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Fosfomycin for the treatment of multidrug-resistant, including extended-spectrum β-lactamase producing, Enterobacteriaceae infections: a systematic review

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Rising rates of resistance to antimicrobial drugs among Enterobacteriaceae limit the choice of reliably active forms of these drugs. We evaluated the evidence on fosfomycin as a treatment option for infections caused by members of the family Enterobacteriaceae with advanced resistance to antimicrobial drugs, including producers of extended-spectrum β-lactamase (ESBL). We systematically reviewed studies evaluating the antimicrobial activity, or the clinical effectiveness of fosfomycin. 17 antimicrobial-susceptibility studies were found and included in our Review, accounting for 5057 clinical isolates of Enterobacteriaceae with advanced resistance to antimicrobial drugs (4448 were producers of ESBL); 11 of the 17 studies reported that at least 90% of the isolates were susceptible to fosfomycin. Using a provisional minimum inhibitory concentration susceptibility breakpoint of 64 mg/L or less, 1604 (96·8%) of 1657 *Escherichia coli* isolates producing ESBL were susceptible to fosfomycin. Similarly, 608 (81·3%) of 748 *Klebsiella pneumoniae* isolates producing ESBL were susceptible to fosfomycin. In two clinical studies, oral treatment with fosfomycin–trometamol was clinically effective against complicated or uncomplicated lower urinary tract infections caused by ESBL-producing *E coli* in, cumulatively, 75 (93·8%) of the 80 patients evaluated. Initial clinical data support the use of fosfomycin for the treatment of urinary tract infections caused by these pathogens, although further research is needed.

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Introduction

The rising rates of resistance to antimicrobial drugs in Enterobacteriaceae reduces the number of reliably effective drugs that can be used to treat infections with these pathogens.[1–3] Of particular public health importance is the spread of extended-spectrum β-lactamases (ESBLs) among isolates of Enterobacteriaceae both from community and health-care settings.[4,5] The presence of these enzymes confers resistance to third-generation and fourth-generation cephalosporins and monobactams, and is frequently associated with co-resistance to other classes of antimicrobial drugs, such as fluoroquinolones, co-trimoxazole, tetracyclines, and aminoglycosides.[6] Other types of β-lactamases that also confer resistance to extended-spectrum cephalosporins or even carbapenems, such as AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases, are also identified with increasing frequency among isolates of Enterobacteriaceae.[7]

Nevertheless, during the past few years there has been a shortage of antimicrobial drugs introduced into clinical practice with substantial antimicrobial activity against Enterobacteriaceae isolates resistant to commonly used drugs. Tigecycline, the first marketed glycylcycline-class antibiotic, is one of the few exceptions because it has high antimicrobial activity against isolates of, primarily, *Escherichia coli* and also isolates of *Klebsiella pneumoniae* that produce ESBLs or have a multidrug-resistance phenotype.[8] Still, the example of polymyxins shows that older drugs that have been left out of routine clinical use might have retained activity against otherwise multidrug-resistant isolates.[9,10]

Fosfomycin, known for nearly four decades, 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.[11] Fosfomycin has a broad spectrum of antimicrobial activity, including activity against several Gram-negative and Gram-positive aerobic bacteria.[12–15] We evaluate fosfomycin as a potential treatment option for infections caused by Enterobacteriaceae isolates with advanced resistance to antimicrobial drugs.

Methods

Study selection

We systematically reviewed the published work on Enterobacteriaceae isolates with an advanced drug resistance profile and their susceptibility to fosfomycin, and the clinical effectiveness of treatment with fosfomycin for infections with these pathogens. For the purposes of this Review, we deemed advanced resistance to antimicrobial drugs to be denoted by multidrug resistance (as defined within each study), carbapenem resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases. We searched PubMed, Scopus, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to January, 2009, along with the bibliographies of relevant studies.

Our search strategy consisted of the combination of the terms "fosfomycin", "phosphomycin", or "phosphonomycin" with either terms relating to antimicrobial-drug resistance ("drug resistance", "beta-lactamases", "extended-spectrum beta-lactamases", "ESBL", "CTX-M", "AmpC", "carbapenem resistance", "metallo-beta-lactamases", or "MBL") or terms referring to the bacteria of interest ("Enterobacteriaceae", "Escherichia", "Klebsiella", "Proteus", "Enterobacter", "Morganella", "Salmonella", or "Shigella"). We excluded studies written in languages other than English, Spanish, French, German, Italian, and Greek, and studies presented solely as abstracts in scientific conferences.

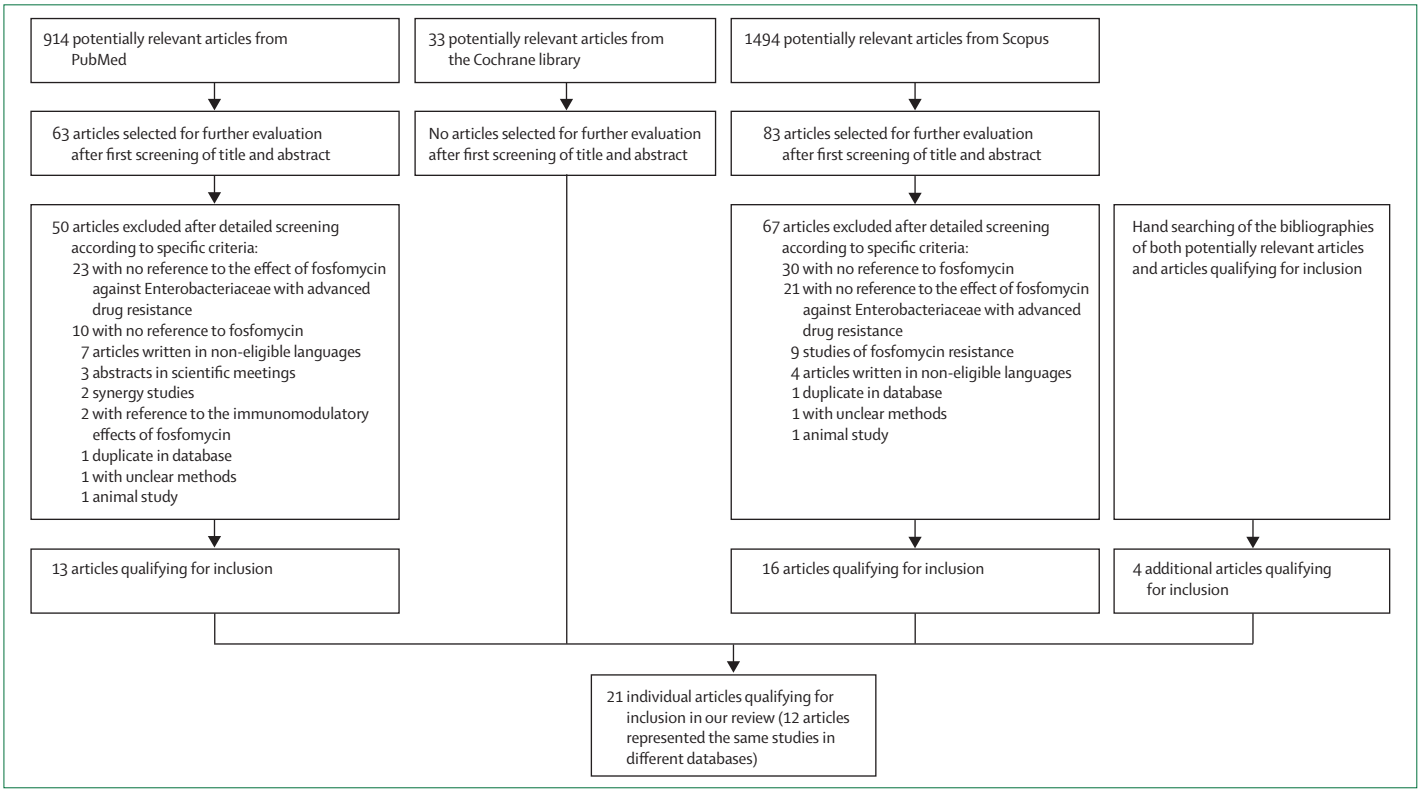

Figure: **Article selection**

Data extraction and synthesis

We extracted fosfomycin susceptibility data as reported in antimicrobial susceptibility studies or presented in tables of susceptibilities or relevant graphs according to the criteria and methods used in each study. For studies where more than one method for susceptibility testing was used, we extracted the relevant data preferentially obtained by use of the agar dilution method, disc diffusion method, Etest, or broth microdilution method.[16–18]

To collate the antimicrobial susceptibility data reported in different studies, we deemed reliable antimicrobial activity of fosfomycin to be denoted by susceptibility to this drug of at least 90% of the isolates studied, and poor antimicrobial activity by susceptibility of fewer than 50% of the isolates. We selected the cut-off values as corresponding to the 90% and 50% minimum inhibitory concentration (MIC) measures that are commonly used to describe the antimicrobial activity of a drug against a group of isolates. Furthermore, we calculated the crude cumulative susceptibility rate to fosfomycin of the isolates included in different studies by use of the most relevant Clinical and Laboratory Standards Institute (CLSI) criteria that refer to urinary isolates of *E coli*.[16]

The figure depicts the process of selecting studies for inclusion in our Review. Specifically, a total of 21 studies were included.[18–38] Of these studies, 17 referred to antimicrobial susceptibility data,[18–34] and four referred to clinical data.[35–38]

Antimicrobial activity of fosfomycin

In table 1, we present the data extracted from each of the 17 microbiological studies included in our Review on the pattern of resistance to antimicrobial drugs, source, site of isolation, and the susceptibility of the evaluated Enterobacteriaceae isolates to fosfomycin. Among the 17 selected studies, four involved isolates from Spain,[18,20,23,27] three from France,[30,33,34] two from the UK,[26,32] and two from Thailand.[29,31] The remaining six studies involved isolates from Greece,[22] Hong Kong,[24] Japan,[28] Korea,[25] Turkey,[21] or the USA.[19] The majority of the studies included involved clinical isolates collected after the year 2000.[19–26,28,29,31,32]

11 of the 17 included studies used criteria corresponding to the CLSI breakpoints for *E coli* urinary isolates (susceptibility defined as MIC of 64 mg/L or less[16]),[18–25,27,29,31] two studies used criteria corresponding to the former British Society for Antimicrobial Chemotherapy breakpoints for Gram-negative rods isolated from urinary tract infections (susceptibility defined as MIC of 128 mg/L or less[39]),[26,32] and two studies used criteria corresponding to the Comité de l'Antibiogramme de la Société Française de Microbiologie breakpoints for Enterobacteriaceae (susceptibility defined as MIC of 32 mg/L or less[40]).[30,34] The two remaining studies from France[33] and Japan,[28] did not specify the fosfomycin MIC breakpoints used. The methods for establishing susceptibility to fosfomycin used in each of the studies included in this Review were mainly disc diffusion[20,21,24,29–31,33,34] and agar dilution.[18,19,22,25,26]

	Country; study period; susceptibility testing method	Isolates with advanced drug resistance	Origin of isolates (number)	Fosfomycin MIC breakpoint of susceptibility	Susceptible isolates (MIC range [mg/L])	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Prakash et al, 2009[19]	USA; 2002–08; agar dilution	57 ESBL Enterobacteriaceae, predominantly *Escherichia coli* (46 CTX-M; 11 SHV or TEM-10 producing)	Urinary isolates	Clinical and Laboratory Standards Institute	42 of 46, 91·3% (CTX-M); 11 of 11, 100% (SHV or TEM-10)	0·5 (CTX-M), 4 (SHV or TEM-10)	64 (CTX-M); 8 (SHV or TEM-10)
Andreu et al, 2008[20]	Spain; February–June, 2006; automated broth microdilution or disc diffusion	105 ESBL *Escherichia coli*	Community-acquired, complicated or uncomplicated, lower UTIs	Clinical and Laboratory Standards Institute	103 of 105, 98%	..	..
Pullucku et al, 2008[21]	Turkey; January–December, 2005; disc diffusion	344 ESBL *E coli*	Nosocomial (241) or outpatient (103) urinary tract infections	Clinical and Laboratory Standards Institute	231 of 241, 95·9% (nosocomial); 101 of 103, 98·1% (outpatient)	..	..
Falagas et al, 2007[22]	Greece; 2006–07; agar dilution	30 both ESBL and MBL *Klebsiella pneumoniae*	Any clinical site from patients at a tertiary hospital	Clinical and Laboratory Standards Institute	30 of 30, 100% (8–64)	16	32
Goyanes et al, 2007[23]	Spain; 2004–06; automated microdilution system	1449 ESBL plus 499 AmpC Enterobacteriaceae†	Urinary isolates collected in a tertiary hospital	Clinical and Laboratory Standards Institute	1304 of 1449, 90% (ESBL); 254 of 499, 51% (AmpC)	..	..
Ho et al, 2007[24]	Hong Kong; third and fourth quarters of 2004 and 2005; disc diffusion	157 MDR *E coli* (resistant to ampicillin, ciprofloxacin, and co-trimoxazole), 89 ESBL *E coli* with a CTX-M phenotype‡	Urinary isolates from outpatient adult women	Clinical and Laboratory Standards Institute	156 of 157, 99·4% (MDR); 88 of 89, 98·9% (ESBL)§	..	..
Ko et al, 2007[25]	Korea; May–September, 2005; agar dilution	24 ESBL *E coli* (14 both TEM and CTX-M, 7 CTX-M, 1 SHV, 1 TEM, and 1 both SHV and CTX-M producing)	22 urinary and 2 blood isolates from patients at a tertiary hospital	Clinical and Laboratory Standards Institute	24 of 24, 100%	..	32
De Cueto et al, 2006[18]	Spain; 1995–2001; agar dilution	290 ESBL *E coli*, 138 ESBL *K pneumoniae*	Isolates collected at multiple hospitals (148 from outpatients with community-acquired infections, including 75 from women with uncomplicated urinary tract infections)	Clinical and Laboratory Standards Institute	289 of 290, 99·7% (0·5–128; *E coli*); 128 of 138, 92·7% (0·5–512; *K pneumoniae*)	1 (*E coli*), 16 (*K pneumoniae*)	4 (*E coli*), 64 (*K pneumoniae*)
Ellington et al, 2006[26]	UK; 2003–04; agar dilution	220 ESBL (CTX-M) *E coli*¶	Isolates from urinary tract infections collected at a reference laboratory (172 sporadic isolates and 48 representatives of 5 major UK clones)	British Society for Antimicrobial Chemotherapy‖	220 of 220, 100%	..	..
Ena et al, 2006[27]	Spain; January, 1999, to December, 2004; automated broth microdilution	161 ESBL *E coli*	Isolates from urinary tract infections of ambulatory (100) or patients admitted to hospital (61)	Clinical and Laboratory Standards Institute	159 of 161, 99%	..	..
Muratani et al, 2006[28]	Japan; January–September, 2003; ..	200 ESBL *E coli*	Inpatient urinary tract infections	..	146 of 200, 73%**	..	..
Waiwarawooth et al, 2006[29]	Thailand; January, 2005, to December, 2005; disc diffusion	607 ESBL *E coli* 537 ESBL *K pneumoniae*	Isolates from various sites from inpatients (collected within or after 48 h from admission to hospital)	Clinical and Laboratory Standards Institute	573 of 607, 94·3 (<48 h: 169 of 190, 89%; >48 h: 404 of 417, 97%; *E coli*); 412 of 537, 76·7 (<48 h: 72 of 90, 80%; >48 h: 340 of 447, 76%; *K pneumoniae*)	..	..
Dubois et al, 2005[30]	France; November, 1996, to December, 2002; disc diffusion	17 ESBL Enterobacteriaceae (5 Proteus mirabilis, 4 *K pneumoniae*, 3 *E coli*, 3 *Providencia stuartii*, 2 *Morganella morganii*)	Isolates from urine or bedsores from nursing home residents	Comité de l'Antibiogramme de la Société Française de Microbiologie	2 of 5, 40% (*P mirabilis*); 4 of 4, 100% (*K pneumoniae*); 3 of 3, 100% (*E coli*); 0 of 3, 0% (*P stuartii*); 0 of 2, 0% (*M morganii*)	..	..
Tharavichitkul et al, 2005[31]	Thailand; January, 2003, to December, 2003; disc diffusion, Etest	43 ESBL *K pneumoniae*, 37 ESBL *E coli*	Randomly selected ESBL clinical isolates among those isolated from inpatients at single hospital	Clinical and Laboratory Standards Institute	38 of 43, 88·4% (<0·5 to >512; *K pneumoniae*); 36 of 37, 97·3% (<0·5 to 128; *E coli*)	12 (*K pneumoniae*), 0·7 (*E coli*)	32 (*K pneumoniae*), 1·8 (*E coli*)

(Continues on next page)

	Country; study period; susceptibility testing method	Isolates with advanced drug resistance	Origin of isolates (number)	Fosfomycin MIC breakpoint of susceptibility	Susceptible isolates (MIC range [mg/L])	MIC_{50} (mg/L)	MIC_{90} (mg/L)
(Continued from previous page)							
Woodford et al, 2004[32]	UK; January, 2003, to March, 2004; agar dilution	57 ESBL (group 1 CTX-M) *E coli* (45 representatives of 5 major UK strains and 12 representatives of non-major UK strains)¶	Isolates from various sites collected at a reference laboratory	British Society for Antimicrobial Chemotherapy‖	45 of 45, 100% (0·5–2; major-strains); ·· (0·5–256; non-major strains)††	··	··
Gouby et al, 1994[33]	France; August, 1991, to March, 1993; disc diffusion	12 ESBL *K pneumoniae*	Outbreak strains from patients in a geriatric hospital	··	0 of 12, 0%	··	··
Arpin et al, 1996[34]	France; 1993; disc diffusion	73 MDR‡‡ *Enterobacter aerogenes* (31 ESBL-producing, mainly SHV-4)	70 isolates from medical ICU and hospital ward patients and 3 environmental isolates from medical ICU	Comité de l'Antibiogramme de la Société Française de Microbiologie	3 of 73, 4·1% (MDR); 2 of 31, 6·5% (ESBL)	··	··

MIC=minimum inhibitory concentration. ESBL=extended-spectrum β-lactamase. MDR=multidrug resistance. MBL=metallo-β-lactamase. *Multidrug resistance, carbapenem-resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases. †We calculated absolute numbers from percentile data provided in the study. ‡‡MDR: resistant to aminoglycosides and β-lactams (chromosomally derepressed cephalosporinase). ‡47 isolates were both MDR and ESBL-producing. §Data refer to both fully and intermediately susceptible isolates. ¶Isolates included in Ellington and colleagues might overlap with those included in Woodford and colleagues. ‖Refers to the former to 2009 breakpoints. **Data extracted from a bar chart. ††The MIC geometric mean of isolates belonging to non-major-strains was 1·9 mg/L.

Table 1: **Microbiological studies on the activity of fosfomycin against Enterobacteriaceae with advanced resistance to antimicrobial drugs***

In table 2, we summarise the percentage of studies that included isolates of Enterobacteriaceae with a greater than 90% susceptibility to fosfomycin according to the criteria used in each study. Also presented is the cumulative susceptibility of the isolates to fosfomycin using the CLSI susceptibility breakpoint for urinary isolates of *E coli*, in studies from which such data could be extracted. We have stratified this data by different types of pathogens, resistance patterns, and origin of the isolates.

The 17 included studies reported data on the susceptibility to fosfomycin of 5057 isolates of Enterobacteriaceae with advanced resistance to antimicrobial drugs. These isolates were mainly *E coli* (2205 isolates), *Klebsiella pneumoniae* (764), and *Enterobacter* spp (73); in two studies[19,23] the type of the pathogens was not specified. In 11 of the 17 included studies, 90% or more of the isolates of Enterobacteriaceae with advanced resistance to antimicrobial drugs were susceptible to fosfomycin.[18–22,24–27,31,32] By contrast, in two studies,[33,34] fewer than 50% of the isolates (which were isolates of *Enterobacter aerogenes* and *K pneumoniae*, respectively) were susceptible to fosfomycin.

Isolates of Enterobacteriaceae that produced ESBL accounted for 4448 (88·0%) of the 5057 isolates with advanced resistance to antimicrobial drugs evaluated in the included studies. In 11 of 17 studies that reported specific relevant data 90% or more of 4448, in total, isolates were susceptible to fosfomycin.[18–22,24–27,31,32] By the most relevant CLSI criteria, the cumulative susceptibility to fosfomycin of the isolates of Enterobacteriaceae that produced ESBL was 91·3% (3569 of 3911 isolates) in the 11 studies where relevant data could be retrieved.[18,19,20–25,27,29,31] Differentiating between ESBL-producing Enterobacteriaceae isolates collected from outpatients and patients admitted to hospital, 90% or greater susceptibility to fosfomycin was reported in three of three[20,21,24] and four of eight[21,22,25,28,29,31,33,34] studies providing specific relevant data, respectively, whereas the cumulative susceptibility rate by the CLSI criteria was 98·3% (292 of 297),[20,21,24] and 88·5% (1344 of 1519),[21,22,25,29,31] respectively.

Clinical effectiveness of fosfomycin

In table 3, we present the data from the four studies that evaluated the clinical effectiveness of fosfomycin against infections caused by Enterobacteriaceae with advanced resistance to antimicrobial drugs.[35–38] Specifically, two studies evaluated oral treatment with fosfomycin–trometamol for lower urinary tract infections with ESBL-producing *E coli* in patients with various risk factors.[35,36] Cumulatively, treatment with fosfomycin was associated with clinical cure in 75 of the 80 (93·8%) patients included in these studies. However, one of these studies found a lower rate of microbiological success (41 of 52; 78·8%).[36] In the remaining study,[35] single-dose fosfomycin–trometamol was equally effective to co-amoxiclav given for 5–7 days in patients with susceptible pathogens. Two additional studies[37,38] reported that treatment with fosfomycin was effective in two cases of infection due to multidrug-resistant *Salmonella* spp.

Discussion

The main finding of our Review is that fosfomycin has a good level of antimicrobial activity against clinical isolates of Enterobacteriaceae that produce ESBL. *E coli* seem to be the most susceptible to fosfomycin of the Enterobacteriaceae that produce ESBL. Fosfomycin, in particular, has high-levels of antimicrobial activity against isolates of *E coli* that produce ESBL, originating both from patients with community-acquired and hospital-acquired infections. Additionally, the antimicrobial activity of fosfomycin does not seem to be influenced by the site from which the

pathogen is isolated, either specifically the urinary tract or mixed sites. Furthermore, there are preliminary clinical data that support the idea that fosfomycin is a valuable option for the treatment of lower urinary tract infections caused by *E coli* that produce ESBL.

The low level of cross-resistance to fosfomycin noted in Enterobacteriaceae that produce ESBL is not seen in antimicrobial drugs that are commonly used for the treatment of infections caused by this group of pathogens.[6] This finding could be because resistance to fosfomycin in Enterobacteriaceae does not seem to be mediated primarily by plasmids, since it is more commonly chromosomally encoded.[41,42] However, cotransmission of resistance to fosfomycin and resistance to other antimicrobials through plasmids has been shown.[43–45] Furthermore, fosfomycin seems to be spared from the effect of various mechanisms of multiple resistance to antimicrobial drugs, because of its unique chemical structure and mechanism of action.[12,46] Apart from the Enterobacteriaceae that produce ESBL evaluated in our Review, high levels of antimicrobial activity of fosfomycin have also been reported in Enterobacteriaceae resistant to fluoroquinolones.[25,47–49]

Our Review has found that fosfomycin is a reliably active antimicrobial drug against Enterobacteriaceae that produce ESBL, particularly *E coli*. This finding might be important for the treatment of community-acquired ESBL-associated infections involving the urinary tract, which are mostly caused by *E coli*.[5,50] Oral single-dose fosfomycin–trometamol is reliably effective for the treatment of uncomplicated urinary tract infections.[51] Other traditional empirical antibiotic regimens for uncomplicated urinary tract infections, such as fluoroquinolones and co-trimoxazole, might be inactive against pathogens that produce ESBL,[6,52] potentially leading to suboptimum outcomes.[53,54]

Apart from fosfomycin, nitrofurantoin, pivmecillinam, and co-amoxiclav could be further options for oral antimicrobial treatment of ESBL-associated, but otherwise uncomplicated, urinary tract infections.[52,55] Specifically, nitrofurantoin has been used for the treatment of acute uncomplicated cystitis, and, has high rates of antimicrobial activity against *E coli* urinary isolates in vitro.[56,57] Studies specifically evaluating the susceptibility of isolates of ESBL-producing *E coli* to nitrofurantoin have reported varying findings.[19,20,24,25,27,28,58,59] Co-resistance between nitrofurantoin and fluoroquinolones in urinary isolates of *E coli* has also been noted.[60] Nitrofurantoin is not reliably active against common Enterobacteriaceae uropathogens, such as *K pneumoniae* and *P mirabilis*.[56,57] Moreover, the production of ESBLs has been associated with decreased susceptibility to nitrofurantoin in *K pneumoniae*.[61]

Pivmecillinam, an oral β-lactam, has also been used in the treatment of acute uncomplicated cystitis, particularly in northern Europe.[62] In vitro, pivmecillinam has high levels of antimicrobial activity against common uropathogens, particularly *E coli*.[56,57] It seems relatively stable to the hydrolytic activity of AmpC β-lactamases;[63] however, the evidence of its activity against Enterobacteriaceae that produce ESBL is scarce and less convincing.[64] Of note, treatment with pivmecillinam was successful in a case of relapsing pyelonephritis caused by ESBL-producing *E coli*, where other treatments had failed.[65]

	Studies showing susceptibility to fosfomycin of 90% or more compared with total number of studies	Cumulative susceptibility of isolates according to the CLSI criteria†
All Enterobacteriaceae isolates		
Any advanced antimicrobial drug resistance profile	11 of 17 (64·7%)[18–34]	3891 of 4478 (86·9%)[18–25,27,29,31]
ESBL-producing	11 of 17 (64·7%)[18–34]	3569 of 3911 (91·3%)[18–25,27,29,31]
Isolates from urinary tract	8 of 10 (80·0%)[19–21,23–28,30]	2061 of 2227 (92·5%)[19–21,23–25,27]
Isolates from mixed sites‡	5 of 8 (62·5%)[18,22,25,29,31–34]	1508 of 1684 (89·5%)[18,22,25,29,31]
Isolates from outpatients	3 of 3 (100·0%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 8 (50·0%)[21,22,25,28,29,31,33,34]	1344 of 1519 (88·5%)[21,22,25,29,31]
***Escherichia coli* isolates**		
Any advanced antimicrobial drug resistance profile	11 of 12 (91·7%)[18,20,21,24–32]	1672 of 1725 (96·9%)[18,20,21,24,25,27,29,31]
ESBL-producing	11 of 12 (91·7%)[18,20,21,24–32]	1604 of 1657 (96·8%)[18,20,21,24,25,27,29,31]
Isolates from urinary tract	6 of 7 (85·7%)[20,21,24–28]	704 of 721 (97·6%)[20,21,24,25,27]
Isolates from mixed sites‡	5 of 6 (83·3%)[18,25,29–32]	900 of 936 (96·2%)[18,25,29,31]
Isolates from outpatients	3 of 3 (100%)[20,21,24]	292 of 297 (98·3%)[20,21,24]
Isolates from hospitalised patients	4 of 5 (80·0%)[21,25,28,29,31]	864 of 909 (95·0%)[21,25,29,31]
***Klebsiella pneumoniae* isolates**		
Any advanced antimicrobial drug resistance profile	3 of 6 (50·0%)[18,22,29–31,33]	608 of 748 (81·3%)[18,22,29,31]
ESBL-producing	3 of 6 (50·0%)[18,22,29–31,33]	608 of 748 (81·3%)[18,22,29,31]
Isolates from mixed sites‡	2 of 5 (40·0%)[18,22,29,31,33]	608 of 748 (81·3%)[18,22,29,31]
Isolates from hospitalised patients	2 of 4 (50·0%)[22,29,31,33]	480 of 610 (78·7%)[22,29,31]

ESBL=extended-spectrum β-lactamase. CLSI=Clinical and Laboratory Standards Institute. *Multidrug resistance, carbapenem-resistance, or production of ESBLs, AmpC β-lactamases, serine carbapenemases, or metallo-β-lactamases. †CLSI fosfomycin susceptibility criteria refer specifically to urinary isolates of *Escherichia coli*. ‡Urinary tract isolates are potentially included.

Table 2: **Summary of data reported on fosfomycin susceptibility of Enterobacteriaceae isolates with advanced resistance to antimicrobial drugs***

Co-amoxiclav has moderate in vitro antimicrobial activity against Enterobacteriaceae that produce ESBL.[19,25,27–29,66] Although the clinical effectiveness of β-lactam and β-lactamase inhibitor combinations against serious infections caused by ESBL-producing Enterobacteriaceae remains uncertain,[52] the use of co-amoxiclav in a series of 37 patients with cystitis caused by ESBL-producing *E coli* has been associated with a favourable overall cure rate of 84%.[35] Yet, the effectiveness of co-amoxiclav seemed to be substantially lower in the subgroup of patients infected with pathogens having elevated MICs to this treatment. In vitro data also show that the combination of oral third-generation cephalosporins with clavulanic acid might help overcome the resistance conferred by the ESBLs.[19,67] However, the clinical effectiveness of such a treatment is uncertain.

The value of intravenous fosfomycin (available in Germany, France, Spain, Italy, and Japan) for the treatment of systemic infections by isolates of Enterobacteriaceae with advanced resistance to antimicrobial drugs warrants

	Country; period; study design	Type of infection	Patient characteristics	Underlying condition	Causative pathogens	Antibiotic treatment	Treatment outcome
Rodriguez-Bano et al, 2008[35]	Spain; February, 2002, to May, 2003; prospective study	Community-acquired cystitis	Outpatients	Various risk factors reported for the whole cohort of 112 cases with community-acquired infections	ESBL *Escherichia coli*, susceptible to fosfomycin	3 g fosfomycin–trometamol single-dose	Cure (26 of 28; 93%)
Rodriguez-Bano et al, 2008[35]	Spain; February, 2002, to May, 2003; prospective study	Community-acquired cystitis	Outpatients	Various risk factors reported for the whole cohort of 112 cases with community-acquired infections	ESBL *Escherichia coli*, susceptible to fosfomycin	Amoxicillin-clavulanate potassium 625 mg 3-times daily for 5-7 days	Cure (31 of 37; 84% [26 of 28; 93% for infections with susceptible isolates])
Pullucku et al, 2007[36]	Turkey; September, 2004, to July, 2006; retrospective study	Lower urinary tract infections	52 inpatients or outpatients, mean age 55 years (SD 18·3), 27 (52%) women	None (16 patients), indwelling catheter (7), hemiparesis or quadriparesis (2), malignancy in urinary tract (4), other malignancies (4), diabetes mellitus (5), renal transplantation (5), nephrolithiasis (3), recent urological intervention (6)	ESBL *Escherichia coli*, resistant to ciprofloxacin and co-trimoxazole, susceptible to fosfomycin	3 g oral fosfomycin–trometamol once every other night for three doses	Clinical success (49 of 52; 94·2%), microbiological success at 7–9 days post-treatment (41 of 52; 78·8%), microbiological relapse at 28 days post-treatment (0 of 28; 0%)
Nakaya et al, 2003[37]	Japan; September, 2000; case report	Acute gastroenteritis	A 35 day-old boy	None	MDR *Salmonella typhimurium*	Oral followed by intravenous fosfomycin	Clinical and microbiological cure
Kohbata et al, 1983[38]	Japan; February, 1982; case report	Typhoid fever	A 45 year-old man	Cholecystectomy 27 days earlier	MDR *Salmonella typhi*	Fosfomycin plus latamoxef, given after failure of cephalothin, tobramycin, cephalexin, and cefmetazole	Rapid clinical improvement, microbiological cure

ESBL=extended-spectrum β-lactamase. MDR=multidrug resistant.

Table 3: **Effectiveness of treatment with fosfomycin against infections with MDR or ESBL-producing Enterobacteriaceae**

further investigation. A recent review[10] highlighted that the reported use of fosfomycin for the treatment of various types of infections, other than those involving the urinary or the gastrointestinal tract, has been associated with a high rate of clinical success. However, the level of evidence is not strong. In our Review we did not identify data on the clinical use of intravenous fosfomycin against infections caused by Enterobacteriaceae with advanced resistance to antimicrobial drugs. However, fosfomycin had good antimicrobial activity against isolates originating from various clinical sites. In this respect, intravenous fosfomycin could be used in clinical practice as a last resort option for the treatment of Enterobacteriaceae infections for which traditional antimicrobial drugs are not active, have failed, or are otherwise contraindicated.

Nonetheless, the assessment of the degree of the antimicrobial activity of fosfomycin depends on the specific breakpoints of susceptibility used. Stricter breakpoints might be more appropriate for systemic infections rather than those involving the lower urinary tract, since fosfomycin becomes highly concentrated in urine. The most relevant CLSI breakpoints of susceptibility to fosfomycin (64 mg/L or less) refer specifically to urinary isolates of *E coli*.[16] However, the European Committee on Antimicrobial Susceptibility Testing has recently adopted a breakpoint of susceptibility of Enterobacteriaceae to fosfomycin of 32 mg/L or less, irrespective of the site of infection.[68]

Additionally, the use of fosfomycin for the treatment of systemic infections relates to the potential for resistance to emerge during treatment. In vitro, the spontaneous mutation rate to fosfomycin in strains of Enterobacteriaceae seems to be high.[26,69] However, this finding does not relate with the low levels of resistance to fosfomycin noted in isolates of Enterobacteriaceae in countries where fosfomycin has frequently been used in routine clinical practice.[45,70,71] This could be because the development of chromosomal resistance to fosfomycin seems to entail a biological cost that reduced the resistant mutants' capacity for survival.[69,72]

This systematic review has several limitations. Particularly, some potentially relevant studies done in countries where fosfomycin is widely used were published in local languages and could not be further evaluated for eligibility for inclusion in our Review. Moreover, there was substantial variability in the fosfomycin MIC breakpoints[16,39,40] and the methods of susceptibility testing used in the included studies, making it difficult to compare their findings.

The agar dilution method is the preferred one for fosfomycin susceptibility testing,[16] whereas broth dilution tests might provide inconsistent findings.[73,74] Susceptibility testing to fosfomycin is recommended to be done with the addition of glucose-6-phosphate in the testing medium at a concentration of 25 mg/L. Glucose-6-phosphate, a substance physiologically found in human cells, enhances in vitro the susceptibility to fosfomycin for most Enterobacteriaceae pathogens.[73] This detail was not specifically reported in several of the studies included in our Review.

Conclusion

The available evidence shows that fosfomycin has a high level of antimicrobial activity against Enterobacteriaceae isolates with advanced resistance to antimicrobial drugs, such as the production of ESBLs. This was more pronounced for the evaluated isolates of *E coli* that

produce ESBL. Although the clinical evidence is still limited, fosfomycin might be a valuable treatment option for community-acquired urinary tract infections caused by these pathogens. This is particularly important since resistance rates to other oral drugs are increasing, making the selection of appropriate empirical treatment problematic. Further research on the use of fosfomycin for complicated urinary tract infections or even additional clinical indications is recommended.

Search strategy and selection criteria

These are described in detail in the Methods section.

Contributors

MEF had the idea for the study and contributed to the study design, data interpretation, and the revision of the paper. ACK contributed to search of published work, data extraction, data analysis, and wrote parts of the first draft of the paper. AMK contributed to search of published work, data extraction, data analysis, and the revision of the paper. DEK contributed to the study design, search of published work, data extraction, analysis and interpretation, wrote parts of the first draft of the paper, and contributed to its revision. All authors approved the final version of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

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