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Research Article

ANTIBIOTIC RESISTANCE TRENDS OF UROPATHOGENIC ESCHERICHIA COLI ISOLATED FROM INPATIENTS IN A TERTIARY CARE HOSPITAL IN NORTH EAST INDIA

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ABSTRACT

Background: Urinary tract infections (UTIs) are amongst the most common infections encountered in clinical practice. The commonest bacterial agent involved in causation of UTIs is *Escherichia coli*. Cotrimoxazole is the recommended drug for the treatment of UTIs. Several studies have reported increasing trends in resistance against cotrimoxazole, fluoroquinolones and other antibiotics, including ciprofloxacin. The aims and objects of this study are isolation and identification of Escherichia coli from cases of urinary tract infections from inpatients and to find out its antibiotic resistance trends.

Methods: This Study was conducted in the Department of Microbiology, RIMS, Imphal from October 2015 to September 2016. Urine specimens sent to the laboratory from inpatients (wards and ICU) were collected and further processed following standard operative procedures. Antibiotic susceptibility test was performed by Kirby Bauer's disc diffusion method using Muller Hinton Agar as per Clinical and Laboratory Standards Institute (CLSI) guidelines and susceptibility pattern was noted.

Results: Among 105 E.coli isolated, highest resistance was found for ceftazidime(91.4%), amoxicillin/clavulanic acid(87.6%) and ampicillin(85.7%) followed by ceftazidime/clavulanic acid (75.2%), ceftriaxone(75.2%), ciprofloxacin(73.3%), piperacillin/tazobactum(58%), and cotrimoxazole(46.6%). Few isolates (12.3%) were resistant to meropenem, amikacin (5.7%) gentamicin (23.8%) and oral nitrofurantoin (8.5%). 79(75.2%) isolates were found multidrug resistant (MDR) and 10 (9.5%) isolates were extensively drug resistant (XDR). Extended spectrum beta lactamase (ESBL) enzyme was detected in 34 (32.3%) E. coli isolates.

Conclusion: Empirical therapy should be tailored to the surveillance data on the epidemiology and resistance patterns of common uropathogens to reduce treatment failures and the emergence of bacterial resistant strains.

INTRODUCTION

Urinary tract infections (UTIs) are amongst the most common infections encountered in clinical practice (Borreillo *et al*). The commonest bacterial agent involved in causation of UTIs is *Escherichia coli*, being the principal pathogen both in the community as well as in the hospital (Karlowsky *et al,* 1999 and Gorbach *et al*, 2004). The treatment of UTIs varies according to the age of the patient, sex, underlying disease, infecting agent and whether there is lower or upper urinary tract involvement. Cotrimoxazole is the recommended drug for the treatment of UTIs in settings where the prevalence of resistance is <10-20 per cent and ciprofloxacin is recommended where this resistance is >20 per cent, according to the Infectious Diseases Society of America (IDSA) guidelines (Warren *et al*, 1999 and Zervos *et al*, 2000). Several studies have reported increasing trends in resistance against cotrimoxazole (Sahm *et al*, 2001 and Nys *et al*, 2006), fluoroquinolones and other antibiotics, including ciprofloxacin (Karlowsky *et al*, 2006 and Park *et al*, 2006). To reduce the rate of morbidity, an early treatment of UTIs is mandatory, which relays on empirical therapies. However, to initiate an effective empirical treatment, several factors must be taken into consideration, including geographical location, age and sex of the patient, and local antimicrobial resistance profiles of the pathogens.

In most cases of UTI, empirical antibiotic therapy is initiated before the laboratory results of urine cultures are received. Such therapy should be tailored to the surveillance data on the epidemiology and resistance patterns of common uropathogens to reduce treatment failures and the emergence of bacterial

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resistant strains (Gupta *et al*, 1999). Since the last two to three decades, just as many community and hospital acquired bacterial infections, UTIs due to multidrug resistant uropathogens have caused a growing concern worldwide (Moges *et al*, 2002 and Gonzalez *et al*, 1999). The aims and objects of this study are isolation and identification of Escherichia coli from cases of urinary tract infections from inpatients and to find out its antibiotic resistance trends.

METHODS

This Study was conducted in the Department of Microbiology, RIMS, Imphal from October 2015 to September 2016. Urine specimens sent to the laboratory from inpatients (wards and ICU) were collected and inoculated onto Blood agar and MacConkey agar and incubated at 37ºC for 24 hours. A specimen was considered positive for UTI if the bacterial colony count is $>10^5$ cfu/ml. They were further processed for identification following standard operative procedures (Collee *et al*, 2007). Antibiotic susceptibility test was performed by Kirby Bauer's disc diffusion method using Muller Hinton Agar as per Clinical and Laboratory Standards Institute (CLSI) guidelines and susceptibility pattern was noted (Wayne, 2007). The following antibiotic discs (drug concentrations in µg) were used: ampicillin (10µg), amikacin (30µg), gentamicin (10µg), ciprofloxacin (5µg), cotrimoxazole(25µg), nitrofurantoin (300µg), amoxyclav (20/10µg), piperacillin/ tazobactam (100/10µg), ceftriaxone (30µg), ceftazidime (30µg), ceftazidime/clavulanic acid (30µg/10µg), meropenem(10µg).

Identification of Multidrug Resistant (MDR), Extensive Drug Resistant (XDR) and potential ESBL Escherichia coli

MDR and XDR isolates were identified according to the combined guidelines of the European Centre for Disease Prevention and Control (ECDC) and the Centers for Disease Control and Prevention (CDC) (Magiorakos *et al*, 2012). In this study, the isolate resistant to at least one antimicrobial from three different group of first line drugs tested was regarded as multidrug resistant (MDR). Extensively drug resistant (XDR) isolates were identified when the isolates are resistant to at least one agent in all but two or fewer antimicrobial categories (i.e., bacterial isolates remain susceptible to only one or two categories). Confirmatory test of ESBL Isolates considered potential ESBL producers by initial screening were emulsified with nutrient broth to adjust the inoculum density equal to that of 0.5 Mac Farland turbidity standards. Combination Disk test (CDT), as recommended by the CLSI, was performed in all isolates presumed to be ESBL producers. In this test, Ceftazidime (30 µg) disks alone and in combination with clavulanic acid (Ceftazidime + clavulanic Acid, 30/10 µg) disks, were applied onto a plate of Mueller Hinton Agar (MHA) which was inoculated with the test strain and then incubated in ambient air for 16-18 h of incubation at 35 ± 2 °C. Isolate that showed increase of ≥ 5 mm in the zone of inhibition of the combination discs in comparison to that of the Ceftazidime disk alone was considered an ESBL producer (Wayne, 2007).

RESULTS

A total of 2200 urine samples were processed during the study period, out of that approximately 25% (550) samples showed significant growth. *Escherichia coli* was isolated from 250 (45.4% of growth positive samples) samples. 105(42% of total *Escherichia coli*) were from inpatients 96(38.4%) were from wards and 9 (3.6%) from ICU. The majority (62%) of the positive cases were females while the remaining (38%) were males (Fig.1). The frequency of *Escherichia coli* positive urine cultures were highest among the age group 40-50 years (31%) followed by 50-60 years (23%) as shown in fig. 2.

Antimicrobial resistance pattern of E. coli

High level of drug resistance was seen in E. coli isolates. Among 105 E. coli isolated, highest resistance was found for ceftazidime(91.4%), amoxicillin/clavulanic acid(87.6%) and ampicillin(85.7%) followed by ceftazidime/ clavulanic acid(75.2%), ceftriaxone (75.2%) and ciprofloxacin(73.3%). Resistance for piperacillin/ tazobactum(58%), and cotrimoxazole (46.6%) was found to be moderate. Very few isolates (12.3%) were resistant to meropenem, whereas resistance rate for injectable aminoglycosides (amikacin 5.7% and gentamicin 23.8%) and oral nitrofurantoin (8.5%) is also less (Table 1).

Multidrug resistant (MDR) and Extensive drug resistant (XDR) isolates

Among total 105 E. coli isolates subjected for antimicrobial susceptibility testing, 79(75.2%) isolates were found to be multidrug resistant (MDR) and 10 (9.5%) isolates were extensively drug resistant (XDR). MDR isolates were resistant to ampicillin (100%), ciprofloxacin (100%), third generation cephalosporins eg. Ceftazidime (100%), cefixime (100%) and cefpodoxime (100%), amoxicillin/clavulanate (98%), cotrimoxazole (96%) and ceftriaxone (96%) respectively. However, MDR isolates were susceptible towards amikacin (90.2%), meropenem (88.3%), nitrofurantoin (86.3%) and gentamicin (69%). Although the number of XDR isolates was low, they were completely resistant to all antibiotics except meropenem, amikacin and nitrofurantoin (Table 1).

ESBL E.coli and their susceptibility pattern

Extended spectrum beta lactamase (ESBL) enzyme was detected in 34 (32.3%) E. coli isolates. Penicillins, cephalosporins and monobactam group of antibiotics were appeared completely ineffective (100% resistance) against ESBL producers. However, ESBL producing E.coli strains were susceptible to reserve class of antibiotics including meropenem 29 (86.6%).

Table 1 Antibiotic susceptibility pattern of total MDR, and XDR E coli isolates

Name of the antibiotic	Total no. of isolates (%age resistance)	MDR isolates=XDR isolates=10 79 (%age resistance)	(%age resistance)
Ampicillin	90(85.7%)	79(100%)	10(100%)
Amoxicillin/Clavulanic acid	92(87.6%)	103(98%)	10(100%)
Ciprofloxacin	77(73.3%)	79(100%)	9(90%)
Cotrimoxazole	49(46.6%)	101(96%)	10(100%)
Gentamicin	25(23.8%)	33(31%)	3(30%)
Amikacin	6(5.7%)	10(9.8%)	5(50%)
Nitrofurantoin	9(8.5%)	14(13.7%)	2(20%)
Meropenem	13(12.3%)	12(11.7%)	6(60%)
Ceftazidime	96(91.4%)	79(100%)	10(100%)
Ceftazidime/Clavulanic acid	79(75.2%)	98(94%)	10(100%)
Piperacillin/Tazobactum	61(58%)	76(72.5%)	10(100%)
Ceftriaxone	79(75.2%)	101(96%)	10(100%)
Cefixime	95(90.4%)	79(100%)	10(100%)
Cefpodoxime	96(91.4%)	79(100%)	10(100%)

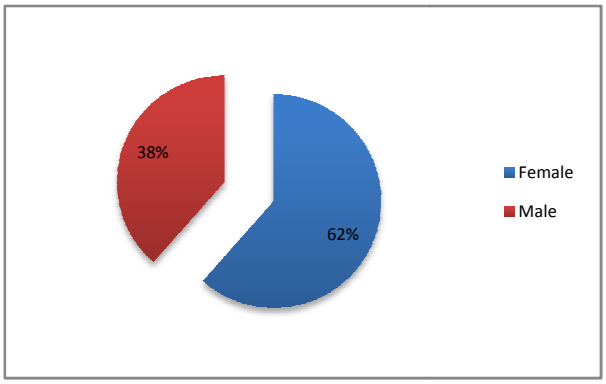

Fig 1 Pie chart showing gender predisposition of UTI for females

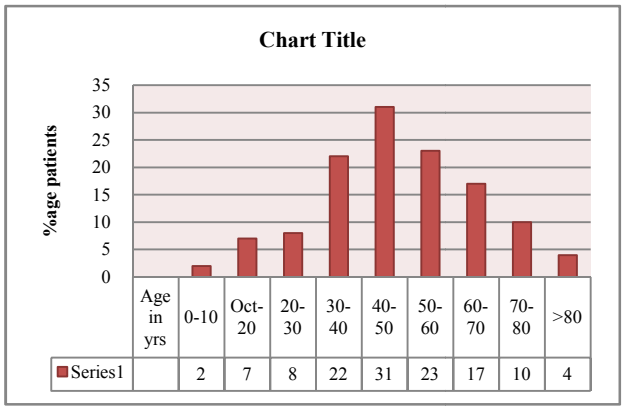

Fig 2 Bar diagram showing age wise distribution of patients.

DISCUSSION

E. coli and other uropathogens are becoming increasingly resistant to commonly used antimicrobial agents, reducing the effectiveness of some standard regimens. Meanwhile, epidemiologic and resistance patterns of the pathogens in UTIs show inter-regional variability, and the susceptibility patterns are continuously changing depending on different regional antibiotic treatment regimens (Friedrich *et al*, 1999, Karlowsky *et al*, 2002 and Hooton *et al*, 1997). Antibiotic resistance is a major factor contributing to therapeutic failure. The present study illustrates the demographic variables of E.coli associated UTI and antimicrobial susceptibility patterns from inpatients in a tertiary care hospital in north east India over a period of 1 year.

The anatomical differences in the female urinary system, including a short urethra and the proximity to the vulvar and perianal areas, result in a higher prevalence of UTI in females (Sobel and Kaye, 2002). The guidelines of the Infectious Diseases Society of America (IDSA) for the treatment of UTI recommend avoiding empirical treatment with a specific antibiotic when the local level of resistance among *E. coli* strains exceeds 20%. Previously, the first empirical antibiotic for UTI treatment was cotrimoxazole. However, resistance rate to cotrimoxazole in *E. coli* was reached at 50% in studies done by Ko *et al*., 2003; Shin *et al*., 2005 and 36.06% in study done by Hong *et al* in 2004 while resistance rate is 46.6% in our study. And these finding demonstrated that cotrimoxazole was no longer reasonable choice in empirical treatment of UTI. Furthermore, the most alarming finding in our study was the exceedingly high resistance rate of *E.coli* to ciprofloxacin (73.3%). This rate is higher than that reported by Hong *et al* in 2013 (33.55%) and lower than a study done by Parajuli *et al*, 2016 (78%). These results imply that quinolones, which are commonly used in the management of UTI, might gradually lose their utility in the empiric treatment of UTI.

In addition, the resistance rates for first generation and third generation cephalosporins in *E. coli* is increasing over time. In our study the resistance rate for ceftazidime is 91.4% and cefixime is 90.4% while in a study done by Ali *et al*, 2006 this resistance is 57.5% and 53.5% respectively. In a study done by Parajuli *et al*, 2006 resistance rate for ceftazidime (45%), ceftriaxone (45%) and cefixime (71%) which is lower than our study.

The percentage of isolates of *E.coli* resistant to ampicillin was found to be as much as 85.7 per cent in our set up. Such high levels of resistance to ampicillin have been quoted by many other studies from different parts of India. Gupta *et al*, 2007 in a study from the northern part of the country reported 76 per cent resistance to *E.coli* isolates for ampicillin. A more recent study from Karnataka and Pondicherry reported a resistance rate of 80.6 per cent and 80 percent for ampicillin (Manjunath *et al*, 2011, Mandal *et al*, 2012, Niranjan and Malini, 2014).

A low degree of resistance to amikacin (5.7% and 9.8%) and gentamicin (23.8% and 31%) (aminoglycoside drug) was observed for total and MDR isolates respectively which is less than study done by Bajpai *et al*, 2014 (12.5% and 36.8%) for amikacin and (31.3% and 51.5%) for gentamicin in ESBL and non ESBL produers respectively and hence may be helpful in combating severe infections. Aminoglycosides being injectables are used restrictively in the community care setting and have showed lesser resistance rates and hence may be helpful in combating severe infections (Sood and Gupta, 2012). Another oral antibiotic nitrofurantoin (8.5% and 13.7% resistance among total and MDR cases) was found to be more effective in treatment of UTI in our case and the findings are in agreement with similar surveillance studies by Sasirekha *et al*, 2013 and Bajpai *et al*, 2014 and other Indian studies, which have demonstrated nitrofurantoin as an appropriate agent for first line treatment of community acquired UTI. Low antimicrobial resistance for nitrofurantoin can be attributed to its localized action on urinary tract and not being exposed outside urinary tract (Rajesh *et al*, 2010).

Resistance to meropenem 12.3% in our study is quite alarming. Carbapenem resistance is usually multifactorial. Resistance to carbapenems occurs through bacterial production of betalactamase enzymes that hydrolyze the antibacterial agent or through porin changes in the bacterial cell wall that reduce the permeability of the drug into the organism. In addition, upregulation of efflux pumps result into reduced susceptibility of organisms toward meropenem (Rodriguez *et al*, 2009). Resistance shown by Bajpai *et al*, 2014 for meropenem is 52.1%. This may be because patients in Intensive Care Unit are directly being treated with carbapenems that has led to development of such multidrug-resistant isolates in our health-care setting.

In this study, multidrug resistant (MDR) and extensively drug resistant E coli were found 75.2% and 9.5% respectively while this resistance is 64.9% and 5% by study done by Parajuli *et al*, 2017 in Nepal. In another study done by Niranjan and Malini, 2014 in puduchery the MDR rate for E.coli isolated from cases

of UTI was found to be 76.5%. Increasing pattern of resistance of urinary tract pathogens against common antibiotics is reported from other studies in India (Mandal *et al*, 2012).

ESBL-producing *E. coli* is an emerging cause of nosocomial healthcare-associated, and community-acquired infection worldwide (Eliopoulos and Bush, 2001). Inadequate empirical antibiotic therapy for infections caused by this microorganism is associated with poor outcomes and the use of carbapenem or cefepime is only effective for patients infected by ESBL (Ramphal and Ambrose, 2006). Our prevalence rate of ESBL producing E coli (32.3%) is less than the findings reported by other studies in different parts of Asian region including Shettigar *et al*, 2016 (37.7%) from India, Pourakbari *et al*., 2010 (37%) and Moore *et al*, 2016 (44%) from Cambodia and Kizilca *et al*, 2012 (41.4%) from Turkey. Extremely higher rates of ESBL E coli have also been reported, notably by Chinnasami *et al*, 2016 (83%) from India, Masud *et al*, 2014 (53.8%) from Bangladesh and Shah *et al*, 2015 (50.9%) from Pakistan. The increased rate of ESBL-producing bacteria causing infection in community as well as hospital settings constitutes an undeniable trend.

CONCLUSION

The sensitivity pattern of microorganisms to various antibiotics varies over time and among different geographical locations. Therefore, continuous analysis of the antibiotic resistance pattern acts as a guide in initiating the empirical treatment of UTI and the therapy must be started only after the gold-standard test like urine culture and sensitivity have been done. Since, according to the present study the susceptibility for injectable amikacin and oral nitrofurantoin is found to be high so these drugs can be used for empirical treatment of UTI, moreover carbapenem drugs should never be used for empirical treatment, it should be used only as a last line resort to avoid its developing resistance in the community.

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Conflicts Of Interest: None declared.

Ethical Statement: Ethical approval has been taken from the Institutional ethics committee for this study.

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