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Study of antibiotic sensitivity pattern of extended spectrum β-lactamase (ESBL) producing organisms in pediatric patients at a tertiary care hospital

[1]Parag Mahankar, [2]Bibhudatta Dash, [3]Dr. Priyanka Badjate

[1]Assistant Professor, Department of Pediatrics, Bharati Vidyapeeth Medical College and Hospital, Pune, Maharashtra, India
[2]Assistant Professor, Department of Pediatrics, IMS & SUM Hospital, Bhubaneswar, Odisha, India
[3]Associate Professor, Department of Pediatrics, Bharati Vidyapeeth Medical College and Hospital, Pune, Maharashtra, India

Corresponding Author:
Dr. Priyanka Badjate (dr.priyanka_b@yahoo.com)

Abstract

Background: The broad spectrum ß-lactam antibiotics are commonly used empirically for the treatment of gram negative sepsis. But the emergence of ESBL producing organisms has posed a serious threat for their continuing use. Present study was undertaken to find out the magnitude of the problem of infections due to extended spectrum β-lactamase producing organisms.
Material and Methods: Present study was a descriptive & observational study, conducted in patients < 18 years age, all cultures showing a significant growth of ESBL producing organisms from any of the clinical specimens, as per CLSI guidelines.
Results: Infections by ESBL producing organisms were found more common in 13-18 years of age group (36.25%) & males (71.25%). *K. pneumoniae* has been found to be the most commonly isolated ESBL producing organism (56.25%) followed by *E. coli* (38.75%). ESBL producing organisms were most commonly grown in urine samples (51.25%) followed by pus culture (11.25%) and blood (10%). All were sensitive to tigecycline and colistin (100%). In the carbapenem group, sensitivity to imipenem was highest (93.75%) followed by ertapenem (66.25%), doripenem (65%) and meropenem (53.75%). Among the 45 isolates of ESBL *K. pneumoniae*, all were sensitive to tigecycline and colistin. Sensitivity to imipenem is 93.33% while that to meropenem, doripenem and ertapenem were 46.66%, 62.22% and 64.44% respectively. Out of the 31 isolates of ESBL producing *E. coli*, all were sensitive to tigecycline and colistin. Sensitivity to Imipenem was 96.77% while that to meropenem, doripenem and ertapenem were 64.71%, 70.96% and 70.96% respectively. Sensitivity to meropenem has gone down dramatically from 71.42% to 22.22%, which is significant.
Conclusion: A growing resistance in the ESBL producing organisms is noted which is very alarming. A limited number of drugs are available against these ESBL producing organisms and the drug of choice is carbapenem.

Keywords: ESBL, antibiotic sensitivity, paediatric patients, carbapenem

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Introduction

Emergence of resistance to β-lactam antibiotics began even before the first β- lactam, penicillin was developed. The first β-lactamase was identified in *E. coli* prior to the release of penicillin for use in medical practice [1]. Now, extended spectrum β-lactamase (ESBL) producing organisms have been reported from all parts of the world [2].
Prevalence of ESBL in many parts of the world was 10-40% among *E. coli* and *K. pneumonia* [3]. In 2007, the Asia Pacific region was found to harbor plasmid borne ESBL to the magnitude of 62% and 75% in *E. coli* and *K. pneumoniae* respectively [4]. The prevalence of ESBL producing clinical isolates is more than 20% in Asia and South Africa [3, 4].
The broad spectrum ß-lactam antibiotics are commonly used empirically for the treatment of gram negative sepsis. But the emergence of ESBL producing organisms has posed a serious threat for their continuing use. Presumably, the selective pressure imposed by the use and overuse of new antibiotics in the treatment of patients has resulted in the emergence of new variants of β-lactamase. Present study was undertaken to find out the magnitude of the problem of infections due to extended spectrum β-lactamase producing organisms recovered from various clinical specimens in pediatric setup & the antimicrobial susceptibility pattern of these strains.

Material and Methods

Present study was a descriptive & observational study, conducted in department of pediatrics, at XXX medical college & hospital, XXX, India. Study duration was of 2 years (July 2012 to June 2014). Study was approved by institutional ethical committee.

Inclusion criteria

- Patients < 18 years age, all cultures showing a significant growth of ESBL producing organisms from any of the clinical specimens, as per CLSI guidelines.

Exclusion criteria

- Cultures showing the growth of two or more organisms.
- Urine cultures showing insignificant colony count.

Demographic data, clinical details, clinical course details were collected from case records. All the clinical specimens were processed and organisms identified as per standard microbiological techniques. Isolates were screened for ESBL production by using Kirby Bauer disc diffusion of cefotaxime (CTX), ceftazidime (CAZ) and ceftriaxone (CRX) placed on inoculated plates containing Muller Hinton agar according to the CLSI recommendations. Isolates showing inhibition zone size of ≤ 22 mm with ceftazidime (30mcg), ≤25 mm with ceftriaxone (30mcg), ≤ 27 mm with cefotaxime (30mcg) were suspected for ESBL production. *E. coli* ATCC 25922 was used as a quality control strain.
Data was collected and compiled using Microsoft Excel, analysed using SPSS 23.0 version & statistical analysis was done using descriptive statistics. Difference of proportions between qualitative variables were tested using chi- square test or Fisher exact test as applicable. P value less than 0.5 was considered as statistically significant.

Results

Infections by ESBL producing organisms were found more common in 13-18 years of age

group (36.25%) followed by 6-12 years of age group (31.25%). Out of the 80 patients, 57 were male and 23 were female patents.

Table 1: General characteristics

Characteristics	No. of patients	Percentage
Age groups		
< 1 year	4	5%
1-5 years	22	27.5%
6-12 years	25	31.25%
13- 18 years	29	36.25%
Gender		
Male	57	71.25%
Female	23	28.75%

K. pneumoniae has been found to be the most commonly isolated ESBL producing organism (56.25%) followed by *E. coli* (38.75%).

Table 2: Organism grown on culture

Organism	No. of patients	Percentage
K. pneumoniae	45	56.25%
E. coli	31	38.75%
P. mirabillis	2	2.5%
E. aerogenes	2	2.5%

ESBL producing organisms were most commonly grown in urine samples (51.25%) followed by pus culture (11.25%) and blood (10%).

Table 3: Clinical specimen showing growth of ESBL organisms (n=80)

Body fluid involved	No. of patients	Percentage
Urine	41	51.25%
Pus	9	11.25%
Blood	8	10%
Cerebrospinal fluid	6	7.5%
Sputum	6	7.5%
Stool	5	6.25%
Wound swab	2	2.5%
Tracheal secretions	2	2.5%
Broncho-alveolar lavage	1	1.25%

Out of the 41 urine samples showing growth of ESBL producing organisms, 22 (53.65%) samples have grown *E. coli* and 16 (39.02%) samples have showed growth of *K. pneumonia*. *K. pneumonia* was found to be the most commonly grown organism in the rest of the clinical samples like blood, pus, CSF, sputum, stool, wound swab and tracheal secretions.

Table 4: Distribution of different organisms in clinical specimens

Clinical specimen	*K. pneumoniae*	*E. coli*	*E. aerogenes*	*P. mirabillis*
Urine (n=41)	16 (39.02%)	22(53.65%)	1(2.4%)	2 (4.81%)
Pus (n=9)	8 (88.8%)	1(1.1%)	-	-
Blood (n=8)	4 (50%)	4 (50%)	-	-
CSF (n=6)	4 (66.66%)	2 (33.33%)	-	-
Sputum (n=6)	6 (100%)	-	-	-

Stool (n=5)	3 (60%)	2 (40%)	-	-
Wound swab(n=2)	2 (100%)	-	-	-
Tracheal secretion (n=2)	2 (100%)	-	-	-
BAL (n=1)	-	-	1(100%)	-

Out of the 80 ESBL isolates, all were sensitive to tigecycline and colistin (100%). In the carbapenem group, sensitivity to imipenem was highest (93.75%) followed by ertapenem (66.25%), doripenem (65%) and meropenem (53.75%). 62.5% of isolates were found sensitive to piperacillin + tazobactam while 65% to cefoperazone + sulbactam. Sensitivity to amikacin and chloramphenicol was found to be 75%. Out of the 41 urinary isolates, 65.85% were sensitive to nitrofurantoin.

Table 5: Sensitivity pattern of ESBL isolates (n=80)

Antibiotics	No. of sensitive isolates	Percentage
Tigecycline	80	100%
Colistin	80	100%
Imipenem	75	93.75%
Meropenem	43	53.75%
Doripenem	52	65%
Ertapenem	53	66.25%
Piperacillin + tazobactam	50	62.5%
Ticarcillin + clavulanate	6	7.5%
Cefoperazone + sulbactam	52	65%
Trimethoprim + sulfamethoxazole	12	15%
Chloramphenicol	60	75%
Amikacin	60	75%
Gentamicin	34	42.5%
Netilmicin	55	68.75%
Tobramycin	54	67.5%
Nalidixic acid	7	8.75%
Ciprofloxacin	12	15%
Moxifloxacin	13	16.25%
Ofloxacin	14	17.5%
Levofloxacin	39	48.75%
Cephalosporins	0	0%
Nitrofurantoin (n=41)	27	65.85%

Among the 45 isolates of ESBL *K. pneumoniae*, all were sensitive to tigecycline and colistin. Sensitivity to imipenem is 93.33% while that to meropenem, doripenem and ertapenem were 46.66%, 62.22% and 64.44% respectively. 55.55% isolates of *K. pneumonia*e were found sensitive to piperacillin + tazobactam and cefoperazone + sulbactam combination. 66.66% of isolates were sensitive to amikacin and chloramphenicol.

Table 6: Sensitivity pattern of *K. pneumoniae* (n=45)

Antibiotics	No. of sample sensitive	Percentage
Tigecycline	45	100%
Colistin	45	100%
Imipenem	42	93.33%
Meropenem	21	46.66%
Doripenem	28	62.22%
Ertapenem	29	64.44%
Piperacillin + tazobactam	25	55.55%

Ticarcillin + clavulanate	4	8.88%
Cefoperazone +sulbactam	25	55.55%
Trimethoprim + sulfamethoxazole	6	13.33%
Chloramphenicol	30	66.66%
Amikacin	30	66.66%
Gentamicin	16	35.55%
Netilmicin	29	64.44%
Tobramycin	28	62.22%
Nalidixic acid	7	15.55%
Ciprofloxacin	8	17.77%
Moxifloxacin	9	20%
Ofloxacin	11	24.44%
Levofloxacin	19	42.22%
Cephalosporins	0	0%

Out of the 31 isolates of ESBL producing *E. coli*, all were sensitive to tigecycline and colistin. Sensitivity to Imipenem was 96.77% while that to meropenem, doripenem and ertapenem were 64.71%, 70.96% and 70.96% respectively. Sensitivity to piperacillin + tazobactam and cefoperazone + sulbactam combinations was found to be 77.4% and 67.74% respectively. 90.32% of isolates were sensitive to chloramphenicol while 93.54% were sensitive to amikacin.

Table 7: Sensitivity pattern of *E. coli* (n=31)

Antibiotics	**No. of sample sensitive**	**Percentage**
Tigecycline	31	100%
Colistin	31	100%
Imipenem	30	96.77%
Meropenem	20	64.51%
Doripenem	22	70.96%
Ertapenem	22	70.96%
Piperacillin + tazobactam	24	77.41%
Ticarcillin + clavulanate	2	6.45%
Cefoperazone + sulbactam	21	67.74%
Trimethoprim + sulfamethoxazole	5	16.12%
Chloramphenicol	28	90.32%
Amikacin	29	93.54%
Gentamicin	17	54.83%
Netilmicin	25	80.64%
Tobramycin	24	77.41%
Nalidixic acid	0	0%
Ciprofloxacin	3	9.67%
Moxifloxacin	3	9.67%
Ofloxacin	3	9.67%
Levofloxacin	18	58.06%
Cephalosporins	0	0%

We found that tigecycline and colistin have maintained 100% sensitivity to ESBL producing organisms over the period of 3 years. In the carbapenem group, sensitivity of imipenem has been maintained consistently during this study period. Sensitivity to meropenem has gone down dramatically from 71.42% in 2012 to 22.22% in 2014, which is significant (p value <0.0001). Similarly, the sensitivity of doripenem and ertapenem have reduced significantly over the period of 3 years (p value <0.0001).

Piperacillin + tazobactam and cefoperazone + sulbactam combinations have significant

reduction in sensitivity from 76.19% (2012) to 51.81% (2014) (p=0.016) and 71.42% (2012) to 55.55% (2014) (p=0.041) respectively. Sensitivity of levofloxacin has also reduced from 80.95% in 2012 to 29.63% in 2014, p value <0.0001 which is significant. While comparing the sensitivity of chloramphenicol over the last 3 years, sensitivity has been actually found to be increased from 2012 to 2014 with p value <0.0001, which is significant.

Table 8: Trend of antibiotic sensitivity pattern over period of 3 years

Antibiotic	No. of sample sensitive in year			p-value significance
	2012 (n=21)	2013 (n=32)	2014 (n=27)	
Tigecycline	21 (100%)	32 (100%)	27 (100%)	
Colistin	21 (100%)	32(100%)	27 (100%)	
Imipenem	20 (95.21%)	30 (93.75%)	25 (95.59%)	0.78 (NS)
Meropenem	15 (71.42%)	22 (68.5%)	6 (22.22%)	P<0.0001(S)
Doripenem	18 (85.71%)	26 (81.25%)	8 (27.58%)	P<0.0001(S)
Ertapenem	18 (85.71%)	25 (78.12%)	10 (37.3%)	P<0.0001(S)
Piperacillin + tazobactam	16 (76.19%)	20 (62.5%)	14 (51.85%)	0.016 (S)
Ticarcillin + Clavulanate	1 (4.76%)	3 (9.37%)	2 (7.4%)	
Cefoperazone + sulbactam	15 (71.42%)	22 (68.75%)	15 (55.55%)	0.041 (S)
Trimethoprim + sulfamethoxazole	2 (9.52%)	3 (9.37%)	2 (7.4%)	
Chloramphenicol	13 (61.9%)	22 (68.75%)	25 (92.59%)	P<0.0001(S)
Amikacin	16 (76.19%)	25 (78.12%)	19 (70.37%)	0.78 (NS)
Gentamicin	10 (47.61%)	10 (31.25%)	14 (51.85%)	0.24 (NS)
Netilmicin	16 (76.19%)	21 (65.62%)	18 (66.66%)	0.69 NS
Tobramycin	19 (90.47%)	22 (68.75%)	18 (66.66%)	P<0.0001(S)
Nalidixic acid	1 (4.7%)	1 (3.12%)	5 (18.51%)	
Ciprofloxacin	2 (9.52%)	4 (12.5%)	6 (22.22%)	
Moxifloxacin	2 (9.52%)	6 (18.75%)	5 (18.51%)	
Ofloxacin	3 (14.28%)	5 (15.62%)	6 (22.22%)	
Levofloxacin	17 (80.95%)	19 (59.37%)	8 (29.62%)	P<0.0001(S)

Discussion

The susceptibility pattern of ESBL isolates changes from time to time and place to place. With the spread of ESBL organisms in hospitals all over the world, it is necessary to know the prevalence of ESBL producing strains in a particular hospital so as to formulate a policy of antibiotics therapy in high risk units where infections due to resistant organisms are much fatal.

Also the treatment options for the ESBL isolates are expensive and many times not available in resource-limited settings. The limited pipeline of new antibiotics is particularly an issue for children as safety, pharmacokinetic data and FDA approval typically lag years behind that for adults. A knowledge of the resistance pattern of bacterial strains in a community helps to guide appropriate and judicious antibiotic use.

In this study, we observed that out of the 80 samples, 57 were male patients (71.25%) while 23 were female patients (28.75%). Similar results were obtained in the study conducted by Shah AA *et al*., [5] and Zakaria Al Muharrami *et al*. [6]

We have observed that urine (51.25%) is the most common clinical specimen showing growth of extended spectrum β-lactamase producing organisms. Similar results were obtained in the study by Zakaria Al Muharrami *et al*., [6] (46.2%), L K Logan *et al*., [7] (63%). Also, Nema Shashwari *et al*., [8] found that maximum ESBL producing isolates were isolated from urine samples (52.53%). Similar results were also observed in the study by Parul Agrawal *et al*., [9] However, Vemula Sarojamma *et al*., [10] found that higher percentages of ESBL producing organisms were isolated from blood followed by stool, sputum, urine and pus. Also

S.M. Rudresh *et al*., [11] observed that ESBL production was more common among isolates from exudates (70%) followed by blood (66.7%).

K. pneumoniae was the most commonly isolated extended spectrum β-lactamase producing organism from clinical isolates (56.25%) followed by *E. coli* (38.75%) and *P. mirabillis* (2.5%) in our study. Nandini Vijaykanthi *et al*., [12] found that *K. pneumoniae* (60%) was the most common ESBL producing organism followed by *E. coli (30%)* which is similar to the observation of our study.

We observed that out of the 41 urinary isolates, ESBL producing *E. coli* was the most common isolated organism (53.65%) followed by ESBL producing *K. pneumoniae* (39.02%). ESBL producing *K. pneumonia* was more commonly isolated than *E. coli* from rest of clinical samples like pus (88.8%), cerebrospinal fluid (66.6%), stool (60%), sputum, broncho-alveolar lavage and tracheal secretions (100%).

Napoporn Chaiittisuk *et al*., [7] found that ESBL *E. coli* isolates were most frequently obtained from the urinary tract (39%) than K. pneumonia (25%). They also found that ESBL *K. pneumonia* was more commonly obtained from respiratory tract (35%) and blood (18%) as compared to ESBL *E. coli* obtained from respiratory tract (22%) and blood (11%).

In our study, we concluded that all isolates were sensitive to tigecycline and colistin. In the carbapenem group, sensitivity to imipenem was maximum (93%) followed by ertapenem (66.25%), doripenem (65%) and meropenem (53.75%). Ponnusamykonar Poovendram *et al*., [13] and Swaminathan Rajan *et al*., [14] found 100% susceptibility to imipenem.

Nandini Vijaykanthi *et al*., [12] noted that 50% of ESBL producing organisms were sensitive to meropenem while the sensitivity to piperacillin + tazobactam combination was 80%, which is comparable with our study. Neha Shashwati *et al*., [8] found that the sensitivity to imipenem was 100%, piperacillin + tazobactam 89.28%, meropenem 87.5% and amikacin 83.92%.

Muhammad Roshan *et al*., [15] had showed that among the ESBL producing isolates, more than 99% were susceptible to carbapenems, 84% were to piperacillin + tazobactam, 81% were to cefoperazone + sulbactam, 12% were to Fluoroquinolones, 13% were to trimethoprim + sulfamethoxazole, 59% were to amikacin and 18% were to gentamicin. These results are comparable with our study results. Similar results were also obtained in a study by Gaurav Dalele *et al*., [16] where they had concluded that maximum susceptibility was seen to imipenem (95.1%) followed by piperacillin + tazobactam (71.8%) and amikacin (66.9%).

Umadevi *et al*., [17] noted that ESBL producing *E. coli* showed maximum susceptibility to imipenem (100%), followed by piperacillin + tazobactam (84%), amikacin (68%) and gentamicin (9%), while *K. pneumoniae* showed susceptibility to imipenem (98%), piperacillin + tazobactam (60%) and gentamycin (18%).

B. N. Chaudhari *et al*. [18] found that among the ESBL producing isolates of *E. coli*, 94% were susceptible to ertapenem, 96% were susceptible to imipenem and 76% to piperacillin + tazobactam. Corresponding figures for *K. pneumoniae* were 80%, 94% and 59%, which are similar to our study. Similar results were also obtained in study by Mitali Chattergee *et al*., [19] on comparing the sensitivity of different antimicrobial agents over the period of 3 years we concluded that most sensitive antimicrobials like tigecycline and colistin have maintained the sensitivity among the ESBL producing organisms. This may be because they are not in the use very frequently and considered as reserve drugs for resistant cases. In the carbapenem group, sensitivity to imipenem is seen to be unchanged over a period of 3 years, while meropenem shows a significant decrease in sensitivity from 71.42% to 22.22%. Similarly the sensitivity of doripenem and ertapenem has reduced significantly over a period of 3 years.

Selective pressure imposed by the use and overuse of new antibiotics in the treatment of patients has resulted in the emergence of new variants of β-lactamase. Antimicrobial resistance surveillance is necessary to determine the size of the problem and to guide empirical selection of antimicrobial agents for treating the infected patients. So this study will help to formulate a policy of empirical therapy in pediatric high risk units where infection due

to resistant organisms is much higher and fatal.
Once an ESBL producing pathogen is detected from a clinical specimen, cephalosporinsshould not be used and β-lactam + β-lactamase inhibitor combinations may be considered in cases of non-serious infections. Carbapenem is drug of choice unless, sensitivity pattern shows resistance. Tigecycline and colistin, though consistently effective in this group, should be strictly reserved for isolates resistant to carbapenems. Constant vigil is required in each and every hospital for early pick up of changing resistance pattern.

Conclusion

A growing resistance in the ESBL producing organisms is noted which is very alarming. A limited number of drugs are available against these ESBL producing organisms and the drug of choice is carbapenem. However, considering the emerging resistance to carbapenems, choice of antibiotics in the near future is very limited. Infection-control practitioners and clinicians need the clinical laboratory to rapidly identify and characterize different types of resistant bacteria especially ESBL efficiently, in order to minimize the spread of these bacteria and help to select more appropriate antibiotics.

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