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Original Article

Cost Effective Antibiotics Versus Meropenem Against Extended Spectrum Beta Lactamase Producing *Escherichia Coli* from Urine

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ABSTRACT

Introduction: urinary tract infections are one of the most common infectious diseases in the world. *Escherichia coli* is the most common cause of Urinary tract infection. Antibiotics are the routine therapy of urinary tract infection but due to misuse of them there is increasing resistance to them.

Objective: To compare the in-vitro efficacy of cost effective antibiotics versus meropenem against Extended Spectrum Beta Lactamase producing *Escherichia coli* in urine.

Methodology:

Material and Methods: This Cross sectional descriptive study was conducted from 1st January 2018 to 31st May 2018 at the Department of Microbiology Army Medical College. *Escherichia coli* isolated from urine samples were first tested for the production of beta-lactamase. The susceptibility of Extended Spectrum Beta Lactamase producing *Escherichia coli* to fosfomycin, nitrofurantoin and meropenem was checked and compared.

Results: A total of 133 extended spectrum beta lactamase producing *Escherichia coli* were isolated and tested. Out of these 99.25 % were susceptible to fosfomycin, 97% to nitrofurantoin and 95.5% to meropenem. Isolates were 3.75% more susceptible to fosfomycin and 1.75% more susceptible to nitrofurantoin than meropenem.

Conclusion: Fosfomycin and nitrofurantoin was much more efficient against extended spectrum beta lactamase producing *Escherichia coli* as compared to meropenem. Easy to administer and being cost effective Fosfomycin and nitrofurantoin are very good options if to be used as first line therapy against extended spectrum beta lactamase producing *Escherichia coli*.

Keywords: *Escherichia coli,* extended spectrum beta lactamase (ESBL), fosfomycin, nitrofurantoin, meropenem

Introduction

The incidence of Urinary tract infection in general population reached 18/1000 persons per year and it is considered most prevalent infectious disease. Urinary tract infection is more common in females. The most common pathogen in urinary tract infection is *Escherichia coli*.[1]

In current situation, inappropriate and frequent use of antibiotics has led to increase in rate of resistance in Gram negative bacteria. As a result treatment of urinary tract infections is becoming more difficult. In Enterobacteriaceae most common pathogen is *Escherichia coli* and *Klebsiella pneumoniae ; in* addition to other resistance mechanisms to standard antibiotics there is also emergence of extended spectrum beta lactamase.[2] Group of beta lactamases which has ability to hydrolyze aztreonam and 3rd generation cephalosporins are known as extended spectrum beta lactamases (ESBL).

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The ESBL are mostly plasmid encoded so the choice of antibiotics in treating ESBL are very limited.[3]

For the treatment of serious infections caused by ESBL producing Enterobacteriaceae, carbapenems are the drug of choice and in tertiary care centers it is most frequently used antibiotic against Gram negative rods.[4] But the drawbacks of carbapenems include parenteral route of administration, high cost, need of hospitalization and potential of resistance .[5]

Fosfomycin is an old antimicrobial drug but it is among the very few options available for the treatment of multidrug resistant strains.[6] It prevents the synthesis of peptidoglycan by inhibiting MurA. Fosfomycin is now again gaining attention for treatment of Enterobacteriaceae especially ESBL producing isolates.[7]

In addition fosfomycin needs only one dose, has very low resistance reported worldwide and there are multiple studies that support its use in UTI against multidrug resistant pathogens.[8] Fosfomycin is very low molecular weight derivative of phosphonic acid It is very active against *Escherichia coli* and its Minimum inhibitory concentrations are very low.[9] It is available

both intravenous and oral forms. In urinary tract infections it is used in oral form as single dose for treatment but as intravenous dose it is used in combination with other antibiotics in bacteremia and pneumonia due to multidrug resistance of Gram negative bacteria.[10] The resistance mechanism of fosfomycin is an enzymatic modification by plasmid encoded glutathione transferase and also binding site modification of fosfomycin Cys 115 .[11]

Nitrofurantoin belongs to a group nitrofurans which are compounds containing nitro groups. The mode of action of nitrofurantoin is reduction to compounds that interfere in the synthesis of RNA, DNA and protein. The resistance is mainly due to mutations in nfsA and nfsB.[11] It is available in oral form and it reaches a very high concentration in urine when taken orally so it is given in lower urinary tract infections. It is very effective against *Escherichia coli, Klebsiella pneumoniae, Enterococcus* and *Citrobacter*. Recommended dosage is 50mg to 100mg four times a day.[12]

Infectious Disease Society of America reported ESBL producing *Escherichia coli* and *Klebsiella pneumoniae* among six drug resistant microbes for which new treatment options are immediately needed.[13]

Material and Methods

The Study was cross sectional descriptive and was conducted at Army Medical College/ National University of Medical Sciences in department of microbiology from 1st January 2018 to 31st May 2018. Non probability consecutive sampling technique was used and SPSS (version 22) was used for data analysis. In this period of time all urinary samples received in microbiology department were plated out on cysteine lactose electrolyte deficient agar plates and incubated for 48 hours at 35°C +/-2。C for the isolation of uropathogens. During this period any growth observed was dealt by using colony morphology, Gram stain, motility and biochemical profile (Analytical Profile Index 20E Biomerieux, France). After identifying organism, modified Kirby-Bauer disc diffusion method was used to test antibiotic sensitivity of the organism on Muller –Hinton agar. For sensitivity, antibiotic disks of Nitrofurantoin 300µg, Fosfomycin 50µg and Meropenem10µg were used. After incubation, bacterial growth's zone of inhibition was measured and checked with the clinical and laboratory standards institute (CLSI, 2018) guidelines. In the presence of clavulanate by observing enhancement of zone of inhibition around ceftriaxone and aztreonam ESBL production was confirmed. The rationale of study was to compare the sensitivity of *Escherichia coli* to meropenem, nitrofurantoin and fosfomycin.

Results

Total 2890 urine samples received in microbiology department during the study period. Out of them significant bacteriuria was noted in 816 (28.2%) samples while the 2074 samples were either sterile or were non-significant bacteriuria.

Out of total 437(88.6%) Enterobacteriaceae, the extended spectrum beta lactamase producing organisms were 154 (35.2%) as shown in Table 1.

Table 1: Frequency and Percentages

Samples	N (%)
Total samples	2890
Positive samples	816(28.2%)
Gram negative rods	493(60.41%)
Enterobacteriaceae	437(88.6%)
ESBL	154(35.2%)

Out of total 154 ESBL producing isolates 133 (86.3%) were *Escherichia coli* followed by *Klebsiella pneumoniae* 12 (7.7%) as shown in table 2. Among ESBL producing *Escherichia coli* 48.87% were males and 51.12% were females. The mean age of males were 58.8 years while females were 51.12 years.

Table 2: Frequency and Percentages of ESBL Producing Isolates

Pathogens	n(%)
Escherichia coli	133(86.3%)
Klebsiella pneumoniae	12(7.7%)
Others	9(5.8%)

ESBL producing *Escherichia coli* showed 99.25% sensitivity to fosfomycin, 97% sensitivity to nitrofurantoin and 95.5% to meropenem as shown in table 3.

Table 3: Sensitivity % of ESBL Producing *Escherichia coli* to Antibiotics

Antibiotics	Sensitivity% of *Escherichia coli*
Fosfomycin	99.25%
Nitrofurantoin	97%
Meropenem	95.5%

Discussion

In this era of antibiotic resistance, Fosfomycin and nitrofurantoin are proved to be of much value. According to the European guidelines for the antimicrobial therapy they recommended oral fosfomycin and nitrofurantoin against *Escherichia coli* as it is still susceptible to these antibiotics over 90%.[14] The main worry with fosfomycin is development of resistance during treatment .But while treating urinary tract infection the frequency of resistance to fosfomycin is very less for *Escherichia coli* as compared to other microbes.[15]

A survey conducted in Spain showed resistance frequency of ESBL producing *Escherichia coli* to fosfomycin as 0.3% and declared fosfomycin as first line of treatment for cystitis .It is an effective alternative and is used for treatment of asymptomatic UTI in pregnancy.[16] A study conducted in teaching hospital Taiwan showed 95.5% of ESBL producing *Escherichia coli* were sensitive to fosfomycin.[17] A systemic review was carried out to evaluate fosfomycin as treatment option for ESBL producing Enterobacteriaceae and it reported 96.8% ESBL producing *Escherichia coli* were susceptible to fosfomycin.[18] Our study also showed 99% ESBL producing *Escherichia coli* was susceptible to fosfomycin. Hence fosfomycin is better therapeutic choice for the treatment of UTI.

Nitrofurantoin is an old antibiotic and in our study ESBL producing *Escherichia coli were* 97% susceptible to nitrofurantoin and our results are nearly same as the study conducted in India which showed nearly 90% susceptibility to nitrofurantoin and 99.6% to fosfomycin[19] .The study conducted in Turkey showed 98% susceptibility to nitrofurantoin.[20] So for ESBL producing *Escherichia coli* nitrofurantoin is also a promising therapeutic option.

Pakistan is a developing country and by prescribing fosfomycin and nitrofurantoin we not only decrease the burden on health budget as they are cost effective They are also available in oral form and patient does not need hospitalization. As a result carbapenems can be spared for complicated and multidrug resistant infections.

Conclusion

Fosfomycin and nitrofurantoin is more efficient and cost effective in ESBL producing *Escherichia coli* as compared to meropenems.They can be regarded as good options if use as first line of therapy in UTI.

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A. Conception/Study/Designing/Planning
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C. Interpretation/ Analysis and Discussion