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Review

Fusidic acid for the treatment of bone and joint infections caused by meticillin-resistant *Staphylococcus aureus*

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ABSTRACT

There is a lack of surveillance data on resistance to fusidic acid (FA) in Asia, and no reviews of FA usage for the treatment of orthopaedic infections have been conducted since the year 2000. In this study, we present a systemic literature review of FA resistance in Asia and the clinical use of FA for the treatment of bone and joint infections (BJIs). The in vitro activity of FA against meticillin-resistant *Staphylococcus aureus* (MRSA) isolates remains good, with low (<10%) resistance rates in most Asian countries. FA in Asia appears to be a better oral anti-MRSA agent than trimethoprim/sulfamethoxazole and clindamycin. More than 80 cases of FA use for BJI have been reported since 2000 and the recurrence or failure rate is <10%. There is much evidence supporting the use of FA in combination with other antibiotics (e.g. rifampicin) as an oral treatment following intravenous glycopeptide treatment for BJIs.

1. Introduction

There is a need for safe, oral antibiotics against meticillin-resistant *Staphylococcus aureus* (MRSA) for effective step-down therapy after hospitalisation or for initial therapy for community-acquired infections [1]. Fusidic acid (FA), manufactured by Leo Pharmaceuticals, has been widely used in Europe, Canada, Australia and some Asian countries for decades. Although FA has not been approved for use in the USA by the US Food and Drug Administration (FDA), Cempra Pharmaceuticals has designed a dosing regimen for the use of FA as monotherapy if and when it is approved for use in the USA [1,2].

A number of review papers on FA were published in the *International Journal of Antimicrobial Agents* in the 1990s [3–7] and, in 2010, Schöfer and Simonsen reviewed the clinical efficacy of FA for skin and soft-tissue infections (SSTIs) [8]. The evidence provided in those review papers showed that FA is an effective treatment for SSTIs, acute osteomyelitis, chronic osteomyelitis, vertebral infection, septic arthritis, and prosthetic and other device-related infections due to meticillin-susceptible *S. aureus* (MSSA). There are few oral antibiotics listed in the treatment guidelines for treatment of MRSA infections [3–8]. The therapeutic guidelines in Australia list the combination of rifampicin (RIF) and FA as a treatment option for recurrent staphylococcal skin infections (including

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MRSA-positive infections) and MRSA osteomyelitis involving the bone or joint prostheses, both in adult and paediatric patients [9].

Treatment guidelines in the UK recommend FA and RIF for bone and joint infections (BJIs) [10]. In several reviews on BJIs, FA is listed as the treatment of choice [11–15].

Here we provide a review of FA resistance patterns in Asia and focus on the use of FA for the treatment of BJIs due to MRSA after the year 2000. Comprehensive searches were conducted of Medline, PubMed, Google Scholar, CINAHL, EMBASE and the CNKI (Chinese National Knowledge Infrastructure) database as well as reference lists of retrieved articles. Search terms were 'fusidic acid', '*Staphylococcus aureus*', 'MRSA', 'osteomyelitis', 'septic arthritis' and 'bone and joint infection', with each of the target country names in turn. Studies with a percentage of FA resistance in MRSA in Chinese articles are included.

2. Pharmacology

FA inhibits polypeptide chain elongation by binding to the ribosome elongation factor G (EF-G)–GDP complex. FA has good oral bioavailability and is metabolised and excreted by the liver [16]. This bacteriostatic agent is highly protein-bound and has been shown to have good concentrations in soft tissue, bone and synovial fluid [3,17,18]. FA is active against several *Staphylococcus* spp., including MSSA and MRSA, but has poor activity against *Streptococcus pyogenes* [4]. Rates of resistance to FA are higher among coagulase-negative staphylococci (CoNS) than among *S. aureus* [4,19–21]. The recommended dose of FA is 250–500 mg every 8–12 h; however, new pharmacokinetic data show that front-loaded dosing [≥1200 mg every 12 h (q12h) × 2 doses followed by ≥600 mg q12 h] has better activity against MRSA and *S. pyogenes* than non-front-loaded dosing (600 mg q12 h) [2].

3. In vitro activity of fusidic acid in combination with other antibiotics

Most in vitro and in vivo studies on FA combinations have concentrated on the effects of FA with RIF. Other common oral combinations with FA include minocycline, linezolid and fosfomycin. Checkerboard dilution and time–kill methods have revealed that FA combined with RIF had partial synergistic effects [22–26]. A combination of FA and minocycline has been reported for the treatment of vancomycin-intermediate *S. aureus* (VISA) infection, but there is a lack of in vitro data [27]. FA combined with linezolid has been successful in the treatment of VISA infection and endocarditis [28–30]. When combined with FA, linezolid was shown to prevent selection of resistant mutants but showed no synergy in one study [31]. Saginur et al. found that RIF and FA, plus either ciprofloxacin or vancomycin, were consistently bactericidal against MRSA biofilms [32]. Another study in China showed 88% synergism when FA was combined with fosfomycin [33]. Tang et al. found that the in vitro killing effects of fosfomycin combined with FA were better than the killing effects of RIF combined with FA [34].

4. Fusidic acid resistance in North America and Europe

The prevalence of resistance to FA in *S. aureus* remained low well into the 1990s. In staphylococci, high-level FA resistance is usually caused by mutations in *fusA*, the gene encoding EF-G, and low-level resistance is generally caused by the horizontally transferable genes *fusB* and *fusC* [35–37]. FusB-type proteins bind to EF-G on the ribosome, which allows the ribosomes to resume translation. There is also a concern that recent exposure to topical FA is correlated with the presence of FA-resistant *S. aureus* [38–40]. In addition, there is also a significant trend towards increased FA resistance among *S. aureus* with increased duration of use [40,41].

Updated surveillance data on FA resistance in MRSA have been reported in studies from North America, Australia and Europe [20,21,41,42,36]. *Staphylococcus aureus* resistance rates are very low in the USA (0.3%) and are relatively high in Canada and Australia (ca. 7.0%) [20,21]. In Canada, the occurrence of *fusB* and *fusC* is similar among *S. aureus*, whereas in Australia *S. aureus* isolates tend to be *fusC*-positive [20,21].

The increase in FA resistance in Europe appears to be due to clonal expansion of a strain called the epidemic European FA-resistant impetigo clone. This clone has been reported in the UK, France and other European countries [43–45]. In an updated surveillance report on FA resistance in 13 European countries, 10.7% of *S. aureus* isolates displayed FA minimum inhibitory concentrations (MICs) ≥2 mg/L [41]. Israel, Italy, Poland, Spain and Sweden had low rates (1.4–3.1%) of FA resistance [41]. Greece (62.4%) and Ireland (19.9%) had the highest resistance rates. Many of the FA-resistant *S. aureus* isolates in Greece and Ireland were spread clonally and showed high fusidic MIC values (≥512 mg/L), especially among isolates that carried the *fusA* L461 K mutation [41]. It is unclear whether the emerging FA resistance patterns seen in some European countries are also present in Asia [37,41,42], mainly because there is an overall lack of surveillance data in Asian countries.

5. Fusidic acid resistance in Asia

Resistance rates to FA in Asian countries are shown in Table 1 (references S1–S31 in Supplementary data). Resistance rates from 2000 to the present are available for 13 Asian countries, namely China, Japan, South Korea, Taiwan, Hong Kong, Singapore, Malaysia, Thailand, Cambodia, Kuwait, Iran, Saudi Arabia and Pakistan. Resistance was determined by the disk diffusion method in most of those studies. In most Asian countries, with the exception of Kuwait, Pakistan and South Korea, resistance rates are relatively low (<10%). In general, clindamycin resistance is high in Asia (>60%). Although most isolates are more susceptible to trimethoprim than to clindamycin, the rates of resistance to these two antimicrobial agents are higher than those to FA. Few studies have provided data on resistance to doxycycline and minocycline (data not shown).

In Kuwait, most MRSA isolates have high FA MICs (>256 mg/L), possibly because of the circulation of epidemic clones. Transmission of these clones and their maintenance in different hospitals may explain their high prevalence in Kuwaiti hospitals. The circulating strains with sequence type (ST) 80 commonly isolated from patients with community-acquired (CA) MRSA in Kuwait are not seen in other Asian countries. In contrast, ST59 is the most common CA-MRSA strain, and ST239 is the most common nosocomial MRSA strain in most Asian countries. In contrast to other CA-MRSA clones, the ST80 clone commonly carries the *fusB* gene, which appears to confer reduced susceptibility to FA. Studies from Greece and Kuwait have reported a high incidence of ST80 among CA-MRSA isolates and high rates of FA resistance [46,47]. According to recent data gathered by the Asian Network for Surveillance of Resistant Pathogens (ANSORP), which is a prospective, multinational surveillance study, ST80 has not been isolated in any Asian country [48]. ST80 is common in the Mediterranean and Balkan regions as well as in the Middle East. The reason for the relatively high prevalence of FA resistance in Pakistan and South Korea is not known. FA resistance among MSSA is also high in South Korea [49,50].

In Kuwait, the rate of FA resistance increased dramatically from 22% in 1994 to 92% in 2004 [51]. In Malaysia, the rate of resistance to FA among MRSA isolates increased from 3–5% during the

Table 1
Resistance profiles of fusidic acid (FA) in Asian countries.

Country	Reference[a]	Study year	Susceptibility testing method	No. of isolates tested	% of resistant isolates			
					FA	CLI	SXT	RIF
High FA resistance								
South Korea	Lee et al. [S1]	1996	DDM	90	12.2	86.7	N/A	N/A
South Korea	Kim et al. [S2]	1999–2001	DDM	439	14.1	84.3	8.9	18.0
South Korea	Kim et al. [S3]	2008	ADM	40	52.5	50	10	17.5
Kuwait	Udo et al. [S4]	2004	DDM	930	92	N/A	27	4.7
Kuwait	Udo et al. [S5]	2005	DDM	588	84	N/A	81	1
Pakistan	Idrees et al. [S6]	2005–2007	DDM	501	9	79	59	50
Pakistan	Zafar et al. [S7]	2006–2007	DDM	126	18	N/A	43	N/A
Pakistan	Shabir et al. [S8]	2010	DDM	60	20	N/A	N/A	52
Low FA resistance								
Cambodia	Chheng et al. [S9]	2006–2007	DDM	17	0	77	88	N/A
China[b]	Chen et al. [S10]	2001–2003	DDM	50	2.0	N/A	36	14
China[b]	Ni [S11]	2002	DDM	57	1.7	95.9	23.5	22.7
China[b]	Chang [S12]	2002–2003	DDM	280	1.7	95.9	23.5	22.7
China[b]	Pan [S13]	2002–2003	DDM	50	12	100	40	10
China	Liu et al. [S14]	2003–2007	ADM	11	0	90.9	N/A	N/A
China[b]	Hu et al. [S15]	2006–2007	DDM	56	1.8	92.8	25.0	N/A
China	Liu et al. [S16]	2008–2009	DDM	66	3	N/A	N/A	N/A
Hong Kong	Ip et al. [S17]	2000–2001	DDM	200	1	67.5	6	N/A
Iran	Askarian et al. [S18]	2006	DDM	32	0	69	N/A	3
Iran	Japoni et al. [S19]	2008–2009	Etest	156	0	76	69	11
Japan	Takizawa et al. [S20]	2003	ADM	54	0	N/A	N/A	0
Japan	Nakaminami et al. [S21]	2006	DDM	76	1.3	35.5	N/A	N/A
Malaysia	Norazah et al. [S22]	1997–1999	DDM	640	5	N/A	N/A	5
Malaysia	Thong et al. [S23]	2003–2007	DDM	66	11	19	N/A	12
Taiwan	Chen et al. [S24]	1995–2006	ADM	257	0	88	75.8	N/A
Taiwan	Lin et al. [S25]	2003–2007	DDM	94	1.1	85.6	4.8	N/A
Taiwan	Lo et al. [S26]	2004–2006	DDM	131	0	88.5	0	0
Taiwan	Lo et al. [S26]	2007–2009	DDM	240	0	89.6	2.9	1.3
Thailand	Hortiwakul et al. [S27]	2000–2001	Etest	100	0	N/A	N/A	N/A
Thailand	Mekviwattanawong et al. [S28]	2005	DDM	184	6.1	91.4	85.9	53.8
Thailand	Nickerson et al. [S29]	2006–2007	DDM	23	13	65	96	35
Saudi Arabia	Baddour et al. [S30]	2004–2005	Etest	512	4.3	N/A	33.8	N/A
Singapore	Hsu et al. [S31]	2005	DDM	197	<5	N/A	N/A	<5

CLI, clindamycin; SXT, trimethoprim/sulfamethoxazole; RIF, rifampicin; DDM, disk diffusion method; N/A, not available; ADM, agar dilution method.
[a] References are given in the Supplementary data.
[b] Article in Chinese.

period 1992–1996 to 11% in 2009 [52]. In Singapore, the rate of FA resistance was <5% during 1997–2004 [53]. Data from one medical centre in Taiwan revealed that FA usage remained stable from 2002 to 2009 and that the prevalence of FA-resistant Gram-positive bacteria causing healthcare-associated infections also remained stable (ca. 3–7%) [54].

Only three papers have been published on FA resistance gene determinants in Asia. In one study from central Taiwan, the most common FA resistance determinant in 34 isolates was *fusC* (74%) [55]. In northern Taiwan, Chen et al. found that 84% of 45 FA-resistant MRSA isolates had *fusA* mutations [56]. A small study in China showed that *fusB* and *fusC* were the main resistance determinants in four FA-resistant clinical isolates [57].

6. Fusidic acid in bone and joint infections caused by meticillin-resistant *Staphylococcus aureus*

No randomised controlled trials of FA as treatment for BJIs due to MRSA have been conducted. Trampuz and Zimmerli recommended a 2-week regimen of vancomycin and RIF followed by FA for treatment of prosthetic joint infections due to MRSA [13]. Oral antimicrobial therapy for osteomyelitis is important given the associated costs and potential morbidity of prolonged courses of intravenous (i.v.) therapy [14]. Unfortunately, the only oral antibiotics that are active against MRSA include pristinamycin, linezolid, trimethoprim/sulfamethoxazole (SXT), doxycycline and FA.

Table 2 presents the results of the literature search for reviews of treatment of osteomyelitis and septic arthritis [30,58–70]. The three large series of FA use for BJIs involved prosthetic joint infections with or without implant removal [63,67,69]. In most cases, FA was administered along with RIF following administration of i.v. glycopeptides. Other oral antibiotics that are used in combination with FA for the treatment of osteomyelitis and septic arthritis with or without removal of the prosthesis include chloramphenicol, doxycycline, linezolid and pristinamycin. In general, oral FA is appropriate for long-term use. In more than 80 reported cases of infections treated with FA, only 7 patients (<10%) had treatment failure or recurrence. In one study of a two-stage revision in total knee arthroplasty infected with MRSA (89%) or meticillin-resistant CoNS (11%) in Taiwan [69], i.v. vancomycin or teicoplanin was used for ≥2 weeks or until clinical infection control was observed and C-reactive protein (CRP) had decreased to <2.0 mg/dL. Oral sodium fusidate tablets were then administered for ≥4 weeks until the CRP value returned to normal. The criteria for re-implantation were CRP < 1.0 mg/dL and no clinical signs of infection 2 weeks after discontinuing the oral regimen. In that series, there were only three cases of recurrent infection [69]. In a retrospective cohort study of patients with MRSA orthopaedic device-related infections between 2000 and 2008 at Geneva University Hospital (Switzerland), none of the patients who received RIF plus FA ($n = 12$) experienced treatment failure [67]. In a large series from Australia involving patients with MRSA prosthetic joint infections treated with surgical debridement and prosthesis retention, RIF combined with FA was administered for a mean duration of 12 months (range 6–33 months) and only 1 of 11 MRSA infections recurred [63]. Other case reports of FA use for the treatment of BJIs caused by MRSA after 2000 are listed in Table 2 [30,58–70].

Table 2
Literature review of fusidic acid use for the management of bone and joint infections caused by meticillin-resistant *Staphylococcus aureus*.

Reference	Publication year	Country	No. of patients	Prosthetic device	Duration of i.v. antibiotic treatment	Oral antibiotic in combination	No. of patients with treatment failure or recurrence
Howden et al. [30]	2004	Australia	4	Yes	N/R	RIF, CHL	1
Ng and Gosbell [58]	2005	Australia	4	No	N/R	PRI	0
Nather et al. [59]	2005	Singapore	3	No	6–8 weeks	CLI	0
Chiang et al. [60]	2005	Taiwan	1	No	4 weeks	None	0
Donaldson et al. [61]	2006	Australia	2	No	7 weeks	RIF	2
Inverarity et al. [62]	2006	UK	1	No	6 weeks	DOX	0
Aboltins et al. [63]	2007	Australia	11	Yes	1–4 weeks	RIF	1
Apisarnthanarak and Mundy [64]	2007	Thailand	1	No	2 weeks	RIF	0
Murray et al. [65]	2008	Australia	7	No	N/R	RIF	0
Ahamed Puthiyaveetil [66]	2009	Australia	1	No	N/R	RIF	0
Ferry et al. [67]	2010	Switzerland	12	Yes	N/R	RIF	0
O'Neill et al. [68]	2011	Ireland	1	No	2 weeks	LZD	0
Chiang et al. [69]	2011	Taiwan	39	Yes	2–4 weeks	N/R	3
Wolfe [70]	2011	USA	1	No	10 weeks	None	0

i.v., intravenous; N/R, not reported; RIF, rifampicin; CHL, chloramphenicol; PRI, pristinamycin; CLI, clindamycin; DOX, doxycycline; LZD, linezolid.

7. Conclusions

The in vitro activity of FA in Asia is good and most countries, with the exception of Kuwait, South Korea and Pakistan, have low resistance rates (<10%). FA appears to be a better oral anti-MRSA agent than SXT, doxycycline/minocycline and linezolid. For the treatment of MRSA BJIs, most studies support the use of FA in combination with other antibiotics (e.g. RIF) as step-down oral antibiotic regimens following administration of i.v. glycopeptides.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.ijantimicag.2012.03.010.

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