Original Article

Extraintestinal Infections due to *Escherichia Coli*: An Emerging Issue

Microbiology Section

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ABSTRACT

Background: Infections due to Extraintestinal pathogenic Escherichia coli (ExPEC) represent a major but little-appreciated health threat. Proper antibiotic sensitivity testing and judicious use of antibiotics are crucial in treatment of such infections.

Aims: This study was done to determine the spectrum of infections caused by ExPEC and their antimicrobial susceptibility pattern.

Settings and Design: Department of Microbiology, Bowring and Lady Curzon Hospital which is a tertiary care, teaching hospital attached to Bangalore Medical College and Research Institute. This is a prospective study from January 2009 to December 2010.

Materials & Methods: A total of 379 *E. coli* isolates from various extraintestinal infections were studied for the antimicrobial sensitivity. The isolates were processed using standard procedures. All strains of *E.coli* were tested for antimicrobial susceptibility pattern by modified Kirby Bauer disc diffusion method. The results were interpreted using CLSI guidelines and statistically analyzed.

Results: A total of 379 strains of *E.coli* were isolated from extraintestinal infections. Out of these 253 (66.7%) were from urine, 101 (26.6%) were from pus & exudates, 23 (6.1%) from sputum and 2 (0.5%) from blood. The analysis of drug resistance pattern shows that among 349 isolates of *E.coli* maximum number 357 (94.2%) were resistant to ampicillin and least, 0(0%) were resistant to carbapenams followed by 59 (15.6%) to netilmicin.

Conclusions: This study demonstrates a significant increase in the prevalence of antimicrobial resistance among *E.coli* isolates. When selecting empirical therapy, in vitro susceptibility patterns must be considered along with other factors, such as expected efficacy, adverse effects, cost, cost-effectiveness, and selection of resistant strains.

Key Words: Drug Resistance, Multiple, Bacterial, Escherichia coli Infections/Microbiology

KEY MESSAGE

- The continued development of antimicrobial resistance among *E.coli* isolates is increasing and requires both further surveillance and new approaches to slow the emergence of resistance. Carbapenam group of antimicrobials seem to be the last resort though emerging resistance in this groups has also been reported. When selecting empirical therapy, in vitro susceptibility patterns must be considered and judicious use of antibiotics and good antibiotic policy are the need of the day.

INTRODUCTION

Escherichia coli is an important nosocomial and community acquired pathogen and one of the commensals of the human intestinal tract [1]. The pathogenic strains of *Escherichia coli* have long been recognized as the agents of foodborne diarrhoea [2]. It is not always appreciated that *E coli* is an important cause of extraintestinal diseases-diseases that occur in bodily sites outside the gastrointestinal tract [3]. These include the urinary tract, the central nervous system, the circulatory system, and the respiratory system [4]. The ability of *E. coli* to cause extra intestinal infections depends largely on several virulence factors which help in the survival of E. coli under adverse conditions which are present at those sites. *E.coli* strains that induce extraintestinal diseases are termed as extraintestinal pathogenic *E. coli* (ExPEC) [5]. In terms of morbidity and mortality, ExPEC has a great impact on public health, with an economic cost of several billion dollars annually [4].

Pathogenic isolates of *E.coli* have relatively high potentials for developing resistance[6]. Therefore, the treatment of E. coli infections is increasingly becoming difficult. Extended spectrum β-lactamase (ESBL) producing organisms pose a major problem for clinical therapeutics [7]. The knowledge of the drug resistance pattern in a geographical area and the formulation of an appropriate hospital antibiotic policy will go a long way in the control of these infections. Therefore, it is necessary to know the antibiotic susceptibility pattern of pathogenic *E. coli* to select the correct antibiotic(s) for the proper treatment of the infections which are caused by it [8].The objective of the present study was to demonstrate the spectrum of the infections which were caused by ExPEC and its drug resistance pattern [Table/Fig-1].

MATERIAL AND METHODS

A total of 379 isolates of *E. coli* from extraintestinal infections which were obtained from January 2009 to December 2010, were

Antibiotics	Disc Content	Resistant	Sensitive
Ampicillin	10µg	<13	>17
Trimethoprim/ Sulphamethoxazole (Cotrimoxazole)	1.25/23.75µg	<10	>16
Ciprofloxacin	5µg	<15	>21
Cefotaxime	30µg	<14	>23
Gentamicin	30µg	<12	>15
Amikacin	30µg	<14	>17
Netilmicin	30µg	<12	>15
Imipenam	10µg	<13	>16

[Table/Fig-1]: Sensitivity of *E coli* to Antibiotics

included in the study. The study population included hospitalised patients of all age groups in a tertiary care referral hospital which was attached to a medical college. Due permission was obtained from the institutional head to conduct this study. The specimens which were received by the Department of Microbiology were pus,exudates, clean catch midstream urine, sputum and blood from patients who were suffering from wound infections, intra-abdominal infections, urinary tract infections (UTI), respiratory infections and blood stream infections. The samples were processed immediately and were identified by using standard techniques [9].

Antibiotic susceptibility was tested with the Kirby–Bauer disc diffusion method, according to the CLSI guidelines [10].

THE KIRBY BAUER DISK DIFFUSION METHOD

This was done on Mueller Hinton agar (Hi Media, Mumbai) which was prepared from a dehydrated base according to the manufacturer's instructions. The preparation of the inoculum for the sensitivity testing was done by emulsifying 3-5 morphologically similar colonies in peptone broth and incubating them at 37°C until the turbidity was comparable to a 0.5 Mc Farland's Turbidity standard. The control was prepared by using the *E coli* ATCC 25922 strain. A sterile cotton swab was dipped into the inoculum and rotated several times against the wall of the test tube above the fluid level, to remove the excess inoculum. The dried surface of a Mueller Hinton plate was then inoculated with the swab as a lawn culture. Once the surface was dried, the antibiotic disks (from Hi Media, Mumbai) were placed on the surface by evenly spacing them in such a way that any two disks were not closer than 24mm from centre to centre. After 18 hours of incubation at 37°C, the inner diameter of the zone of inhibition was measured by using a millimetre scale around each antimicrobial disk, on the undersurface of the plate. The zone size around each antimicrobial disk was interpreted as sensitive, intermediate or resistant according to the CLSI guidelines of 2009 [10] as follows.

RESULTS

As [Table/Fig-2] shows, of the 7864 samples which were received by our department, 2428(30.9%) were from suspected UTI cases,

Sample	Total Screened	Total Culture Positive	*E.Coli* Positive
Urine	2428	943	253
Sputum	1858	538	23
Pus	1591	987	65
Ear swab	637	394	26
Ascitic fluid	245	153	10
Blood	1105	166	2

[Table/Fig-2]: Samples received, positive on culture and positive for *E.coli*

Sample	No. of Isolates	Percentage of total
Urine	253	66.7%
Pus and exudates	101	26.6%
Sputum	23	6.1%
Blood	2	0.5%
TOTAL	379	100%

[Table/Fig-3]: Samples obtained from extraintestinal infections.

1858(23.6%) were from respiratory tract infections, 2473(31.4%) were from skin and soft tissue infections/ear infections/intra-abdominal infections and 1105(14.0%) were from blood stream infections.

Out of the 2428 urine samples which were received, 943(38.8%) were culture positive and 538(29.0%) out of 1858 sputum samples, 1534(62.0%) out of 2473 pus/exudates and 166(15.0%) out of 1105 blood samples were culture positive respectively.

Of the 943 culture positive urine samples, 253(26.8%) were caused by *E.coli*, so also 23(4.3%) out of 538 culture positive sputum samples, 101(6.5%) out of 1534 culture positive pus/exudate samples out of which 65(4.2%) were from skin/soft tissue infections, 26(1.7%) were from ear infection and 10(0.7%) were from intra-abdominal infections. 2(1.2%) out of 166 blood samples were positive for *E.coli*.

The analysis of the drug resistance pattern in [Table/Fig-3] shows that among 379 isolates of *E.coli*, a maximum number i.e 357(94.2%) were resistant to ampicillin and the resistance was lowest in carbapenams 0(0%), followed by netilmicin 59(15.6%)

Among the isolates from urine, the maximum resistance was observed for ampicillin 238(94.1%), followed by cotrimaxazole 171(67.6%), gentamicin 120 (47.4%), cefotaxime 81(32.0%), amikacin 60(23.7%), ciprofloxacin 48(19%) and netillin 30(11.8%), as shown in [Table/Fig-4]

In isolates from pus and exudates, the maximum resistance was observed for ampicillin 97(96.0%), followed by cotrimaxazole 84(83.2%), ciprofloxacin 69(68.3%), gentamicin 68(67.3%), amikacin 45(44.6%), cefotaxime 44(43.6%), and netilmicin 23(22.8%), as shown in [Table/Fig-5]

Among the sputum isolates, maximum resistance was observed for ampicillin 22(95.6%), followed by cotrimoxazole 16(69.5%),

Clinical Samples	Ampicillin	Cotrimoxazole	Ciprofloxacin	Cefotaxime	Gentamicin	Amikacin	Netilmicin	Imipenam
Urine (253)	238 (94.1%)	171 (67.6%)	48 (19%)	81 (32%)	120 (47.4%)	60 (23.7%)	30 (11.8%)	0 (0%)
Exudate (101)	97 (96%)	84 (83.4%)	69 (68.3%)	44 (43.6%)	68 (67.3%)	45 (44.6%)	23 (22.8%)	0 (0%)
Sputum (23)	22 (95.6%)	16 (69.5%)	15 (65.2%)	7 (30.4%)	12 (52.2%)	9 (39.1%)	6 (26.1%)	0 (0%)
Blood (2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total (379)	357 (94.2%)	271 (71.5%)	132 (34.8%)	132 (34.8%)	180 (47.5%)	114 (30.0%)	59 (15.6%)	0 (0%)

[Table/Fig-4]: Resistance pattern of *E coli* from different isolates to various antibiotics used

ciprofloxacin 15(65.2%), gentamicin 12(52.2%), amikacin 9(39.1%), cefotaxime 7(30.4%), and netilmicin 6(26.1%), as shown in [Table/Fig-6]

The *E.coli* which was isolated from blood was sensitive to all the antibiotics. None of the E.coli which was isolated from the various samples was resistant to carbapenams.

[Table/Fig-5] shows the resistance of the *E coli* isolates in paediatric patients (0-18 years). The maximum cases were of UTI (85.9%). Ampicillin was the most resistant antibiotic (79.5%), followed by Cotrimoxazole which was resistant in 60.2% isolates. All the other antibiotics which were used were moderately sensitive. All isolates were sensitive to Imipenam.

[Table/Fig-6] shows the resistance of the *E coli* isolates in adults (18-65 years). The maximum number of isolates were from UTIs(61.8%). Ampicillin was the most resistant antibiotic (98%), followed by Cotrimoxazole which was resistant in 74.4% isolates and gentamicin was resistant in 56.5% isolates. All other antibiotics were moderately sensitive. All isolates were sensitive to Imipenam.

[Table/Fig-7] shows the resistance of the *E coli* isolates in inpatients. The maximum number of cases were of UTIs (58.1%). The maximum resistance was for ampicillin (96.4%), followed by Cotrimoxazole which was resistant in 74.2% isolates and gentamicin resistant to 56.3% isolates. All other antibiotics were moderately sensitive. All isolates were sensitive to Imipenam.

[Table/Fig-8] shows the resistance of the *E coli* isolates in outpatients. The maximum number of cases were of UTIs(73.6). The maximum resistance was for Ampicillin (92.4%) followed by Cotrimoxazole which was resistant in 69.3% isolates and Gentamicin resistant in 50% isolates. All other antibiotics were moderately sensitive. All isolates were sensitive to Imipenam.

DISCUSSION

E. coli has widely been implicated in various clinical infections, namely hospital acquired and community infections, as reported by Shah et al [11]. Extraintestinal, pathogenic Escherichia coli (ExPEC) possesses virulence traits that allow it to invade, colonize, and induce diseases in bodily sites outside of the gastrointestinal tract[2] by overcoming the host defence mechanisms. The virulence of the individual strains in a given infection is determined by the presence and actual expression of the virulence genes which are present in them, and also by the environmental conditions in the host [3]. *E. coli* is therefore able to cause a variety of infections such as urinary tract infections (UTIs), soft tissue infections, bacteraemias, respiratory tract infections, etc, as was seen in our study, with UTIs being the predominant type of infection. This was similar to the findings of a study which was done by Olowe et al [12].

Clinical Samples	Ampicillin	Cotrimoxazole	Ciprofloxacin	Cefotaxime	Gentamicin	Amikacin	Netilmicin	Imipenam
Urine (67)	53 (79.1%)	39 (58.2%)	9 (13.4%)	19 (28.3%)	24 (35.8%)	14 (20.9%)	6 (8.9%)	0 (0%)
Exudate (10)	8 (80%)	7 (70%)	5 (50%)	4 (40%)	5 (50%)	4 (40%)	3 (30%)	0 (0%)
Sputum (1)	1 (100%)	1 (100%)	1 (100%)	0 (0%)	1 (100%)	0 (0%)	0 (0%)	0 (0%)
Blood (0)	–	–	–	–	–	–	–	–
Total (78)	62 (79.5%)	47 (60.2%)	15 (19.2%)	23 (29.5%)	30 (38.5%)	18 (23.1%)	9 (11.5%)	0 (0%)

[Table/Fig-5]: Resistance patterns of *E coli* isolates from patients 0-18 years of age to various antibiotics used

Clinical samples	Ampicillin	Cotrimoxazole	Ciprofloxacin	Cefotaxime	Gentamicin	Amikacin	Netilmicin	Imipenam
Urine (186)	185 (99.5%)	132 (71%)	39 (21%)	62 (33.3%)	96 (51.6%)	46 (24.7%)	24 (12.9%)	0 (0%)
Exudate (91)	89 (97.8%)	77 (84.6%)	64 (70.3%)	40 (43.9%)	63 (69.2%)	41 (45%)	21 (23.1%)	0 (0%)
Sputum (22)	21 (95.4%)	15 (68.2%)	14 (63.6%)	7 (31.8%)	11 (50%)	9 (40.9%)	6 (27.3%)	0 (0%)
Blood (2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total (301)	295 (98%)	224 (74.4%)	117 (38.9%)	109 (36.2%)	170 (56.5%)	96 (31.9%)	51 (16.9%)	0 (0%)

[Table/Fig-6]: Resistance pattern of *E coli* isolates from patients between 18-65 years of age to various antibiotics used

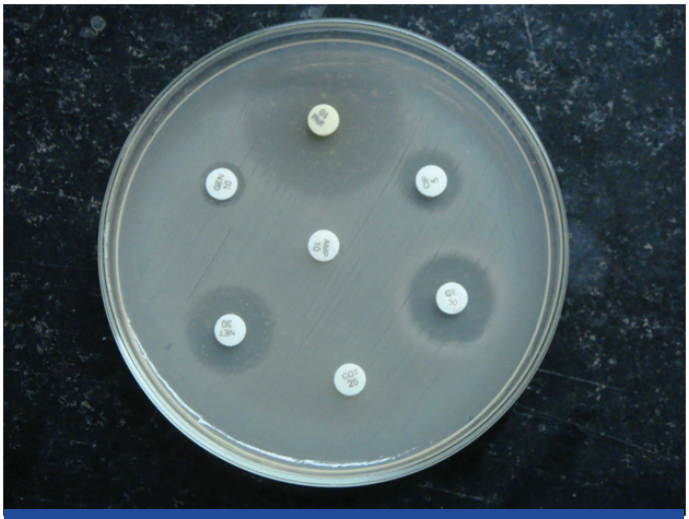
Clinical samples	Ampicillin	Cotrimoxazole	Ciprofloxacin	Cefotaxime	Gentamicin	Amikacin	Netilmicin	Imipenam
Urine (97)	95 (97.9%)	68 (70.1%)	24 (24.7%)	36 (37.1%)	47 (48.4%)	26 (26.8%)	13 (13.4%)	0 (0%)
Exudate (57)	55 (96.5%)	49 (86%)	42 (73.7%)	27 (47.4%)	41 (71.9%)	28 (49.1%)	14 (24.6%)	0 (0%)
Sputum (11)	11 (100%)	7 (63.3%)	7 (63.3%)	4 (36.4%)	6 (54.5%)	5 (45.4%)	3 (27.3%)	0 (0%)
Blood (2)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Total (167)	161 (96.4%)	124 (74.2%)	73 (43.7%)	67 (40.1%)	94 (56.3%)	59 (35.3%)	30 (18%)	0 (0%)

[Table/Fig-7]: Resistance pattern of *E coli* from in-patient isolates to various antibiotics used

Clinical samples	Ampicillin	Cotrimoxazole	Ciprofloxacin	Cefotaxime	Gentamicin	Amikacin	Netilmicin	Imipenam
Urine (156)	143 (91.7%)	103 (66%)	24 (15.4%)	45 (28.8%)	73 (47%)	34 (21.8%)	17 (11%)	0 (0%)
Exudate (44)	42 (95.4%)	35 (79.5%)	27 (61.4%)	17 (38.6%)	27 (61.2%)	17 (38.6%)	9 (20.4%)	0 (0%)
Sputum (12)	11 (91.7%)	9 (75%)	8 (66.7%)	3 (25%)	6 (50%)	4 (33.3%)	3 (25%)	0 (0%)
Blood (0)	–	–	–	–	–	–	–	–
Total (212)	196 (92.4%)	147 (69.3%)	59 (27.8%)	65 (30.7%)	106 (50%)	55 (25.9%)	29 (13.7%)	0 (0%)

[Table/Fig-8]: Resistance pattern of *E coli* from out-patient isolates to various antibiotics

[Table/Fig-9]: Antimicrobial susceptibility testing by Kirby Bauer disc diffusion method showing sensitivity to Imipenam and Netilmicin



[Table/Fig-10]: Pure culture of E coli isolated froma sample of urine on blood agar and McConkey Agar

Drug resistance is on the rise among the *E. coli* strains that cause human infections. The studies from other developing countries have shown that the trend in enteric pathogens is towards increasing antibiotic resistance[13].

In our study, the antibiotic susceptibility pattern was studied for all the isolates of *E. coli*. Resistance was observed to the commonly used antibiotics such as ampicillin, ciprofloxacin, co-trimoxazole, cefotaxime, gentamicin, amikacin and netillin. A greater prevalence of the resistance to the common antibiotics has also been reported by other workers[14,15]. The presence of multidrug resistance may be related to the dissemination of antibiotic resistance among the hospital isolates of *E. coli*. Such multi drug resistance has serious implications for the empiric therapy of the infections which are caused by *E. coli* and for the possible co-selection of the antimicrobial resistance which is mediated by multi drug resistance plasmids[16]. Among the aminoglycosides, netilmicin was found to have an edge over gentamicin and amikacin. Similar observations have been made by a previous group of researchers [14]. A maximum number of isolates (76.9%) were resistant to ampicillin and the least number (42.8%) to netillin. These results were consistent with those of the previous studies on drug resistance in *E coli* [17,18].

When divided into age groups, the most *E. coli* resistance was seen in the adult population (age more than 18 years). This was similar to other studies which were done by Iqbal[19] et al and Aypak[20] et al. The highest resistance was seen for ampicillin (98%) and cotrimoxazole (74.4%) in the age group of more than 18 years. A similar pattern was seen with quinolones, cephalosporins and aminoglycosides. Imipenem was sensitive to all the isolates.

Another finding was a relatively low resistance to most of the antibiotics in the paediatric age group. This was because the maximum patients were of UTI, which could be because of the community acquired strains with a lesser degree of antimicrobial resistance. Also, children were not treated with higher antibiotics previously. This was in contrast to the findings of a study which was done by Iqbal et al[19], who found a relatively high resistance in the age group of 1-20 years, though they have not given supporting evidence for the same.

The rates of resistance were different among the inpatient and outpatient isolates. Our data shows the increased rates of resistance to all the antibiotics except Imipenam in the inpatient cases, as compared to that in those who were treated on an outpatient basis. This may be due to the increased use of antimicrobials in our hospital setting. These findings are similar to those of the study which was done by Al-Tawfiq in Saudi Arabia[21]. While in the outpatients, the oral, first generation cephalosporins and fluoroquinolones were effective, in the inpatients, only the newer aminoglycosides and carbapenams seemed to be effective. These findings were comparable to those of the study which was done by Gupta et al [22]. The high rate of antimicrobial resistance in the pathogens which were isolated our the hospital can possibly be explained by the selective effect of the treatment with multiple antimicrobials for a single patient, which may have resulted in the amplification of the antimicrobial resistance in some organisms [23].

On the specific subject of uropathogens, a number of alarming papers concerning the rising resistance rates have been published[17],[24],[25] and a recent case-control study by Hillier et al[26] provided evidence that the exposure to antibiotics was a strong risk factor for UTIs which were caused by resistant *E. coli*. Our study was similar to the above mentioned one, in having a high degree of resistance to ampicillin, cotrimoxazole and gentamicin. Though carbapenam resistance has been reported from other studies [27], we have not encountered any such resistance among the *E.coli* strains at our centre. Hence, the judicious use of this group of antibiotics still holds a ray of hope for the patients who are infected with multi-drug resistant organisms.

Therefore, the correct detection of drug resistant *E.coli* is important. The judicious use of antibiotics and a good antibiotic policy are needed to limit the emergence and spread of antibiotic resistance in bacteria. When selecting empirical therapy, in vitro susceptibility patterns must be considered along with other factors such as expected efficacy, adverse effects, cost, cost-effectiveness, and the selection of the resistant strains [17].

CONCLUSIONS

The continued development of antimicrobial resistance among *E.coli* isolates is disturbing and it requires both further surveillance and new approaches to slow the emergence of resistance. The trends which are seen with *E. coli* may also occur with other pathogenic organisms. The proper selection of antibiotics for the treatment depends on the results of the antibiotic sensitivity test. Since antimicrobial resistant patterns are constantly evolving, and as this is a present global public health problem, there is a necessity

for constant antimicrobial sensitivity surveillance. This will help the clinicians to provide safe and effective empiric therapies.

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