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

Matthew E Falagas, Antonia C Kastoris, Anastasios M Kapaskelis, Drosos E Karageorgopoulos

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.

**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.1,2 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.3,4 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, tetracyclines, and aminoglycosides.5 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.6,7 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 glycyclcline-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-acetylgalactosamine 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.12,13 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 “phosphonopyrimidines” with either terms relating to antimicrobial-drug resistance (“drug resistance”, “β-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.

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**References**


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.11–18 Of these studies, 17 referred to antimicrobial susceptibility data,16–18 and four referred to clinical data.15–16

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,16,20,23,27 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.24 The majority of the studies included involved clinical isolates collected after the year 2000.19–24,26,28,31,32

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).16,20,23,27,29,31 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),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).30,34 The two remaining studies from France29 and Japan28 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,20,21,24–26,29,31,34 and agar dilution.29,32,33,32,36

Figure: Article selection

914 potentially relevant articles from PubMed
90 articles excluded after detailed screening according to specific criteria:
23 with no reference to the effect of fosfomycin against Enterobacteriaceae with advanced drug resistance
10 with no reference to fosfomycin
7 articles written in non-eligible languages
3 abstracts in scientific meetings
2 synergy studies
2 with reference to the immunomodulatory effects of fosfomycin
1 duplicate in database
1 with unclear methods
1 animal study

33 potentially relevant articles from the Cochrane library
No articles selected for further evaluation after first screening of title and abstract

1494 potentially relevant articles from Scopus
83 articles selected for further evaluation after first screening of title and abstract
67 articles excluded after detailed screening according to specific criteria:
30 with no reference to fosfomycin
21 with no reference to the effect of fosfomycin against Enterobacteriaceae with advanced drug resistance
9 studies of fosfomycin resistance
4 articles written in non-eligible languages
1 duplicate in database
1 with unclear methods
1 animal study

21 individual articles qualifying for inclusion
20,21,24–26,29,31,34

63 articles selected for further evaluation after first screening of title and abstract
23 articles qualifying for inclusion
20,21,24–26,29,31,34

83 articles selected for further evaluation after first screening of title and abstract
16 articles qualifying for inclusion
20,21,24–26,29,31,34

Hand searching of the bibliographies of both potentially relevant articles and articles qualifying for inclusion
4 additional articles qualifying for inclusion
20,21,24–25,32,36

No articles selected for further evaluation after first screening of title and abstract

67 articles excluded after detailed screening according to specific criteria:
30 with no reference to fosfomycin
21 with no reference to the effect of fosfomycin against Enterobacteriaceae with advanced drug resistance
9 studies of fosfomycin resistance
4 articles written in non-eligible languages
1 duplicate in database
1 with unclear methods
1 animal study

63 articles selected for further evaluation after first screening of title and abstract
13 articles qualifying for inclusion
20,21,24–26,29,31,34

90 articles excluded after detailed screening according to specific criteria:
23 with no reference to the effect of fosfomycin against Enterobacteriaceae with advanced drug resistance
10 with no reference to fosfomycin
7 articles written in non-eligible languages
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1 duplicate in database
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Hand searching of the bibliographies of both potentially relevant articles and articles qualifying for inclusion
4 additional articles qualifying for inclusion
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<table>
<thead>
<tr>
<th>Country; study period; susceptibility testing method</th>
<th>Isolates with advanced drug resistance</th>
<th>Origin of isolates (number)</th>
<th>Fosfomycin MIC breakpoint of susceptibility</th>
<th>Susceptible isolates (MIC range [mg/L])</th>
<th>$\text{MIC}_{50}$ (mg/L)</th>
<th>$\text{MIC}_{90}$ (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prakash et al, 2009&lt;sup&gt;9&lt;/sup&gt; USA; 2002–08; agar dilution</td>
<td>57 ESBL Enterobacteriaceae, predominantly Escherichia coli (46 CTX-M, 11 SHV or TEM-10 producing)</td>
<td>Urinary isolates</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>42 of 46, 91.3% (CTX-M); 11 of 11, 100% (SHV or TEM-10)</td>
<td>0.5 (CTX-M); 4 (SHV or TEM-10)</td>
<td>64 (CTX-M); 8 (SHV or TEM-10)</td>
</tr>
<tr>
<td>Andreu et al, 2008&lt;sup&gt;10&lt;/sup&gt; Spain; February–June, 2006; automated broth microdilution or disc diffusion</td>
<td>105 ESBL Escherichia coli</td>
<td>Community-acquired, complicated or uncomplicated, lower UTIs</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>103 of 105, 98%</td>
<td>..</td>
<td>..</td>
</tr>
<tr>
<td>Pulkcu et al, 2008&lt;sup&gt;11&lt;/sup&gt; Turkey; January–December, 2005; disc diffusion</td>
<td>344 ESBL E coli</td>
<td>Nosocomial (241) or outpatient (103) urinary tract infections</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>231 of 241, 95.9% (nosocomial); 101 of 103, 98.1% (outpatient)</td>
<td>..</td>
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<tr>
<td>Falagas et al, 2008&lt;sup&gt;12&lt;/sup&gt; Greece; 2006–07, agar dilution</td>
<td>30 both ESBL and MBL Klebsiella pneumoniae</td>
<td>Any clinical site from patients at a tertiary hospital</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>30 of 30, 100% (B-64)</td>
<td>16</td>
<td>32</td>
</tr>
<tr>
<td>Goyanes et al, 2008&lt;sup&gt;13&lt;/sup&gt; Spain; 2004–06; automated microdilution system</td>
<td>1449 ESBL plus 499 AmpC Enterobacteriaceae!</td>
<td>Urinary isolates collected in a tertiary hospital</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>1304 of 1449, 90% (ESBL); 254 of 499, 51% (AmpC)</td>
<td>..</td>
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<tr>
<td>Ho et al, 2007&lt;sup&gt;14&lt;/sup&gt; Hong Kong; third and fourth quarters of 2004 and 2005; disc diffusion</td>
<td>157 MDR E coli (resistant to ampicillin, ciprofloxacin, and co-trimoxazole), 89 ESBL E coli with a CTX-M phenotype&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Urinary isolates from outpatient adult women</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>156 of 157, 99.4% (MDR); 88 of 89, 98.9% (ESBL)§</td>
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<tr>
<td>Ko et al, 2007&lt;sup&gt;15&lt;/sup&gt; Korea; May–September, 2005, agar dilution</td>
<td>24 ESBL E coli (14 both TEM and CTX-M, 7 CTX-M, 3 SHV, 1 TEM, and 1 both SHV and CTX-M producing)</td>
<td>22 urinary and 2 blood isolates from patients at a tertiary hospital</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>24 of 24, 100%</td>
<td>..</td>
<td>32</td>
</tr>
<tr>
<td>De Cueto et al, 2006&lt;sup&gt;16&lt;/sup&gt; Spain; 1995–2001; agar dilution</td>
<td>290 ESBL E coli, 138 ESBL K pneumoniae</td>
<td>Isolates collected at multiple hospitals (148 from outpatients with community-acquired infections, including 75 from women with uncomplicated urinary tract infections)</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>289 of 290, 99.7% (0·5–128; E coli); 128 of 138, 92.7% (0·5–512; K pneumoniae)</td>
<td>1 (E coli); 16 (K pneumoniae)</td>
<td>4 (E coli), 64 (K pneumoniae)</td>
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<td>Ellington et al, 2006&lt;sup&gt;17&lt;/sup&gt; UK; 2003–04; agar dilution</td>
<td>220 ESBL (CTX-M) E coli&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>Isolates from urinary tract infections collected at a reference laboratory (172 sporadic isolates and 48 representatives of 5 major UK clones)</td>
<td>British Society for Antimicrobial Chemotherapy&lt;sup&gt;</td>
<td></td>
<td>&lt;/sup&gt;</td>
<td>220 of 220, 100%</td>
</tr>
<tr>
<td>Ena et al, 2006&lt;sup&gt;18&lt;/sup&gt; Spain; January, 1999, to December, 2004; automated broth microdilution</td>
<td>161 ESBL E coli</td>
<td>Isolates from urinary tract infections of ambulatory (100) or patients admitted to hospital (61)</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>159 of 161, 99%</td>
<td>..</td>
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<tr>
<td>Muratani et al, 2006&lt;sup&gt;19&lt;/sup&gt; Japan; January–September, 2003; ..</td>
<td>200 ESBL E coli</td>
<td>Inpatient urinary tract infections</td>
<td>..</td>
<td>146 of 200, 73%&lt;sup&gt;**&lt;/sup&gt;</td>
<td>..</td>
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<tr>
<td>Wavarawooth et al, 2006&lt;sup&gt;20&lt;/sup&gt; Thailand; January, 2005, to December, 2005; disc diffusion</td>
<td>607 ESBL E coli, 537 ESBL K pneumoniae</td>
<td>Isolates from various sites from inpatients (collected within or after 48 h from admission to hospital)</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>573 of 607, 94.3% (&lt;48 h: 169 of 190, 89%; &gt;48 h: 404 of 417, 97%; E coli); 412 of 537, 76.7% (&lt;48 h: 72 of 90, 80%; &gt;48 h: 340 of 447, 76%; K pneumoniae)</td>
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<tr>
<td>Dubois et al, 2005&lt;sup&gt;21&lt;/sup&gt; France; November, 1996, to December, 2002; disc diffusion</td>
<td>17 ESBL Enterobacteriaceae (5 Proteus mirabilis, 4 K pneumoniae, 3 E coli, 3 Providencia stuartii, 2 Morganella morganii)</td>
<td>Isolates from urine or bedside cultures from nursing home residents</td>
<td>Comité de l’Antibiogramme de la Société Française de Microbiologie</td>
<td>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)</td>
<td>..</td>
<td>..</td>
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<tr>
<td>Tharavichitkul et al, 2005&lt;sup&gt;22&lt;/sup&gt; Thailand; January, 2001, to December, 2003; disc diffusion, Ettest</td>
<td>43 ESBL K pneumoniae, 37 ESBL E coli</td>
<td>Randomly selected ESBL clinical isolates among those isolated at single hospital</td>
<td>Clinical and Laboratory Standards Institute</td>
<td>38 of 43, 88.4% (&lt;0·5 to &gt;512; K pneumoniae); 36 of 37, 97·3% (&lt;0·5 to 128; E coli)</td>
<td>12 (K pneumoniae), 18 (E coli)</td>
<td>0·7 (E coli)</td>
</tr>
</tbody>
</table>

(Continues on next page)
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 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 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. By contrast, in two studies, 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. 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. 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 and four of eight studies providing specific relevant data, respectively, whereas the cumulative susceptibility rate by the CLSI criteria was 98.3% (292 of 297), 20.12.14 and 88.5% (1344 of 1519), 11.12.25.29.31 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. 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. 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%). In the remaining study, single-dose fosfomycin–trometamol was equally effective to co-amoxiclav given for 5–7 days in patients with susceptible pathogens. Two additional studies 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

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<th>Fosfomycin MIC breakpoint of susceptibility</th>
<th>Susceptible isolates (MIC range [mg/L])</th>
<th>MIC50 (mg/L)</th>
<th>MIC90 (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Woodford et al, 2004†</td>
<td>57 ESBL (group 1 CTX-M) E coli (45 representatives of 5 major UK strains and 12 representatives of non-major UK strains)</td>
<td>Isolates from various sites collected at a reference laboratory</td>
<td>British Society for Antimicrobial Chemotherapy</td>
<td>45 of 45, 100% (0.5–2; major-strains); (0.5–256; non-major-strains)</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Gouby et al, 1994‡</td>
<td>12 ESBL K pneumoniae</td>
<td>Outbreak strains from patients in a genicatal hospital</td>
<td>...</td>
<td>0 of 12, 0%</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Arpin et al, 1996§</td>
<td>73 MDR Enterobacter aerogenes (31 ESBL producing mainly SHV-4)</td>
<td>20 isolates from medical ICU and hospital ward patients and 3 environmental isolates from medical ICU</td>
<td>Comité de l’Antibiogramme de la Société Française de Microbiologie</td>
<td>3 of 73, 4.1% (MDR); 2 of 31, 6.5% (ESBL)</td>
<td>...</td>
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</tbody>
</table>

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

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). ‡‡The MIC geometric mean of isolates belonging to non-major-strains was 1.9 mg/L.
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.5 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.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.14,46 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.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,5,51 potentially leading to suboptimum outcomes.52

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.52,53 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.54,55 Studies specifically evaluating the susceptibility of isolates of ESBL-producing *E coli* to nitrofurantoin have reported varying findings.52,53,55,56,57 Co-resistance between nitrofurantoin and fluoroquinolones in urinary isolates of *E coli* has also been noted.41 Nitrofurantoin is not reliably active against common Enterobacteriaceae uropathogens, such as *K pneumoniae* and *P mirabilis*.58,59 Moreover, the production of ESBLs has been associated with decreased susceptibility to nitrofurantoin in *K pneumoniae*.60

Pivmecillinam, an oral β-lactam, has also been used in the treatment of acute uncomplicated cystitis, particularly in northern Europe.42 In vitro, pivmecillinam has high levels of antimicrobial activity against common uropathogens, particularly *E coli*.24,25 It seems relatively stable to the hydrolytic activity of AmpC β-lactamases;42 however, the evidence of its activity against Enterobacteriaceae that produce ESBL is scarce and less convincing.42 Of note, treatment with pivmecillinam was successful in a case of relapsing pyelonephritis caused by ESBL-producing *E coli*, where other treatments had failed.42

Co-amoxiclav has moderate in vitro antimicrobial activity against Enterobacteriaceae that produce ESBL.31,27–31,36 Although the clinical effectiveness of β-lactam and β-lactamase inhibitor combinations against serious infections caused by ESBL-producing Enterobacteriaceae remains uncertain,42 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%.32 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.58,59 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

<table>
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<tr>
<th>Studies showing susceptibility to fosfomycin of 90% or more compared with total number of studies</th>
<th>Cumulative susceptibility of ESBL according to the CLSI criteria*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Enterobacteriaceae isolates</strong></td>
<td></td>
</tr>
<tr>
<td>Any advanced antimicrobial drug resistance profile</td>
<td>11 of 17 (64.7%)38,49,54</td>
</tr>
<tr>
<td>ESBL-producing</td>
<td>11 of 17 (64.7%)38,49,54</td>
</tr>
<tr>
<td>Isolates from urinary tract</td>
<td>8 of 10 (80.0%)39,40,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from mixed sites</td>
<td>5 of 8 (62.5%)39,40,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from outpatients</td>
<td>3 of 3 (100.0%)39,40,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from hospitalised patients</td>
<td>4 of 8 (50.0%)39,40,54,62,63,64,65</td>
</tr>
<tr>
<td><strong>Escherichia coli isolates</strong></td>
<td></td>
</tr>
<tr>
<td>Any advanced antimicrobial drug resistance profile</td>
<td>11 of 12 (91.7%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>ESBL-producing</td>
<td>11 of 12 (91.7%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from urinary tract</td>
<td>6 of 7 (85.7%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from mixed sites</td>
<td>5 of 6 (83.3%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from outpatients</td>
<td>3 of 3 (100.0%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from hospitalised patients</td>
<td>4 of 5 (80.0%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td><strong>Klebsiella pneumoniae isolates</strong></td>
<td></td>
</tr>
<tr>
<td>Any advanced antimicrobial drug resistance profile</td>
<td>3 of 6 (50.0%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>ESBL-producing</td>
<td>3 of 6 (50.0%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from mixed sites</td>
<td>2 of 5 (40.0%)38,49,54,62,63,64,65</td>
</tr>
<tr>
<td>Isolates from hospitalised patients</td>
<td>2 of 4 (50.0%)38,49,54,62,63,64,65</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Patient characteristics</th>
<th>Underlying condition</th>
<th>Causative pathogens</th>
<th>Antibiotic treatment</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outpatients</td>
<td>Various risk factors reported for the whole cohort of 112 cases with community-acquired infections</td>
<td>ESBL Escherichia coli, susceptible to fosfomycin</td>
<td>3 g fosfomycin-trometamol single-dose</td>
<td>Cure (26 of 28; 93%)</td>
</tr>
<tr>
<td>Outpatients</td>
<td>Various risk factors reported for the whole cohort of 112 cases with community-acquired infections</td>
<td>ESBL Escherichia coli, susceptible to fosfomycin</td>
<td>3 g oral fosfomycin-trometamol once every other night for three doses</td>
<td>Clinical success (4 of 52; 94%), microbiological success at 7–9 days post-treatment (41 of 52; 78%), microbiological relapse at 28 days post-treatment (0 of 28; 0%)</td>
</tr>
<tr>
<td>None</td>
<td>None</td>
<td>MDR Salmonella typhimurium</td>
<td>Oral followed by intravenous fosfomycin</td>
<td>Clinical and microbiological cure</td>
</tr>
<tr>
<td>A 35 day-old boy</td>
<td>None</td>
<td>MDR Salmonella typhi</td>
<td>Fosfomycin plus talamoxef, given after failure of cephalothin, tobramycin, cephalaxin, and cefmetazole</td>
<td>Rapid clinical improvement, microbiological cure</td>
</tr>
<tr>
<td>A 45 year-old man</td>
<td>Cholecystectomy 27 days earlier</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

Further investigation. A recent review 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. 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.

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. 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. 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.

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 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, whereas broth dilution tests might provide inconsistent findings. 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. 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.

**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.

**References**


