-lactamases. ESBL production confers resistance to all the β-lactam antibiotics, except carbapenems and cephamycins. Organisms producing ESBLs are clinically relevant and remain an important cause for failure of therapy with cephalosporins (Bush, 2001). Indeed, the failure of cephalosporin therapy in an infection where the pathogen was reported to be susceptible to the drug in routine susceptibility testing has often been the first indicator that the infecting strain produced an ESBL (Pitout *et al.*, 2005.)

ESBL encoding plasmids also carry genes which encode resistance to other class of antibiotics such as fluoroquinolones, aminoglycosides and sulfonamides (Wilcox, 2009). Thus, limited antibiotic choices are available for the treatment of infections caused by these strains. The determinations of antimicrobial susceptibility of a clinical isolate are often crucial for the optimal antimicrobial therapy of infected patients. This need is only increasing with increasing resistance and the emergence of multidrug-resistant microorganisms (Holten and Onusko, 2000). In these circumstances, it is essential to quantify the problem and reinforce the strategy promoting an appropriate antibiotic use.

Although the occurrence of ESBL-producing organisms has been extensively reported in the literature, the clinical significance of ESBL production and the treatment outcome has received comparatively little attention.

In this study, the clinical outcome of cephalosporin treatment in patients with infections due to ESBL producing bacteria was studied.

Materials and Methods

This was a prospective observational study carried out in a multi-specialty teaching hospital in South India, over a period of 24 months from February 2008 to January 2010. Consecutive patients admitted in various wards and intensive care units (ICUs), who had blood stream infections caused by ESBL producing *K. pneumoniae* and *E. coli* were included.

Only the adult patients (>12 years old) were included. Patients aged <12 years, bacteremia of polymicrobial etiology, repeat cases and outpatients were excluded. Antimicrobial susceptibility pattern of the ESBL producing isolates were recorded. Each patient was followed up after the diagnosis of bacteremia to assess the clinical outcome.

The patient's details were obtained from their case records. Patient's demographic data, ward, organism isolated, drug administration etc were recorded as per a proforma designed. Treatment changes made by the treating physician during the course of the patient's hospital stay on the basis of the susceptibility reports as well as the nature and severity of the infection were also recorded. The effectiveness of 3GCs administration was monitored thrice a week.

An episode of bacteremia is defined as blood culture positivity for *E coli or Klebsiella* spp

Empirical treatment defined as antimicrobial agents prescribed for fever or other systemic signs of infection without identifying specific source of infection (Kollef, 2000).

Definitive treatment defined as antimicrobial agents prescribed for specific clinically localized source of infection. The identified source of infection was required to be documented in the patient's medication record (Kollef, 2000).

Inappropriate therapy defined as, if the patient was prescribed 3GCs for an infection with ESBL producing *K. pneumoniae* or *E. coli.*

Appropriate therapy defined as use of non-3GCs for an infection with ESBL producing *K. pneumoniae* or *E. coli*, to which the bacterial isolate was susceptible in-vitro

Cure defined as absolute remission of local and systemic sign and symptoms of infection without addition of other antibiotics and without evidence of recurrence

Early improvement defined as decrease of local and systemic signs and or symptoms of infection without complete remission

Early failure defined as unchanged or deterioration of systemic signs and or symptoms of infection.

Results and Discussion

One hundred and sixty two in-patients were followed up during the study period of 24 months from February 2008 to January 2010. Of the 162 patients, 114 (70.3%) had blood culture positive for ESBL producing *K. pneumoniae*, 48 (29.6%) for ESBL producing *E. coli*. Sixty four patients were male and 98 were female. Eighty three (51.2%) patients were in intensive care units, and 79 (48.7%) in other wards.

Antibiotic profile of the ESBL producers showed a high degree of resistance to multiple classes of antibiotics with >90% of resistant to 3GCs, 83 % to ciprofloxacin, 49.6% to amikacin and 13% to meropenem (Figure 1). For all the isolates, MIC of the

3GCs were in the range of 32 to >512 µg/mL.

Appropriateness of initial antimicrobial choice in the treatment of infection due to ESBL producer:

Among the 162 patients infected with ESBL producing bacteria, 98 (60.4%) received appropriate empirical therapy, and 64 (39.5%) received inappropriate therapy. Of those who received appropriate therapy, 31(31.6%) patients received carbapenems, followed by 21 (21.4%) received aminoglycosides. Combination therapy with two active drugs was given to 17(17.3%) patients (Table 1).

Among the inappropriate group, 43 (67.1%) of the patients were empirically given 3GCs and 4GC alone. The combination therapy was found to be inappropriate in 18.7% of patients receiving cephalosporins and fluoroquinolones and in 9% of the patients receiving cephalosporin and aminoglycosides (Table 1).

Change of therapy in ESBL infections

After antimicrobial susceptibility reports were available, in the inappropriate group, out of 43 patients who were given empirical treatment with 3GCs, 18 and 11 patients were changed over to guided therapy with carbapenem and amikacin respectively. Similarly, among the 12 patients who were given cephalosporins and fluoroquinolones combinations empirically, 7 patients were changed over to guided therapy with carbapenems. However, no change of the therapy was noted for 25 (39%) patients who were infected with ESBL producers and resistant to 3GCs (Table 2).

Similarly, among 98 patients in the appropriate group, change of guided therapy was noted in 41 (41.8%) patients and no change in 57 (58.1%) patients. No change of therapy was observed in a maximum of patients treated with carbapenems empirically (Table 3).

Clinical outcome of the patients treated with cephalosporins

Of the 98 patients in the appropriate antimicrobial prescribed group, early improvement was seen in 64 (65.3%), early failure in 28 (28.5%) patients. Similarly, among the 64 patients in the inappropriate antimicrobial prescribed group, early improvement was noted in 37 (57.8%), early failure in 22 (34.3%) patients. The clinical outcome of the patients treated with 3GCs infected with ESBL producing *K. pneumoniae* and *E. coli* is given in Table 4.

The mortality was higher, 17.1% in inappropriate group than the 4% in appropriate group (Figure 2). The overall mortality in both the group is 9.2% (15 patients).

ESBL-producing *K. pneumoniae* and *E. coli* have been responsible for numerous out-breaks of infection throughout the world and pose challenging infection control issues (Kang *et al.,* 2004). Clinical outcomes data indicate that ESBLs are clinically significant and, when detected, indicate the need for the use of appropriate antimicrobial agents. In this study, the outcome of cephalosporin treatment in 162 cases of bacteremia due to ESBL producing *E. coli* and *K. pneumoniae* among in-patients in our hospital was evaluated.

In treating bacteremic infections, of the 162 patients, 64 (39.5%) were given cephalosporins inappropriately, as the empirical antimicrobial of choice. In this hospital, cefotaxime was the commonest cephalosporin administered followed by ceftriaxone and ceftazidime. Cefepime was

used less frequently. In the appropriate therapy, carbapenem was given to a maximum of 31.6% patients followed by aminoglycosides in 21.4% (Table 1)

In clinical outcome, early improvement was seen in 65.3% vs 57.8% and early failure in 28.5% s 34.3% in the appropriate and inappropriate groups respectively. For bacteremias caused by ESBL-producing strains, a 7.5% difference as early improvement treatment response was observed in regimens that did not included a cephalosporin. However, a difference of 5.8% as early failure was observed in cephalosporin included regimens. Though these variations were not statistically significant, it is of importance in the patient care. These discrepancies could be due to the differences between the in *vitro* results of the antimicrobial susceptibility testing and the dynamics of i*n vivo* activity of these antimicrobials.

The overall mortality was 9.2% due to BSI caused by ESBL producing bacteria. The mortality was higher, 17.1% in inappropriate group and 4% in appropriate group (P>0.05). The effect of cephalosporin resistance on mortality was probably mediated by the failure to provide effective antimicrobial therapy. It to be noted that, the mortality increases four times when inappropriate antimicrobial is prescribed. Moreover, changing antimicrobial therapy based on available and susceptibility results might not reduce the excess risk of mortality associated with inappropriate initial antimicrobial treatment. The outcome in patients infected with ESBL producing bacteria could be influenced by an enhanced virulence of these resistant organisms. In this study, only the clinical outcome was assessed. Hence, the bacteriological outcome is not available, which is a limitation.

It was observed that, among the 64 patients empirically given cephalosporins alone and/ with other combinations, no change to guided definitive therapy was noted in 25 (39%) patients. In spite of treatment change, 8 patients expired and 3 recovered in this group. In the appropriate group of 98 patients, 41(41.8%) were given definitive therapy and in 57(58.1%) patients no change of antibiotics was effected. In this group, four patients died, out of which in 2 patients, therapy was changed to the appropriate antibiotics and in 2 patients empirical therapy was continued.

The cause of death in patients receiving the appropriate therapy may not only due to infections but also other causes such as respiratory failures, liver failure and multi-organs failure. The association of various risk factors for acquisition of ESBL-producing organisms and their outcomes has been reported in many studies earlier such as severity of illness, length of hospital stay, length of intensive care unit stay, invasive procedures, intravascular devices, administration of total parenteral nutrition, poor nutritional status etc. (Ho *et al.*, 2002; Rup and Fey, 2003). These factors might have played a role in these cases; however, they were not analyzed in this study.

Studies have indicated that choosing an appropriate therapy soon after the onset of infection is an important factor in determining outcome. Du *et al.*, did not find an association between ESBL status and outcome, nevertheless he reported that ESBL production in *E. coli* and *K. pneumoniae* bacteremia was more likely to lead to the choice of inappropriate empirical therapy, which, in turn, increased the risk of treatment failure or death (Du *et al*., 2002) In contrast, Ariffin *et al.* found that overall sepsis-related mortality was significantly higher among patients infected with

ceftazidime-resistant *K. pneumoniae* (50.0%) than among patients infected with ceftazidime-susceptible *K. pneumoniae* (13.3%) (Ariffin *et al.*, 2000). Not all studies have found that inappropriate empirical therapy administered prior to the availability of culture results always leads to a poor outcome (Ramphal and Ambrose, 2006).

In the appropriate group, 57 (58.1%) patients did not receive therapy as per the guidance. This may be because of the clinical improvement of the patient, as noted by the clinician. However, the bacteriological outcomes of these cases were not assessed. Two patients despite change of therapy in this group expired. An inoculum effect, in which the MIC increases with increasing inoculum, has been proposed as a possible explanation for treatment failure occurring in the face of apparent in vitro susceptibility. This reveals that treatment failure can occur even when the organism appears to be susceptible to the chosen antibiotic. Similar results were observed by Paterson *et al.* in a prospective study of 10 patients who received treatment for bacteremia caused by ESBL-producing *K. pneumoniae*, noticed that, in all cases, in vitro tests indicated that the infecting strains were susceptible to the utilized cephalosporin yet treatment failure was recorded for 7 of the patients (Paterson, 2000).

In the perspective of microbiologists, these organisms which show resistance to an antibiotic *in vitro*, when the same is administered this may up regulate the efflux mechanism resulting in resistance and it may confer resistance to other antibiotic classes also. Further, loss of OMP porins with ESBLs/ AmpCs production in them may cause carbapenem resistance. Resistance to carbapenems by altered permeability is usually difficult in infection control procedures than the enzyme production (Quale *et al.* 2003).

Antibiograms are currently used to estimate the impact of changes in antibiotic usage and to determine infection control strategies and antibiotic usage policies (Critchely *et al.* 2004). Furthermore, within the nosocomial setting, antibiograms are often taken into account to define a rational selection of the empirical antimicrobial therapy for treating patients with hospital-acquired infections. However it is shown that, the reliability of antibiograms to be used for this purpose has rarely been assessed (Fridkin *et al.*, 2003). In this study, all the ESBL isolates showed high MIC to 3GCs in the range of 32 to >512 µg/mL. Antibiotic susceptibility pattern of the ESBL producers showed multi-drug resistance with >90% of resistant to 3GCs, 83 % to ciprofloxacin, 50% to amikacin. Because ESBL-containing plasmids often carry resistance genes for other antibiotics, gentamicin, tobramycin, and fluoroquinolones may be ineffective (Paterson, 2000).

Although β-lactam/β-lactamase inhibitors combinations have been suggested as an option for ESBL producers, these drugs must be given in high doses (Gold and Moellering, 1996). In this study, in the appropriate group, empirically β-lactam/β-lactamase inhibitor combination was given to 9 patients, all the isolates found to be resistant *in vitro.* Change of therapy was effected in 7 patients. Two patients continued the same, despite being no change, they recovered. Similarly, in the inappropriate group, one of the 2 patients receiving guided β-lactam/β-lactamase inhibitor combination expired. This discrepancy may be because, in *in vitro* tests, the activity of β-lactam/β-lactamase inhibitor combination agents is influenced by the bacterial inoculum, dose

administration regimen and specific type of ESBL present. In addition, organisms expressing multiple β-lactamases as well as porin deficient mutants are being described showing variable results with β-lactamase inhibitor combination drugs (Bradford, 2001).

Cefepime, a fourth-generation cephalosporin, is active against most ESBL-producing organisms; particularly those with SHV derived enzymes. In addition, there are some data from in vivo models to support the use of cefepime in the treatment of infections due to ESBL- producing Enterobacteriaceae (Andes and Craig, 2001). However, cefepime resistance may be more frequent in strains which produce the CTX-M-type ESBLs (Fernandes *et al.,* 2014). Extensive clinical experience with cefepime in the treatment of infections due to ESBL-producing microbes is lacking but clinical failures have been observed (Paterson *et al.*, 2001). In this study, it was observed that cefepime was not used as frequently as 3GCs in Gram negative infections in this hospital. In addition, in an environment where AmpC producers equally exist as ESBLs, cefepime should not be administered as a first line of therapy.

Restriction of the use of extended-spectrum cephalosporins is the most common antibacterial-restriction measure employed in controlling outbreaks of ESBL-producing organisms (Pfeifer *et al.,* 2010). Often, restriction of extended-spectrum cephalosporin use is accompanied by switching empirical therapy for serious infections to other classes of antibacterials. Currently, carbapenems are generally regarded as the preferred agent for treatment of infections due to ESBL-producing organisms. Carbapenems are resistant to ESBL-mediated hydrolysis and exhibit excellent in vitro activity against strains of *Enterobacteriaceae* expressing ESBLs (Livermore, 1995). Clinical data supports the use of carbapenems for treatment of infections due to ESBL-producing organisms (Paterson *et al*., 2000).

In the early 1980s, prior to the antibiotic era, CLSI established breakpoints for expanded-spectrum cephalosporins. Correlations of MICs to clinical outcome were excellent; indeed, an MIC of ≤8 ug/ml correlated with ≥92% clinical success in Gram negative infections including *K. pneumoniae and E. coli.* Later in 1990s, after the emergence of ESBLs, MICs of cephalosporins showed an upward tread (Paterson *et al.,* 2004). Although a particular ESBL will typically confer resistance to at least one particular expanded-spectrum cephalosporin or aztreonam, the minimum inhibitory concentration (MIC) may not be high enough for the strain to be called 'resistant'. Hence, guidelines were formulated by CLSI for initial screening and confirmation of ESBL producers. Further, due to the wide range of enzymes, use of more than one indicator cephalosporin for screening was recommended.

But, in 2010, CLSI approved the lowering of susceptibility breakpoints for most of the third generation cephalosporins based on new pharmacokinetic, pharmacodynamic and clinical data. The effort to lower the cephalosporin breakpoints were originally undertaken to differentiate ESBL positive from ESBL negative isolates and eliminate the need for laboratories to perform ESBL screening and confirmation testing.

Table.1 List of antibiotics prescribed appropriately or inappropriately

Initial antimicrobial choice	Appropriate therapy (n=98)	Inappropriate therapy (n=64)
3GCs and 4GC	-	43 (67.1%)
β-lactam/ β-lactamase inhibitors	10 (10.2%)	-
Fluoroquinolones	11 (11.2%)	-
Aminoglycoside	21 (21.4%)	-
Carbapenems	31 (31.6%)	-
Others	8 (8.1%)	-
Combination of two groups:		
Cephalosporins + Aminoglycoside	-	9 (14.0%)
Cephalosporins + Fluoroquinolones	-	12 (18.7%)
Carbapenem + Aminoglycoside	17(17.3%)	-

Where, n= no.of patients

Table.2 Effect of antimicrobial susceptibility testing on antibiotic prescription

Antimicrobial choice		Inappropriate empirical therapy (n)	Change over to definitive guided therapy (n)	No change of therapy, (n)
3GCs and 4GC		43	Carbapenems (16),	14
		-	Aminoglycoside (11)	
		-	β-lactam/ β-lactamase inhibitors (2)	
Combination of two groups	Cephalosporins and aminoglycoside	9	Carbapenem (2)	7
	Cephalosporins and fluoroquinolones	12	Carbapenem (8)	4
Total		64	39 (60.9%)	25 (39%)

where, n= no.of patients

Table.3 Effect of antimicrobial susceptibility testing on antibiotic prescription in the 'appropriate group'

Antimicrobial choice	**appropriate empirical therapy (n)**	**Change over to definitive guided therapy (n)**	**No change of therapy, (n)**
β-lactam/ β-lactamase inhibitors	9	Carbapenems (4) Aminoglycoside (3)	2
Fluoroquinolones	11	Carbapenem (5) β-lactam/ β-lactamase inhibitors (2)	4
Aminoglycoside	21	Carbapenems (9)	12
Carbapenems	36	β-lactam/ β-lactamase inhibitors (2) Higher antibiotics (7)	27
Carbapenem and aminoglycoside	17	Higher antibiotics (5)	12
Others	4	Carbapenem (4)	0
Total	98	41 (41.8%)	57 (58.1%)

where, n= no.of patients

Table.4 Clinical outcome of the patients treated with 3GCs infected with ESBL producing *K. pneumoniae* and *E. coli*

Total No. of ESBL producers (n=162)	Patient outcome	Antimicrobial prescribed	
		Appropriate therapy (n=98)	Inappropriate therapy (n=64)
Early improvement	Yes	64(65.3%)	37(57.8%)
	No	34(34.6%)	27(42.1%)
Early failure	Yes	28 (28.5%)	22(34.3%)
	No	70(71.4%)	42(65.5%)
Death	Yes	4(4.0%)	11(17.1%)
	No	94(95.9%)	53(82.8%)

Fig.1 Antibiotic profile of the ESBL producers studied

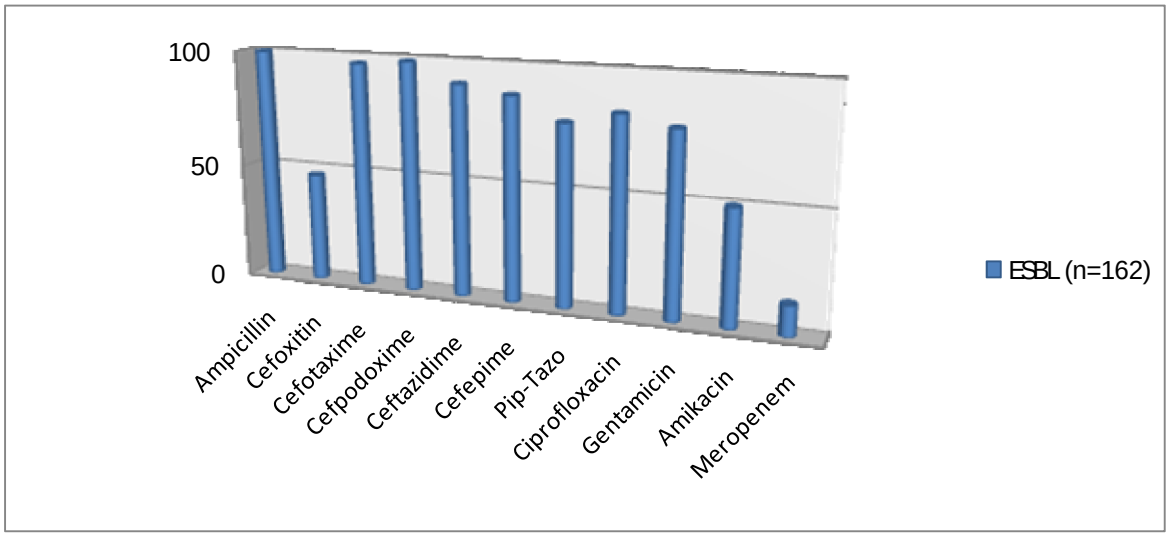
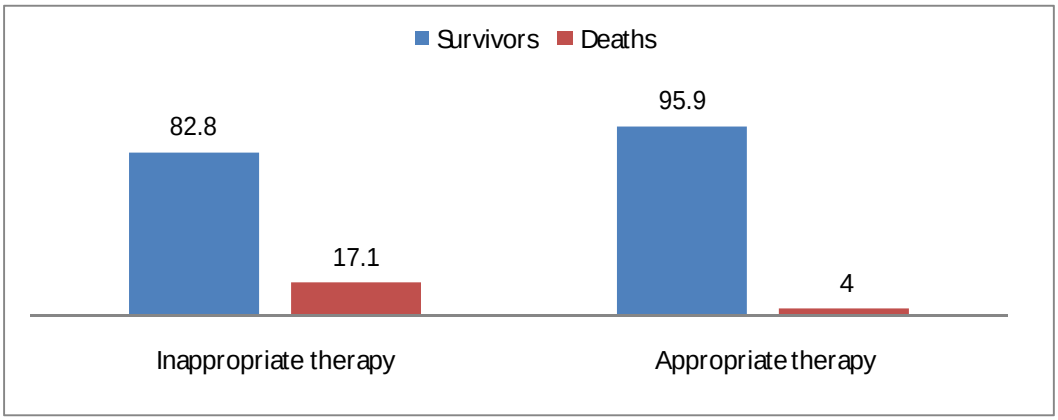


Fig.2 Mortality rate among patients received appropriate and inappropriate therapy with 3GCs due to ESBL infections



When using the new interpretive criteria, routine ESBL testing is no longer necessary before reporting results (i.e., it is no longer necessary to edit results for cephalosporins, aztreonam, or penicillins to resistant as it was prior to the lowering of the breakpoints).

The changes to the cephalosporin breakpoints are a much debated issue among clinical microbiologists and clinicians with two opposing sides. The pro CLSI side debates that based on new clinical data from pharmacokinetic/pharmacodynamic, animal model, and retrospective studies the MIC value was the important factor predicting clinical outcome rather than the presence or absence of an ESBL (MacGowan, 2008; Curello and MacDougall, 2014).

On the other hand, the opposing side debates that some resistant pathogens such as ESBL producers are falsely susceptible in routine tests and could lead to ineffective therapy resulting in adverse clinical outcomes. Thus, they insist special tests are required to detect the resistance mechanisms involved so that susceptibility reports can be modified for patient safety (Paterson and Bonomo 2005). These facts may have both therapeutic and infection control implications in the future.

However, in the environment of high drug resistance, though not relevant to patient care directly, ESBL testing is useful for epidemiological and infection control purposes as the presence of both ESBLs and AmpC which cause 3GC resistance. Thus, the continued surveillance of ESBL-producing Enterobacteriaceae will be even more vital in the coming years to determine what impact the new cephalosporin breakpoints will have on the spread of these important pathogens.

The empirical therapy with cephalosporins might not be sufficient in our setting because high rate of resistant to cephalosporins in the organisms with multiple β-lactamases producers exists. There is no significant association between the mortality in patients given 3GCs empirically and other antibiotics. The clinical outcome of par could be due to a number of factors of the underlying disease at the time antimicrobial therapy. In view of their excellent in-vitro activity, carbapenems should be the initial empiric choice for serious life threatening infections caused by ESBL producing Enterobacteriaceae, with prompt de-escalation when culture and susceptibility results become available.

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