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Ertapenem Susceptibility in Septicaemia due to Extended Spectrum Beta Lactamase (ESBL) Organisms in Teaching Medical College and Hospital Covering Rural Community

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A B S T R A C T

ESBL producing clinical isolates of gram negative organisms are major burden in hospital as well as in the community. These organisms are the causative agent for septicemia. Carbapenem group (Imipenem and Ertapenem) are the drug of choice for treating such infections. Recently increased incidences of resistance to Imipenem were reported, that makes the management of sepsis difficult. Aim of the study was to evaluate the susceptibility pattern of ertapenem in ESBL producing gram negative bacilli isolated from patients with septicemia in a teaching medical college covering predominantly rural population. Hospital based prospective study was conducted at SRM Medical College Hospital and Research Centre, Potheri, Kancheepuram, from septicemia diagnosed cases. The blood samples were collected and processed by standard methods. Isolation and identification of organisms was done as per standard guidelines. Antimicrobial sensitivity was determined by Kirby Bauer's Disc diffusion method as per CLSI guidelines. Evaluation of susceptible pattern of ertapenem from imipenem resistant ESBL producing gram negative isolates was studied. Among 765, 416 (54.37%) were male and 349 (45.62 %) were female. Of 765, 114 (14.9 %) showed positive. Out of 114, 52.66 % (60/114) were gram positive organisms, 44.73 % (51/114) were gram negative organisms and 2.63 % (3/114) were fungal isolates. Among 51 gram negative isolates, 16 (31.37 %) isolates were ESBL producers. Out of 16 ESBL isolates, 7(43.75%) were Imipenem resistant. Out of 7 Imipenem resistant, 5 (71.42%) were ertapenem sensitive and 2(28.57%) were ertapenem resistant. Present study showed low-level ertapenem resistance in imipenem resistance ESBL producing gram negative isolates. Ertapenem may be a viable alternative to other carbapenems for the treatment of infections caused by ESBL producing clinical isolates. Clinical outcome studies are required to determine if ertapenem is effective for the treatment of infections caused by these organisms.

Introduction

Septicemia means multiplication of microorganisms and production of toxins in blood stream. Bacteraemia may be unimicrobial or polymicrobial. Common pathogens causing septicaemia/bacteraemia are *Staphylococcus aureus*, Coagulase Negative *Staphylococci*, *Escherichia coli, Klebsiella pneumoniae, Pseudomonas aeruginosa, Enterobacter cloacae, Salmonella* species etc., and rare organisms like *Brucella* species, HACEK groups (*Haemophilus* species, *Actinobacillus actinomycetemcomitans, Cardiobacterium hominis*, *Ekinella* species and *Kingella kingae*), *Candida* species etc.,

Extended spectrum β-lactamase (ESBL)-producing strains of Enterobacteriaceae have now emerged as a major problem in hospitalized as well as community-based patients. These organisms are responsible for a variety of infections, such as urinary tract infection, septicemia, hospital-acquired pneumonia, intra-abdominal abscess, brain abscess and device-related infections. (1)

ESBL are enzymes that mediate resistance to extended spectrum cephalosporins (Third generation).Production of extended spectrum β-lactamases (ESBL) by Gram-negative bacteria has become a major issue in the fields of clinical microbiology and infectious diseases in the past 5 years. (2,34) Therapeutic options are few and include aminoglycosides, quinolones, piperacillin-tazobactam and carbapenems. (5)

Carbapenems (Imipenem and Meropenem) are the drugs of choice for the treatment of infections caused by ESBL-producing organisms. Ertapenem is a parenteral carbapenem that was licensed for once daily use in November 2001 in the USA and in April 2002 in Europe. (6)

Ertapenem has in vitro activity against ESBL producing gram negative bacteria.(7)There are only 2 reports of its clinical efficacy in ESBL producing gram negative bacterial infections with few cases of bacteraemia.(8,9) In this study we have evaluated its clinical efficacy in treating ESBL producing and other multi drug resistant gram negative bacteraemia.

Materials and Methods

Hospital based prospective study conducted at SRM Medical College Hospital and Research Centre, Potheri, District: Kancheepuram, Tamil Nadu, India during March 2012 to February 2013. The study group of patients was clinically diagnosed blood stream infections admitted in various units such as Intensive care units (ICU's) and health care units (Wards). The blood samples were collected and processed by standard methods. Isolation and identification of organisms was done as per standard guidelines.**(10)** Antimicrobial sensitivity was determined by Kirby Bauer's Disc diffusion method as per CLSI guidelines.**(11)** *Staphylococcus aureus* (ATCC 25923), *E. coli* (ATCC 25922) and *Pseudomonas aeruginosa* (ATCC 27853) were used as quality control throughout the study for culture and antimicrobial susceptibility testing. ESBL was screened by phenotypic confirmatory test, using Ceftazidime and Ceftazidime/Clavulanate combination disc. Ertapenem susceptibility was screened by double disc synergy test, using imipenem and ertapenem discs.

Statistical analysis

The results were expressed as percentages for analysis of various epidemiological details and for analyzing the distribution of different bacterial isolates and their sensitivity pattern. Microsoft excel was used for the interpretation of these results.

Results and Discussion

Total 765 blood sample was collected during March 2012 to February 2013 from septicemia diagnosed cases. Among those 416 (54.37%) were male while 349 (45.62 %) were female (Table 1).

Out of 765 samples, 114 (14.9 %) were culture positive and 651 (85.09 %) were culture negative. Out of 114, 52.66% (60/114) were gram positive organisms, 44.73% (51/114) were gram negative organisms and 2.63% (3/114) were fungal isolates (Tables 2, 3 and 4). Out of 51 gram negative isolates, 16 (31.37 %) were ESBL producing isolates, which were seen predominantly in *E. coli* (50%) followed by *Pseudomonas aeruginosa* (25%) and *Klebsiella pneumoniae* (12.5%) (Table 5).

Among 16 ESBL isolates 7 (43.75%) were imipenem resistant. Out of 7 Imipenem resistant, 5 (71.42%) were ertapenem sensitive and 2(28.57%) were ertapenem resistant. These 2 ertapenem resistant isolates also shows resistant in Ertapenem with 3-amino phenyl boronic acid (Table 6)

Table.1 Age and sexwise distribution of patients

No. of patients (n=765)	< 15 Years		15 – 40 Years		40 – 60 Years		>60 Years	
	Male	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
	153 (58.95 %)	115 (42.9%)	87 (58.3%)	62 (41.6%)	149 (53%)	132 (46.97%)	27 (40.2%)	40 (59.7%)
Total	268 (35 %)		149 (19.47 %)		**281 (36.73%)**		67 (8.75 %)	

Table.2 Distribution of gram positive organisms isolated from blood culture

Organisms (n=60)	Name of the isolates	No .of Isolates and Percentage
GPC	*Staphylococcus aureus*	11 (18.33 %)
	Enterococcus species	6 (10 %)
	Coagulase Negative staphylococci (CoNS)	3 (60%)
	Streptococcus pyogens	3 (5%)
	Streptococcus pneumoniae	2 (3.33%)
	Other *Streptococcus* species	2 (3.33%)

Table.4 The distribution of fungus isolated from blood culture

Organisms (n=3)	Name of the isolates	No .of Isolates and Percentage
Fungus	*Candida albicans*	2 (66.66%)
	Candida non albicans	1(33.33%)

Table.3 Distribution of gram negative organisms isolated from blood culture

Organisms (n=51)	Name of the isolates	No .of Isolates and Percentage
GNB	*Escherichia coli*	17 (33.33%)
	Pseudomonas aeruginosa	11 (21.56%)
	Klebsiella species	9 (17.64%)
	Citrobacter species	3(5.88%)
	Enterobacter species	3(5.88%)
	Acinetobacter species	3(5.88%)
	Salmonella typhi	2 (3.92%)
	Proteus vulgaris	2 (3.92%)
	Brucella melitensis	1 (1.96%)

Table.5 List of ESBL producing with Imipenem resistant Gram negative isolates

Name of the isolates	No .of ESBL producing GNB Isolates and Percentage (n=16/51)	No. of Imipenem resistant Isolates (n=7/16)
Escherichia coli	8 (50 %)	3 (42.85%)
Pseudomonas aeruginosa	4 (25 %)	2 (28.57%)
Klebsiella species	2 (12.5 %)	1 (14.28%)
Citrobacter species	1 (6.25 %)	1 (14.28%)
Enterobacter species	1 (6.26%)	0 (00)
Total	16 (100%)	7 (100%)

Table.6 Imipenem resistant with Ertapenem sensitive ESBL producing isolates

Name of the isolates	No. of Imipenem resistant Isolates (n=7/16)	No. of Ertapenem sensitive isolates (n=5/7)	No. of Ertapenem resistant Isolates (n=2/7)	Carbapenamase production Ertapenem and Ertapenem with 3 amino phenyl boronic acid
Escherichia coli	3 (42.85%)	2 (28.57 %)	1 (50%)	0
Pseudomonas aeruginosa	2 (28.57%)	2 (28.57 %)	0	--
Citrobacter species	1 (14.28%)	1 (14.28 %)	0	--
Klebsiella species	1 (14.28%)	0	1 (50%)	0
Total	7 (100%)	5 (100%)	2 (100 %)	0

Bacteremia/Septicemia is the leading infectious disease; consisting of 16% of world population and 21% of the world global burden of the diseases. [12] Recent world-wide laboratory based surveillance report said that an attributable mortality rate of 35 – 50 % from bacteremia alone despite emergence of newer antibiotics and improvement in supportive care. [13] The prevalence of bacteremia, the common causative organisms causing this infection and its antibiotic resistant pattern, the morbidity and mortality in a rural population are under reported in most of the developing countries including India.

In the present study the prevalence of bacteremia was 14.90 % among 765 patients of all age groups. The prevalence of bacteraemia varies from place to place and country to country, via: New Delhi 42.1%, Chandigarh 13.17%, Jordan 58.6% reported and Kenya 12.5 %[14, 15,16,)]

In the present study, 57.01 % of male patients were affected by bacteremia, as compare to female patients 42.98 %. Most of the patients were in the age group of 40 – 60 years (36.73%), followed by 0-15 years (35%). Samples received from various ICU's (49.41%) had more positive cultures (59.64%) compared to other units. Among Gram positive organisms, Coagulase negative staphylococci were the predominant isolate (60%), followed by *Staphylococcus aureus* (18.33%), *Streptococci pyogens* (5%), *Streptococci pneumonia* (3.33%), other Streptococci species (3.33%) and Enterococci species (10%). Among Gram negative organisms, *Escherichia coli* was predominant pathogen (33.33%), followed by *Klebsiella pneumoniae* (17.64%), *Citrobacter* species (5.88%), *Enterobacter* species (5.88%), *Pseudomonas aeruginosa* (21.56%), *Acinetobacter* species (5.88%), *Salmonella typhi* (3.92%) and *Brucella* species 1.96%.

In recent south Indian study the gram positive organisms were 51.7% and Gram negative organisms were 48.3% in blood culture samples. In the same study, CoNS were most frequent isolates (29.8%) followed by *Pseudomonas* aeruginosa (19.9%). Other organisms isolated in decreasing order of frequency were staphylococci aureus (16.9%), Nonfermentive gram negative rods (9.9%), *E. coli* (7.55%), *Klebsiella pneumoniae* (6.9%), *Streptococci* species 4.5%), *Salmonella typhi* (3.5%) and one each of *Proteus mirabilis* and *Streptococci pneumoniae*. [17]

The present study shows that 2.63% of fungal organisms isolated from septicaemia patients, in which *Candida albicans* were predominant. All the isolates and proved organisms were subjected to antibiotic susceptibility test for the commonly used antimicrobials using modified Kirby Bauer disc diffusion method.

The β-lactamases are a large family of enzymes representing the major mechanism of resistance of bacteria against β -lactam antibiotics. More than 340 β -lactamase enzymes have been detected until 2004. [2, 3, 4]

Currently, carbapenems are regarded as the preferred agents for treatment of infections caused by ESBL- or AmpC-producing bacteria.[3,18] In a study by Chitnis et al. [19] , 11% of multidrug-resistant isolates were susceptible to meropenem only. However, chromosomally mediated extended-spectrum serine proteases (group 2F) and metallo- β-lactamases active against carbapenems are not uncommon. Carbapenem resistance has been spreading in intensive care units among *Acinetobacter* spp. and *Pseudomonas* strains. In the short run, increased utilization of carbapenems against ESBL-producing bacteria will possibly lead to improved patient outcome, but, in the long run, to widely spread carbapenem resistance. Combination therapy, once multidrug resistance has occurred, was not effective in a study by

Erdem et al.[20]In our study, Out of 51 gram negative isolates, 16 (31.37 %) were ESBL producing isolates, which were seen predominantly in *E. coli* (50%) followed by *Pseudomonas* aeruginosa (25%) and *Klebsiella pneumoniae* (12.5%). Among 16 ESBL isolates 7 (43.75%) Pseudomonas was imipenem resistant. Out of 7 Imipenem resistant, 5 (71.42%) were ertapenem sensitive and 2(28.57%) were ertapenem resistant. These 2 ertapenem resistant isolates also shows resistant in Ertapenem with 3-amino phenyl boronic acid.

In conclusion, Ertapenemcan be used as an alternative to other carbapenems for the treatment of infections caused by ESBL producing clinical isolates. Several studies are required to determine if ertapenem is effective for the treatment of infections caused by these organisms.

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