Kalai et al. | Article 7822
*J Pure Appl Microbiol.* 2023;17(1):345-353. doi: 10.22207/JPAM.17.1.24
Received: 06 May 2022 | Accepted: 20 December 2022
Published Online: 01 March 2023

P-ISSN: 0973-7510; E-ISSN: 2581-690X

RESEARCH ARTICLE OPEN ACCESS

# Susceptibility Profile of Nitrofurantoin and Fosfomycin among Carbapenem-resistant *Enterobacteriaceae* Isolates in UTI from a Tertiary Care Hospital

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## Abstract

**UTI is one of the most common infections requiring antibiotic treatment and hospitalization. The rising trend in multidrug resistance to commonly used antibiotics has reduced the therapeutic options for treating these infections. Reexploring older antibiotics like nitrofurantoin and fosfomycin provide treatment options and help combat resistance. This prospective study was conducted in the Department of Microbiology, SRM Medical College Hospital and Research Center, from July 2021 to February 2022. The study included only clean catch midstream urine isolates of *Escherichia coli* and *Klebsiella pneumonia* from hospitalized patients and outpatients. Standard microbiological procedures were used to process the urine samples. Direct gram stain and conventional biochemical reactions were performed to identify the isolates. The antimicrobial susceptibility testing was carried out by the Kirby Bauer disk diffusion method and Minimum Inhibitory Concentration by E- test gradient method for fosfomycin. MIC for nitrofurantoin was determined by Micro Broth Well Dilution according to CLSI guidelines 2021. Among 150 urine samples, *Escherichia coli* 107 (71.3%) was higher than *Klebsiella pneumonia* 43 (29%). Carbapenemase production was seen in 58 (63.04%) isolates by the Kirby Bauer disc diffusion method. Among the 58 positive carbapenemase producers, E. coli was found to be 33 (56.8%), and *Klebsiella pneumonia* was 25 (43.1%). Fosfomycin susceptibility rates by E test were reported to be high in *Escherichia coli*, ranging from 0.5-1mg/L. *Klebsiella pneumonia* was less susceptible to fosfomycin ranging from 16-32mg/L. Only 7(21%) isolates of *Escherichia coli* showed MIC of 1-4µg/ml to nitrofurantoin by broth microdilution. 21 (63.63%) isolates of *Escherichia coli* and 11(44%) isolates of *Klebsiella pneumonia* were reported to have an intermediate category with MIC of 8-32µg/mL. A higher MIC of 64- > 256µg/ml was shown by 5 (15.15%) isolates of *Escherichia coli* and 14 (56%) isolates of *Klebsiella pneumonia*. Older medications may resurface as useful therapeutic choices as resistance to current treatment options grow.**

**Keywords:** UTI, Carbapenem Resistance, MIC Nitrofurantoin, Fosfomycin, Enterobacteriaceae

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**Citation:** Kalai J, Maheswary D, Leela KV, Gopinathan A. Susceptibility Profile of Nitrofurantoin and Fosfomycin among Carbapenem-resistant *Enterobacteriaceae* Isolates in UTI from a Tertiary Care Hospital. *J Pure Appl Microbiol.* 2023;17(1):345-353. doi: 10.22207/JPAM.17.1.24

## INTRODUCTION

UTI is the most common bacterial illness affecting 150 million people globally each year.[1] In 2007, there were an estimated 10.5 million hospital visits for UTI symptoms (representing 0.9% of all ambulatory visits) and 2-3 million emergency room visits in the United States. Urolithiasis varies by region, with a prevalence of 7.00 per cent and 5.06 per cent in Australia and Spain by 2007, 8.80 per cent in America in 2010, and 6.50 per cent in China in 2015. Urolithiasis has been much more common in the last half-century, with an estimated yearly cost burden of $5.30 billion in 2014.[2] In the United States, an estimated 250,000 instances of pyelonephritis occur each year, with females having a greater incidence. The estimated incidence of pyelonephritis in women aged 18 to 49 is 28 per 10,000, with 7% of cases requiring hospitalization. Cultural and genetic factors may influence prevalence (for example, pyelonephritis affects 59 out of 10,000 people in South Korea).[3] Even though urinary tract infections are the third most frequent infection in India, only a few studies have been published from West Bengal, Aligarh and Odisha on clean catch midstream urine to determine the antibiotic susceptibility and resistance pattern of the uropathogens.[4-6]

The prevalence rate of CRE is recorded differently in different parts of India. Gram-negative bacilli *Escherichia coli* is liable for causing the majority of UTIs, but other organisms of importance include *Klebsiella pneumonia, Proteus spp, Acinetobacter spp, Enterococcus spp, Pseudomonas aeruginosa* and *Serratia spp*.[2]

UTIs due to multidrug-resistant bacteria are becoming more common, related to antibiotic use.[7] The rise in resistance among *Enterobacteriaceae* has made empiric regimen selection difficult, especially in multidrug-resistant infections. Extended-spectrum beta-lactamases (ESBL)-mediated resistance among *Enterobacteriaceae* has been reported worldwide in the last decade, including in Chicago. Other resistance mechanisms among urinary infections have also been discovered.[8]

Carbapenemase enzymes are the leading cause of carbapenem resistance. *Enterobacteriaceae*'s most prevalent carbapenemases are divided into Ambler classes A, B, and D. The *Klebsiella pneumoniae* carbapenemases (KPC) and Imipenem-hydrolysing-lactamase (IMI) are the most common in class A, with KPC being the most common overall. Metallo-lactamases (MBL), New Delhi Metallo-lactamases (NDM), Imipenem-resistant Pseudomonas enzyme (IMP), and Verona integron-mediated Metallo-lactamase are all members of Class B. (VIM). Finally, Oxacillin-hydrolyzing carbapenemases (OXA) are found in class D, with OXA-48 being the most usually isolated. Carbapenemase genes can be acquired or intrinsic.[9]

Treatment is complicated since carbapenemases are resistant to many antibiotics. With only a few antibiotics expected to be in the pipeline in the next five to ten years, we are left with reintroducing old drugs like nitrofurantoin and fosfomycin to help treat UTIs.[10] Fosfomycin inhibits the cell wall synthesis of both gram-negative and gram-positive and acts as a potential alternative for treating uncomplicated UTIs.[11] There is also evidence that fosfomycin exhibits sufficient activity against pathogens causing infections in the critical care unit.[12] Nitrofurantoin interferes with bacterial ribosomal proteins and inhibits protein synthesis. The resistance to nitrofurantoin is uncommon, and many MDR organisms are susceptible.[13]

## METHODS

This prospective study was conducted in the Department of Microbiology, SRM Medical College Hospital and Research Center, from July 2021 to February 2022. The Ethical clearance was approved by the Institutional Ethics Committee of SRM. The study included only clean catch midstream urine isolates of *Escherichia coli* and *Klebsiella pneumonia* from hospitalized patients and outpatients. The study's results will aid in determining the prevalence of carbapenem-resistant organisms and improve patient care by using older drugs such as Nitrofurantoin and Fosfomycin in treating urinary tract infections. Standard microbiological procedures were used to process the urine samples. Urine samples were streaked on UTI Chrom agar and Blood agar and incubated for 18-24 hours at 37°C after a direct gram stain. Conventional biochemical reactions

were performed to identify the isolates. The antimicrobial susceptibility testing was carried out by the Kirby Bauer disk diffusion method. Minimum Inhibitory Concentration was determined by E-the test gradient method and Micro Broth Well Dilution according to CLSI guidelines 2021.

Data was taken regarding the patient's age and gender, urine culture characteristics, organism isolation, and antibiotic susceptibility profile by the Kirby Bauer disk diffusion method according to CLSI guidelines 2021. Antibiotics screened were Amoxicillin clav (20µg), Ceftazidime (30µg), Cefipime (30µg), Ceftriaxone (30µg), Cefuroxime (10µg), Ertapenem (10µg), Meropenem (10µg), Piperacillin Tazobacten (100µg/10µg), Amikacin (30µg), Ampicillin (10µg), Ciprofloxacin (5µg), Cotrimoxazole (1.25µg), Cefotaxime (30µg), Cefoxitin (30µg), Cefazolin (30µg), Gentamycin (10µg) Imipenem (10µg), Nitrofurantoin (300µg) Ofloxacin (5µg), Tetracycline (300µg), Tigecyclin (15µg). The susceptibility patterns of CRE *Escherichia coli* and *Klebsiella pneumonia* were analyzed and entered in the MS excel sheets. Fosfomycin (Ezy MIC strips Hi-media) susceptibility rates were determined with the E test gradient method, and the Minimum inhibitory concentration of Nitrofurantoin (Sigma Aldrich Chemical Pvt.Ltd.) for CRE *Escherichia coli* and *Klebsiella Pneumoniae* were determined by Broth microdilution method as per CLSI guidelines 2021.[14] The interpretation of MIC for broth microdilution was determined using a Resazurin dye (Sisco Research Laboratories Pvt.Ltd.).

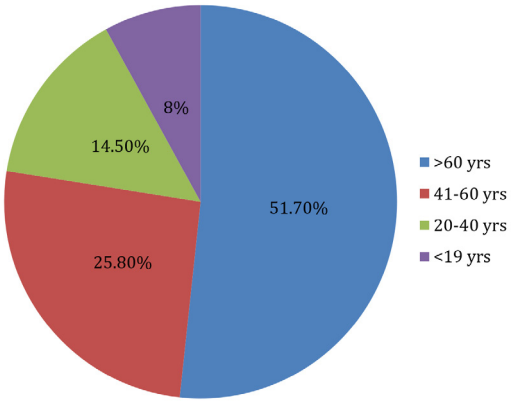


**Figure 1.** Distribution of CRE isolates among the various age groups from urine samples

**E-Test Gradient Method**

After incubation, the test bacterium was inoculated into Muller Hinton Agar supplemented with 25 µg/ml of glucose-6- phosphate. Antibiotic strips impregnated with an increasing concentration gradient of fosfomycin are laid on the agar surface and incubated for 24 hours at 37°C.[15]

According to CLSI guidelines 2021, the MIC breakpoints categories for the *Enterobacteriaceae* are:

| | S | I | R |
|---|---|---|---|
| Fosfomycin | <64 | 128 | >256 |

**Broth Micro dilution**

The commercially available antimicrobial powder was dissolved within the diluent (phosphate buffer), and a standard inoculum was prepared using the direct colony suspension method from a 24 hours cultured agar plate. Muller Hinton Broth is added to each of the micro titre plate's wells, 25L of nitrofurantoin dilution 256g/ml to column 1, 128g/ml to column 2, and so on until column 10 of the plate has 0.5g/ml is added. Column 11 is a growth control that only contains media and bacterial inoculum, while column 12 is a media control that contains medium 100L. Incubate the plates at 37°C for 24 hours in an

**Table.** Minimum Inhibitory Concentration of Nitrofurantoin for CR *Escherichia coli* & *Klebsiella pneumoniae* by Broth microdilution method

| ORGANISM | MIC of Nitrofurantoin (1- >256) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | >256 µg/mL | 128 µg/mL | 64 µg/mL | 32 µg/mL | 16 µg/mL | 8 µg/mL | 4 µg/mL | 2 µg/mL | 1 µg/mL |
| *Escherichia coli* | 4 | - | 1 | 4 | 11 | 6 | 7 | - | - |
| *Klebsiella pneumoniae* | 8 | 6 | - | 5 | 6 | - | - | - | - |

ambient air incubator within 15 minutes of adding inoculum.[15]

According to CLSI guidelines 2021, the MIC breakpoints for *Enterobacteriaceae* are:

| | S | I | R |
|---|---|---|---|
| Nitrofurantoin | <32 | 64 | >128 |

**Preparation of Resazurin Dye**

0.015g of Resazurin powder (Sisco Research Laboratories Pvt.Ltd.) is diluted in 100 ml distilled water. After incubation for 24 h at 37°C, resazurin (0.015 %) was added to all wells (30 µl per well) and further incubated for 2–4 h for the observation of colour change. The colour changes from blue to pink if the organism grows.[16]

## RESULTS

The study conducted in the Department of Microbiology, SRM Medical College Hospital & Research Centre between July 2021 and February 2022 included 150 urine samples containing both *Escherichia coli* and *Klebsiella pneumonia*. *Escherichia coli* 107 (71.3%) were found to be high than *Klebsiella pneumonia* 43 (29%) among the 150 samples collected for urine culture. The study found that people aged 61 years and over (51.7%) had the highest CRE, followed by those aged 41-60 years (25.8% ), (14.5.%) in 20-40 yrs of age and only 8 % in < 19 years old Figure 1. Carbapenemase production was seen in 58 (63.04%) isolates from the urine samples collected by Kirby Bauer disc diffusion methods. Among the 58 positive carbapenemase producers, *E. coli* was found to be 33 (56.8%), and *Klebsiella pneumonia* was 25 (43.1%). The routine antibiotic susceptibility and resistant pattern of carbapenem-resistant *Escherichia coli* and *Klebsiella pneumonia* by the Kirby Bauer disk diffusion method are shown in Figures 2 and 3.

The MICs of Fosfomycin by E test method for *Escherichia coli* and *Klebsiella Pneumoniae* is shown in Figure 4, 5 and 6. The rates of Fosfomycin susceptibility were reported to be high in *Escherichia coli*, ranging from 0.5 to 1mg/L. *Klebsiella pneumonia* was less susceptible to fosfomycin ranging from 16-32mg/L. MIC for nitrofurantoin by broth microdilution method-carbapenem-resistant *Escherichia coli* and *Klebsiella pneumonia* demonstrated that only 7(21%) isolates of *Escherichia coli* showed MIC of 1-4µg/ml. 21 (63.63%) isolates of *Escherichia coli* and 11(44%) isolates of *Klebsiella pneumonia* were reported to have an intermediate category with

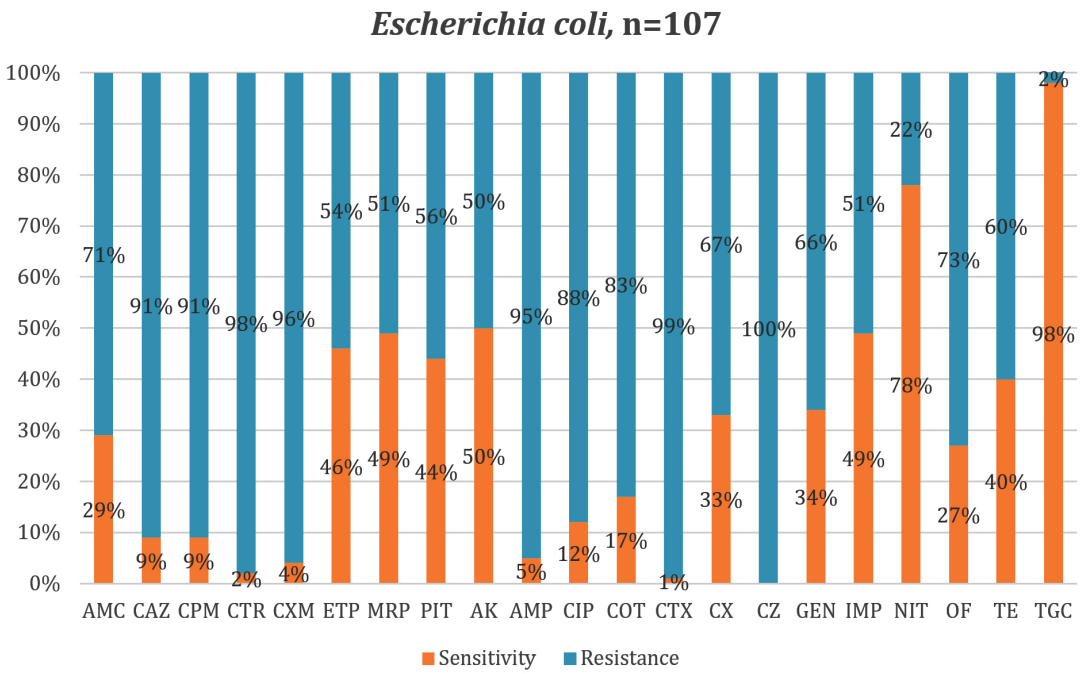


**Figure 2.** Antibiotic susceptibility and resistant pattern of CR *Escherichia coli* by Kirby Bauer disk diffusion method

MIC of 8-32µg/ml. A higher MIC of 64- > 256µg/mL was shown by 5 (15.15%) isolates of *Escherichia coli* and 14 (56%) isolates of *Klebsiella pneumonia*, as summarised in Table.

## DISCUSSION

A total of 150 samples were recruited for the study. Of these, 58 were positive for

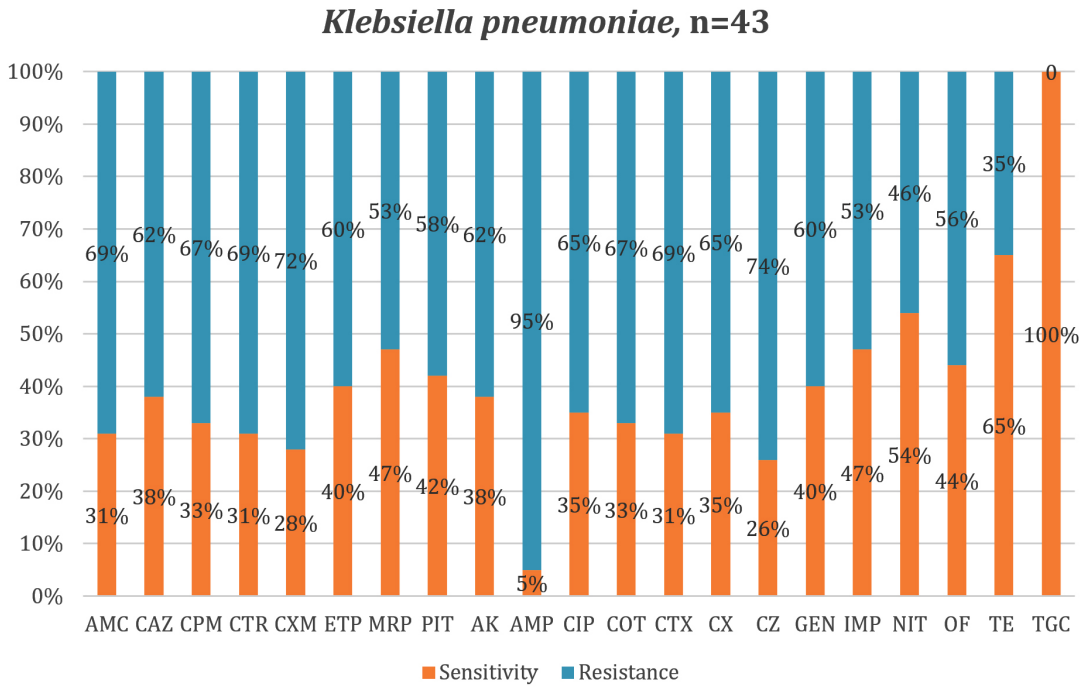


**Figure 3.** Antibiotic susceptibility and resistant pattern of CR *Klebsiella pneumoniae* by Kirby Bauer disk diffusion method

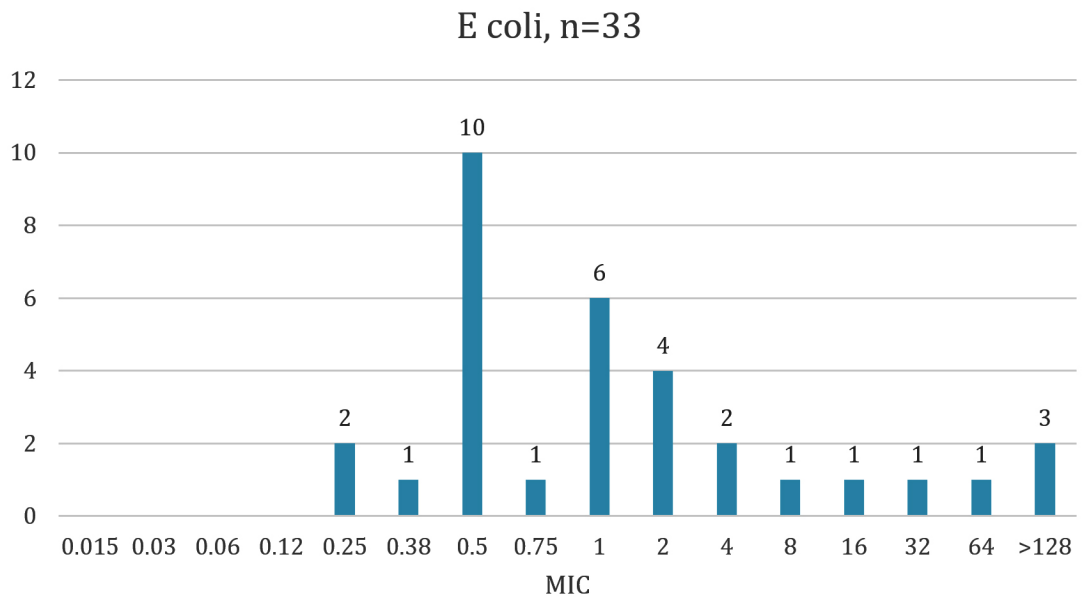


**Figure 4.** Fosfomycin susceptibility rates of CR *Escherichia coli* by E test method

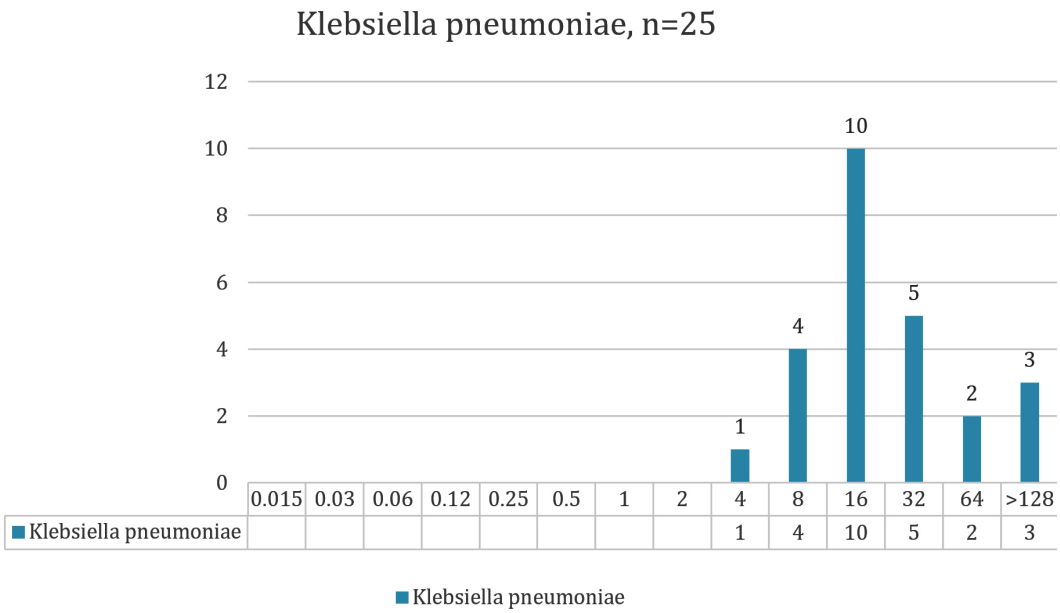


**Figure 5.** Fosfomycin susceptibility rates of CR *Klebsiella pneumoniae* by E test method

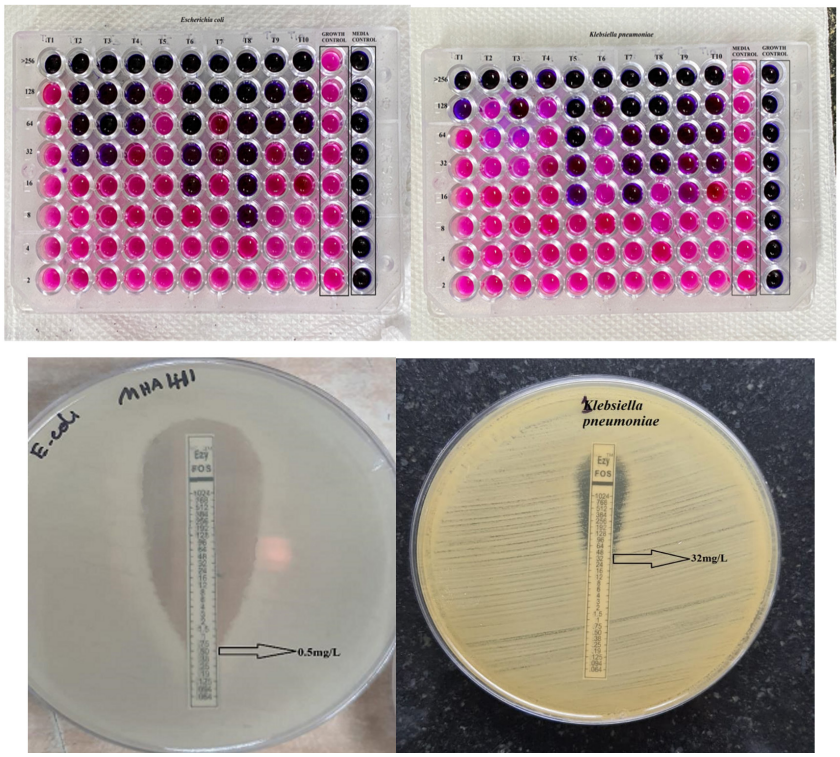


**Figure 6.** MIC of Nitrofurantoin for *Escherichia coli* and *Klebsiella pneumonia* by Broth Microdilution and E test

Carbapenemase production, giving a prevalence of 38%. In the present study, the prevalence of CRE in UTI in the hospital was relatively high. Wattal et al. conducted a similar study, which reported a high CRE prevalence rate ranging from 13 to 51% in tertiary care hospitals in Delhi.[17]

Multidrug-resistant *Escherichia coli* and *Klebsiella pneumonia* strains are rising, contributing to higher morbidity and mortality. All isolates were resistant to multiple antibiotics. Out of 150 urine samples, 58 were carbapenem-resistant, and *Escherichia coli* was more frequently isolated 33 (56.8%) than *Klebsiella pneumonia* 25 (43.1%)

The study found that people aged 61 years and over (51.7%) had the highest CRE, followed by those aged 41-60 years (25.8%); a similar finding was observed by Herdiyanti et al.[18] Probably because these age groups are most exposed to antibiotics, they have higher co-morbidities such as hypertension, type 2 diabetes mellitus, COPD, and other conditions for which they are more frequently hospitalized than the general population.

The highest prevalence of carbapenem resistance in the present study was observed in *E. coli* (56.8%), which correlates with Sanjeev K et al.(Udaipur),[19] and Parimala et al. (63%).[20] The predominance of *Escherichia coli* might be due to urine samples and *Escherichia coli* being a major urinary pathogen. In contrast, the study conducted by Wattal et al. on urinary samples.[16] displays a predominance of *Klebsiella pneumonia*.

Carbapenem-resistant *Escherichia coli* had the highest sensitivity to tigecycline (96.9%) and nitrofurantoin (90%) which correlates with the findings of Chauhan et al. Meerut (tigecycline 98%)[21] and Dusi Ratna Harika et al. (nitrofurantoin 88.4%),[22] whereas, *Klebsiella pneumonia* showed maximum sensitivity to tigecycline (100%) and tetracycline (48%) followed by nitrofurantoin (24%). Other studies conducted by Chauhan et al.[21] reported the least susceptibility to meropenem and imipenem, which correlates to our present study.

*E.coli* was highly resistant to Cephalosporins (first & second) generation (100%), ciprofloxacin and cotrimoxazole, followed by amikacin (24%). The overall resistance to meropenem in this study was found to be (6%) in contrast to the study by Behewa et al.[23] who reported 19.50% meropenem resistance. However, *Klebsiella pneumoniae* was highly resistant to ceftazidime, cefepime, ceftriaxone, cefuroxime, ertapenem, piperacillin-tazobactam, amikacin, ampicillin, ciprofloxacin, cefotaxime, cefazolin and gentamicin (100%).

The MICs of fosfomycin were far lower for *E.coli* than for *Klebsiella pneumonia*. The mode MIC for *E. coli* was 0.5 mg/L compared with 16 mg/L for *Klebsiella pneumonia*. Susceptibility to fosfomycin was high in *E.coli* (90.9%), followed by *Klebsiella pneumonia* (80%) which had a MIC < 32mg/L, which correlates with the study of Wouter van den Bijllaardt et al. [24]

Micro broth dilution was performed for nitrofurantoin to obtain the MIC values. MIC ranged from 4-32mg/L for *E. Coli* strains to 16-32mg/L for *Klebsiella pneumoniae* strains, which correlates to a study by Fiona Fransen et al.[25] and Karolina Klesiewicz et al.[26] A higher MIC of 64- > 256µg/mL was shown by 5 (15.15%) isolates of *Escherichia coli* and 14 (56%) isolates of *Klebsiella pneumonia*. In this study, the susceptibility rate of *Escherichia coli* isolates for nitrofurantoin was 84% in comparison to *Klebsiella pneumonia* which was only around 44% sensitive, correlating with the findings of Neeraj K.Tulara.[27]

## CONCLUSION

There is a scarcity of antibiotics for therapy in the face of developing multidrug resistance. Antibiotics like nitrofurantoin and fosfomycin, which are no longer commonly recommended, can treat infections like UTIs. However, regular monitoring is essential to detect trends in resistance to these antibiotics.

## ACKNOWLEDGMENTS

None.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## AUTHORS' CONTRIBUTION

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

## FUNDING

None.

## DATA AVAILABILITY

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

## ETHICS STATEMENT

This study was approved by the Institutional Ethics Committee of SRM Medical College Hospital & Research Centre, Chennai, Tamil Nadu, India, with reference number 2890/IEC/2021.

## INFORMED CONSENT

Written informed consent was obtained from the participants before enrolling in the study.

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