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Fosfomycin for the treatment of infections caused by multidrug-resistant non-fermenting Gram-negative bacilli: a systematic review of microbiological, animal and clinical studies

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Abstract

The treatment of multidrug-resistant (MDR), extensively drug-resistant or pandrug-resistant non-fermenting Gram-negative bacterial infections constitutes a challenge in an era of few new antibiotic choices. This mandates the re-evaluation of already existing antibiotics such as fosfomycin. We systematically reviewed the literature to assess the clinical and microbiological effectiveness of fosfomycin in the treatment of these infections by searching PubMed, Scopus and the Cochrane Library databases. In 23 microbiological studies identified, 1859 MDR non-fermenting Gram-negative bacterial isolates were examined. The susceptibility rate to fosfomycin of MDR *Pseudomonas aeruginosa* isolates was $\geq 90\%$ and 50–90% in 7/19 and 4/19 relevant studies, respectively. Cumulatively, 511/1693 (30.2%) MDR *P. aeruginosa* isolates were susceptible to fosfomycin. Serotype O12 isolates exhibited greater susceptibility. Only 3/85 (3.5%) MDR *Acinetobacter baumannii* and 0/31 MDR *Burkholderia* spp. isolates were susceptible to fosfomycin. Variable criteria of susceptibility were used in the included studies. Fosfomycin was synergistic in combination with a β -lactam, aminoglycoside or ciprofloxacin in 46/86 (53.5%) MDR *P. aeruginosa* isolates. One animal study found a good therapeutic effect of the combination fosfomycin/gentamicin against MDR *P. aeruginosa* endocarditis. In six clinical studies, 33 patients with MDR *P. aeruginosa* infections (mainly pulmonary exacerbations of cystic fibrosis) received fosfomycin (25/33 in combination with other antibiotics); 91% of the patients clinically improved. In conclusion, fosfomycin could have a role as a therapeutic option against MDR *P. aeruginosa* infections. Further research is needed to clarify the potential utility of this agent.

1. Introduction

In an era of extensive bacterial drug resistance, especially among non-fermenting Gram-negative species such as *Pseudomonas aeruginosa* and *Acinetobacter baumannii* [1], emphasis should be given not only to the development of new drugs but also to the re-evaluation of older and ‘forgotten’ drugs [2–4]. Fosfomycin is a drug representing the latter category, discovered almost 40 years ago. It inhibits bacterial cell wall biosynthesis by inactivating the UDP-*N*-acetyl-glucosamine-3-*o*-enolpyruvyltransferase [5].

The oral form of this broad-spectrum antibiotic [6] has principally been used in the treatment of uncomplicated urinary tract infections (UTIs) in the USA, UK and other countries. However, the intravenous form has been used for indications beyond UTIs in only a few countries such as Germany, France, Spain and Japan [7]. Recent data suggest that it may be considered as an alternative in the treatment of Gram-negative and Gram-positive infections other than of UTIs [7,8].

Thus, we sought to evaluate human and animal studies that examined the clinical effectiveness and/or microbiological activity of fosfomycin against multidrug-resistant (MDR), extensively drug-resistant (XDR) or pandrug-resistant (PDR) non-fermenting Gram-negative bacilli.

2. Methods

2.1. Literature search

We systematically searched PubMed, Scopus and the Cochrane Library databases up to January 2009. The keywords used were (fosfomycin OR phosphomycin OR phosphonomycin) AND (drug resistance OR *Pseudomonas* OR *Acinetobacter* OR *Stenotrophomonas* OR *Burkholderia*). Bibliographies of relevant articles were also hand-searched.

2.2. Study selection

Studies were selected if they included microbiological, animal experimental or clinical data on the effect of fosfomycin against MDR non-fermenting Gram-negative pathogens such as *Pseudomonas* spp., *Acinetobacter* spp., *Stenotrophomonas* spp. and *Burkholderia* spp. Studies were considered eligible for inclusion if they referred to well defined MDR, XDR or PDR non-fermenting Gram-negative bacilli or to Gram-negative bacilli with resistance to two or more classes of potentially effective antimicrobial agents. The full text was retrieved for articles considered as potentially eligible for inclusion. No limitations were used regarding the study sample size and study design. Studies written in languages other than English, French, German, Italian or Spanish were excluded from the review as well as studies representing abstracts in scientific conferences.

2.3. Data extraction

For the microbiological studies, data were extracted regarding the number, site of isolation, resistance characteristics and susceptibility to fosfomycin of the pathogens isolated. Data regarding the antimicrobial effect of the combination of fosfomycin with other antimicrobial agents were also extracted. The fosfomycin minimum inhibitory concentration (MIC) breakpoint values of the relevant standards-developing organisation and the test method(s) used by the authors of each study to define and determine fosfomycin susceptibility were noted. If more than one test method was used to determine fosfomycin susceptibility, data were extracted on all test methods used. Data were extracted for the clinical and animal studies regarding the study population, type of infection, pathogens isolated, treatment administered and the outcome of infection.

3. Results

The process of study selection is depicted as a flow diagram in Fig. 1. A total of 30 studies published between 1985 and 2008 were included in the review [8–37]. Twenty-three of these are microbiological studies on the activity of fosfomycin against clinical isolates of MDR non-fermenting Gram-negative bacteria [8–30], one is an animal study [31] and six are clinical studies referring to the treatment of MDR bacterial infections with fosfomycin [32–37].

3.1. Microbiological studies

Data extracted from the 23 microbiological studies on the in vitro activity of fosfomycin against MDR non-fermenting Gram-negative bacilli are summarised in Table 1 [8–30]. Eleven studies included non-fermenting Gram-negative isolates originating from France [9,10,12,15,20,23–26,28,29], three studies included isolates originating from Japan [11,17,18], two from Italy [19,30] and one each from Thailand [16], Taiwan [14], Greece [8], Spain [27], the UK [22], Germany [21] and Bulgaria [13]. Fifteen of the twenty-three studies reported on the site of isolation of the isolates examined [9,10,12,13,15,17–21,23,25,26,29,30]. Ten studies evaluated susceptibility to fosfomycin according to the disk diffusion method [9,15,16,21,24–26,28–30] and three studies each according to the agar dilution method [8,12,20], the broth microdilution method [17,18,27] and Etest [13,14,22], whilst three studies did not state the method of determination of fosfomycin susceptibility [10,19,23]. In one study more than one test method was used to determine susceptibility to fosfomycin [11]; in this study, the Etest method was selected to evaluate fosfomycin susceptibility, as the Clinical and Laboratory Standards Institute (CLSI) does not recommend the relevant broth dilution methods [39].

Regarding the interpretative MIC breakpoints of susceptibility to fosfomycin used, eight studies used a susceptibility breakpoint of ≤ 64 mg/L [8,11,12,14,16,17,21,27], four studies used a breakpoint of ≤ 32 mg/L [23,24,28,29], one study used a breakpoint of ≤ 16 mg/L [18], whereas specific data were not reported in 10 studies [9,10,13,15,19,20,22,25,26,30]. The majority of the latter (six of ten) were performed in France [9,10,15,20,25,26]. In total, 1859 MDR non-fermenting Gram-negative bacilli

were analysed, of which 1743 (93.8%) were *P. aeruginosa* isolates [8–12,14–16,18–21,23–26,28–30], 85 (4.6%) were *A. baumannii* [8,13,17,27] and 31 (1.7%) were *Burkholderia* spp. [22]. There was no report on isolates of the *Stenotrophomonas* spp.

Nineteen studies in total provided data on the susceptibility to fosfomycin of MDR *P. aeruginosa* isolates [8–12,14–16,18–21,23–26,28–30]. Seven of these nineteen studies found that $\geq 90\%$ of the isolates evaluated were susceptible to fosfomycin [10–12,19,21,23,29] and four additional studies found that 50–90% of the isolates were susceptible to fosfomycin [8,15,24,28]. Data for the specific susceptibility rate to fosfomycin were available for all but 50 of the 1743 MDR *P. aeruginosa* isolates evaluated [16]. Cumulatively, 511 (30.2%) of 1693 isolates were found by the individual study authors to be susceptible to fosfomycin.

The great majority of the abovementioned isolates were included in the study conducted by Bert and Lambert-Zechovsky [25]. This study evaluated 1348 *P. aeruginosa* isolates collected from Intensive Care Unit patients. Although the rate of multidrug resistance of these isolates was not specified, relevant data were included in our review since these demonstrated substantial resistance rates to imipenem (nearly 30%), antipseudomonal penicillins or cephalosporins, aminoglycosides or ciprofloxacin [25]. Moreover, in this study 1604 additional clinical isolates of *P. aeruginosa* originating from patients located in hospital wards were recovered and examined. The predominant serotypes of the total of 2952 isolates evaluated were O6 (16.2%), O11 (14.6%), O1 (9.8%) and O16 (7.2%).

Forty-three (10%) of the 431 *P. aeruginosa* O11 isolates in contrast to 49 (72.1%) of the 68 *P. aeruginosa* O12 isolates examined were susceptible to fosfomycin.

Six studies reported on the susceptibility to fosfomycin of a total of 193 *P. aeruginosa* isolates belonging to serotype O12 [21,25,26,28–30]. Of the 193 *P. aeruginosa* O12 isolates examined, 123 (63.7%) were found to be susceptible to fosfomycin. In four of the above six studies that provided specific relevant data, the susceptibility rate to fosfomycin of isolates belonging to other *P. aeruginosa* serotypes was markedly lower (20.7%) than for isolates of the O12 serotype [25,28–30]. In contrast, these isolates had higher rates of susceptibility to antimicrobial agents other than fosfomycin compared with isolates of serotype O12.

Regarding MDR *A. baumannii* isolates, 3 (3.5%) of the 85 total isolates were susceptible to fosfomycin, as reported in four studies [8,13,17,27]. Regarding *Burkholderia* spp., none of the 31 isolates examined in one relevant study was found to be susceptible to fosfomycin [22].

Seven studies reported on the microbiological effect of the combination of fosfomycin with other antibiotics [16,18,21,24,27,29,38]. Among a total of 86 *P. aeruginosa* MDR isolates, a synergistic effect of the combination of fosfomycin with another antibiotic, either a β -lactam (carbapenem, meropenem, imipenem, ceftazidime, aztreonam), an aminoglycoside or ciprofloxacin was shown for 46 isolates (53.5%). Most of the abovementioned 86 isolates were resistant to all of the antibiotics used in combination

with fosfomycin. Regarding MDR *A. baumannii* isolates, one study showed that the combination of fosfomycin with amikacin and tobramycin had a synergistic effect in 15 (44%) of 34 and in 11 (32%) of 34 isolates, respectively, for which fosfomycin alone had no in vitro activity [27].

3.2. Animal studies

One animal experimental study relevant to our review was identified in the literature. A rabbit model of aortic valve endocarditis induced by *P. aeruginosa* was studied in this in vivo study [31]. The study showed that fosfomycin combined with ciprofloxacin was the best therapeutic option, whereas fosfomycin alone was ineffective and ciprofloxacin was effective only when administered at high doses.

3.3. Clinical studies

Data extracted from the six included clinical studies examining fosfomycin therapy for infections caused by non-fermenting Gram-negative bacilli are presented in Table 2 [32–37]. Specifically, the relevant literature consists of three cohort studies (two conducted in the UK [32,36] and one in Israel [37]) and three case reports from Australia [33], Thailand [35] and Saudi Arabia [34]. A total of 33 patients (17 female) were included in the clinical studies; 26 (78.8%) were adults (15 females) and 7 (21.2%) were juveniles (2 females) [33,37]. In addition, 31 (93.9%) of the 33 patients were cystic fibrosis (CF) patients (17 female) with pulmonary exacerbation of infectious aetiology [32,33,36,37]. Two of the studies conducted on patients with CF referred to 7 (21.2%)

juveniles (3 females) [33,37]. All of the six studies referred to infections caused by MDR *P. aeruginosa*.

Overall, in the clinical studies 33 patients with infections caused by MDR *P. aeruginosa* received fosfomycin (25 in combination with other antibiotics and 8 as monotherapy). A favourable clinical course was reported with fosfomycin treatment for the great majority of these patients (30/33; 90.9%). Exceptions included one patient in whom fosfomycin treatment was discontinued due to adverse events [36] and two patients who died after the end of fosfomycin treatment [37]. Favourable clinical outcomes were associated with fosfomycin therapy regardless of the susceptibility of the causative pathogens to this agent in one study [36] and despite microbiological persistence of the causative pathogens in an additional study [37].

4. Discussion

The main finding of our review is that fosfomycin may play a role in the treatment of infections caused by MDR *P. aeruginosa*. One has to acknowledge that relatively few studies have examined the clinical or microbiological effects of fosfomycin on infections due to MDR non-fermenting Gram-negative bacilli. Interestingly, the great majority of relevant studies regard *P. aeruginosa*, whilst there is a dearth of relevant data for MDR *A. baumannii*, *Burkholderia* spp. and *Stenotrophomonas* spp.

The available clinical data indicate that fosfomycin might be an effective and safe drug in patients with severe infections caused by MDR *P. aeruginosa*. Specifically, the

majority of the evaluated data, derived from studies on CF patients, suggest that fosfomycin may lead to clinical resolution of pulmonary exacerbations caused by MDR *P. aeruginosa* in these often difficult-to-treat patients, without significant adverse events. A particular value of fosfomycin for the treatment of infective pulmonary exacerbations in CF, as well as other chronic infections or foreign body-associated infections, may relate to the good penetration and activity of this agent in biofilms [40,41].

However, the in vitro data examined in this review showed that less than one-third of the MDR *P. aeruginosa* isolates were susceptible to fosfomycin. Yet some studies noted that the activity of fosfomycin against *P. aeruginosa* differed depending on the strain serotype [21,25,26,28–30]. Specifically, serotype O12 isolates appeared to have substantially higher rates of susceptibility to fosfomycin compared with isolates of other serotypes. This may be important since isolates of serotype O12 are usually associated with a MDR phenotype and have been linked to nosocomial outbreaks in various countries [42,43].

It is also noteworthy that in our review the combination of fosfomycin with antibiotics such as carbapenems, ceftazidime, aminoglycosides, aztreonam and ciprofloxacin showed good synergistic effects against the MDR *P. aeruginosa* isolates tested. This is of special interest as the majority of these MDR *P. aeruginosa* isolates were resistant to the specific antibiotics mentioned above [16,18,24,29]. Moreover, electron microscopy data have shown that fosfomycin combined with ciprofloxacin induces bacteriolysis in ciprofloxacin-resistant *P. aeruginosa* isolates [44]. This may provide a rationale to

administer fosfomycin combinations with other antibiotics in MDR *P. aeruginosa* infections. However, it should be stressed that in clinical practice it is mandatory to perform synergy testing to evaluate the potential benefit of antimicrobial combinations with fosfomycin, as occasionally antagonistic effects have been observed when combining fosfomycin with β -lactams or aminoglycosides [16].

In addition, one of the potential disadvantages of fosfomycin monotherapy is the emergence of resistance during treatment. In this regard, physicians frequently use this medication usually in combination with other antibiotics for the treatment of systemic infections [7]. Data regarding the emergence of resistance to fosfomycin in the studies included in this review were lacking. Yet studies performed in France, where fosfomycin has been used routinely in clinical practice for the treatment of systemic infections, have generally found high rates of resistance of *P. aeruginosa* isolates to fosfomycin [25,45].

However, the latter finding may relate to the lack of universally accepted fosfomycin interpretative MIC breakpoints. The standards-developing organisations that have defined fosfomycin MIC breakpoint values are, amongst others, the British Society for Antimicrobial Chemotherapy (BSAC), the Comité de l'Antibiogramme de la Société Française de Microbiologie (CA-SFM) and the CLSI. Specifically, BSAC suggests a fosfomycin MIC resistance breakpoint of >128 mg/L for Gram-negative rods isolated from UTIs [46]. The CA-SFM suggests a fosfomycin MIC resistance breakpoint of >32 mg/L for Enterobacteriaceae and *P. aeruginosa* [47]. The CLSI recommends a fosfomycin MIC breakpoint of >64 mg/L for Enterobacteriaceae for use with *Escherichia*

coli only [39]. The interpretation of susceptibility to fosfomycin in *P. aeruginosa* isolates may considerably depend on the relevant criteria used, as the MIC mode of *P. aeruginosa* isolates may correspond to one of the abovementioned breakpoints [45].

In contrast to MDR *P. aeruginosa*, *A. baumannii* was resistant to fosfomycin in the in vitro studies in this review. A synergistic effect with aminoglycosides was reported in one of the included studies. However, the clinical significance, if any, of such a combination remains elusive.

There are several limitations to this review. First, a significant number of studies relevant to our review have been conducted in Japan, where fosfomycin is widely used. These studies were published in Japanese journals and thus did not fulfil our language criteria. Another limitation is the lack of homogeneity in the definition of MDR, XDR or PDR bacterial infections. For example, one study referred to 'pandrug resistance' in 26 *P. aeruginosa* isolates, defining it as resistance to β -lactams, aminoglycosides and fluoroquinolones [10]. However, this resistance pattern does not signify pandrug resistance [48]. Another limiting factor was also that the authors of the included studies suggested variable MIC breakpoint values for fosfomycin. Moreover, as Kobayashi et al. [11] report in their study, different MIC values may be obtained when using different test media.

5. Conclusions

Fosfomycin could potentially be considered in the treatment of infections caused by MDR *P. aeruginosa* if established therapeutic options are not available. An appreciable number of studies have documented good antimicrobial activity of fosfomycin against MDR *P. aeruginosa* isolates, which is difficult to quantitate given the lack of universally accepted specific species-related susceptibility breakpoints. The antimicrobial activity of fosfomycin against MDR *P. aeruginosa* may also be enhanced in combination with other antibiotics. However, further research is necessary to establish the clinical or microbiological effectiveness of fosfomycin therapy in infections caused by MDR, XDR or PDR non-fermenting Gram-negative bacilli. Randomised clinical trials or case–control studies evaluating the clinical effectiveness and safety in infections caused by these pathogens would offer more insight into the question at hand.

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Fig. 1. Flow diagram of the detailed selection process of articles eligible for inclusion in the review.

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Table 1

Microbiological studies on the susceptibility of multidrug-resistant (MDR) non-fermenting Gram-negative bacilli to fosfomycin (FOS)

Reference	Country, period, method(s)	MDR isolates [n/N (%)]; resistance characteristics	Origin of isolates; sites of isolation (n)	Resistance patterns	MIC range (mg/L) (susceptibility n/N, %), MIC ₅₀ (mg/L), MIC ₉₀ (mg/L)	MIC susceptibility criteria (mg/L)	Combination of FOS with other antibiotics
Falagas et al., 2008 [8]	Greece, 2006–2007, agar dilution	30 ESBL <i>Pseudomonas aeruginosa</i> [ESBL + MBL 6/30 (20%)], 30 MDR <i>Acinetobacter baumannii</i>	Patients in a general hospital	Resistance to at least three classes of potentially effective antimicrobial agents	ESBL <i>P. aeruginosa</i> : 4 to >512 (24/30, 80%), 32, 128 MBL + ESBL <i>P. aeruginosa</i> : 4–64 (6/6, 100%), 32,	CLSI	NR

					64 A. <i>baumannii</i> : 64 to >512 (1/30, 3%), 256, >512		
Corvec et al., 2008 [9]	France, 01/1996–12/2004, disk diffusion	14/59 (23.7%) <i>P. aeruginosa</i> MBL (VIM-2), outbreak strains	Urine, stool, sputum, blood	MDR: resistance to all β -lactams, aminoglycosides, fluoroquinolones, RIF, but not COL	NR (0/14, 0%), NR, NR	NR	NR
Dinh et al., 2008 [10]	France, 05/2006 for a 10-week period, NR	28/56 (50%) <i>P. aeruginosa</i>	RT, blood, soft tissue, urine	Resistance to β -lactams, aminoglycosides, quinolones	<i>P. aeruginosa</i> : NR (28/28, 100%), NR, NR	NR	NR
Kobayashi et al., 2007 [11]	Japan, 2004–2006, broth microdilution	45 <i>P. aeruginosa</i>	NR	MDR	Broth microdilution: nutrient broth, 1 to	CLSI	NR

n, Etest					>1024 (42/45, 93.3%), 2, 32; MHB, 16 to >1024 (41/45, 91.1%), 32, 64 Etest: nutrient agar, 4 to >1024 (42/45, 93.3%), 16, 32; MHA, 128 to >1024 (0/45, 0%), >1024, >1024		
Corvec et al, 2006 [12]	France, 2004–2005,	4 <i>P.</i> <i>aeruginosa</i>	Urine (2), bronchial	Resistance to all available	NR (4/4, 100%) NR,	CLSI	NR

	agar dilution	MBL (VIM-1)	aspirate (2)	antibiotics, except COL, AMK, ATM	NR		
Dobrewski et al., 2006 [13]	Bulgaria, 2000–2002, Etest	18/56 (32.1%) <i>A. baumannii</i>	Bronchial aspirate (7), surgical wound (4), urine (4), blood (2), central catheter (1)	MDR	NR (2/18, 11.1%), NR, NR	NR	NR
Yan et al., 2006 [14]	Taiwan, NR, Etest	26 <i>P. aeruginosa</i> MBL: 20/26 (76.9%) VIM-2: 4/20 (20%) VIM-3: 16/20 (80%)	NR	MDR	NR (10/26, 38.5%), NR, NR VIM-3: >256, (0/16, 0%)	CLSI	NR
Dubois et al., 2005 [15]	France, 11/1996– 12/2002, disk	24 ESBL (TEM) <i>P. aeruginosa</i>	Urine (19), bedsores (4), sputum (1)	Resistance to all β -lactams (except IPM), GEN, TOB,	NR (19/24, 79.2%), NR, NR	NR	NR

	diffusion			NET, CIP, RIF			
Pruekprasert and Tunyapanit, 2005 [16]	Thailand, 09/1997–05/2003, disk diffusion	50 <i>P. aeruginosa</i>	Hospitalised patients	Resistance to CAZ and GEN, 98% resistance to IPM	8 to >1024 (NR), 512, >1024	CLSI	IPM, synergy: 11/29 (37.9%) CAZ, synergy: 2/18 (11.1%) GEN, synergy: 1/22 (4.5%)
Nagano et al., 2004 [17]	Japan, 06/2002–04/2003, broth microdilution	3 ESBL <i>A. baumannii</i> (CTX-M)	Transtracheal aspirate (3)	Resistance to PIP, third-generation cephalosporins, ATM	>16 (3/3) NR, NR	CLSI	NR
Okazaki et al., 2002 [18]	Japan, 01/1995–12/1998, broth microdilution	15/30 (50%) <i>P. aeruginosa</i>	Sputum, urine, blood	Resistance to carbapenem, aminoglycosides, fluoroquinolones	16 to >256 (1/15, 6%), >256, >256	Susceptible: ≤16	ETI ≥1: MEM 10/15 (66.7%), FEP 9/15 (60%), ATM 9/15 (60%), IPM 8/15 (53.3%), CAZ 7/15

							(46.6%), GEN 7/15 (46.6%), LVX 7/15 (46.6%), PIP 6/15 (40%)
Mazzariol et al., 1999 [19]	Italy, 02/1997–02/1998, NR	10 MBL <i>P. aeruginosa</i>	RT (5), bile (3), surgical wound (1), blood (1)	MDR with unusually high level of IPM resistance	NR (10/10, 100%), NR, NR	NR	NR
Naas et al., 2001 [20]	France, 08/1998, agar dilution	1 <i>P. aeruginosa</i> (ESBL)	Urine	MDR (resistance to most antibiotics)	NR (0/1, 0%), NR, NR	NR	NR
Traub et al., 1998 [21]	Germany, 01/1996–07/1997, disk diffusion	4/210 (1.9%) <i>P. aeruginosa</i> serotype O12 (1 outbreak strain)	Surgical ICU (4 patients), trachea (4)	MDR, susceptible only to AMK, PMB	8 (4/4, 100%), NR, NR	CLSI	FOS/AMK: bactericidal against 2 FOS-heteroresistant isolates
Baxter et al.,	UK, NR,	31	CF patients	Widespread	NR (0/31,	NR	NR

1997 [22]	Etest	<i>Burkholderia</i> spp. 19/31 (61.3%) <i>B. cepacia</i> 12/31 (38.7%) <i>B. gladioli</i>	(29), septicaemic patients (2)	resistance to TIC, CFS, IPM, aminoglycoside s, COL	0%), NR, NR		
Salauze et al., 1997 [23]	France, 11/1995– 01/1996, NR	7 <i>P. aeruginosa</i> serotype O11	Urine (5), operation wound (1), bronchial aspirate (1)	MDR	NR (7/7, 100%), NR, NR	CA-SFM	NR
Tessier et al., 1997 [24]	France, 01/1994– 01/1995, disk diffusion	16/40 (40%) <i>P. aeruginosa</i>	NR	Resistance to at least two of CAZ, IPM, AMK, CIP	2 to >512 (9/16, 56.3%), 4, 128	Susceptible: ≤32	CIP, synergy: 4/16 (25%) AMK, synergy: 2/16 (12.5%)
Bert and Lambert-Zechovsky, 1996 [25]	France, 6- year period, disk diffusion	1348 <i>P. aeruginosa</i>	ICU patients; RT, urine, wounds, nasopharynx, drainage fluids, blood,	Substantial resistance rates to IPM, antipseudomon al penicillins and	NR (283/1348, 21%), NR, NR	NR	NR

			catheters	cephalosporins, aminoglycoside s, CIP			
Bingen et al., 1996 [26]	France, 12/1993–10/1994, disk diffusion	8 <i>P. aeruginosa</i> serotype O12	Blood (3), urine (3), stool (2)	MDR	NR (1/8, 12.5%), NR, NR	NR	NR
Martinez-Martinez et al., 1996 [27]	Spain, 1990–1995, broth microdilution	34 <i>A. baumannii</i>	NR	MDR	≥128 (0/34, 0%), ≥128, ≥128	CLSI	AMK, synergy: 15/34, 44%, TOB, synergy: 11/34, 32%
Talarmin et al., 1996 [28] (Dubrous et al., 1997 [38] ^a)	France, NR, disk diffusion	25 <i>P. aeruginosa</i> serotype O12 MDR: 18/25 (72%) β-lactamase 25/25 PSE-1, 20/25	NR	Resistance to PIP, GEN, TOB, CIP, TIC, NET	O12: ≤8 to ≥128 (18/25, 72%), 16, ≥128	Susceptible: ≤32	12 isolates examined CAZ, synergy: 10/12 (83.3%) ^a

		(80%)					
		TEM-2, 4/25					
		(16%)					
Watine et al., 1994 [29]	France, 06/1991–06/1993, disk diffusion	<i>P. aeruginosa</i> serotype O12: 37/244 (15.2%)	Urine, tracheobronchial secretions or wounds	≥33/37 (89%) resistance rate to antipseudomonal penicillins, aminoglycosides, fluoroquinolones, respectively	O12: 35/37 (95%)	CA-SFM	CAZ, synergy: 9/12 (75%) ^b
Giammanco et al., 1985 [30]	Italy, 1978–1984, disk diffusion	<i>P. aeruginosa</i> serotype O12: 51/271 (18.8%) ^c	Blood, burn wound, urine, stool, sputum, throat swab	≥96% resistance to PIP, GEN, NET	O12: NR (16/51, 31.3%), NR, NR	NR	NR

ESBL, extended-spectrum β -lactamase; MBL, metallo- β -lactamase; CLSI, Clinical and Laboratory Standards Institute;

NR, not reported; MIC, minimum inhibitory concentration; MIC_{50/90}, MIC for 50% and 90% of the organisms, respectively;

RIF, rifampicin; COL, colistin; RT, respiratory tract; MHB, Mueller–Hinton broth; MHA, Mueller–Hinton agar; AMK,

amikacin; ATM, aztreonam; IPM, imipenem; GEN, gentamicin; TOB, tobramycin; NET, netilmicin; CIP, ciprofloxacin; CAZ,

ceftazidime; PIP, piperacillin; ETI, efficiency time index; MEM, meropenem; FEP, cefepime; LVX, levofloxacin; ICU,

Intensive Care Unit; PMB, polymyxin B; CF, cystic fibrosis; TIC, ticarcillin; CFS, cefsulodin; CA-SFM, Comité de l'Antibiogramme de la Société Française de Microbiologie.

^a Complementary data.

^b Refers to all isolates (not only MDR isolates).

^c Although 100 O12 strains were examined, the susceptibility of only 51 O12 strains was reported.

Table 2

Clinical studies on the effectiveness of fosfomycin (FOS) therapy in infections caused by multidrug-resistant (MDR) non-fermenting Gram-negative bacilli

Reference	Country, period, study design	Type of infection	Underlying condition	Patient characteristics (n, age, sex)	Causative pathogens; resistance characteristics	Resistance patterns	Antibiotic treatment	Treatment outcomes
Faruqi et al., 2008 [32]	UK, 3-year period, prospective cohort study	Pulmonary infection	CF	7, mean age 26.7 years, 5 F (71.4%)	MDR <i>Pseudomonas aeruginosa</i> in 22/26 (85%) episodes	Resistant to more than three antibiotics : CAZ, IPM, ATM, CIP, PIP, PIP/TAZ, GEN, AMK, TOB, COL	'FOS 5 g i.v. q8h' 18 courses FOS + another antibiotic 7 courses FOS + 2 other antibiotics 1 course FOS monotherapy Mean duration of	Symptomatic improvement in 26/26 (100%) episodes No adverse events FEV ₁ improved from 30.9% to 34.4% predicted ($P = 0.14$), regardless of combination of FOS with active or non-

							antibiotic therapy 14.3 days	active antibiotic
Cree et al., 2007 [33]	Australia NR, case report	Pulmonary infection	CF, progressive lung disease, bronchiectas is (frequent hospital admissions)	1, 14 years, F	MDR <i>P. aeruginosa</i>	Susceptible only to COL	1st treatment course: s.c. FOS for 5 days 2nd treatment course: s.c. FOS + CIP p.o. for 14 days 3rd treatment course: s.c. FOS + CIP p.o. for 5 days + intermittent TOB	FEV ₁ : from 70% to 77% FEV ₁ : from 44% to 68% FEV ₁ : from 49% to 51% No serious adverse events,

								localised reactions at infusion site
Guerin et al., 2005 [34]	Saudi Arabia, NR, case report	Prostatitis	HIV, abdominal abscess treated with surgery	1, 46 years, M	MDR <i>P. aeruginosa</i>	VIM-2 MBL-producing (resistant to all antibiotics except COL + FOS)	FOS (12 g/day) + ATM (6 g/day), 21 days	Full recovery, follow-up clear urine samples
Waiwarawooth, 2004 [35]	Thailand, NR, case report	Necrotizing fasciitis	3 weeks prior puncture wound at right pretibial area, DM	1, 50 years, M	MDR <i>P. aeruginosa</i>	Resistant to CAZ, IPM, MEM, AMK, CIP	PIP/TAZ (4.5 g q8h) + AMK (750 mg q24h) + FOS (2 g q12h)	Gradual improvement after 3 weeks of treatment, no clinical relapse
Mirakhur et al., 2003 [36]	UK, NR (5-year period), prospective cohort study	Pulmonary infection	CF	15 (30 episodes of infection), mean age 23 years, 9 F (60%)	MDR <i>P. aeruginosa</i> (61 isolates)	Resistance pattern: CAZ (67.2%), MEM (60.7%),	FOS 5 g three times daily, mean course length 16.6 days,	14/15 (93.3%) clinical resolution 1/15 (6.7%) FOS withdrawal

						IPM (73.8%), PIP (65.5%), GEN (67.3%), TOB (11.5%), COL (0%) FOS- susceptibl e strains: 8/15 (53%) patients	combinatio n with other i.v. antibiotics (CAZ, COL, TOB, MEM) in 20 (67%) courses + with two other antibiotics in 10 (33%) courses	due to nausea Mean FEV ₁ pre vs. post: 41.1% vs. 49.4% ($P <$ 0.001)
Katznelson et al., 1984 [37]	Israel, NR, pre/post study	Pulmonary infection	CF, failure of prior prolonged antibiotic courses with multiple agents	8, mean age 14 years, range 10–23 years, 2 F (25%)	MDR <i>P. aeruginosa</i>	Resistance to most antibiotics	FOS 2.0 g p.o.	(Post-FOS vs. pre-FOS period) Mean FEV ₁ increased from 30.1% to 76.6% FEV ₁ : increase in 6/7 (86%)

patients,
stable in 1/7
(14%) patient
Haemoptysis
(*n*): 5 vs. 2
patients
Hospitalisations
(*n*): 17 vs. 10
(Post-FOS
period)
Deaths (*n*): 2
Microbiological
persistence:
8/8 (100%)
patients

CF, cystic fibrosis; F, female; CAZ, ceftazidime; IPM, imipenem; ATM, aztreonam; CIP, ciprofloxacin; PIP, piperacillin;
TAZ, tazobactam; GEN, gentamicin; AMK, amikacin; TOB, tobramycin; COL, colistin; i.v., intravenous; q8h, every 8 h;
FEV₁, forced expiratory volume in 1 s; NR, not reported; s.c., subcutaneous; p.o., orally; HIV, human immunodeficiency
virus; M, male; MBL, metallo- β -lactamase; DM, diabetes mellitus; MEM, meropenem; q24 h, every 24 h; q12h, every 12 h.

