Frontiers in Health Informatics
ISSN-Online: 2676-7104
www.healthinformaticsjournal.com
2024; Vol 13: Issue 8
Open Access

Role of Fosfomycin activity on ESBL producing E.coli and Klebsiella pneumoniae isolated in clinical samples at a tertiary care hospital, Sudha Medical College, Jagpura, Kota

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Cite this paper as: Dr. Ghanshyam Soni, Dr. Raees Ahmed, Dr. Anubha Vijay, Dr. Gyan Prakash, Dr. Sarita Rani Goyal, Ramnish Kumar, Rifa Parveen (2024). Role of fosfomycin activity on esbl producing e. Coli and klebsiella pneumoniae isolated in clinical samples at a tertiary care hospital, sudha medical college, jagpura, kota. *Frontiers in Health Informatics*, *13 (8) 450-460*

ABSTRACT

Background: The rise of extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae* has significantly complicated the management of infections in healthcare settings. With limited treatment options, the activity of alternative antibiotics like fosfomycin has garnered attention. This study aimed to assess the in vitro susceptibility of ESBL-producing *E. coli* and *K. pneumoniae* to fosfomycin in a tertiary care hospital in India.

Aim and Objective: To study the role of fosfomycin activity on ESBL Producing *E. coli*and *Klebsiellapneumoniae*isolated in clinical samples at a tertiary care hospital.

Methods: A total of 100 ESBL-producing isolates (*E. coli* n=65, *K. pneumoniae* n=35) were isolated from various clinical specimens, including urine, pus, sputum, Respiratory secretions, and wound swabs. ESBL production was confirmed using the combined disc method. Fosfomycin susceptibility was assessed by using the Kirby-Bauer disk diffusion method. Results were interpreted following the Clinical and Laboratory Standards Institute (CLSI) guidelines.

Results: In the present study it was observed that60 (92.3%) ESBL producing E.coli out of 65 shows susceptibility to Fosfomycin and 28 (80%) ESBL producing Klebsiella pneumoniae out of 35 shows susceptibility to Fosfomycin. Maximum 38(58.46%) out of 65ESBL producing*E. coli* and maximum 12 (34.28%) out of 35 ESBL producing*K. pneumoniae* were isolated from urine samples.

Conclusion: Fosfomycin demonstrated high in vitro activity against ESBL-producing *E. coli* and *K. pneumoniae*, especially for urinary tract infections. This study supports the potential use of fosfomycin as an effective alternative

treatment, particularly in infections where other options are limited due to antibiotic resistance. Further studies are needed

to explore its clinical efficacy in combination therapy and in different infection types.
Key words: Fosfomycin, antibiotic susceptibility, extended-spectrum beta-lactamase etc

INTRODUCTION:

The rising tide of antimicrobial resistance poses a severe threat to global public health, with an increasing prevalence of infections caused by multidrug-resistant (MDR) organisms such as extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella pneumoniae*. These organisms, known for their ability to hydrolyse and confer resistance to third-generation cephalosporins, are prevalent in both community and healthcare-associated infections, particularly in tertiary care hospitals [1].

ESBL-producing strains have been identified as major contributors to urinary tract infections (UTIs), bloodstream infections (BSIs), and hospital-acquired pneumonia, complicating therapeutic options and often necessitating the use of last-resort antibiotics, such as carbapenems [2,3].*Escherichia coli* is the most prevalent causative organisms of UTI and is solely responsible for more than 80% of the UTI infections [4].

However, the increasing use of carbapenems has contributed to the emergence of carbapenem-resistant *Enterobacteriaceae* (CRE), further limiting treatment choices and urging the need for alternative therapies [5]. In this context, fosfomycin, a broad-spectrum antibiotic discovered in the 1960s, has re-emerged as a promising option due to its unique mechanism of action and retained efficacy against a variety of resistant pathogens, including ESBL-producing *E. coli* and *Klebsiella pneumoniae* [6].

Fosfomycin exerts its bactericidal effect by inhibiting the enzyme MurA, which is essential for bacterial cell wall synthesis. Unlike many other antibiotics, it does not rely on beta-lactam rings or other structures commonly targeted by resistance mechanisms[6]. Recent studies have demonstrated that fosfomycin retains significant activity against ESBL-producing organisms, making it a viable option in treating infections caused by these resistant strains, especially in settings where other antibiotics fail [7]. In particular, its oral formulation has shown promising results in the treatment of uncomplicated UTIs, while its intravenous formulation is gaining interest for more severe infections such as blood stream infections (BSIs) and pneumonia [8].

Tertiary care hospitals, which often manage complex cases involving MDR organisms, are key settings for evaluating the efficacy of fosfomycin. The rising burden of ESBL-producing *E. coli* and *K. pneumoniae* in these settings has renewed interest in fosfomycin as part of both monotherapy and combination regimens. Ongoing clinical studies are evaluating the optimal use of fosfomycin to manage these challenging infections, with a focus on dosing strategies, resistance development, and clinical outcomes [9]. Fosfomycin is safe in pregnancy and breast feeding. It can be administered in a single dose which represent another importance of this drug. As antimicrobial research continues to evolve, fosfomycin may play a critical role in preserving the effectiveness of existing antibiotics and reducing reliance on carbapenems and other last-resort drugs.Therefore, the present study was undertaken to study the role of fosfomycin activity on ESBL Producing *E. coli*and *Klebsiellapneumoniae*isolated in clinical samples.

MATERIAL AND METHODS:

Study Design:

This study was conducted in the department of microbiology, Sudha Medical College, Jagpura, Kota over a period of 12 months i.e, from September 2023 to August 2024.

The study aimed to evaluate in vitro activity of fosfomycin against ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolated from clinical samples.

Sample Collection:

Clinical samples were collected from OPD patients and IPD patients admitted to various departments, including the Intensive Care Unit (ICU), General Medicine, Surgery, Urology, and Obstetrics and Gynaecology. The samples included urine, pus, sputum, respiratory secretions and wound swabswere processed in the microbiology laboratory. All samples were collected using standard aseptic techniques and transported to the laboratory for culture and sensitivity testing

within 2 hours of collection.

Inclusion Criteria:

1. Samples from patients showing signs of infection (e.g., fever, increased white blood cell count, etc.).
2. Only *E. coli* and *K. pneumoniae* isolates that were confirmed to be ESBL-producers based on phenotypic tests.
3. Age of the patient: 18 years and older.
4. Isolates from both OPD and IPD.

Exclusion Criteria:

1. Duplicate isolates from the same patient during the study period.
2. Isolates showing resistance to all antibiotics tested.
3. Patients who received antibiotic therapy within 48 hours prior to sample collection.

Microbiological Methods:

1. **Isolation and Identification**: Clinical specimens were cultured on MacConkey agar and blood agar plates. Plates were incubated at 37°C for 24–48 hours. Bacterial identification was carried out using standard biochemical tests such as the indole test,methyle red (MR) test, urease test, citrate utilization test and triple sugar iron (TSI) agar test for the differentiation of *E. coli* and *K. pneumoniae*.
2. **ESBL Detection**: ESBL production was confirmed using the combined disc diffusion method as recommended by the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2023). Cefotaxime (30µg) and cefotaxime-clavulanic acid (30/10 µg) discs were placed 20 mm apart on Mueller-Hinton agar plates inoculated with the test organism. A ≥5 mm increase in the zone diameter around the clavulanic acid combination disc compared to cefotaxime alone was indicative of ESBL production.

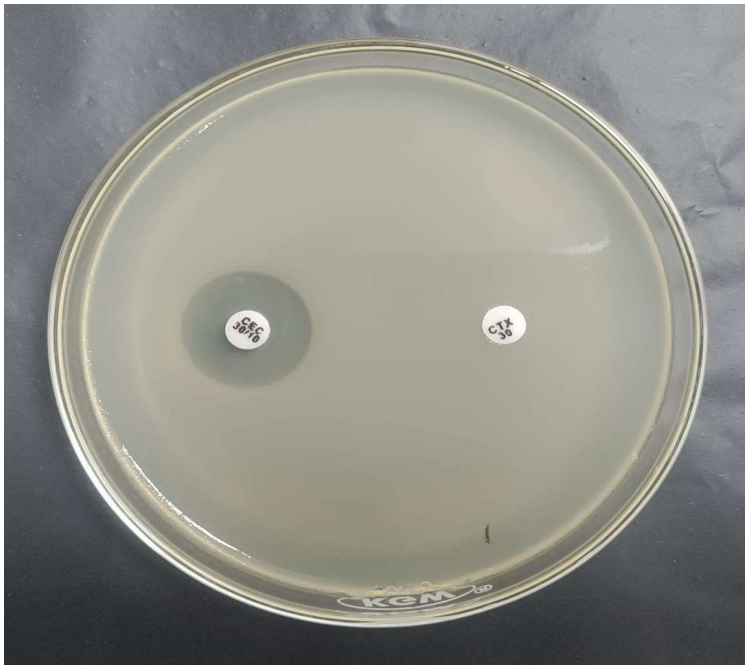


Fig.1: Combined diffusion method to detect ESBL production.

3. **Antibiotic Susceptibility Testing**: Susceptibility testing for fosfomycin was performed by the Kirby Bauer disc diffusion method, using 200 µgfosfomycin disc on Mueller-Hinton agar, in accordance with CLSI guidelines (CLSI, 2023). The isolates were classified as susceptible, intermediate, or resistant based on the zone diameter breakpoints recommended by CLSI.
4. **Control Strains**: Quality control for susceptibility testing was performed using *Escherichia coli* ATCC 25922 and *Klebsiella pneumoniae* ATCC 700603 (ESBL-producing strain) as control organisms.[10]

Data Collection:

Data on patient demographics (age, gender), clinical diagnosis, and the ward of admission were recorded. The source of the isolate and theirantibiotic susceptibility profilewere documented.

Statistical Analysis:

Data were analyzed using SPSS version. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population. The susceptibility of *E. coli* and *K. pneumoniae* to fosfomycin was expressed as a percentage.

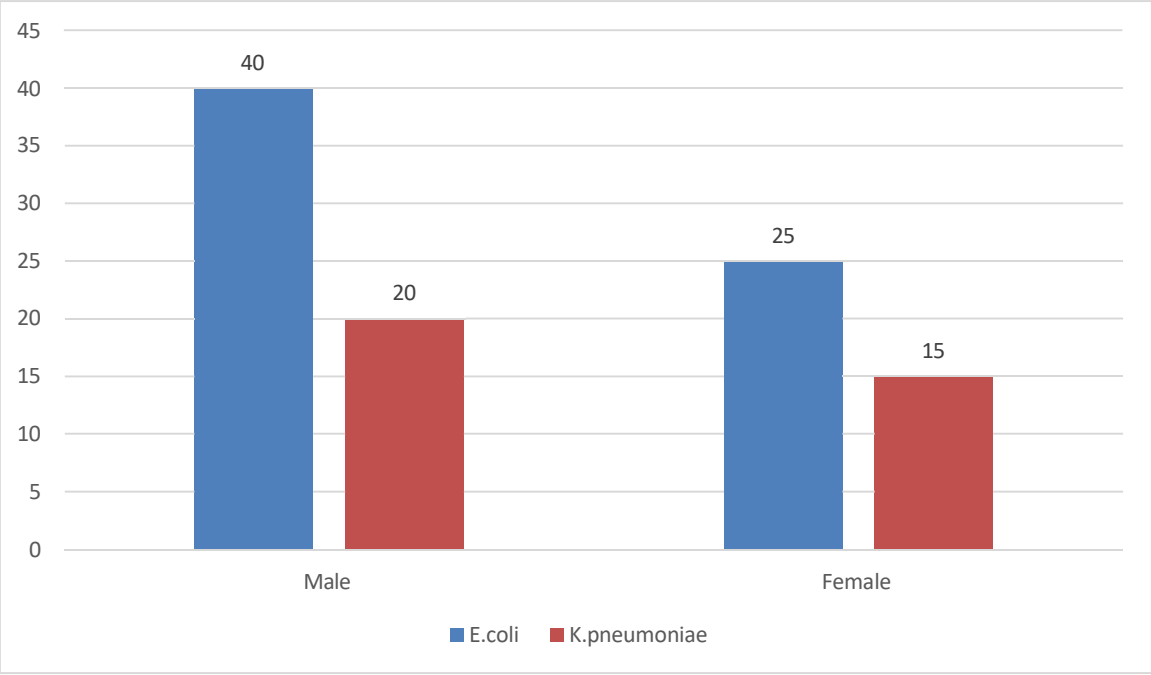
RESULTS:

A total of 100 ESBL-producing isolates, comprising *Escherichia coli* and *Klebsiella pneumoniae*, were included in the study.

Table1:Gender Distribution of ESBL-Producing Isolates.

Gender	*E. coli* (n=65)	*K. pneumoniae* (n=35)	Total (n=100)
Male	40 (61.5%)	20 (57.1%)	60 (60%)
Female	25 (38.5%)	15 (42.9%)	40 (40%)

Fig2: Gender Distribution of ESBL-Producing Isolates.



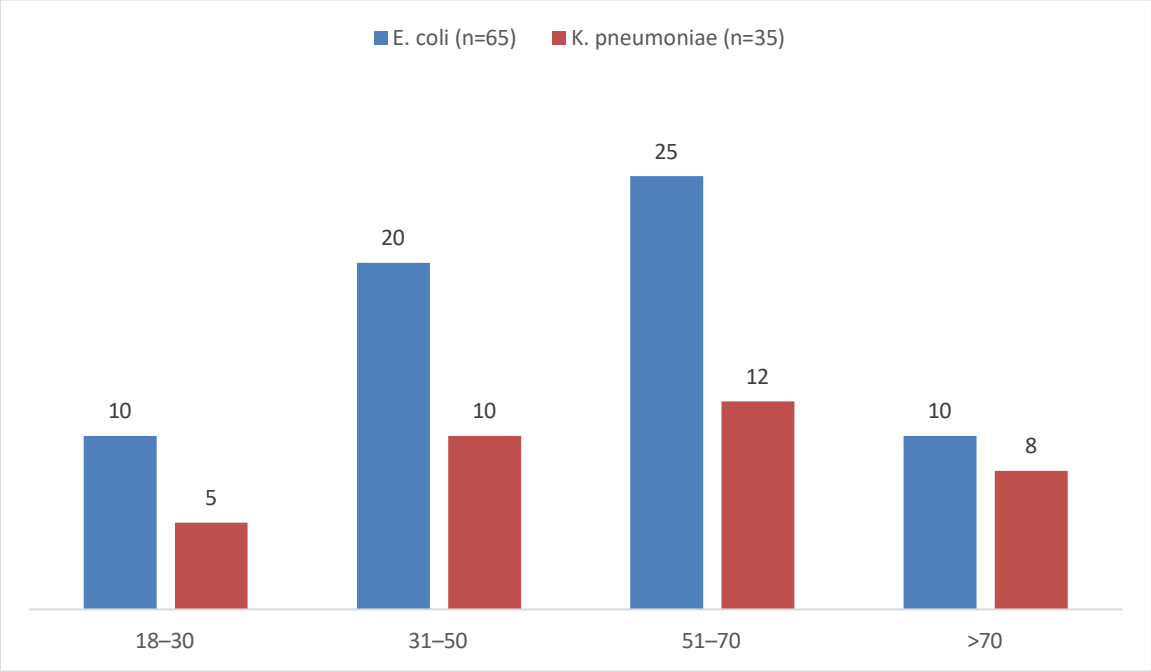
Of the 100 ESBL-producing isolates, 60% were from male patients and 40% from female patients.Among *E. coli* isolates, 61.5% were from males and 38.5% from females and in *K.pneumoniae* isolates, 57.1% were from males and 42.9% from females.This indicates a higher prevalence of ESBL-producing infections among male patients compared to females in this study.

Table2:Age Distribution of ESBL-Producing Isolates

Age Group (Yrs)	*E. coli* (n=65)	*K. pneumoniae* (n=35)	Total (n=100)
18–30	10 (15.4%)	5 (14.3%)	15 (15%)
31–50	20 (30.8%)	10 (28.6%)	30 (30%)

51–70	25 (38.5%)	12 (34.3%)	37 (37%)
>70	10 (15.4%)	8 (22.8%)	18(18%)

Fig3: Age Distribution of ESBL-Producing Isolates



The majority of ESBL-producing isolates were found in patients aged 51–70 years (37%).Among *E. coli* isolates, 38.5% were from patients in the 51–70 age group.*K. pneumoniae* was also most prevalent in patients aged 51–70 years (34.3%).The elderly group (>70 years) represented 18% of the total isolates, showing a relatively high burden of ESBL infections in older patients.This suggests that older adults, especially those in the 51–70 age group, are more likely to ESBL-producing *E. coli* and *K. pneumoniae*.

In the present study the distribution of these isolates, their clinical sources, and their susceptibility to fosfomycin were analyzed.

Table 3: Distribution of ESBL-Producing Isolates

Organism	**Number of Isolates (%)**
Escherichia coli	65 (65%)
Klebsiella pneumoniae	35 (35%)
Total	100 (100%)

Fig.4: Distribution of ESBL-Producing Isolates

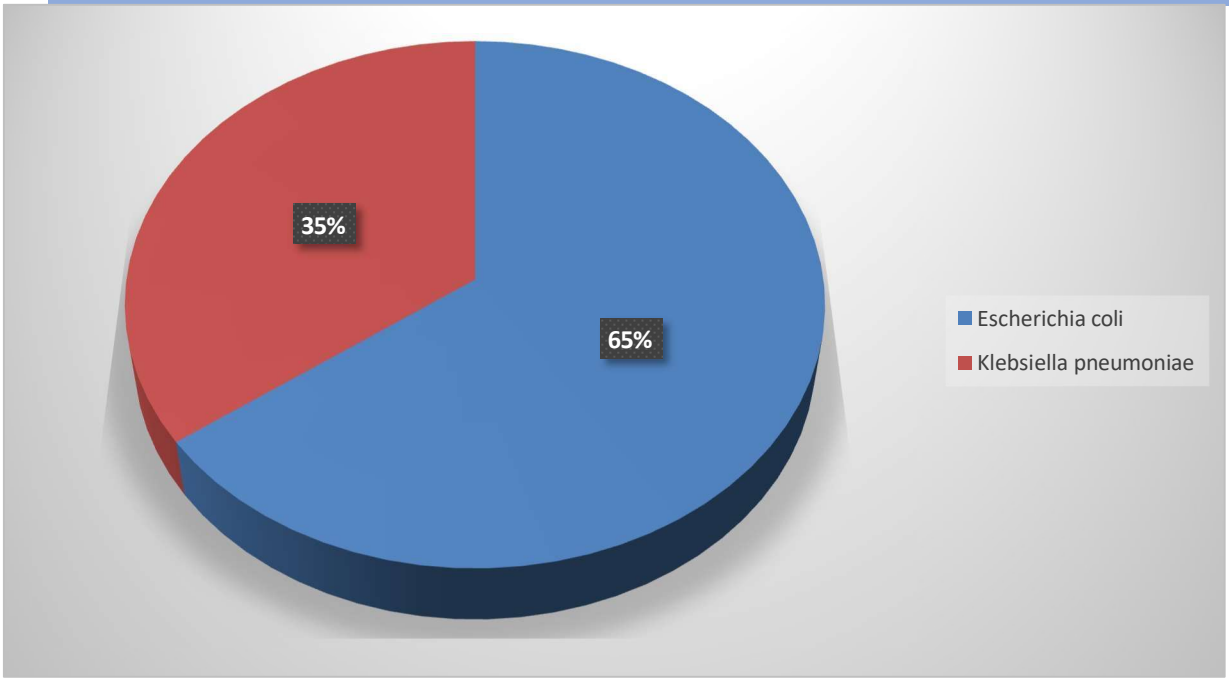


Table4: Clinical Source of Isolates.

Clinical source	E. coli (n=65)	K. pneumoniae (n=35)	Total (n=100)
Urine	**43(66.15%)**	**13(37.14%)**	**56(56%)**
Pus	**7 (10.77%)**	**8 (22.86%)**	**15(15%)**
Respiratory/Tracheal Secretions	**5 (7.69%)**	**6 (17.14%)**	**11(11%)**
Sputum	**4 (6.15%)**	**5(14.29%)**	**9(9%)**
Wound Swabs	**6 (9.23%)**	**3 (8.57%)**	**9(9%)**

Maximum number of ESBL producing isolates were found in urine sample (56%). Among *E. coli* isolates, 43 (66.15%) were from urine sample followed by pus 7 (10.77%), respiratory secretions 5 (7.69%), wound swab 6 (9.23%) and sputum 4 (6.15%). *K. pneumoniae* was also most prevalent in urine samples13(37.14%) followed by pus 8 (22.86%), respiratory secretions 6 (17.14%), sputum 5 (14.29%) and wound swab 3 (8.57%).

Table 5: Fosfomycin Susceptibility by Disc Diffusion Method.

Organism	Susceptible (%)	Intermediate (%)	Resistant (%)
***Escherichia coli* (n=65)**	60 (92.3%)	3 (4.6%)	2 (3.1%)
***Klebsiella pneumoniae* (n=35)**	28 (80%)	4 (11.4%)	3 (8.6%)

Fosfomycin demonstrated high in vitro activity against ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae*, with 92.3% of *E. coli* and 80% of *Klebsiella pneumoniae* being susceptible by disc diffusion method.

Table 6:Clinical Sources and Fosfomycin Susceptibility.

Clinical Source	E. coli (n=65)	Susceptible (E. coli) n (%)	K. pneumoniae (n=35)	Susceptible (K. pneumoniae) n (%)	Total (n=100)	Total Susceptible. n (%)
Urine	43	38 (88.37%)	13	6 (46.15%)	56	44 (78.57%)

Pus	7	5 (71.42%)	8	4 (50%)	15	9 (60%)
Respiratory/Tracheal Secretions	5	4 (80%)	6	3 (50%)	11	7 (63.64%)
Sputum	4	3 (75%)	5	3 (60%)	9	6 (66.67%)
Wound Swabs	6	4 (66.67%)	3	1 (33.33%)	9	5 (55.56%)
Total	65	54 (83.08%)	35	17 (48.57%)	100	71 (71%)

Table7: Distribution and Fosfomycin Susceptibility of ESBL-producing *E. coli* and *K. pneumoniae* Isolates Across Different Clinical Sources

Clinical Source	Study	Location	Organism	Fosfomycin Susceptibility (%)	Total Isolates
Urine	**Our Study (2024)**	India	*E. coli*	88.37%	43
			K. pneumoniae	46.15%	13
	Karageorgopoulos et al. (2012)[11]	Greece	*E. coli*	88.0%	55
			K. pneumoniae	79.0%	25
	Rodríguez-Baño et al. (2014)[12]	Europe	*E. coli*	89.4%	200
			K. pneumonia	79.0%	100
	Neetu et al. (2020)[13]	India (North)	*E. coli*	85.0%	65
			K. pneumoniae	77.0%	20
Pus	**Our Study (2024)**	India	*E. coli*	71.42%	7
			K. pneumonia	50%	8
	Falagas et al. (2016)[14]	Global Review	*E. coli*	84.0%	300 (various)
			K. pneumoniae	74.0%	200 (various)
Respiratory/Tracheal Secretions	**Our Study (2024)**	India	*E. coli*	80%	5
			K. pneumoniae	50%	6
	Liu et al. (2020)[15]	China	*K. pneumoniae*	78.0%	40
Sputum	Our study (2024)	India	*E. coli*	75%	4
			K. pneumoniae	60%	5

	Xiang et al. (2022)[16]	China	*E.coli*	78%	40
			K. pneumoniae	40%	40
Wound Swabs	**Our Study (2024)**	India	*E. coli*	66.67%	6
			K. pneumoniae	33.33%	3
	Yahav et al. (2020)[17]	Various Regions	*E. coli*	82.0%	50
			K. pneumoniae	72.0%	40

Table8: Antibiotic Sensitivity Profiles ofClinical Samples

Antibiotic	***E. coli (n=65)***	***K. pneumoniae (n=35)***
Fosfomycin	60 (92.3%)	28 (80.0%)
Tetracycline	32 (49.2%)	16(45.7%)
Ampicillin-Sulbactam	45 (69.2%)	25 (71.4%)
Cefuroxime	23 (35%)	14 (40%)
Ciprofloxacin	39 (60%)	19 (54.3%)
Co-trimoxazole	33 (50%)	16 (45.7%)
Meropenem	60 (92.3%)	32 (91.43%)
Ceftazidime	40 (61.5%)	20 (57.1%)
Gentamicin	48 (73.8%)	25 (71.4%)
Tobramycin	44 (67.7%)	24 (68.6%)
Colistin	61 (93.85%)	32 (91.43%)
Nitrofurantoin	39 out of 43 (90.69%)	10 out of 13 (76.92%)

These findings indicate that fosfomycin is a viable treatment option for infections caused by ESBL-producing *E. coli* and *K. pneumoniae* in tertiary care hospitals.

DISCUSSION:

The increasing prevalence of extended-spectrum beta-lactamase (ESBL)-producing organisms, especially *Escherichia coli* and *Klebsiella pneumoniae*, presents a significant challenge in managing infections in healthcare settings. These resistant pathogens complicate treatment options, often requiring the use of last-resort antibiotics like carbapenems. However, the emergence of carbapenem-resistant strains has driven interest in alternative treatment options, such as fosfomycin. In this study, we evaluated the in vitro activity of fosfomycin against 100 ESBL-producing *E. coli* and *K. pneumoniae* isolates collected from a tertiary care hospital in India. Our results indicate high susceptibility rates for both organisms, supporting the potential use of fosfomycin as an effective treatment option.

Comparison with Other Studies:

In our study, 92.3% of *E. coli* and 80% of *K. pneumoniae* isolates were susceptible to fosfomycin by disc diffusion. These results are in line with similar studies conducted globally. A study by Neetu et al. (2020) [13] in northern India reported a fosfomycin susceptibility rate of 89% for ESBL-producing *E. coli*, with a slightly lower susceptibility for *K. pneumoniae* (76%). Similarly, a study by Gupta et al. (2017) [18] also conducted in India, demonstrated that fosfomycin was highly effective against ESBL-producing *E. coli*, with susceptibility rates exceeding 90%.

An international study by Michalopoulos and Falagas et al. (2010) [6] highlighted the broad-spectrum activity of

fosfomycin, showing an average susceptibility rate of 85-95% for ESBL-producing *Enterobacteriaceae* across different regions. These findings are comparable to ourstudy, underscoring the global relevance of fosfomycin as a viable treatment option for ESBL-producing organisms.In other study, *K. pneumoniae* exhibited slightly lower susceptibility (80%) compared to *E. coli* (92.3%), which is consistent with the findings of Grabein et al. (2017) [19]. In their systematic review, they reported that *K. pneumoniae* often displays slightly lower susceptibility rates to fosfomycin compared to *E. coli*. This may be due to the presence of chromosomal resistance mechanisms or other resistance factors unique to *K. pneumoniae*, which might reduce the efficacy of fosfomycin in some isolates.

Age and Sex Distribution:

In our study, ESBL infections were more prevalent in males (60%) than females (40%), which is consistent with other studies. The study by Prakash et al. (2019) [20] similarly reported a higher prevalence of ESBL-producing *E. coli* and *K. pneumoniae* in male patients, particularly in older age groups. This may be due to the higher incidence of comorbid conditions such as diabetes and prostate enlargement in older males, predisposing them to recurrent UTIs.

The age distribution in our study revealed that patients aged 51–70 years were most affected by ESBL-producing infections, accounting for 37% of the total cases. This observation is consistent with findings from a study conducted by Nair et al. (2018) [21], which reported that the majority of ESBL-producing isolates were found in older adults, particularly those with underlying chronic diseases. The high prevalence of infections in this age group can be attributed to weakened immune systems, frequent hospitalizations, and the use of indwelling devices such as catheters, which are common risk factors for ESBL colonization and infection.

Clinical Implications:

Given the high susceptibility rates observed in our study, fosfomycin appears to be a viable treatment option, especially for uncomplicated UTIs caused by ESBL-producing *E. coli*, which constituted the majority of isolates in this study. The single-dose oral regimen of fosfomycin for UTIs provides a convenient and effective treatment option, particularly in outpatient settings. Study by Mataseje et al. (2016) [22] have demonstrated that fosfomycin remains highly effective in treating lower urinary tract infections caused by resistant *E. coli*, including ESBL-producing strains.

However, the slightly lower susceptibility rates observed in *K. pneumoniae* isolates highlight the need for cautious use in severe infections such as bloodstream infections or pneumonia, where combination therapy may be more appropriate. Fosfomycin has been successfully used in combination with other agents, such as carbapenems, to enhance its effectiveness in serious infections Rossi et al. (2020) [23]. Fosfomycin presents a valuable option for treating UTIs, particularly those caused by Escherichia coli, including strains that produce ESBLs. Given the limited number of effective antibiotics available for these cases, older antibiotics, including Fosfomycin, have been re-evaluated for their efficacy against multi-resistant bacteria. Fosfomycin has shown good in vitro sensitivity against these resistant strains [24,25].

Antibiotic Sensitivity Profiles of ESBL producing E. coli and K. pneumoniae.

The results of our study indicate a variable susceptibility of *E. coli* and *Klebsiella pneumoniae*, to commonly used antibiotics, with notable effectiveness of fosfomycin and nitrofurantoin, particularly for *E. coli* isolates (90.8%). This is consistent with findings from other studies, such as that by Neetu et al. (2021)[26], which reported a 92% susceptibility rate of *E. coli* to nitrofurantoin, underscoring its continued relevance in treating urinary tract infections caused by ESBL-producing strains. Other similar study by Faibr M et al. (2017) [27], Kalai J et al. (2023)[28] and Mohamed A.H et al.(2023) [29] .

Limitations of study:

While our study demonstrates encouraging results, it has some limitations. The study was conducted at a single tertiary care hospital and the sample sizewas relatively small. Moreover, fosfomycin resistance, although low, has been reported in some settings, particularly with long-term use. Therefore, regular surveillance of resistance patterns and more extensive multicentre studies are required to further validate the clinical utility of fosfomycin in treating infections caused

by ESBL-producing organisms in India.

CONCLUSION:

This study confirms the high in vitro activity of fosfomycin against ESBL-producing *E. coli* and *K. pneumoniae* isolates in a tertiary care hospital in India. Given the increasing resistance to other antibiotics, fosfomycin represents a promising alternative, especially for UTIs caused by ESBL-producing *E. coli*. However, continued monitoring of resistance patterns and further clinical studies are warranted to guide its optimal use in both monotherapy and combination regimens.

DECLARATIONS:

Conflicts of interest: There is no any conflict of interest associated with this study

Consent to participate: There is consent to participate.

Consent for publication: There is consent for the publication of this paper.

Authors' contributions: Author equally contributed the work.

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