Review Article

Susceptibility of fosfomycin for the treatment of Multidrug-Resistant *Escherichia coli:* a systematic review

Nishadi Jayathilaka[1], Thamarasi Senaratne[2*], Varuna Navaratne[3], Dilini Nakkawita[4]

ABSTRACT

Background

To overcome the problem of urinary tract infections (UTIs) caused by antibiotic resistant *E. coli* (EC), either new drugs should be discovered or traditional, forgotten antibiotic options like fosfomycin should be reconsidered. This systematic review enlightens the usage of fosfomycin in different countries and based on the recommendations, seek to find the applicability of using fosfomycin as a first line drug of choice in Sri Lanka like settings.

Method

A systematic review of literature following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis was conducted from 1st of January 2011 to 31st of December 2021 in PubMed using different search terms. Initially, 498 potentially relevant articles were identified. Out of which, 29 articles were included in this review, based on inclusion and exclusion criteria.

Results

Out of 29, 18 studies reported fosfomycin sensitivity data, accounting for total of 14,306 bacterial isolates. Majority of the isolates were *E. coli* (n=9806) followed by *Klebsiella* spp. (n=1444). All these studies reported more than 80% sensitivty to fosfomycin, out of which 11 studies reported fosfomycin resistance ranging from 0.19% to 22%.

Conclusions

Multi-drug resistant, extended spectrum of β-lactamase (ESBL) producing bacteria are increasingly reported. Fosfomycin is the most effective antibiotic against ESBL-EC with a high sensitivity rate against urinary isolates of both community and hospital-acquired UTIs. The findings shed some light on the applicability of fosfomycin as a potential treatment option against *E. coli* in countries with a high burden of antibiotic resistance. However, further clinical studies should be performed before administration.

Keywords

Antibiotic resistance; *Escherichia coli*; fosfomycin; MDR organisms; Urinary tract infections

INTRODUCTION

Urinary tract infections (UTIs) are one among the most common community-acquired bacterial infections in humans. Mortality and occurrence of serious infections associated with UTIs have increased over the years.[1] Annually over 150 million people are affected with UTIs all over the world.[2] *Escherichia coli, Klebsiella pneumoniae*, *Staphylococcus aureus, Enterococcus faecalis,* and,[2] *Proteus mirabilis* are some of the organisms causing UTIs. Out of which *E. coli* is the most common etiological agent.[3, 4, 5]

Oral antibiotics recommended for uncomplicated UTIs include nitrofurantoin, trimethoprim-sulfamethoxazole, fosfomycin, cephalexin, and quinolones like nalidixic acid, norfloxacin, ciprofloxacin etc. Depending on the condition of the patient and the type of bacteria present, suitable antibiotics are prescribed. Due to incomplete recovery of patients and frequent recurrence of UTIs, antibiotic usage has been increased globally.[6]

1. Nishadi Jayathilaka, Faculty of Graduate Studies, General Sir John Kotelawala Defence University, Sri Lanka.
2. Thamarasi Senaratne, Department of Medical Laboratory sciences, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Sri Lanka.
3. Varuna Navaratne
4. Dilini Nakkawita

Department of Para Clinical Sciences, Faculty of Medicine, General Sir John Kotelawala Defence University, Sri Lanka.

Correspondence

Dr. Thamarasi Senaratne, Department of Medical Laboratory Sciences, Faculty of Allied Health Sciences, General Sir John Kotelawala Defence University, Ratmalana, Sri Lanka
E mail: thamarasis@kdu.ac.lk

Bangladesh Journal of Medical Science Vol. 24 No. 02 April'25

DOI: https://doi.org/10.3329/bjms.v24i2.81527

Antibiotic resistance is the process of bacteria becoming resistant to the antibiotics, rather than the body becoming resistant to antibiotics. As a result, bacteria will not be killed by antibiotics. Infections including UTIs, caused due to antibiotic-resistant organisms are very difficult to cure. In USA, approximately 250 million people are infected with antibiotic-resistant bacteria and fungi annually. Of which, over 35,000 people deaths were reported.[7] Due to increased usage of the broad-spectrum antibiotics and increase of Extended Spectrum Beta-Lactamase (ESBL) producers, uropathogens are becoming multi-drug resistant (MDR). Acquisition of resistance to at least one antibiotic in three or more antibiotic classes are defined as MDR.[8,9] The rate of prevalence of MDR *E. coli* in USA has elevated from 9% to 17% from 2009 to 2010[1]. As a result, prevailing effective antibiotics to treat UTIs are limited. The lack of novel antibiotics is provided as a good motivation for the clinicians to use antibiotics like fosfomycin, which has shown good activity against MDR bacteria.[10]

Fosfomycin is a traditional antibiotic with very low molecular weight and a broad spectrum of activity against both Gram-negative and Gram-positive MDR bacteria.[11] It's a proven alternative antibiotic for MDR *E. coli* and *Klebsiella* spp. but, effectiveness for *E. coli* was higher than that for *Klebsiella* spp.[8, 12] Fosfomycins' activity is not affected by beta-lactamases.[12] Many studies have revealed fosfomycin as the potent antibiotic for *E. coli* among all other antibiotics, with a low minimum inhibitory concentration (MIC).[13, 14] Although many foreign studies have suggested fosfomycin as an effective antibiotic for MDR UTIs, limited data is available from Sri Lanka on usage of fosfomycin for research purposes only. However, this is currently not being used in the Sri Lankan clinical setting. Thus, this review was aimed at gathering available literature on fosfomycin, as an alternative for MDR *E. coli*, for Sri Lanka like developing county settings to reduce the burden of antibiotic resistance.

METHODOLOGY

This systematic review was conducted following the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

Study selection

The MEDLINE/ PubMed database was searched for published articles from 1st of January 2011 to 31st of December 2021 to recognize the eligible studies. The search strategy was designed by combining search terms for 'fosfomycin' along with 'susceptibility', 'susceptible', 'resistance', 'resistant'. The search terms related to antibiotic resistance were 'antimicrobial resistance', 'antibiotic resistance', 'multi-drug resistant', 'ESBL production', 'ESBL producing *E. coli*', 'Sri Lanka', 'South Asia', 'Asia', and 'world'.

Selection criteria

The following were the inclusion criteria of this study; (1) *in-vitro* studies reported fosfomycin susceptibility and resistance related data, (2) data from studies that have followed agar dilution method, disc diffusion method, E test, broth micro dilution method or automated methods (VITEK and BD Phoenix), and interpreted using CLSI or EUCAST guidelines. The studies that fulfilled these criteria were excluded; (1) studies published in languages other than English, (2) animal studies, (3) studies that have focused on resistance to other antibiotics instead of fosfomycin and (4) studies with unclear methods.

Data extraction and analysis

This systematic search of literature identified 498 articles for initial title and abstract screening. Precisely, a total of 29 studies were included in this review based on the inclusion and exclusion criteria. The figure 1 demonstrates the method used for selecting studies to include in this review. Out of these 29 studies, 18 referred to fosfomycin susceptibility data, 9 referred to fosfomycin resistance data and 2 referred to both susceptibility and resistance data.

The data extraction was conducted by two independent reviewers and conflicts were discussed by the consensus of two reviewers or with the help of a third senior reviewer. The extracted data were entered in to a Microsoft Excel sheet under column headings such as; name of the first author, publication year, country, microbiological testing method, origin of isolates, number of positive isolates, number of organisms included in the study, and fosfomycin sensitivity and resistance percentages. The extracted data were analyzed and interpreted by using GraphPad Prism 9.3.1 software.

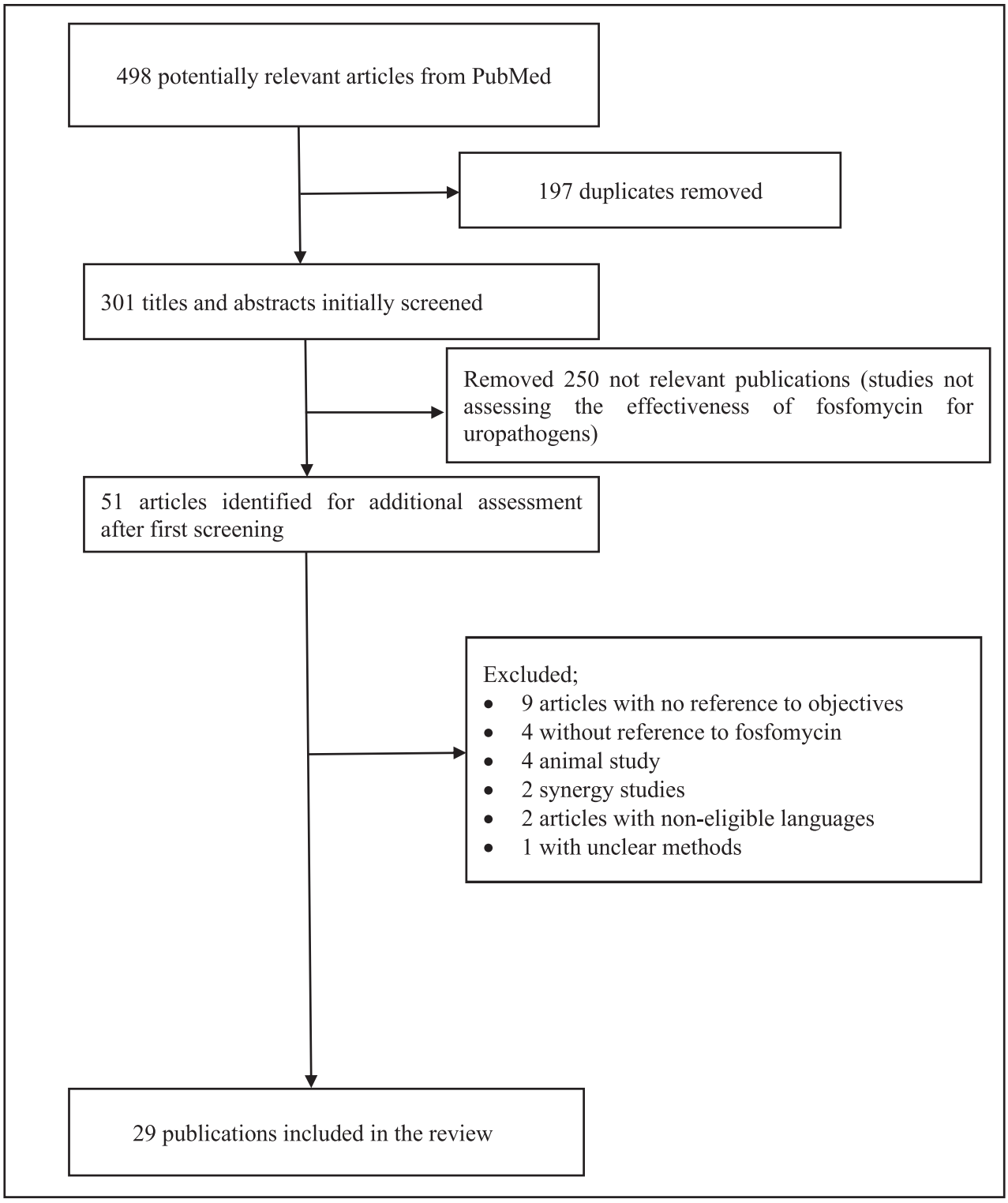

Figure 1: Flowchart of the study selection process for the systematic review

RESULTS

Mode of action of fosfomycin

Fosfomycin was discovered in Spain in 1969. Originally it was named as 'phosphonomycin' which is produced by *Streptomyces spp.*[4,15] and it is an antibacterial agent with a broad spectrum of activity for both Gram-positive and Gram-negative bacteria by inhibiting phosphoenolpyruvate synthetase. Fosfomycin drug enters the cell wall of fosfomycin susceptible bacteria by two transporting systems known as the L-a-glycerophosphate transport system (GlpT) and the hexose phosphate uptake system (UhpT). Thereby, inhibit cell wall peptidoglycan synthesis of bacteria.[16] This is a unique antibiotic that does not show any interaction with other antibacterial agents and has no cross-resistance with other antibiotics. Hence, it acts synergistically with other antibiotics.[17] Fosfomycin is a smaller molecular weighted antibiotic with no ability of binding to proteins. It is less toxic and well tolerated by the body, with few incidences of side effects such as, allergic reactions, vomiting and diarrhea.[4]

There are three formulations of fosfomycin; two oral forms with tromethamine and calcium salts and intravenous form with disodium.[18] Oral fosfomycin is well distributed into tissues. It is mostly used for the treatment of uncomplicated UTIs caused by *E. coli and Enterococcus faecalis*. Fosfomycin possesses a renal clearance of 90%, with no secretion to renal tubular epithelial cells. It is having a long elimination half-life, which is in between 4 and 8 hours.[19] There's a favorable environment inside the urinary tract for fosfomycin,[20] by concentrating the drug in the bladder and by maintaining an acidic pH.

The antimicrobial susceptibility of fosfomycin

Antibiotic susceptibility testing of fosfomycin is important in clinical practice. Clinical Laboratory Standard Institute (CLSI) guidelines has categorized fosfomycin under the "Group U supplement for urine only category". Fosfomycin is the only antibiotic in the fosfomycins family and it is recommended only for the testing of urinary isolates. Fosfomycin 200µg disk is the standard disk for antibiotic susceptibility testing (ABST) by disk diffusion method. Recommended method for Minimum Inhibitory Concentration (MIC) detection is the agar dilution method in CLSI 2022.[21]

Fosfomycin showed a high cure rate around 90%.[22] It was proven as an effective and safe treatment for uropathogens with less toxicity.[23] The articles reviewed, have mentioned that randomized clinical trials are underway, which would provide greater evidence. Fosfomycin was considered as an effective treatment option for ESBL-producing *E. coli* [24, 25] but, limited applicability was reported against ESBL-producing *Klebsiella* spp.[8] Since, the records available on the effectiveness of fosfomycin for MDR bacteria are still limited, further research studies are required to validate the effectiveness of fosfomycin for complicated UTIs in the context of emerging MDR bacteria.[15]

Table 1. Characteristics of studies describing fosfomycin sensitivity data

Sr. No	First author (year)	Study year	Country	Microbiological testing method	Origin of isolates	No: of positive isolates (n)	Number and name of organism/s studied	Fosfomycin sensitivity percentage
1	Saeed (2021)[26]	2018-2019	Bahrain	DD	Urinary isolates	3044	3044-EC	97.6
2	Aprile (2020)[27]	Not mentioned	Italy	AD, GT, BMD and automated systems*	Different clinical isolates	120	35- ESBL EC 50- KPC KP 8- NDM-OXA 48- KP 27- OXA-48 KP	88.6 24.0 100.0 37.5
3	Karaiskos (2019)[23]	2014-2018	Greece	Automated system* E test	Urinary isolates	44	29- EC 6- KP 9- Other	100.0 100.0 100.0
4	Gopichand (2019)[28]	2016-2017	India	DD, BMD	Urinary isolates	326	217- EC 52- KP 57- Other	100.0 70.0

Sr. No	First author (year)	Study year	Country	Microbiological testing method	Origin of isolates	No: of positive isolates (n)	Number and name of organism/s studied	Fosfomycin sensitivity percentage
5	Bielen 2019)[29]	2012-2014	Croatia	DD, AD	Urinary isolates	42	34- ESBL EC 7- ESBL KP 2- Other	100.0 100.0
6	Priyadharshana (2019)[30]	2016-2017	Sri Lanka	DD	Urinary isolates	178	149- EC 16- KP 13- Other	100.0 100.0
7	Ny (2019)[31]	2015-2017	Multicenter (Finland, Germany, Latvia, Poland, Russia and Sweden)	DD	Urinary isolates	775	775- EC	98.7
8	Amladi (2019)[32]	2016-2017	India	DD	Urinary isolates	150	81- EC 69- *Klebsiella* spp.	98.9 94.0
9	Fajfr (2017)[33]	2013-2014	Czech Republic	DD	Urinary isolates	3295	1703- EC 643- KP 949- Other	97.0 80.4
10	Bi (2017)[34]	2011-2015	China	AD	Urinary isolates	356	356- ESBL EC	93.3
11	Ohkoshi (2017)[35]	2008-2009	Japan	DD, AD	Urine, pus, sputum, vaginal secretions, aspirations and stool	211	211- EC	98.6
12	Yeganeh (2016)[24]	2014-2015	Iran	DD	Urinary isolates	219	177- EC 28- *Klebsiella* spp. 14- Other	>90.0 >90.0
13	Matthews (2016)[4]	2013-2015	United Kingdom	Automated system*	Urinary isolates	75	52- EC 23- KP	99.0 81.0
14	Cho (2015)[8]	2011-2015	Korea	Semi-automated system (Microscan)	Urinary isolates	277	217- ESBL EC 60- ESBL KP	93.2 19.6
15	Rajenderan (2014)[36]	2012	South India	BMD	Urinary isolates	925	11- EC 207- *Klebsiella* spp. 707- Other	90.0 90.0
16	Sahni (2013)[37]	2009-2012	South India	DD	Urinary isolates	3141	2416- EC 725- *Enterococcus* spp.	83.0 99.0
17	Lee (2012)[38]	2009	Korea	AD	Not mentioned	347	165- ESBL EC 182- ESBL KP	92.9 95.2
18	Liu (2011)[25]	2008-2009	Taiwan	DD, AD, BMD	Urinary isolates	200	134- ESBL EC 66- ESBL KP	95.5 57.6

AD-Agar Dilution, BMD-Broth Micro Dilution, DD-Disc Diffusion, EC-*Escherichia coli*, ESBL- Extended Spectrum of Beta Lactamase Producing, GT-Gradient Test, KP-*Klebsiella pneumoniae*, KPC- *Klebsiella pneumoniae* carbapenemase, NDM- New Delhi metallo-betalactamase, OXA-48-Oxacillinase-48

*VITEK 2 and/or BD Phoenix

The data that was collected from each of the reviewed 18 studies on fosfomycin susceptibility is shown in Table 1. Here, two studies involved isolates from Korea,[8, 38] two from India[28, 32] and two from South India.[36, 37] The remaining 11 studies included articles from Italy,[27] China,[34] Greece,[23] Taiwan,[25] United Kingdom,[4] Iran,[24] Croatia,[29] Czech Republic,[33], Bahrain,[26] Sri Lanka,[30] Japan,[35] and a combined study of several countries.[31] These 18 studies reported fosfomycin susceptibility data, accounting for total of 14,306 bacterial isolates. Most of these were *E. coli* isolates (n=9806) followed by *Klebsiella* spp. isolates (n=1444). In each of these

studies, fosfomycin susceptibility was tested mainly by disc diffusion method[24-26, 28, 29-33, 35, 37] and agar dilution method.[27, 29, 35, 38, 25] In figure 2, we have represented cumulative yearly percentage susceptibilities of *E. coli* isolates to fosfomycin. Here, 17 of 18 studies reported more than 90% sensitivity to fosfomycin[4, 8, 23-26, 28-36] except one study.[27] All the sensitivity percentages were in between the range of 80% and 100%.

Fosfomycin resistance

The development of resistance to other antibiotics during the therapeutic process, was the primary factor which caused the re-consideration of fosfomycin as a first line drug of choice for UTIs. CTX-M beta lactamases producing *E.coli* are emerging worldwide, which is the most predominent causative organism for both nosocomial and community acquired UTIs.[39] Fosfomycin resistance is observed in CTX-M producing *E. coli*, due to the mutation in the chromosomal locus like glpT and plasmid-mediated fosA3 and fosC2. Another study also determined the plasmid-mediated fosfomycin resistance in both ESBL-producing *E. coli* and *K. pneumoniae.*[38] Transfer of plasmid-mediated genes may increase the worldwide emergence of resistance to fosfomycin. Effective monitoring and surveillance are important to stop further distribution of fosfomycin resistance. As fosfomycin resistance rate is also increasing, it should be used carefully under proper medical advice.[34]

Table 2. Characteristics of studies describing fosfomycin resistance data

Sr. No	First author (year)	Organism/s present	Origin of isolates	Fosfomycin resistance detection method	Percentage resistance to fosfomycin	Amino acid substitution/s or sequence variation/s or resistance gene/s
1	Kansak (2021)[40]	EC	Urinary isolates	DD, AD, NP	15.8	-
		Klebsiella spp.			75.0	
2	Carolina (2020)[41]	EC	Urinary isolates	E-test	9.0	murA
3	Mowlabococcus (2020)[42]	EC	Urinary isolates	DD, AD	0.19	fosA4
4	Mueller (2019)[43]	EC	Urine, blood, stool, genial and anal swabs, expectorations, abscesses	NP, AD,	1.38	fosA3, fosA4
5	Nordmann (2019)[44]	EC	Different clinical samples	NP	22.0	fosA3
6	Bi (2017)[34]	EC	Urinary isolates	AD	6.7	fosA3
7	Ohkoshi (2017)[35]	EC	Isolates from urine, pus, sputum, vaginal secretions, aspirations and stool	DD, AD	1.4	murA, uhpT, uhpA, glpT, ptsI, cyaA
8	Bahramian (2018)[45]	EC	Urinary isolates	NP, AD	6.6	fosA3, fosC2
9	Benzerara (2017)[46]	EC	Urine, blood, stool, joint fluid	DD, E-test, AD	0.9	fosA3, fosA5
10	Li (2015)[47]	EC	Urine, sputum, blood, pus	AD	7.8	fosA3, glpT, murA, uhpT
11	Lee (2012)[38]	EC	Not mentioned in the study	AD	4.5	FosA3
		KP			42.4	-

AD-Agar Dilution, BMD-Broth Micro Dilution, DD-Disc Diffusion, EC-*Escherichia coli*, KP-*Klebsiella pneumoniae*, NP-Rapid fosfomycin/ *E. coli* NP test.

The table 2 displays information on fosfomycin resistance, with regards to the responsible genes or amino acid substitutions or sequence variations. Out of the 11 studies, two comprised of isolates from Switzerland[43,44] and two from China.[34, 47] The remaining seven studies comprised of isolates from Turkey,[40] Brazil,[41] Australia,[42] Japan,[35] Iran,[45] France,[46] and Korea.[38] The most commonly isolated resistance gene was fosA3 gene.[34, 38, 43-47] Of the selected studies, only two have analyzed the resistance genes of *Klebsiela* spp.[38,40] and showed higher resistance rates compared to *E. coli*, irrespective of the sample which the organism was isolated.

The cumulative yearly percentages of fosfomycin resistance among selected 11 studies are graphically represented in Figure 2. Out of these 11 studies, nine showed less than 10% resistance rates[34, 35, 38, 41-43, 45-47] except two which showed 15.8%[40] and 22%[44] resistant rates. Among the selected 11 studies, none of the studies have assessed fosfomycin resistance in 2017 and 2018.

(Susceptibility % [4, 8, 23-38], resistance %[34, 35, 38, 40-47])

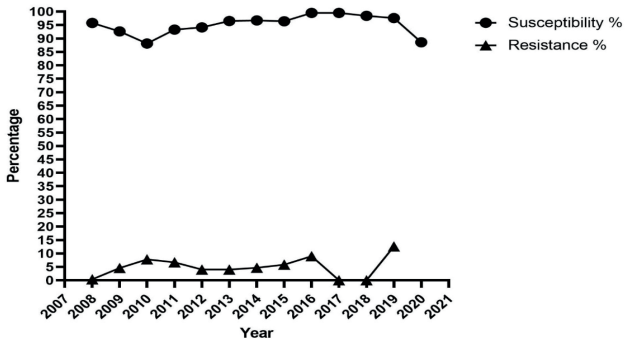

Figure 2: Summary on the percentage sensitivity and resistance rates of fosfomycin to *E. coli,* from 2011 to 2021

DISCUSSION

A thorough assessment of alternative treatment options is needed due to the increased incidence of antibiotic resistant *E. coli* strains that cause UTIs. The importance of this systematic review is to assesses the possibility of using fosfomycin as an effective treatment for MDR, ESBL-producing *E. coli*, focusing specifically on its application in clinical contexts such as Sri Lanka where, the antibiotic resistance to UTI causing organisms is high and fosfomycin is not currently in use. Available literature was analyzed in depth and showed that fosfomycin exerts an excellent effectiveness against a wide population of antibiotic resistant *E. coli.* When assessing the potential use of fosfomycin, it is essential to consider the antibiotic resistance rates in each country, as its influenced by various epidemiological factors and the treatment is challenging due to lack of therapeutic antibiotic options. Thus, to maximize the use of fosfomycin as a frontline treatment, it is imperative to understand the local resistance trends.

Reported high susceptibility rates and low resistance rates of fosfomycin in this review are encouraging and demonstrate its effectiveness in treating UTIs caused by antibiotic resistant bacteria. Fosfomycin showed an increased susceptibility rate to *E. coli* isolates originating from patients with both hospital-acquired and community-acquired infections. Globally available preliminary data validates fosfomycin as a valuable option for the treatment of lower UTIs caused by ESBL-producing *E. coli.*[48] Oral fosfomycin is administered as a single dose to treat uncomplicated UTIs. Recent studies suggest fosfomycin as a therapeutic option for complicated UTIs as well. However, it should be further investigated pharmacodynamically and by clinical trials.[15, 49]

According to the findings of this review, among the ESBL-producing *Enterobacteriaceae* isolates, fosfomycin seems to be more effective to *E. coli* than *Klebsiella* spp. Although, fosfomycin was mostly tested against urinary *Enterobacteriaceae* isolates, its activity does not seem to be affected by the origin of the clinical isolate, as isolates from mixed sites also showed higher susceptibility rates in comparison with urinary isolates. However, there is an observable change in sensitivity rates from one geographic location to another. Although, the emergence of fosfomycin resistant strains were reported, resistant rates following treatment with fosfomycin are largely unknown.[20, 50] In this review, we noted that the reported resistance rates to fosfomycin were lower in comparison to other antibiotics. A low level of cross-resistance was observed in fosfomycin among ESBL producing *Enterobacteriaceae* when compared to commonly used antibiotics for the treatment of uropathogens. This could be because, the resistance to fosfomycin is being mediated by a chromosomal encoding mechanism but,

co-transmission of fosfomycin resistance has also been shown.[51] As Fosfomycin is having a distinctive chemical structure and mechanism of action, it has been spared from various antibiotic resistance mechanisms.[17, 52]

Apart from ESBL-producing *E. coli*, fosfomycin demonstrated a high sensitivity rate for other MDR organisms as well. This finding is important for the treatment of community-acquired and hospital-acquired UTIs caused by MDR and ESBL- producing *E. coli*.[31] The likelihood of fosfomycin to serve as a therapeutic alternative has become more significant, due to the limited availability of susceptible antibiotics and increased emergence of MDR, ESBL-producing *E. coli*. The global data reported in this review provides an essential viewpoint for evaluating the effectiveness of fosfomycin. However, local studies are required in country level to determine its efficacy in clinical context.

This systematic review has few limitations. Particularly, some potentially relevant research studies conducted in countries where fosfomycin is widely used were published in their native languages. Agar dilution method is the gold standard for susceptibility testing of fosfomycin and recommended to be done with the addition of 25 mg/L, glucose-6-phosphate to the agar medium.[21] Glucose-6-phosphate is an enzyme found in human cells which has the capability to enhance the *in-vitro* susceptibility of fosfomycin for bacteria. This fact was not explicitly mentioned in most of the research studies that were included in this review.[53] Although, many studies have been conducted worldwide on the effectiveness of fosfomycin, only one *in-vitro* study has been conducted in the Sri Lankan clinical setting to study the effectiveness of fosfomycin for MDR bacteria. Since, the antibiotic resistance patterns reported in other South-Asian countries showed a similarity to Sri Lanka, the findings of this review can be applied to minimize the burden of antibiotic resistance in the Sri Lankan setting as well as, in other countries where, high antibiotic resistance rates were reported and fosfomycin is currently not in use.

CONCLUSION

MDR organisms and ESBL-producers are emerging increasingly. Global results demonstrated the ability of fosfomycin to combat the threat of antimicrobial resistance in the context of UTI causing, MDR, ESBL-producing *E. coli*. However, the global data conveyed in this review highlighted the need of performing comprehensive context specific local investigations to determine the usefulness of fosfomycin in clinical settings. In order to minimize the antibiotic resistance threat, health care professionals should consider necessary steps to implement the use of fosfomycin to treat antibiotic resistant uropathogens, specifically *E. coli*.

Financial support- No financial support is used

Authors contribution statement

Conception and design: NJ, TS, DN, VN
Analysis and interpretation of the data: NJ, TS
Drafting of the article: NJ

Critical revision of the article: NJ, TS, DN, VN
Final approval of the article: TS, DN, VN

All the authors read and approved the final version of this manuscript

REFERENCES

1. Walker E, Lyman A, Gupta K, Mahoney MV, Snyder GM, and Hirsch EB. Clinical Management of an Increasing Threat: Outpatient Urinary Tract Infections Due to Multidrug-Resistant Uropathogens. *Clin Infect Dis*. 2016;**63**(7): 960-9655
2. Flores-Mireles AL, Walker JN, Caparon M, and Hultgren SJ. Urinary tract infections: Epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015;**13**(5): 269–284.
3. Sharma M, Soneja S, Oberoi L, Malhotra A, Singh K, Mahindroo B. Bacterial IsolateProfile in Gram-Negative Urinary Isolates: Role ofNitrofurantoin. *Int J Hum Heal Sci*. 2023;**07**(2): 162–165
4. Matthews PC, Barrett LK, Warren S, Stoesser N, Snelling M, Scarborough M, et al. Oral fosfomycin for treatment of urinary tract infection : a retrospective cohort study. *BMC Infect Dis*. 2016;1–11.
5. Seitz M, Stief C, and Waidelich R. Local epidemiology and resistance profiles in acute uncomplicated cystitis (AUC) in women: A prospective cohort study in an urban urological ambulatory setting. *BMC Infect Dis*. 2017;**17**(1): 1–5
6. Barber AE, Norton JP, Spivak AM, and Mulvey MA. Urinary tract infections: Current and emerging management strategies. *Clin Infect Dis*. 2013;**57**(5): 719–724
7. US Department of Health and Human Services, CDC. Antibiotic Resistance Threats in the United States. Centers Dis Control Prev. 2019;1–113. Available from: https://www.cdc.gov/drugresistance/biggest_threats.html
8. Cho YH, Jung S Il, Chung HS, Yu HS, Hwang EC, Kim SO, et al. Antimicrobial susceptibilities of extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae in health care-associated urinary tract infection: focus on susceptibility to fosfomycin. *Int Urol Nephrol*. 2015;**47**(7): 1059–1066
9. Bitsori M, and Galanakis E. Treatment of Urinary Tract Infections Caused by ESBL-producing Escherichia coli or Klebsiella pneumoniae. *Pediatr Infect Dis J*. 2020;**38**(12): E332–335
10. Mazzariol A, Bazaj A, and Cornaglia G. Multi-drug-resistant Gram-negative bacteria causing urinary tract infections: a review. *J Chemother*. 2017; **29**(sup1), 2-9.
11. Michalopoulos AS, Livaditis IG, and Gougoutas V. The revival of fosfomycin. *Int J Infect Dis*. 2011;**15**(11)
12. Mączyńska B, Paleczny J, Oleksy-Wawrzyniak M, Choroszy-Król I, and Bartoszewicz M. In Vitro Susceptibility of Multi-Drug Resistant *Klebsiellapneumoniae* Strains Causing Nosocomial Infections to Fosfomycin. A Comparison of Determination Methods. *Pathogens*. 2021;**10**(5): 512.
13. Gardiner BJ, Stewardson AJ, Abbott IJ, and Peleg AY. Nitrofurantoin and fosfomycin for resistant urinary tract infections: old drugs for emerging problems. *Aust Prescr*. 2019;**42**(1): 14-19.
14. Ballestero-Téllez M, Docobo-Pérez F, Rodríguez-Martínez JM, Conejo MC, Ramos-Guelfo MS, Blázquez J, et al. Role of inoculum and mutant frequency on fosfomycin MIC discrepancies by agar dilution and broth microdilution methods in Enterobacteriaceae. *Clin Microbiol Infect*. 2017;**23**(5): 325-331.
15. López-Montesinos I, and Horcajada JP. Oral and intravenous fosfomycin in complicated urinary tract infections. *Rev Esp Quimioter*. 2019;**32**(Suppl 1):37-44.
16. Bassetti M, Graziano E, Berruti M, and Giacobbe DR. The role of fosfomycin for multidrug-resistant gram-negative infections. *Curr Opin Infect Dis*. 2019;617–625.
17. Karaiskos I, and Giamarellou H. Multidrug-resistant and extensively drug-resistant Gram-negative pathogens: Current and emerging therapeutic approaches. *Expert Opin Pharmacother*. 2014;**15**(10):1351–1370
18. Raz R. Fosfomycin: an old--new antibiotic. *Clin Microbiol Infect.* 2012;**18**(1):4-7.
19. Falagas ME, Vouloumanou EK, Samonis G, and Vardakas KZ. Fosfomycin. *Clin Microbiol Rev.* 2016;**29**(2): 321-347.
20. Karageorgopoulos DE, Wang R, Yu X hong, and Falagas ME. Fosfomycin: Evaluation of the published evidence on the emergence of antimicrobial resistance in gram-negative pathogens. *J Antimicrob Chemother*. 2012;**67**(2): 255–268
21. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 32nd ed. CLSI supplement M100. Clinical and Laboratory Standards Institute; 2022
22. Candel FJ, Matesanz David M, and Barberán J. New perspectives for reassessing fosfomycin: applicability in current clinical practice. *Rev Esp Quimioter*. 2019;**32**(Suppl 1): 1–7.
23. Karaiskos I, Galani L, Sakka V, Gkoufa A, Sopilidis O, Chalikopoulos D, et al. Oral fosfomycin for the treatment of chronic bacterial prostatitis. *J Antimicrob Chemother*. 2019;**74**(5): 1430–1437
24. Yeganeh Sefidan F, Azargun R, and Ghotaslou R. Fosfomycin, a Therapeutic Option for Infections Produced by Multiple Drug-Resistant *Enterobacteriaceae*. *Microbiol Res*. 2016; **7**(1): 6407.
25. Liu HY, Lin HC, Lin YC, Yu S hua, Wu WH, and Lee YJ. Antimicrobial susceptibilities of urinary extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae to fosfomycin and nitrofurantoin in a teaching

hospital in Taiwan. *J Microbiol Immunol Infect*. 2011;**44**(5): 364–368.

26. Saeed NK, Al Khawaja S, and Al-Biltagi M. Antimicrobial Susceptibilities of Urinary Extended-spectrum β-lactamase *Escherichia coli* to Fosfomycin. *Oman Med J*. 2021;**36**(6): e314.
27. Aprile A, Scalia G, Stefani S, and Lina M. Journal of Global Antimicrobial Resistance In vitro fosfomycin study on concordance of susceptibility testing methods against ESBL and carbapenem-resistant Enterobacteriaceae. *Integr Med Res* 2020;**23**: 286–289.
28. Gopichand P, Agarwal G, Natarajan M, Mandal J, Deepanjali S, Parameswaran S, et al. In vitro effect of fosfomycin on multi-drug resistant gram-negative bacteria causing urinary tract infections. *Infect Drug Resist*. 2019;**12**: 2005–2013.
29. Bielen L, and Likic R. Experience with fosfomycin in the treatment of complicated urinary tract infections caused by extended-spectrum beta-lactamase-producing Enterobacteriaceae. *Ther Adv Infect Dis*. 2019;**6**: 1–11.
30. Priyadharshana U, Piyasiri LB, and Wijesinghe C. Prevalence , antibiotic sensitivity pattern and genetic analysis of extended spectrum beta lactamase producing Escherichia coli and Klebsiella spp among patients with community acquired urinary tract infection in Galle district , Sri Lanka. *Ceylon Med J*. 2019;**64**(4): 140–145.
31. Ny S, Edquist P, Dumpis U, Gröndahl-Yli-Hannuksela K, Hermes J, Kling AM, et al. Antimicrobial resistance of Escherichia coli isolates from outpatient urinary tract infections in women in six European countries including Russia. *J Glob Antimicrob Resist.* 2019;**17**: 25–34
32. Amladi AU, Abirami B, Devi SM, Sudarsanam TD, Kandasamy S, Kekre N, et al. Susceptibility profile , resistance mechanisms & efficacy ratios of fosfomycin , nitrofurantoin & colistin for carbapenem-resistant Enterobacteriaceae causing urinary tract infections. *Indian J Med Res*. 2019;**149**(2): 185-191.
33. Fajfr M, Louda M, Paterová P, Ry L, Pacovský J, Ko J, et al. The susceptibility to fosfomycin of Gram- negative bacteria isolates from urinary tract infection in the Czech Republic : data from a unicentric study. *BMC Urol*. 2017;**17**(33): 1–6.
34. Bi W, Li B, Song J, Hong Y, Zhang X, Liu H, et al. Antimicrobial susceptibility and mechanisms of fosfomycin resistance in extended-spectrum β-lactamase-producing Escherichia coli strains from urinary tract infections in Wenzhou, China. *Int J Antimicrob Agents.* 2017;**50**(1): 29–34.
35. Ohkoshi Y, Sato T, Suzuki Y, Yamamoto S, Shiraishi T, Ogasawara N, et al. Mechanism of reduced susceptibility to fosfomycin in Escherichia coli clinical isolates. *Biomed Res Int*. 2017;2017.
36. Rajenderan S, Balaji V, Anandan S, Sahni RD, Tansarli GS, and Falagas ME. Determination of MIC distribution of arbekacin, cefminox, fosfomycin, biapenem and other antibiotics against gram-negative clinical isolates in South India: A prospective study. *PLoS One*. 2014;**9**(7): 1–8.
37. Sahni RD, Balaji V, Varghese R, John J, Tansarli GS, and Falagas ME. Evaluation of fosfomycin activity against uropathogens in a fosfomycin-naive population in South India: A prospective study. *Future Microbiol*. 2013;**8**(5): 675–680
38. Lee SY, Park YJ, Yu JK, Jung S, Kim Y, Jeong SH, et al. Prevalence of acquired fosfomycin resistance among extended-spectrum β-lactamase-producing Escherichia coli and klebsiella pneumoniae clinical isolates in korea and IS26-composite transposon surrounding fosA3. *J Antimicrob Chemother*. 2012;**67**(12): 2843–2847
39. Oteo J, Pérez-Vázquez M, and Campos J. Extended-spectrum β-lactamase producing Escherichia coli: Changing epidemiology and clinical impact. *Curr Opin Infect Dis*. 2010;**23**(4): 320–326
40. Kansak N, Arıcı N, Adaleti R, Nakipoglu Y, and Aksaray S. Rapid detection of fosfomycin resistance in Escherichia coli and Klebsiella spp . strains isolated from urinary tract infections. *J Microbiol Methods*. 2021;**188**(July): 106296.
41. Carolina A, Campos C, Andrade NL, Couto N, Mutters NT, Vos M De, et al. Characterization of fosfomycin heteroresistance among multidrug-resistant Escherichia coli isolates from hospitalized patients in Rio de Janeiro , Brazil. *J Glob Antimicrob Resist.* 2020;**22**: 584–593.
42. Mowlaboccus S, Daley D, Pang S, Gottlieb T, Merlino J, Nimmo GR, et al. Identification and Characterisation of Fosfomycin Resistance in Escherichia coli Urinary Tract Infection Isolates from Australia. *Int J Antimicrob Agents*. 2020;106121. https://doi.org/10.1016/j.ijantimicag.2020.106121
43. Mueller L, Cimen C, Poirel L, Descombes M, and Nordmann P. Prevalence of fosfomycin resistance among ESBL-producing Escherichia coli isolates in the community, Switzerland. *Eur J Clin Microbiol Infect Dis*. 2019;**38**(5): 945–949.
44. Nordmann P, and Poirel L. Rapid Detection of Fosfomycin Resistance in Escherichia coli. *J Clin Microbiol*. 2019;**57**(1): e01531-18.
45. Bahramian A, Eslami G, Hashemi A, Tabibi A , and Heidary M. Emergence Of Fosfomycin Resistance Among Isolates Of Escherichia Coli Harboring Extended-Spectrum and AmpC β -Lactamases. *Acta Microbiol Immunol Hung*. 2018;**65**(1): 15–25.
46. Benzerara Y, Gallah S, Hommeril B, Genel N, Decré D, Rottman M, et al. Emergence of Plasmid-Mediated Fosfomycin-Resistance Genes among Escherichia coli Isolates, France.

Emerg Infect Dis. 2017;**23**(9): 6–9.

47. Li Y, Zheng B, Li Y, Zhu S, Xue F, and Liu J. Antimicrobial Susceptibility and Molecular Mechanisms of Fosfomycin Resistance in Clinical Escherichia coli Isolates in Mainland. *PLoS One*. 2015;**10**(8): 1–7.
48. Sultana T, Fakruddin M, Datta S, and Shishir MA. Fighting Urinary Tract Infection: Fosfomycin's Efficacy against Uropathogenic Escherichia coliIsolates. *Int J Hum Heal Sci.* 2023;**07**(04): 338–343.
49. Babiker A, Clarke L, Doi Y, and Shields RK. Fosfomycin for treatment of multidrug-resistant pathogens causing urinary tract infection: A real-world perspective and review of the literature. *Diagn Microbiol Infect Dis.* 2019;**95**(3): 114856. https://doi.org/10.1016/j.diagmicrobio.2019.06.008
50. Aris P, Boroumand MA, Rahbar M, and Douraghi M. The Activity of Fosfomycin Against Extended-Spectrum Beta-Lactamase-Producing Isolates of Enterobacteriaceae Recovered from Urinary Tract Infections: A Single-Center Study over a Period of 12 Years. *Microb Drug Resist*. 2018;**24**(5): 607–612.
51. Falagas ME, Kastoris AC, Kapaskelis AM, and Karageorgopoulos DE. Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review. *Lancet Infect Dis.* 2010;**10**(1): 43–50.
52. Silver LL. Fosfomycin : Mechanism and Resistance. *Cold Spring Harb Perspect Med.* 2017;1–11.
53. Fuchs PC, Barry AL, and Brown SD. Susceptibility testing quality control studies with fosfomycin tromethamine. *Eur J Clin Microbiol Infect Dis*. 1997;**16**(7): 538-540.