

**Fosfomycin and Nitrofurantoin Susceptibility among Extended Spectrum betalactamase (ESBL) Producing Uropathogenic *Escherichia Coli***Vijetha Sajjanar<sup>1</sup>, Premalatha D E<sup>2</sup>, Siddesh K C<sup>3</sup><sup>1</sup>Assistant Professor, Department of Microbiology, KLE JGMMMC, Hubli, Karnataka KLE Academy of Higher Education and Research (KAHER)<sup>2</sup>Assistant Professor, Shimoga Institute of Medical Sciences and Hospital, Shivamogga, Karnataka<sup>3</sup>Associate Professor, Shimoga Institute of Medical Sciences and Hospital, Shivamogga, Karnataka

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Conflict of interest: Nil

**Abstract:**

**Introduction:** Urinary tract infections(UTI) are most common bacterial infections encountered in clinical practice and *Uropathogenic Escherichia. Coli( UPEC)* is predominant organism which causes UTI. Misuse of antibiotics has led to multidrug resistance in *UPEC*. Extended spectrum beta lactamase (ESBL) producing organisms has led to emergence of multidrug resistance to routinely used antibiotics. Fosfomycin and Nitrofurantoin have unique mechanism to delay the evolvement of resistance and are most preferred drugs in multidrug-resistant uropathogenic *E.coli*. The present study was undertaken to analyse trends of fosfomycin and nitrofurantoin susceptibility among Extended spectrum beta lactamase (ESBL) producing *Uropathogenic Escherichia coli*.

**Objectives:**

1. To detect extended spectrum beta lactamase production in uropathogenic *E. coli*.
2. To analyse the fosfomycin and Nitrofurantoin susceptibility pattern of extended spectrum beta lactamase producing uropathogenic *E. coli*.

**Materials and Methods:** The study was conducted on 365 urine samples received from patients with suspected UTI during the period of January 2018 to June 2018 received at Microbiology laboratory from Mc Gann Teaching Hospital, attached to Shivamogga Institute of Medical Sciences, Shivamogga. These samples were processed on blood agar, chocolate agar, and MacConkey agar media and incubated at 37°C under aerobic conditions. The organisms were identified as per standard conventional methods. ESBL detection was done as per CLSI guidelines. Fosfomycin and Nitrofurantoin susceptibility testing will be performed by Kirby Bauer Disk Diffusion method and interpreted as per CLSI guidelines.

**Results & Discussion:** Among 365 samples 240 samples showed significant bacteriuria, 105 samples showed no growth, 20 samples showed non-significant bacteriuria. *Escherichia coli* was most predominant organism isolated accounting for 45.83% (110/240). Out of 110 *E. coli* isolates 97(88.18%) were ESBL positive by screening method and 95(97.93%) were ESBL positive by confirmatory method. Antibiotic sensitivity in ESBL positive UPEC shows.

Fosfomycin(100%), Nitrofurantoin(90.52%) and ESBL negative UPEC shows Fosfomycin (100%), Nitrofurantoin(100%).

**Conclusion:** Multidrug resistance among uropathogenic *Escherichia* requires implementation of alternative treatment strategies for the Urinary tract infection. Thus Fosfomycin and Nitrofurantoin are potential antibiotics for empirical treatment of UTI.

**Keywords:** Fosfomycin, Nitrofurantoin, Uropathogenic *Escherichia Coli (UPEC)*, ESBL

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**Introduction**

Uropathogenic *Escherichia coli (UPEC)* is important cause of community acquired Urinary Tract Infection (CA-UTI) and Hospital acquired UTI accounting for mortality and morbidity worldwide.[1] UPEC is subsets of fecal *E. coli* that can enter colonize urinary tract and cause infection.[2] Extended spectrum beta lactamase (ESBL) are growing class of plasmid mediated beta lactamases which hydrolyse oxyamino beta lactams.

TEM, SHV, and CTX-M are three classes of ESBL.[3] blaESBLs are encoded by plasmids which carry resistance genes against antibiotics such as aminoglycosides, sulfonamides, and quinolones. Multidrug-resistant ESBL-producing UPEC strains are major public health threat and have treatment options. [2,3] Beta lactamase enzymes survive in periplasmic space and attack the antibiotic preventing it to reach target site causing antibiotic

resistance. Therefore, Beta lactamase production remains most important contributing factor for beta lactam resistance in gram negative pathogens like *Escherichia coli*, *Klebsiella species*, *Pseudomonas species*. [3] Extensive and inappropriate use of antibiotics as empirical treatment has also resulted in emergence of multidrug-resistant bacteria. This multidrug resistance leads to failure of treatment regime, delay in clinical response, high-cost treatment, higher mortality and morbidity. [3,4] Fosfomycin and Nitrofurantoin are most preferred drugs in multidrug resistant uropathogenic *E.coli*(UPEC).[4,5]

Nitrofurantoin has ability to act at multiple targets in the bacterial cell and thus resistance has not evolved as fast as other drugs with a single bacterial target. Fosfomycin, has a unique mechanism of antimicrobial action that involves the inhibition of UDP- N-acetylglucosamine enolpyruvyl transferase (MurA), an enzyme that catalyses the first step in bacterial cell-wall synthesis within the cell.[5] The present study was undertaken to analyse trends of fosfomycin and nitrofurantoin susceptibility among Extended spectrum betalactamase (ESBL) producing *Uropathogenic Escherichia coli*.

#### Materials and Methods

A prospective study was conducted in the Department of Microbiology, Shimoga Institute of Medical Sciences and Mcghan Teaching Hospital, Shivamogga. between January 2018 and June 2018. A total of 365 clean catch midstream urine samples collected in wide mouthed sterile container were received and analysed for urine culture and sensitivity profile along with detection of ESBL production at Department of Microbiology, Shimoga Institute of Medical Sciences, Shivamogga

#### Isolation and Identification

Wet mount preparation of urine specimen was examined and looked for the presence of pus cells, red blood cells, urinary casts, epithelial cells.[6] Samples were further processed by Standard loop technique (A semiquantitative method) where a loopful (0.001 ml) of well mixed uncentrifuged urine was inoculated onto the surface of blood agar and MacConkey agar plates. Plates were then incubated at 37°C degree celcius aerobically for 24hrs. Positive urine culture was determined by significant bacteriuria (count > 10<sup>5</sup> CFU /ml in a carefully taken and promptly examined sample).[6,7] The organisms isolated were identified by their colony morphology, Gram stain and relevant standard biochemical methods. Catalase and oxidase test was done.[6,7]

#### ESBL detection as per CLSI guidelines

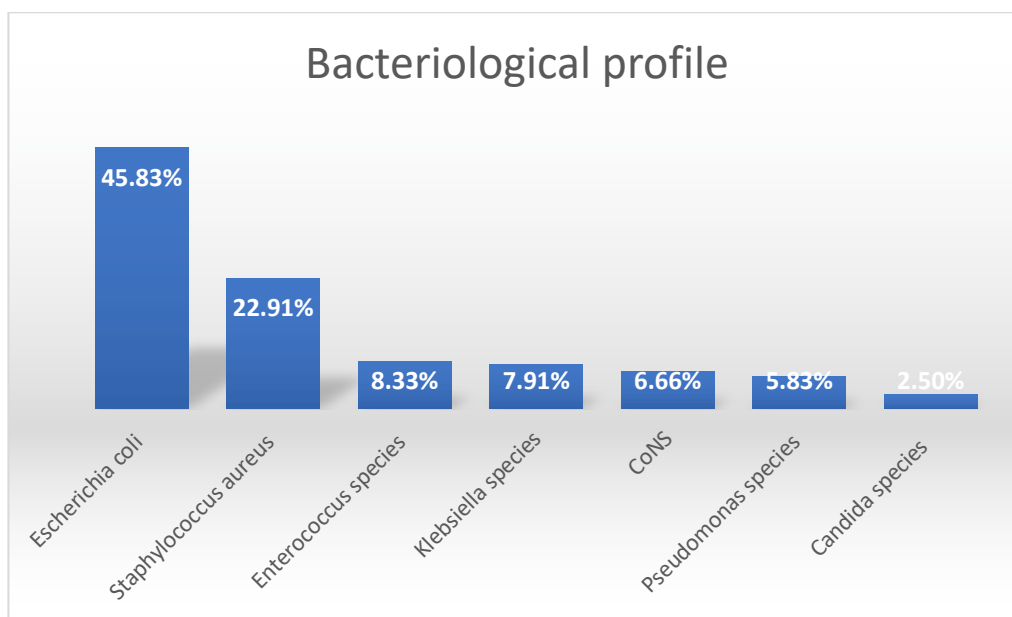
Detection of ESBL production was done by Screening method and Confirmatory method. Screening method of ESBL detection was by Disk diffusion method. According to CLSI guidelines, zone diameter of *E.coli* strain for ceftazidime <22mm and for cefotaxim < 27mm is presumptively taken to indicate ESBL production. Confirmatory methods of ESBL detection was by Combined Disk diffusion method.[8] According to CLSI guidelines, ESBLs will be confirmed by placing a disc of Cefotaxime and Ceftazidime at a distance of 20mm from a disc of Cefotaxime/clavulanic acid(30/10µg) and Ceftazidime/clavulanic acid(30/10µg) respectively on a lawn culture of test strain(0.5 Mcfarland inoculums size)on Muller hinton agar. After overnight incubation at 37°C, ESBL production will be confirmed if there is a ≥5mm increase in zone diameter for either antimicrobial agent in combination with clavulanic acid versus its zone when it is tested alone.[8]

#### Antimicrobial susceptibility testing

Antibiotic susceptibility testing was carried out by Kirby Bauer Disk Diffusion method.[6,7] Following antibiotics were used for gram negative organisms Fosfomycin(200µg), Ampicillin(10µg), Gentamicin (10µg) Nitrofurantoin (300µg), Cotrimoxazole (1.25/23.75µg), norfloxacin (10µg), Ofloxacin (5µg), Aztreonam (30µg), Ceftazidime (30µg), Cefotaxim (30µg) Amikacin (30µg), Amoxiclavulanic acid (30µg), Ciprofloxacin (5 µg), Levofloxacin (5µg), Imipenam (10µg), Piperacillin Tazobactam (100:10 µg). Antibiotics used for gram positive organisms Fosfomycin (200µg), Nitrofurantoin (300µg), Linezolid (10µg), Vancomycin (30µg), Erythromycin (15µg), Azithromycin (15µg), Clindamycin (2µg) Doxycycline (30µg), Gentamycin (10µg), Ciprofloxacin (5µg), Norfloxacin (10µg), Cotrimoxazole (1.25/23.75µg), Cefoxitin (30µg). Interpretation was as per Clinical Laboratory Standard Institute (CLSI) guidelines.[6,7,8]

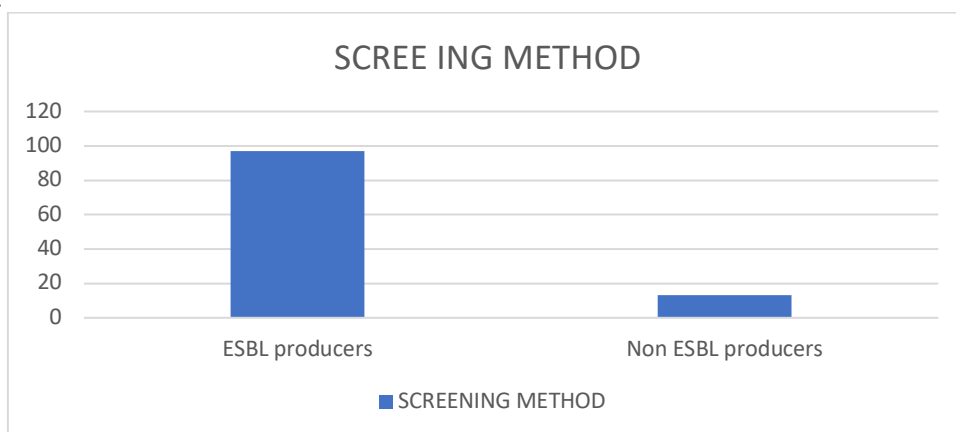
#### Result

A total of 365 urine samples were received at clinical laboratory from patients with suspected UTI during the period of January 2018 to June 2018. Among 365 samples 240 samples showed significant bacteriuria, 105 samples showed no growth, 20 samples showed non-significant bacteriuria. *Escherichia coli* was most predominant organism isolated accounting for 45.83% (110/240) followed by *Staphylococcus aureus* 22.91% (55/250), *Enterococcus species* 8.33% (20/240), *Klebsiella species* 7.91% (19/240), *CoNS (coagulase negative Staphylococcus)* 6.66% (16/240) *Pseudomonas species* 5.83% (14/240), *Candida species* 2.5% (6/240).

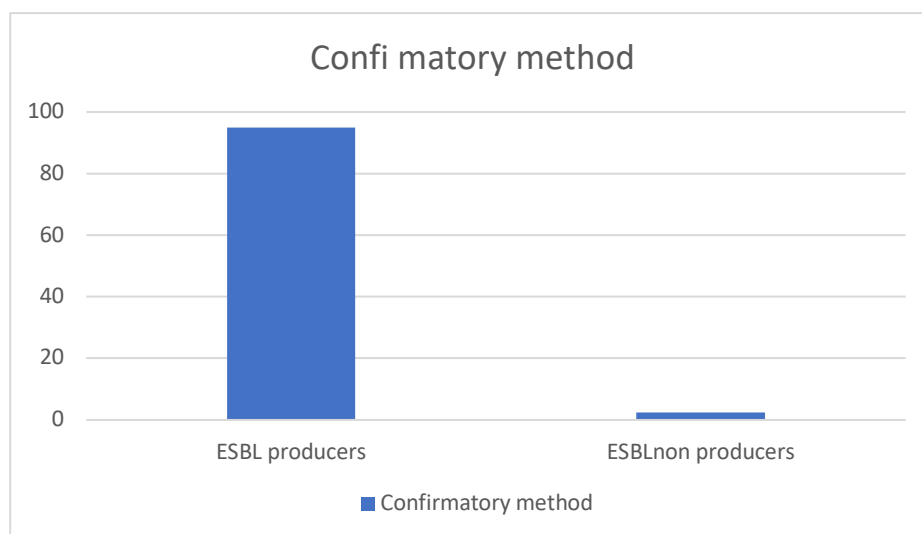


**Figure 1: Bacteriological profile**

Out of 110 *E.coli* isolates 97(88.18%) were ESBL positive and 13(11.81%) were ESBL negative by screening method as per CLSI guidelines. A total of 97 isolates were subjected to ESBL confirmatory test by combined disc diffusion method. Among 97 isolates 95(97.93%) were ESBL positive by confirmatory method as per CLSI guidelines.



**Figure 2: Screening Method**

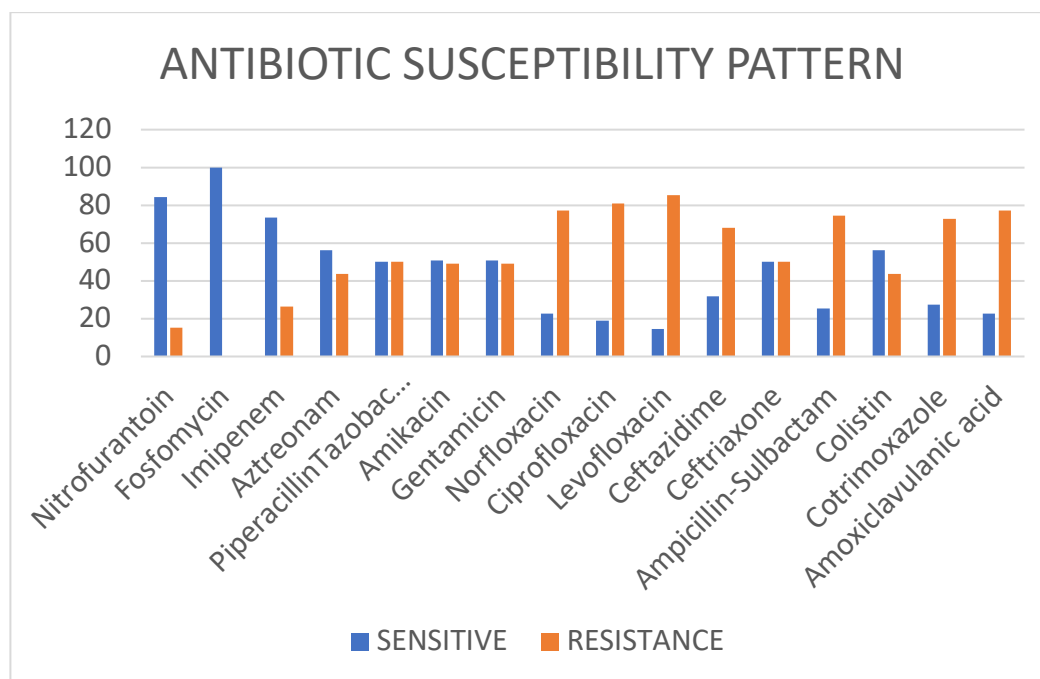


**Figure 3: Confimatory Method**

Antibiotic susceptibility pattern of uropathogenic Escherichia coli is as follows: Nitrofurantoin 84.45%(93), Fosfomycin 100% (110), Imipenem 73.63%(81), Aztreonam 56.36%(62), Piperacillin Tazobactam 50%(55), Amikacin 50.90%(56), Gentamicin 50.90%(56), Norfloxacin 22.72% (25), Ciprofloxacin 19.09%(21), Levofloxacin 14.54%(16), Ceftazidime 31.81%(35), Ceftriaxone 50%(55), Ampicillin-Sulbactam 25.45%(28), Colistin 56.36%(62), Cotrimoxazole 27.27%(30), Amoxiclavulanic acid 22.72% (25).

**Table 1:**

Antibiotic	Sensitive (%)	Resistance (%)
Nitrofurantoin	84.45% (93)	15.14% (17)
Fosfomycin	100% (110)	0% (0)
Imipenem	73.63% (81)	26.36% (29)
Aztreonam	56.36% (62)	43.63% (48)
Piperacillintazobactam	50% (55)	50% (55)
Amikacin	50.90% (56)	49.09% (54)
Gentamicin	50.90% (56)	49.09% (54)
Norfloxacin	22.72% (25)	77.27% (85)
Ciprofloxacin	19.09% (21)	80.90% (89)
Levofloxacin	14.54% (16)	85.45% (94)
Ceftazidime	31.81% (35)	68.18% (75)
Ceftriaxone	50% (55)	50% (55)
Ampicillin-Sulbactam	25.45% (28)	74.54% (82)
Colistin	56.36% (62)	43.63% (48)
Cotrimoxazole	27.27% (30)	72.72% (80)
Amoxiclavulanic Acid	22.72% (25)	77.27% (85)



**Figure 4: Antibiotic Susceptibility Pattern**

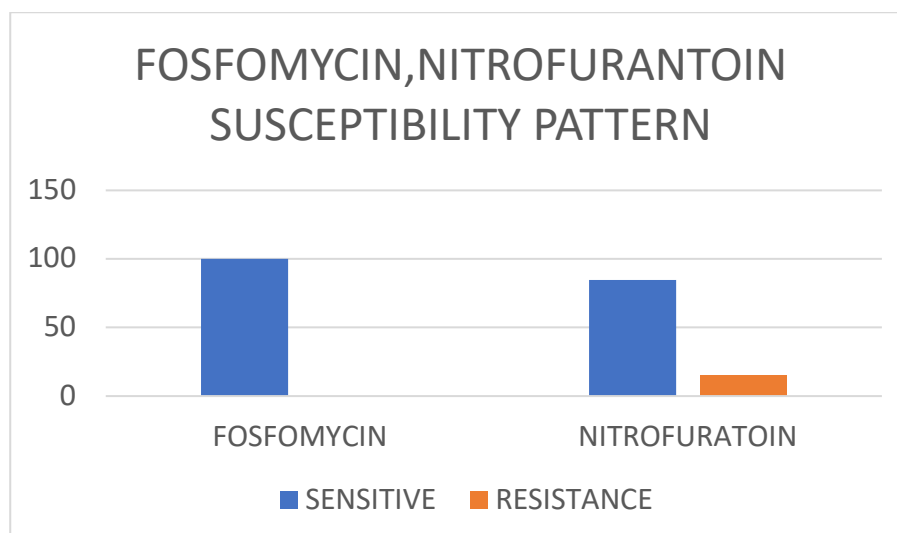


Figure 5: Fosfomycin, Nitrofurantoin Susceptibility Pattern

Table 2:

Antibiotics	ESBL positive UPEC sensitivity(%)	ESBL negative UPEC sensitivity(%)
Nitrofurantoin	90.52%(86)	100%(15)
Fosfomycin	100% (95)	100%(15)
Imipenem	74.73%(71)	100%(15)
Aztreonam	68.42%(65)	80%(12)
Piperacillin Tazobactam	50.52%(48)	73.33%(11)
Amikacin	48.42%(46)	73.33%(11)
Gentamicin	48.42%(46)	73.33%(11)
Norfloxacin	18.94%(18)	40%(6)
Ciprofloxacin	21.05%(20)	53.33%(8)
Levofloxacin	22.10%(21)	60%(9)
Ceftazidime	32.63%(31)	66.66%(10)
Ceftriaxone	41.05%(39)	66.66%(10)
Ampicillin-Sulbactam	23.15%(22)	73.33%(11)
Colistin	68.42%(65)	80%(12)
Cotrimoxazole	36.84%(35)	73.33%(11)
Amoxiclavulanic acid	40%(38)	73.33%(11)

Antibiotic sensitivity in ESBL positive UPEC shows Fosfomycin (100%), Nitrofurantoin (90.52%), Imepenem (74.73%), Aztreonam (68.42%), Piperacillin- Tazobactam (50.52%), Amikacin (48.42%), Genntamicin (48.42%), Norfloxacin (18.94%), Ciprofloxacin (21.05%), Levofloxacin (22.10%), Ceftazidime (32.63%), Ceftriaxone (41.05%), Ampicillin sulbactam (23.15%), Colistin (68.42%), Cotrimoxazole (36.84%), Amoxiclavulanic acid (40%).

Antibiotic sensitivity in ESBL negative UPEC shows Fosfomycin (100%), Nitrofurantoin (100%), Imepenem (100%), Aztreonam (80%), Piperacillin-Tazobactam (73.33%), Amikacin (73.33%), Gentamicin (73.33%), Norfloxacin (40%), Ciprofloxacin (53.33%), Levofloxacin (60%), Ceftazidime (66.66%), Ceftriaxone (66.66%), Ampicillin-sulbactam (73.33%), Colistin (80%), Cotrimoxazole (73.33%), Amoxiclavulanic acid(73.33%).

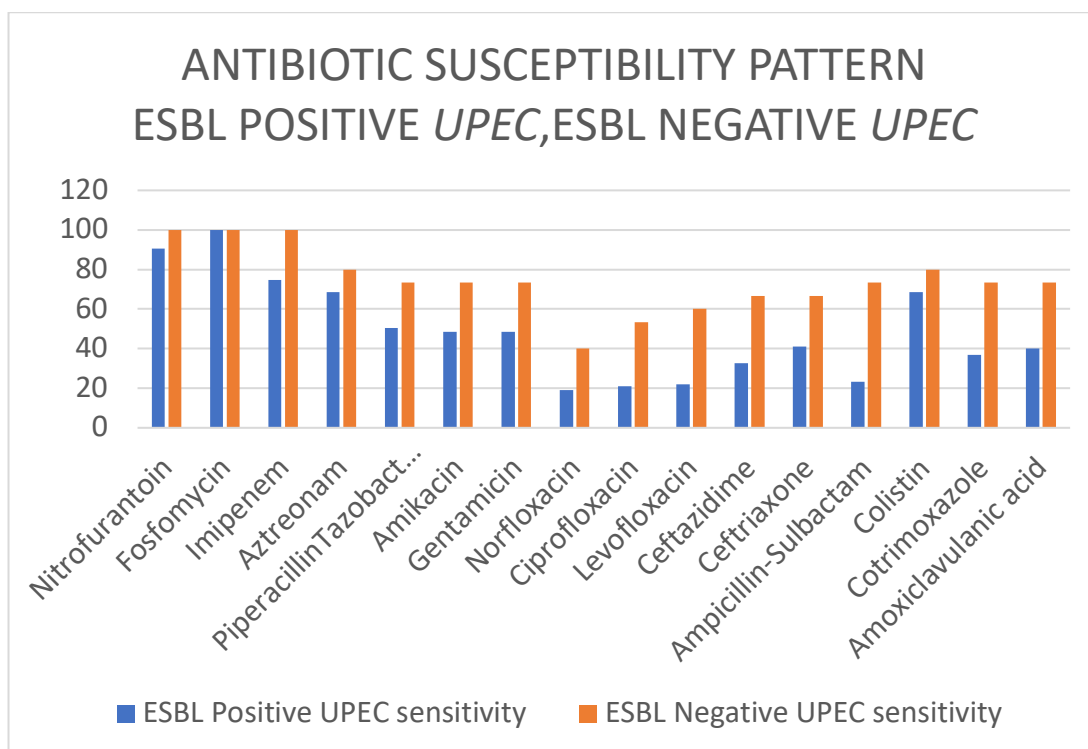


Figure 6: Antibiotic Susceptibility Pattern ESBL Positive UPEC, ESBL Negative UPEC

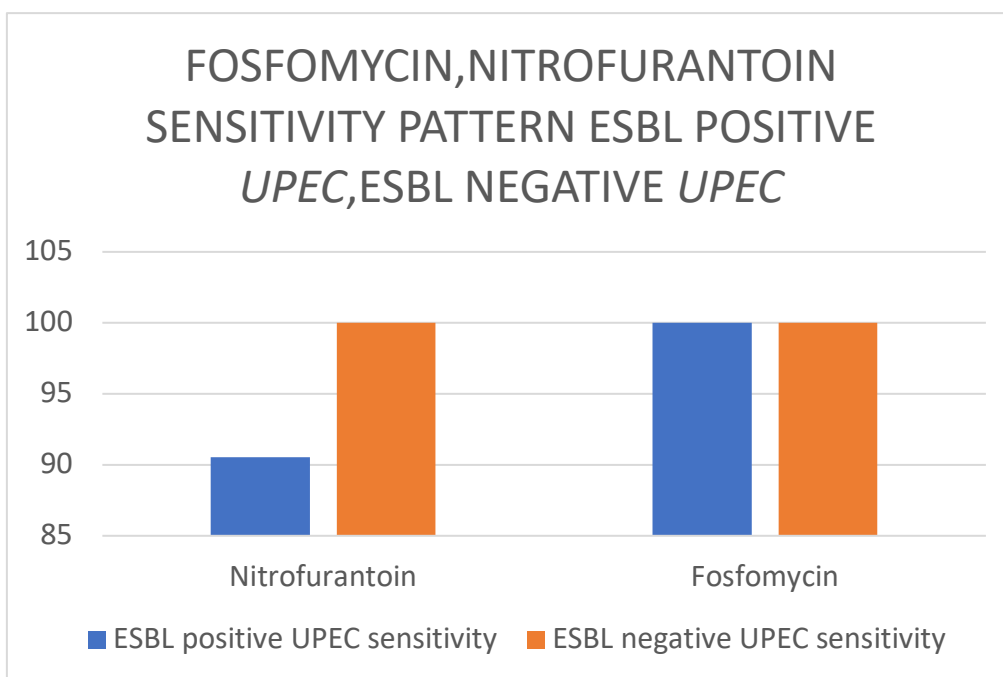


Figure 7: Fosfomicin, Nitrofurantoin Sensitivity Pattern ESBL POSITIVE UPEC, ESBL Negative UPEC

Table 3:

Antibiotics	ESBL positive UPEC resistance(%)	ESBL negative UPEC resistance(%)
Nitrofurantoin	9.47%(9)	0%(0)
Fosfomicin	0%(0)	0%(0)
Imipenem	25.26%(24)	0%(0)
Aztreonam	31.57%(30)	20%(3)
Piperacillin Tazobactam	49.47%(47)	26.66%(4)
Amikacin	51.57%(49)	26.66%(4)

Gentamicin	51.57%(49)	26.66%(4)
Norfloxacin	81.05%(77)	60%(9)
Ciprofloxacin	78.94%(75)	46.66%(7)
Levofloxacin	77.89%(74)	40%(6)
Ceftazidime	67.36%(64)	33.33%(5)
Ceftriaxone	58.94%(56)	33.33%(5)
Ampicillin-Sulbactam	76.84%(73)	26.66%(4)
Colistin	31.57%(30)	20%(3)
Cotrimoxazole	63.15%(60)	26.66%(4)
Amoxiclavulanic acid	60%(57)	26.66%(4)

Antibiotic resistance in ESBL positive UPEC shows Fosfomycin (0%), Nitrofurantoin (9.47%), Imepenem (25.26%), Aztreonam (31.57%), Piperacillin-Tazobactam (49.47%), Amikacin (51.57%), Gentamicin (48.42%), Norfloxacin (81.05%), Ciprofloxacin (78.94%), Levofloxacin (77.89%), Ceftazidime (67.36%), Ceftriaxone (58.94%), Ampicillin-sulbactam (76.84%), Colistin (68.42%), Cotrimoxazole (63.15%), Amoxiclavulanic acid(60%).

Antibiotic resistance in ESBL negative UPEC shows Fosfomycin (0%), Nitrofurantoin (0%) Imepenem (0%), Aztreonam (20%), Piperacillin-Tazobactam (26.66%), Amikacin (26.66%), Gentamicin (26.66%), Norfloxacin (60%), Ciprofloxacin (46.66%), Levofloxacin (40%), Ceftazidime (33.33%), Ceftriaxone (33.33%) Ampicillin-sulbactam (26.66%), Colistin (20%) Cotrimoxazole (26.66%), Amoxiclavulanic acid (26.66%).

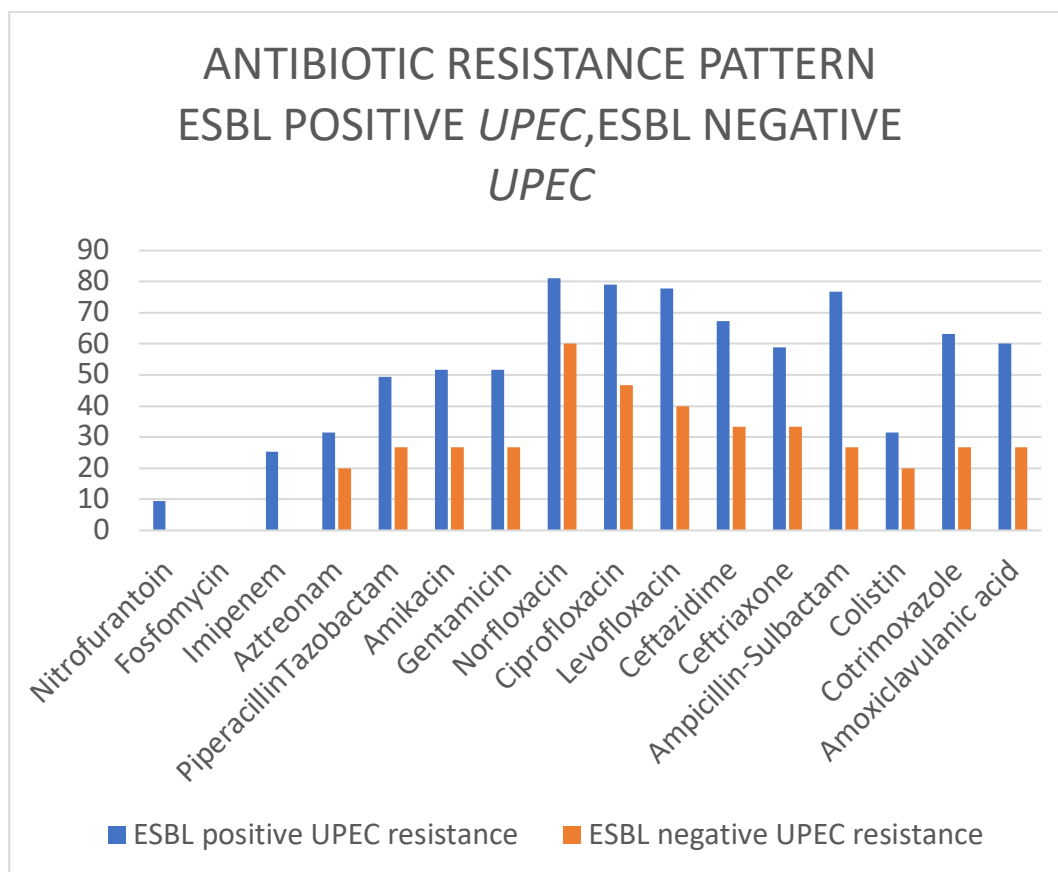
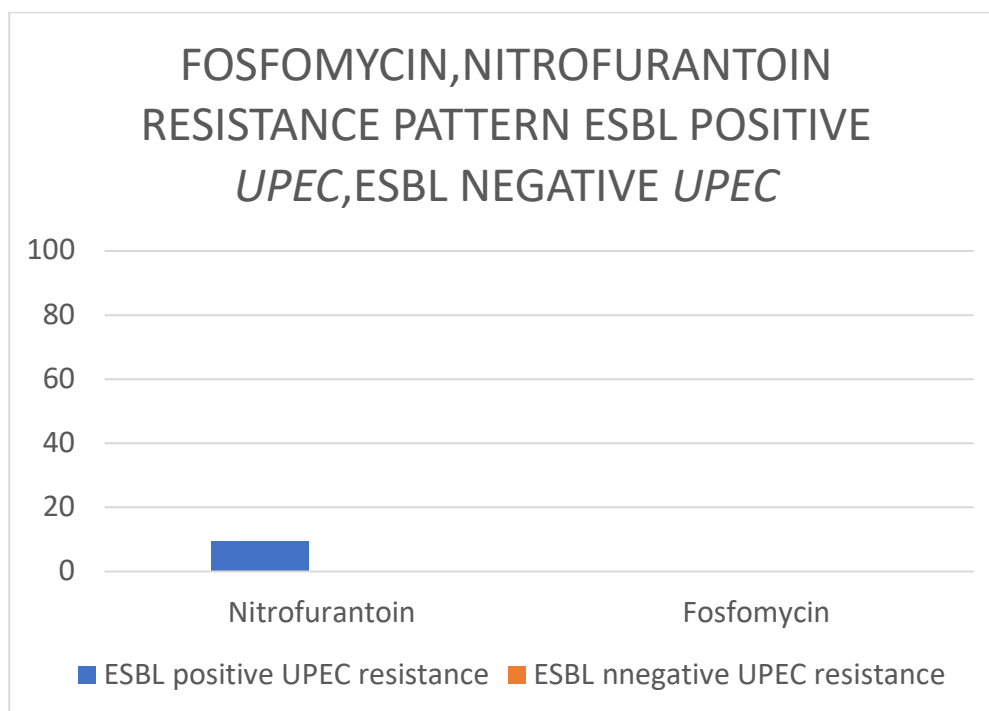


Figure 8: Antibiotic Resistance Pattern Esbl Positive UPEC, ESBL Negative UPEC



**Figure 9: Fosfomycin, Nitrofurantoin Resistance Pattern ESBL POSITIVE UPEC, ESBL Negative UPEC**

### Discussion

In our study Fosfomycin (84.45%) & Nitrofurantoin (100%) showed better sensitivity compared to other antibiotics imipenem (73.63%), aztreonam (56.36%), piperacillin-tazobactam (50%), amikacin (50.90%), gentamicin (50.90%), norfloxacin (22.72%), ciprofloxacin (19.09%), levofloxacin (14.54%), ceftazidime (31.81%), ceftriaxone (50%), ampicillin-sulbactam (24.45%), colistin (56.36%), cotrimoxazole (27.27%), amoxiclavulanic acid (22.72%).

Similar Study done by Lawhale MA et al showed Fosfomycin (84.45%) & Nitrofurantoin (100%) showed better sensitivity compared to other antibiotics imipenem (73.63%), aztreonam (56.36%), piperacillin-tazobactam (50%), amikacin (50.90%), norfloxacin (22.72%), ciprofloxacin (19.09%), levofloxacin (14.54%), ceftazidime (31.81%), ceftriaxone (50%), ampicillin-sulbactam (24.45%), cotrimoxazole (27.27%), amoxiclavulanic acid (22.72%). [9] Similar Study done by Vijayanapathy S et al showed E. coli from inpatients was susceptible to imipenem (260; 97%), amikacin (212; 79%), piperacillin-tazobactam (206; 77%), nitrofurantoin (198; 73%), and cefoperazone-sulbactam (206; 77%). [10] Study done by Banerjee S et al showed among the 216 isolates of E. coli All 216 (100%) were susceptible to colistin, and 212 (98.14%) were susceptible to Fosfomycin. Fosfomycin and Nitrofurantoin has better susceptibility compared to routinely used empirical drugs. Inappropriate use of quinolones has led to its resistance in UPEC causing urinary tract infection. [11] In our study Out of 110 E. coli isolates 97 (88.18%) were ESBL

positive and 13 (11.81%) were ESBL negative by screening method and among 97 isolates 95 (97.93%) were ESBL positive by confirmatory method. Study done by Gupta et al shows among 150 strains of E. coli, ESBLs positive strains was 79 (52.6%) and ESBLs negative strains was 71 (47.3%). [12] Similar study done by Banerjee S et al shows Among total 284 isolates 184 (64.78%) were ESBL producers, of which 137 were E. coli and 100 (35.21%) were non-ESBL producers, of which 79 were E. coli. [11] In our study ESBL producing UPEC showed sensitivity Nitrofurantoin 90.52% fosfomycin 100% and non ESBL producing UPEC showed sensitivity to Nitrofurantoin 100%, Fosfomycin 100%. Study done by Banerjee S et al shows Fosfomycin sensitivity among ESBL producing E. coli was 134/137 (97.81%) and non ESBL producing E. coli was 78/79 (98.74%). Study done by Gupta et al shows ESBL positive UPEC showed sensitivity to Nitrofurantoin 92.4% Fosfomycin 100% and ESBL negative showed nitrofurantoin (97.2%) and Fosfomycin 100%. [12] Similar study done by Tular NK showed esbl producing E. coli showed Fosfomycin (99.6%), Nitrofurantoin (93.7%). [13] ESBL positive UPEC showed lower sensitivity to Fosfomycin and nitrofurantoin compared to ESBL negative UPEC causing UTI. [14,15,16] Fosfomycin and Nitrofurantoin have unique mechanism to delay the evolution of resistance and are most preferred drugs in multidrug resistant uropathogenic E. coli. [17,18]

### Conclusion

Extended Spectrum Beta Lactamase producing UPEC presence and its potential for plasmid-



mediated resistance has caused significant therapeutic problems. Infection outbreak of ESBL-producing UPEC in a hospital or specialized unit of a hospital is of critical importance. Alarming increase in multidrug resistance among *Uropathogenic Escherichia coli* makes it necessary for the implementation of alternative treatment strategies for the Urinary tract infection. Fosfomycin inhibits an enzyme-catalyzed reaction in the first step of the synthesis of the bacterial cell wall and Nitrofurantoin acts at multiple targets in the bacterial cell and resistance is developed through stepwise mutations leading delay in resistance evolution. Thus Fosfomycin and Nitrofurantoin are potential antibiotics for empirical treatment Extended Spectrum Beta Lactamase producing *Uropathogenic Escherichia Coli* causing UTI.

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