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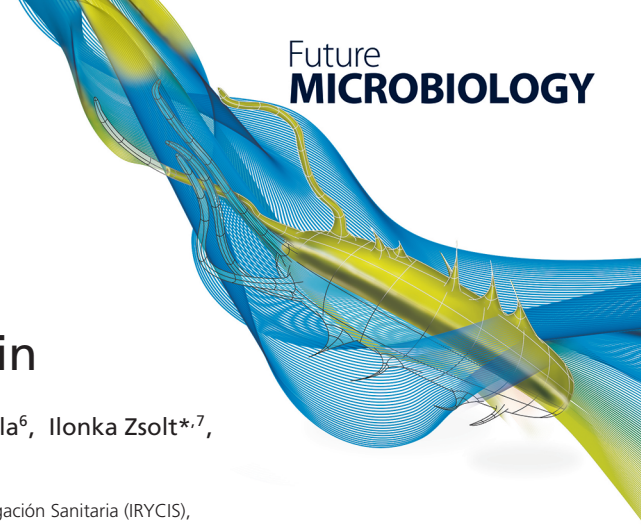

Future MICROBIOLOGY

Microbiological profile of ozenoxacin

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Aim: To explore the antibacterial spectrum of ozenoxacin and compare its *in vitro* activity with that of other antibacterial agents. **Materials & methods:** In 2010, 10,054 isolates were collected from 128 centers worldwide. Minimum inhibitory concentrations against Gram-positive and Gram-negative isolates were determined for 23 and 13 antibacterial agents, respectively. **Results:** Ozenoxacin exhibited high *in vitro* activity against susceptible, and methicillin- or levofloxacin-resistant, Gram-positive bacteria. Ozenoxacin was one or two dilutions less active against Enterobacteriaceae isolates, except for *Escherichia coli,* than other quinolones. **Conclusion:** Ozenoxacin is a potent antimicrobial agent mainly against susceptible and resistant strains of Gram-positive isolates (staphylococci and streptococci), and shows activity against some Gram-negative isolates.

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Impetigo is a common bacterial skin infection affecting children and adults that is caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. It is the most common bacterial skin infection in children aged 2–5 years [1,2].

Impetigo is commonly treated with topically applied antibacterial agents such as mupirocin, fusidic acid and retapamulin [1–5]. A recent evidence-based review supported the clinical efficacy of mupirocin and fusidic acid for treatment of impetigo [5]. However, in some cases, development of resistant isolates limits the uses of these agents [1,5].

An alternative option for treating impetigo in children and adults is a 1% topical cream formulation of ozenoxacin, a nonfluorinated quinolone with bactericidal activity [6], which was recently approved in several countries worldwide [7–10]. Approval of ozenoxacin was granted based on demonstrable clinical benefit in two large Phase III trials of impetigo involving adults and children from 2 months of age [11,12]. Rapid eradication of bacterial load is important in impetigo to hasten symptom resolution and limit person-to-person transmission of infection.

Early *in vitro* characterization of ozenoxacin found that it was 3- to 321-fold more active than other quinolones against quinolone-susceptible and quinolone-resistant Gram-positive bacteria [13]. A subsequent and more comprehensive study showed that ozenoxacin has potent antibacterial activity against staphylococci and streptococci, irrespective of their levofloxacin susceptibility status [14].

This article presents additional surveillance study data generated during development of ozenoxacin. The antibacterial activity of ozenoxacin against Gram-positive and Gram-negative clinical isolates was compared with that of other topical and systemic antibiotics used in the treatment of skin and soft tissue infections (SSTIs). As it had yet to be decided at the time of the study whether ozenoxacin was to be developed as a systemic (oral or intravenous) and/or topical formulation, in order to ascertain its full microbiological profile, its antibacterial

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activity was also investigated against Gram-positive and Gram-negative bacteria causing respiratory tract infections (RTIs) and urinary tract infections (UTIs).

Methods

Clinical isolates collection

During 2010, a total of 10,054 bacterial isolates were collected from 128 centers, with some sites collecting isolates from more than one hospital. Centers were located in the USA (n = 28); Germany (n = 15); France (n = 8); Turkey (n = 8); the UK (n = 7); Spain (n = 6); Italy (n = 5); Belgium, Canada, Greece, Portugal and South Africa (n = 4 each); Argentina, Australia, Austria, Czech Republic, Japan, The Philippines, Slovak Republic, Thailand (n = 2 each); and Hong Kong, Hungary, Ireland, Israel, Malaysia, New Zealand, Poland, Romania, South Korea, Sweden, Switzerland, Taiwan and The Netherlands (n = 1 each).

Isolates were derived from SSTIs (44.8%), RTIs (38.1%), UTIs (1.3%), unknown (8.4%) or other (7.5%) sources. Taxonomic classification of isolates is summarized in Table 1. Isolates were identified following standard microbiological methods, including biochemical test and mass spectrometry (MALDI TOF MS).

Minimum inhibitory concentration determination

Minimum inhibitory concentration (MIC) was determined using broth microdilution methods as recommended by the Clinical and Laboratory Standards Institute (CLSI) [15–17].

Susceptibility was determined using breakpoints set by the CLSI [15,17], except that British Society for Antimicrobial Chemotherapy (BSAC) breakpoints were used for fusidic acid and mupirocin against staphylococci [18].

S. aureus ATCC 29213, *S. pneumoniae* ATCC 49619, *Escherichia coli* ATCC 25922 and *E. coli* ATCC 35218 isolates were used for quality control. All quality control results were within the ranges specified by the CLSI [17,19].

Concentrations of antibacterial agent tested for each isolate are shown in Table 2.

Results

Classification of clinical isolates

Gram-positive bacteria included in the study as principle pathogens were: coagulase-negative staphylococci (CNS), *S. aureus*, β-haemolytic streptococci, viridans streptococci, *S. pneumoniae* and enterococci (Table 1). A high proportion of Gram-positive isolates (69.5% of CNS [618/889]; 63.3% of *S. aureus* [1518/2398]; 78.8% of β-haemolytic streptococci [953/1210]; 66.2% of viridans streptococci [353/533]; and 50.6% of enterococci [84/166]) were derived from SSTIs.

Gram-negative bacteria included in the study as principle pathogens were: Enterobacteriaceae (n = 3190), *Haemophilus* spp. (n = 548) and *Moraxella catarrhalis* (n = 180) (Table 1). A high proportion of Gram-negative isolates classified as *Haemophilus* spp. (95.8%; 525/548) or *M. catarrhalis* (93.9%; 169/180) were derived from RTIs. Similarly, a high proportion of Gram-positive *S. pneumoniae* isolates (90.9%; 843/927) were derived from RTIs.

Comparative antimicrobial activity

Gram-positive bacteria

Staphylococci

Ozenoxacin was highly active against staphylococci with a MIC_{90} of 0.25 mg/l against *S. aureus* and all CNS isolates (Table 3). In general, ozenoxacin had high activity against Gram-positive bacteria irrespective of their resistance/susceptibility to methicillin or nonsusceptibility/susceptibility to levofloxacin.

A comparison of MIC_{90} values in SSTI-derived isolates (Table 4) demonstrated that ozenoxacin (0.5 mg/l) was more active against CNS isolates than 19 of 22 comparator agents tested including vancomycin and linezolid (2 mg/l); moxifloxacin (4 mg/l); amoxicillin-clavulanate and teicoplanin (8 mg/l); levofloxacin (>8 mg/l); fusidic acid and trimethoprim-sulfamethoxazole (16 mg/l); meropenem (>16 mg/l); ampicillin, neomycin and tetracycline (32 mg/l); ceftriaxone and clarithromycin (>32 mg/l); penicillin and piperacillin/tazobactam (64 mg/l); and mupirocin, ceftazidime and cefuroxime (>64 mg/l). Retapamulin was the only comparator tested to have a MIC_{90} value (0.12 mg/l) lower than that of ozenoxacin, while tigecycline and daptomycin each had a MIC_{90} value (0.5 mg/l) equivalent to that of ozenoxacin.

Against *S. aureus* specifically (Table 4), ozenoxacin was equally as active as mupirocin, retapamulin, tigecycline and trimethoprim-sulfamethoxazole (MIC_{90} of 0.25 mg/l), and was more active than 18 of 22 comparator

Table 1. Categorization of isolates (n = 10,054) from skin and soft tissue infections, respiratory tract infections, urinary tract infections and other or unknown sources (≥ 10 in ≥ 1 category).

Group	Pathogen	SSTI	RTI	UTI	Unknown	Other	Total
Gram positive							
Coagulase-negative staphylococci (CNS)	All CNS	618	106	1	146	18	889
	Staphylococcus capitis	30	8		12	3	53
	Staphylococcus epidermidis	365	47		86	9	507
	Staphylococcus haemolyticus	76	18		11	1	106
	Staphylococcus hominis	48	20		22	4	94
	Staphylococcus lugdunensis	53	4		6		63
	Staphylococcus pettenkoferi	10	1		3		14
	Staphylococcus warneri	7	4		4	1	16
Staphylococcus aureus	*Staphylococcus aureus*	1518	666	1	196	17	2398
β-haemolytic streptococci	All β-haemolytic streptococci	953	118	5	127	7	1210
	Streptococcus agalactiae	271	11	5	37	3	327
	Streptococcus dysgalactiae	172	28		21	1	222
	Streptococcus pyogenes	507	78		69	3	657
Viridans streptococci	All Viridans streptococci	353	64	1	108	7	533
	Streptococcus anginosus	91	11		14	1	117
	Streptococcus constellatus	60	6		4		70
	Streptococcus gallolyticus	38	2	1	19		60
	Streptococcus intermedius	15	4		3		22
	Streptococcus mitis	29	13		21	2	65
	Streptococcus oralis	39	8		12	1	60
	Streptococcus parasanguinis	18	4		4		26
	Streptococcus salivarius	23	7		10	1	41
	Streptococcus sanguinis	10	1		7	1	19
– *Streptococcus pneumoniae*	*Streptococcus pneumoniae*	63	843		18	3	927
Enterococci	All Enterococci	84	8	41	26	7	166
	Enterococcus faecalis	81	7	39	26	6	159
Gram negative							
Enterobacteriaceae	All Enterobacteriaceae	895	1329	70	208	688	3190
	Citrobacter freundii	50	33	8	4	38	133
	Citrobacter koseri	40	34	10	1	34	119
	Klebsiella aerogenes	54	45	4	4	51	158
	Enterobacter cloacae	73	74	2	5	65	219
	Escherichia coli	287	508	17	5	234	1051
	Klebsiella oxytoca	51	100	6		40	197
	Klebsiella pneumoniae	94	350	11	2	87	544
	Morganella morganii	144	44	3	2	40	233
	Salmonella spp.	15	5	3	106	34	163
	Serratia marcescens	61	117	4	6	44	232
	Shigella flexneri		1	2	32	5	40
	Shigella sonnei	3	2		34	2	41
Other Gram-negative bacteria	*Haemophilus* spp.	11	525		3	9	548
	Haemophilus influenzae	3	458		2	7	470
	Haemophilus parainfluenzae	8	62		1	2	73
	Moraxella catarrhalis	4	169	6		1	180
	Neisseria gonorrhoeae	2		7	4		13

RTI: Respiratory tract infection; SSTI: Skin and soft tissue infection; UTI: Urinary tract infection.

Table 2. Concentrations of antibacterial agent tested for each bacteria.

Antibacterial	Antibacterial range tested (mg/l)					
	Staphylococci and Enterococci	*Streptococcus* spp. (other than *S. pneumoniae*)	*Streptococcus pneumoniae* and *Moraxella catarrhalis*	Enterobacteriaceae	*Haemophilus* spp.	*Neisseria gonorrhoeae*
Ozenoxacin	0.001–2	0.001–2	0.001–2	0.001–2	0.001–2	0.001–2
Mupirocin	0.03–64	0.03–64				
Fusidic acid	0.03–64	0.03–64				
Levofloxacin	0.004–8	0.03–64	0.03–64	0.004–8	0.008–16	0.004–4
Moxifloxacin	0.004–8	0.015–32	0.015–32	0.004–8	0.008–16	0.004–4
Ciprofloxacin				0.002–4		0.004–4
Ampicillin	0.015–32	0.008–16	0.015–32	0.015–32	0.008–16	
Amoxicillin-clavulanate	0.015–32	0.008–16	0.008–16	0.015–32	0.015–32	
Cefuroxime	0.03–64	0.008–16	0.008–16	0.03–64	0.015–16	0.008–1
Ceftriaxone	0.03–32	0.004–8	0.004–8	0.015–32	0.004–8	0.004–0.5
Ceftazidime	0.03–64	0.015–16	0.015–16	0.03–64	0.008–16	
Clarithromycin	0.03–32	0.015–32	0.015–32		0.015–32	
Daptomycin	0.015–32	0.015–32	0.015–16			
Linezolid	0.015–32	0.015–32	0.015–32			
Meropenem	0.008–16	0.008–16	0.008–16	0.004–8	0.008–16	
Neomycin	0.03–64	0.03–64		0.03–64		
Penicillin G	0.03–64	0.008–16	0.008–16		0.008–16	0.015–8
Piperacillin				0.06–128	0.06–128	
Piperacillin-tazobactam	0.03–64	0.015–32	0.03–64	0.06–128	0.03–64	
Retapamulin	0.008–16	0.008–16				
Teicoplanin	0.015–32	0.015–32	0.015–32			
Tetracycline	0.03–64	0.03–64	0.03–64		0.03–64	0.015–8
Tigecycline	0.004–4	0.004–4	0.002–4	0.004–8	0.002–4	
Trimethoprim-sulfamethoxazole	0.015–32	0.015–32	0.015–32		0.015–32	
Vancomycin	0.03–64	0.03–32	0.015–32			0.001–2

antibacterial agents tested that had MIC_{90} values of 0.5 mg/l (fusidic acid and daptomycin); 1 mg/l (teicoplanin and vancomycin); 2 mg/l (linezolid); 4 mg/l (moxifloxacin); >8 mg/l (levofloxacin); 16 mg/l (amoxicillin/clavulanic acid and meropenem); 32 mg/l (tetracycline); >32 mg/l (ampicillin, ceftriaxone and clarithromycin); 64 mg/l (penicillin and piperacillin-tazobactam); and >64 mg/l (ceftazidime, cefuroxime and neomycin).

Ozenoxacin was consistently among the most active antibacterial agents (as measured by MIC_{90}) against individual CNS spp. derived from SSTIs (Table 4). Ozenoxacin was the most active agent against *Staphylococcus capitis* (0.06 mg/l) and *S. lugdunensis* (0.015 mg/l). Ozenoxacin was the fourth most active agent against *S. epidermidis* (1 mg/l) after retapamulin, daptomycin and tigecycline in order. Ozenoxacin and mupirocin were equal-second most active agents against *S. haemolyticus* (0.25 mg/l) after retapamulin. Ozenoxacin was the third most active agent against *S. hominis* (1 mg/l) after retapamulin and daptomycin.

Resistance rates to fusidic acid identified in several staphylococcal species (*S. aureus* spp. [n = 2398]: 6.5%; methicillin-resistant *S. aureus* [MRSA; n = 1053]: 8.5%; methicillin-susceptible *S. aureus* [MSSA; n = 1345]: 5.1%; and CNS spp. [n = 889]: 24.6%) were higher when antimicrobial activity was tested in isolates derived from SSTIs (*S. aureus* spp. [n = 1518]: 7.8%; CNS spp. [n = 618]: 24.1%; *S. capitis* [n = 30]: 16.7%; *S. epidermidis* [n = 365]: 26.8%; *S. haemolyticus* [n = 76]: 26.3%; and *S. hominis* [n = 48]: 33.3%). Resistance rates to mupirocin in these same species were (*S. aureus* spp.: 4.8%; MRSA: 9.0%; MSSA: 1.6%; and CNS spp.: 27.8%); and in isolates derived from SSTIs were (*S. aureus* spp.: 4.7%; CNS spp.: 27.7%; *S. capitis*: 6.7%; *S. epidermidis*: 40.5%; *S. haemolyticus*: 5.3%; and *S. hominis*: 22.9%).

Table 3. Summary minimum inhibitory concentration data of ozenoxacin stratified by methicillin resistance/susceptibility and/or levofloxacin susceptibility/nonsusceptibility for Gram-positive bacteria (staphylococci, streptococci and enterococci).

Pathogen	Levofloxacin susceptibility	n	Ozenoxacin MIC (mg/l)		
			MIC_{50}	MIC_{90}	Range
Staphylococcus aureus	All	2398	0.004	0.25	≤0.001–2
	Levofloxacin nonsusceptible	877	0.12	0.25	0.002–2
	Levofloxacin susceptible	1521	0.004	0.004	≤0.001–2
– Methicillin-resistant *S. aureus* (MRSA)	All	1053	0.12	0.25	≤0.001–2
	Levofloxacin nonsusceptible	769	0.12	0.25	≤0.001–2
	Levofloxacin susceptible	284	0.004	0.008	0.002–2
– Methicillin-susceptible *S. aureus* (MSSA)	All	1345	0.004	0.008	≤0.001–2
	Levofloxacin nonsusceptible	108	0.12	1	0.004–2
	Levofloxacin susceptible	1237	0.004	0.004	≤0.001–0.5
Coagulase-negative staphylococci (CNS)	All	889	0.015	0.25	≤0.001–2
	Levofloxacin nonsusceptible	395	0.12	1	0.03–2
	Levofloxacin susceptible	494	0.008	0.015	≤0.001–0.12
– Methicillin-resistant CNS	All	500	0.12	1	≤0.001–2
	Levofloxacin nonsusceptible	346	0.12	1	0.03–2
	Levofloxacin susceptible	154	0.008	0.015	≤0.001–0.03
– Methicillin-susceptible CNS	All	389	0.008	0.12	0.002–2
	Levofloxacin nonsusceptible	49	0.12	2	0.03–2
	Levofloxacin susceptible	340	0.008	0.015	0.002–0.12
Staphylococcus capitis	All	53	0.008	0.12	0.002–0.12
	Levofloxacin nonsusceptible	13	0.06	0.12	0.03–0.12
	Levofloxacin susceptible	40	0.008	0.008	0.002–0.015
– Methicillin-resistant *S. capitis*	All	23	0.008	0.12	0.004–0.12
	Levofloxacin nonsusceptible	11	0.06	0.12	0.03–0.12
	Levofloxacin susceptible	12	0.008	0.008	0.004–0.008
– Methicillin-susceptible *S. capitis*	All	30	0.008	0.008	0.002–0.12
	Levofloxacin nonsusceptible	2	0.06	0.12	0.03–0.12
	Levofloxacin susceptible	28	0.008	0.008	0.002–0.15
Staphylococcus epidermidis	All	507	0.06	1	≤0.001–2
	Levofloxacin nonsusceptible	265	0.12	2	0.03–2
	Levofloxacin susceptible	242	0.008	0.015	≤0.001–0.03
– Methicillin-resistant *S. epidermidis*	All	337	0.12	1	≤0.001–2
	Levofloxacin nonsusceptible	237	0.12	2	0.03–2
	Levofloxacin susceptible	100	0.008	0.015	≤0.001–0.015
– Methicillin-susceptible *S. epidermidis*	All	170	0.008	0.12	0.002–2
	Levofloxacin nonsusceptible	28	0.12	2	0.06–2
	Levofloxacin susceptible	142	0.008	0.015	0.002–0.03
Staphylococcus haemolyticus	All	106	0.12	0.25	0.002–1
	Levofloxacin nonsusceptible	67	0.12	0.25	0.03–1
	Levofloxacin susceptible	39	0.004	0.008	0.002–0.008
– Methicillin-resistant *S. haemolyticus*	All	73	0.12	0.25	0.004–1
	Levofloxacin nonsusceptible	62	0.12	0.25	0.06–1
	Levofloxacin susceptible	11	0.004	0.008	0.004–0.008
– Methicillin-susceptible *S. haemolyticus*	All	33	0.008	0.12	0.002–0.25
	Levofloxacin nonsusceptible	5	0.12	0.25	0.03–0.25
	Levofloxacin susceptible	28	0.004	0.008	0.002–0.008

MIC: Minimum inhibitory concentration.

Table 3. Summary minimum inhibitory concentration data of ozenoxacin stratified by methicillin resistance/susceptibility and/or levofloxacin susceptibility/nonsusceptibility for Gram-positive bacteria (staphylococci, streptococci and enterococci) (cont.).

Pathogen	Levofloxacin susceptibility	n	Ozenoxacin MIC (mg/l)		
			MIC_{50}	MIC_{90}	Range
Staphylococcus hominis	All	94	0.008	0.25	0.002–2
	Levofloxacin nonsusceptible	33	0.12	2	0.03–2
	Levofloxacin susceptible	61	0.008	0.008	0.002–0.12
– Methicillin-resistant *S. hominis*	All	51	0.06	1	0.004–2
	Levofloxacin nonsusceptible	29	0.12	2	0.03–2
	Levofloxacin susceptible	22	0.008	0.015	0.004–0.015
– Methicillin-susceptible *S. hominis*	All	43	0.008	0.06	0.002–1
	Levofloxacin nonsusceptible	4	0.12	1	0.06–1
	Levofloxacin susceptible	39	0.008	0.008	0.002–0.12
Staphylococcus lugdunensis	All	63	0.015	0.015	0.004–0.25
	Levofloxacin nonsusceptible	3	0.25	0.25	0.12–0.25
	Levofloxacin susceptible	60	0.015	0.015	0.004–0.03
– Methicillin-resistant *S. lugdunensis*	All	2	0.008	0.12	0.008–0.12
	Levofloxacin nonsusceptible	1	0.12	0.12	0.12–0.12
	Levofloxacin susceptible	1	0.008	0.008	0.008–0.008
– Methicillin-susceptible *S. lugdunensis*	All	61	0.015	0.015	0.004–0.25
	Levofloxacin nonsusceptible	2	0.25	0.25	0.25–0.25
	Levofloxacin susceptible	59	0.015	0.03	0.004–0.03
Staphylococcus pettenkoferi	All	14	0.5	0.5	0.004–1
	Levofloxacin nonsusceptible	10	0.5	1	0.12–1
	Levofloxacin susceptible	4	0.008	0.03	0.004–0.03
– Methicillin-resistant *S. petteternkoferi*	All	4	0.5	1	0.03–1
	Levofloxacin nonsusceptible	3	0.5	1	0.5–1
	Levofloxacin susceptible	1	0.03	0.03	0.03–0.03
– Methicillin-susceptible *S. pettenkoferi*	All	10	0.12	0.5	0.004–1
	Levofloxacin nonsusceptible	7	0.5	1	0.12–1
	Levofloxacin susceptible	3	0.008	0.008	0.004–0.008
– *Staphylococcus warneri*	All	16	0.008	0.015	0.004–0.015
	Levofloxacin nonsusceptible	3	0.008	0.015	0.008–0.015
	Levofloxacin susceptible	13	0.008	0.015	0.004–0.015
β-haemolytic streptococci	All	1210	0.03	0.03	0.004–2
– *Streptococcus agalactiae*	All	327	0.03	0.06	0.008–1
	Levofloxacin nonsusceptible	8	1	1	0.25–1
	Levofloxacin susceptible	319	0.03	0.06	0.008–0.12
– *Streptococcus dysgalactiae*	All	222	0.03	0.03	0.008–0.25
	Levofloxacin nonsusceptible	5	0.25	0.25	0.06–0.25
	Levofloxacin susceptible	217	0.015	0.03	0.008–0.25
– *Streptococcus pyogenes*	All	657	0.015	0.03	0.004–2
	Levofloxacin nonsusceptible	2	0.06	2	0.06–2
	Levofloxacin susceptible	655	0.015	0.03	0.004–0.12
Viridans streptococci	All	533	0.03	0.06	≤0.001–2
– *Streptococcus anginosus*	All	117	0.015	0.03	≤0.001–0.06
– *Streptococcus constellatus*	All	70	0.015	0.03	≤0.001–0.06
– *Streptococcus cristatus*	All	3	0.015	0.03	0.015–0.03
– *Streptococcus equinus*	All	6	0.015	0.06	0.015–0.06

MIC: Minimum inhibitory concentration.

Table 3. Summary minimum inhibitory concentration data of ozenoxacin stratified by methicillin resistance/susceptibility and/or levofloxacin susceptibility/nonsusceptibility for Gram-positive bacteria (staphylococci, streptococci and enterococci) (cont.).

Pathogen	Levofloxacin susceptibility	n	Ozenoxacin MIC (mg/l)		
			MIC_{50}	MIC_{90}	Range
– *Streptococcus gallolyticus*	All	60	0.03	0.06	0.008–2
	Levofloxacin nonsusceptible	4	0.12	2	0.06–2
	Levofloxacin susceptible	56	0.03	0.06	0.008–0.12
– *Streptococcus intermedius*	All	22	0.015	0.03	0.004–0.06
– *Streptococcus mitis*	All	65	0.03	0.06	0.015–0.5
	Levofloxacin nonsusceptible	2	0.25	0.5	0.25–0.5
	Levofloxacin susceptible	63	0.03	0.06	0.015–0.06
– *Streptococcus oralis*	All	60	0.03	0.06	0.015–0.25
	Levofloxacin nonsusceptible	2	0.25	0.25	0.25–0.25
	Levofloxacin susceptible	58	0.03	0.06	0.015–0.06
– *Streptococcus parasanguinis*	All	26	0.03	0.25	0.015–2
	Levofloxacin nonsusceptible	4	0.25	2	0.06–2
	Levofloxacin susceptible	22	0.03	0.03	0.015–0.06
– *Streptococcus peroris*	All	13	0.03	0.06	0.015–1
	Levofloxacin nonsusceptible	1	1	1	1–1
	Levofloxacin susceptible	12	0.03	0.06	0.015–0.06
– *Streptococcus salivarius*	All	41	0.03	0.06	0.015–0.06
– *Streptococcus sanguinis*	All	19	0.03	0.06	0.015–0.06
Streptococcus pneumoniae	All	927	0.03	0.03	≤0.001–2
	Levofloxacin nonsusceptible	11	0.25	2	0.06–2
	Levofloxacin susceptible	916	0.03	0.03	≤0.001–0.12
	Penicillin nonsusceptible	96	0.03	0.03	0.008–2
	Penicillin susceptible	831	0.03	0.03	≤0.001–0.5
Enterococci	All	166	0.06	1	≤0.001–2
– *Enterococcus faecalis*	All	159	0.06	1	≤0.001–2
	Levofloxacin nonsusceptible	48	1	1	0.06–2
	Levofloxacin susceptible	111	0.03	0.06	≤0.001–0.25

MIC: Minimum inhibitory concentration.

Streptococci & enterococci

Ozenoxacin was highly active against levofloxacin nonsusceptible/susceptible streptococci and *Enterococcus* spp. (Table 3) with a MIC_{90} of 0.03 mg/l against combined β-haemolytic streptococci; 0.06 against combined viridans streptococci; 0.03 mg/l against *S pneumoniae*; and 1 mg/l against enterococci including *E. faecalis*.

In SSTI-derived isolates (Table 4), ozenoxacin had the lowest or equal-lowest MIC_{90} compared with 22 other antibacterial agents tested against the following bacteria: combined β-haemolytic streptococci, *S. agalactiae,* combined viridans streptococci, *S. anginosus, S. constellatus, S. oralis* and *S. pneumoniae*. The activity of ozenoxacin against remaining streptococci and enterococci was generally within one dilution of the most active compound. Against combined β-haemolytic streptococci, ozenoxacin had the lowest MIC_{90} (0.03 mg/l) of all 23 antibacterial agents tested. Meropenem, penicillin, amoxicillin-clavulanic acid, ceftriaxone, cefuroxime and retapamulin each had a MIC_{90} of 0.06 mg/l, while ampicillin, teicoplanin and tigecycline each had a MIC_{90} of 0.012 mg/l. MIC_{90} values for all other agents were higher than that of ozenoxacin: 0.25 mg/l for moxifloxacin, daptomycin, piperacillin-tazobactam and trimethoprim-sulfamethoxazole; 0.5 mg/l for vancomycin; 1 mg/l for mupirocin, levofloxacin, ceftazidime and linezolid; 4 mg/l for clarithromycin; 16 mg/l for fusidic acid; and 64 mg/l for tetracycline and neomycin.

Against *E. faecalis* (Table 4), tigecycline (MIC_{90} of 0.12 mg/l) was the most active agent, followed by amoxicillin-clavulanic acid and tetracycline (both 0.05 mg/dl), then ozenoxacin and ampicillin (both 1 mg/dl).

Table 4. Comparative minimum inhibitory concentration data of ozenoxacin and other antibacterial agents for Gram-positive isolates from skin and soft tissue infections.

Pathogen	MIC (mg/l)	Antimicrobial agent(s)																					
		OZN	MUP	FUS	LVX	MXF	AMC	AMP	CAZ	CRO	CXM	CLR	DAP	LZD	MEM	NEO	PEN	TZP	RET	TEC	TET	TGC	SXT	VAN
All coagulase-negative staphylococci (CNS) (n = 618)	MIC_{50}	0.015	0.25	0.12	0.25	0.12	0.5	2	16	8	2	16	0.5	1	1	0.25	4	1	0.06	2	0.5	0.12	0.5	2
	MIC_{90}	0.5	>64	16	>8	4	8	32	>64	>32	>64	>32	0.5	2	>16	32	64	64	0.12	8	32	0.5	16	2
Staphylococcus capitis (n = 30)	MIC_{50}	0.008	0.12	0.12	0.25	0.06	0.12	0.25	4	2	0.5	0.25	0.5	1	0.12	0.06	1	0.5	0.06	0.5	0.25	0.12	0.06	1
	MIC_{90}	0.06	0.5	8	4	1	4	>32	64	>32	>64	>32	1	2	8	16	>64	64	0.12	0.5	2	0.25	0.25	2
Staphylococcus epidermidis (n = 365)	MIC_{50}	0.06	0.25	0.25	2	0.5	1	4	16	8	4	32	0.5	1	2	0.25	4	1	0.06	4	1	0.12	0.5	2
	MIC_{90}	1	>64	16	>8	>8	8	16	64	>32	>64	>32	0.5	2	16	32	32	32	0.12	8	32	0.5	16	2
Staphylococcus haemolyticus (n = 76)	MIC_{50}	0.12	0.12	0.12	8	1	4	32	>64	>32	64	32	0.25	1	8	2	64	16	0.06	4	1	0.25	1	1
	MIC_{90}	0.25	0.25	16	>8	4	>32	>32	>64	>32	>64	>32	0.5	1	>16	64	>64	>64	0.12	8	32	0.5	>32	2
Staphylococcus hominis (n = 48)	MIC_{50}	0.008	0.25	0.12	0.12	0.06	0.5	1	32	8	1	32	0.25	1	1	0.06	0.5	2	0.06	0.5	0.25	0.12	4	1
	MIC_{90}	1	>64	16	>8	8	2	16	>64	32	8	>32	0.25	2	4	4	16	8	0.12	4	64	0.5	8	1
Staphylococcus lugdunensis (n = 53)	MIC_{50}	0.015	0.12	0.12	0.12	0.06	0.25	0.25	16	4	1	0.06	0.25	1	0.25	0.25	0.12	0.5	0.03	0.5	0.12	0.06	0.25	1
	MIC_{90}	0.015	0.12	0.25	0.25	0.12	1	4	16	4	2	>32	0.25	1	0.5	0.25	4	1	0.06	0.5	0.25	0.06	0.5	1
Staphylococcus aureus (n = 1518)	MIC_{50}	0.004	0.12	0.12	0.25	0.06	1	8	16	4	2	0.25	0.5	2	0.12	0.5	16	2	0.12	0.5	0.25	0.12	0.06	1
	MIC_{90}	0.25	0.25	0.5	>8	4	16	>32	>64	>32	>64	>32	0.5	2	16	>64	64	64	0.25	1	32	0.25	0.25	1
All β-haemolytic streptococci (n = 953)	MIC_{50}	0.03	0.12	8	0.5	0.12	0.015	0.015	0.25	0.03	0.015	0.03	0.06	1	≤0.008	32	0.015	0.06	0.03	0.06	0.25	0.06	0.06	0.5
	MIC_{90}	0.03	1	16	1	0.25	0.06	0.12	1	0.06	0.06	4	0.25	1	0.06	64	0.06	0.25	0.06	0.12	64	0.12	0.25	0.5
Streptococcus agalactiae (n = 271)	MIC_{50}	0.03	1	16	1	0.12	0.06	0.12	0.5	0.06	0.06	0.03	0.25	1	0.06	64	0.06	0.25	0.03	0.12	32	0.06	0.12	0.5
	MIC_{90}	0.06	1	32	1	0.25	0.06	0.12	1	0.06	0.06	>32	0.25	1	0.06	>64	0.06	0.25	0.06	0.12	64	0.12	0.12	0.5
Streptococcus dysgalactiae (n = 172)	MIC_{50}	0.03	0.12	4	0.5	0.12	0.015	0.03	0.25	0.03	0.015	0.03	0.06	1	0.015	32	≤0.008	0.06	0.03	0.12	0.25	0.06	0.12	0.25
	MIC_{90}	0.03	0.25	8	1	0.25	0.03	0.03	0.5	0.03	0.015	1	0.12	1	0.015	32	0.015	0.12	0.06	0.12	32	0.25	0.12	0.5
Streptococcus pyogenes (n = 507)	MIC_{50}	0.03	0.06	8	0.5	0.12	0.015	0.015	0.12	0.015	0.015	0.03	0.06	1	≤0.008	32	≤0.008	0.06	0.03	0.06	0.25	0.06	0.06	0.5
	MIC_{90}	0.03	0.25	8	1	0.25	0.015	0.03	0.25	0.03	0.015	0.5	0.06	1	≤0.008	64	0.015	0.06	0.06	0.12	32	0.06	0.25	0.5

AMC: Amoxicillin/Clavulanate; AMP: Ampicillin; CAZ: Ceftazidime; CLR: Clarithromycin; CRO: Ceftriaxone; CXM: Cefuroxime; DAP: Daptomycin; FUS: Fusidic acid; LVX: Levofloxacin; LZD: Linezolid; MEM: Meropenem; MIC: Minimum inhibitory concentration; MUP: Mupirocin; MXF: Moxifloxacin; ND: Not done; NEO: Neomycin; OZN: Ozenoxacin; PEN: Penicillin; RET: Retapamulin; SXT: Sulfamethoxazole/trimethoprim; TEC: Teicoplanin; TET: Tetracycline; TGC: Tigecycline; TZP: Piperacillin/tazobactam; VAN: Vancomycin.

Table 4. Comparative minimum inhibitory concentration data of ozenoxacin and other antibacterial agents for Gram-positive isolates from skin and soft tissue infections (cont.).

Pathogen	MIC (mg/l)	Antimicrobial agent(s)																					
		OZN	MUP	FUS	LVX	MXF	AMC	AMP	CAZ	CRO	CXM	CLR	DAP	LZD	MEM	NEO	PEN	TZP	RET	TEC	TET	TGC	SXT	VAN
All viridans streptococci (n = 353)	MIC_{50}	0.03	0.5	16	1	0.12	0.06	0.06	2	0.12	0.12	0.03	0.25	1	0.03	32	0.06	0.12	0.12	0.06	0.5	0.03	0.12	0.5
	MIC_{90}	0.06	1	64	2	0.25	0.5	1	8	0.25	1	>32	1	2	0.12	64	0.5	2	1	0.25	64	0.12	2	1
Streptococcus anginosus (n = 91)	MIC_{50}	0.015	0.5	8	0.5	0.12	0.06	0.06	2	0.12	0.12	0.03	0.25	1	0.06	32	0.03	0.12	0.12	0.06	0.5	0.03	≤0.015	0.5
	MIC_{90}	0.03	0.5	16	1	0.25	0.12	0.12	4	0.25	0.25	0.5	0.5	2	0.06	64	0.06	0.25	0.5	0.06	16	0.06	0.06	1
Streptococcus constellatus (n = 60)	MIC_{50}	0.015	0.5	16	0.5	0.12	0.03	0.06	2	0.12	0.12	≤0.015	0.25	1	0.06	32	0.03	0.12	0.12	0.03	0.5	0.03	≤0.015	1
	MIC_{90}	0.03	1	32	0.5	0.12	0.12	0.25	8	0.25	0.25	0.03	0.5	1	0.12	64	0.06	0.25	0.5	0.12	8	0.06	0.03	1
Streptococcus gallolyticus (n = 38)	MIC_{50}	0.03	1	32	1	0.12	0.06	0.06	0.5	0.06	0.06	0.06	0.06	1	0.015	8	0.06	0.25	1	0.25	64	0.06	0.25	0.5
	MIC_{90}	0.12	1	64	2	0.25	0.12	0.12	1	0.12	0.25	>32	0.5	2	0.03	64	0.06	0.25	16	0.25	>64	0.12	16	0.5
Streptococcus oralis (n = 39)	MIC_{50}	0.03	1	32	1	0.12	0.06	0.06	2	0.12	0.25	0.25	1	1	0.03	64	0.12	0.12	0.12	0.12	1	0.06	0.12	0.5
	MIC_{90}	0.06	8	32	2	0.25	4	4	>16	4	>16	>32	1	2	1	>64	4	4	0.25	0.12	>64	0.12	1	1
Streptococcus pneumoniae (n = 63)	MIC_{50}	0.03	ND	ND	1	0.12	0.015	0.03	0.25	0.03	0.03	0.03	0.12	1	0.015	ND	0.03	0.03	ND	0.06	0.25	0.06	0.25	0.5
	MIC_{90}	0.03	ND	ND	1	0.25	2	4	16	1	8	>32	0.25	1	0.5	ND	4	4	ND	0.12	32	0.12	8	0.5
All Enterococci (n = 84)	MIC_{50}	0.06	32	4	1	0.25	0.5	1	>64	>32	>64	16	1	2	4	>64	2	4	>16	0.5	64	0.12	0.06	1
	MIC_{90}	1	64	4	>8	>8	0.5	1	>64	>32	>64	>32	4	2	8	>64	4	8	>16	0.5	>64	0.12	>32	2
Enterococcus faecalis (n = 81)	MIC_{50}	0.06	32	4	1	0.25	0.5	1	>64	>32	>64	16	1	2	4	>64	2	4	>16	0.5	64	0.12	0.06	1
	MIC_{90}	1	64	4	>8	>8	0.5	1	>64	>32	>64	>32	4	2	8	>64	4	8	>16	0.5	64	0.12	>32	2

AMC: Amoxicillin/Clavulanate; AMP: Ampicillin; CAZ: Ceftazidime; CLR: Clarithromycin; CRO: Ceftriaxone; CXM: Cefuroxime; DAP: Daptomycin; FUS: Fusidic acid; LVX: Levofloxacin; LZD: Linezolid; MEM: Meropenem; MIC: Minimum inhibitory concentration; MUP: Mupirocin; MXF: Moxifloxacin; ND: Not done; NEO: Neomycin; OZN: Ozenoxacin; PEN: Penicillin; RET: Retapamulin; SXT: Sulfamethoxazole/trimethoprim; TEC: Teicoplanin; TET: Tetracycline; TGC: Tigecycline; TZP: Piperacillin/tazobactam; VAN: Vancomycin.

Table 5. Summary minimum inhibitory concentration data of ozenoxacin for Gram-negative bacteria.

Pathogen	n	Ozenoxacin MIC (mg/l)		
		MIC_{50}	MIC_{90}	Range
All Enterobacteriaceae	3190	0.25	>2	0.004–>2
– *Citrobacter braakii*	11	1	>2	0.06–>2
– *Citrobacter freundii*	133	0.25	>2	0.03–>2
– *Citrobacter koseri*	119	0.06	0.12	0.015–>2
– *Klebsiella aerogenes*	158	0.25	>2	0.03–>2
– *Enterobacter asburiae*	21	0.12	0.5	0.03–>2
– *Enterobacter cloacae*	219	0.12	>2	0.015–>2
– *Enterobacter kobei*	11	0.25	>2	0.03–>2
– *Escherichia coli*	1051	0.06	>2	0.004–>2
– *Klebsiella oxytoca*	197	0.25	1	0.03–>2
– *Klebsiella pneumoniae*	544	0.25	>2	0.008–>2
– *Morganella morganii*	233	0.25	>2	0.03–>2
– *Salmonella* spp.	163	0.12	0.5	0.015–>2
– *Serratia marcescens*	232	1	>2	0.004–>2
– *Shigella flexneri*	40	0.03	0.5	0.008–>2
– *Shigella sonnei*	41	0.03	0.25	0.008–>2
Other Gram-negative bacteria				
– *Haemophilus* spp.	548	0.004	0.03	≤0.001–2
– *Haemophilus influenza*	470	0.004	0.015	≤0.001–1
– *Haemophilus parainfluenza*	73	0.03	0.25	≤0.001–2
– *Moraxella catarrhalis*	180	0.004	0.008	≤0.001–0.03
– *Neisseria gonorrheae*	13	0.12	1	≤0.001–2

MIC: Minimum inhibitory concentration.

Gram-negative bacteria

Enterobacteriaceae

Ozenoxacin had a MIC_{90} of more than 2 mg/l for combined species of the Enterobacteriaceae family, with values ranging from 0.12 mg/l for *Citrobacter koseri*, 0.25 mg/l for *Shigella sonnei,* 0.5 mg/l for *Enterobacter asburiae* and *S. flexneri*, 1 mg/l for *Klebsiella oxytoca,* and more than 2 mg/l for all remaining species (Table 5).

MIC values against Gram-negative bacteria derived from SSTIs were compared for ozenoxacin and 13 other antibacterial agents. Based on MIC_{90}, ozenoxacin was the most active quinolone against combined Enterobacteriaceae, *E. cloacae*, *E. coli*, *K. pneumoniae* and *Morganella morganii*. In contrast, ozenoxacin was the least active quinolone against *C. freundii, C. koseri, E. aerogenes, K. oxytoca* and *Serratia marcescens.* However, the quinolones were generally of similar activity with MIC_{90} values within one or two dilutions of each other.

For combined species of Enterobacteriaceae, the most active compounds (as measured by MIC_{90}) were meropenem (0.06 mg/l), tigecycline (2 mg/l) and ozenoxacin (>2 mg/l), followed by neomycin (4 mg/l), ciprofloxacin (>4 mg/l), levofloxacin and moxifloxacin (each >8 mg/l). All other antibacterial agents had MIC_{90} values of 32 to >128 mg/l (Table 6).

Other Gram-negative bacteria

For other Gram-negative bacteria (Table 5), ozenoxacin was highly active against *Haemophilus* spp. (MIC_{90} of 0.03 mg/l), *H. influenzae* (0.015 mg/l) and *Moraxella catarrhalis* (0.008 mg/l), and was somewhat less active against *H. parainfluenzae* (0.25 mg/l) and *Neisseria gonorrhoeae* (1 mg/l), although it was tested on only 13 *N. gonorrhoeae* isolates.

Ozenoxacin and levofloxacin (MIC_{90} of 0.015 mg/l) were the second most active antibacterial agents against *H. influenzae* after ceftriaxone (0.008 mg/l), followed by piperacillin/tazobactam (≤0.03 mg/l), moxifloxacin (0.03 mg/l), meropenem (0.06 mg/l) and ceftazidime (0.12 mg/l); all other antibacterial agents had MIC_{90} values of 0.5–16 mg/l.

Table 6. Comparative minimum inhibitory concentration data (mg/l) of ozenoxacin and other antibacterial agents for Gram-negative isolates from skin and soft tissue infections.

Pathogen	MIC (mg/l)	Antimicrobial agent													
		OZN	LVX	MXF	CIP	AMC	AMP	CAZ	CRO	CXM	MEM	NEO	PIP	TZP	TGC
All Enterobacteriaceae (n = 895)	MIC_{50}	0.25	0.06	0.12	0.03	16	>32	0.25	0.06	8	0.03	1	8	2	0.5
	MIC_{90}	>2	>8	>8	>4	>32	>32	32	>32	>64	0.06	4	>128	32	2
Citrobacter freundii (n = 50)	MIC_{50}	0.25	0.12	0.25	0.015	32	32	0.5	0.25	4	0.03	1	4	2	1
	MIC_{90}	>2	1	1	0.5	>32	>32	>64	>32	>64	0.06	2	>128	64	2
Citrobacter koseri (n = 40)	MIC_{50}	0.06	0.03	0.03	0.008	2	32	0.12	0.06	4	0.015	0.5	8	2	0.5
	MIC_{90}	0.12	0.06	0.06	0.015	8	>32	0.5	0.25	8	0.03	1	64	8	1
Klebsiella aerogenes (n = 54)	MIC_{50}	0.25	0.06	0.12	0.015	>32	>32	0.25	0.12	8	0.03	0.5	4	4	0.5
	MIC_{90}	0.5	0.12	0.12	0.03	>32	>32	64	32	>64	0.06	1	128	64	1
Enterobacter cloacae (n = 73)	MIC_{50}	0.12	0.06	0.06	0.015	>32	>32	0.5	0.25	16	0.03	0.5	4	4	1
	MIC_{90}	>2	4	4	4	>32	>32	>64	>32	>64	0.06	1	>128	128	2
Escherichia coli (n = 287)	MIC_{50}	0.06	0.06	0.06	0.015	8	>32	0.25	0.03	4	0.015	2	>128	2	0.25
	MIC_{90}	>2	>8	>8	>4	32	>32	32	>32	>64	0.03	4	>128	32	0.5
Klebsiella oxytoca (n = 51)	MIC_{50}	0.25	0.06	0.06	0.015	1	>32	0.12	0.06	4	0.03	0.5	16	2	0.5
	MIC_{90}	0.5	0.12	0.25	0.06	4	>32	0.25	0.12	8	0.03	4	64	8	1
Klebsiella pneumoniae (n = 94)	MIC_{50}	0.25	0.06	0.12	0.03	4	>32	0.5	0.06	4	0.03	1	16	4	1
	MIC_{90}	>2	>8	>8	>4	>32	>32	>64	>32	>64	0.06	8	>128	>128	2
Morganella morganii (n = 144)	MIC_{50}	0.5	0.06	0.25	0.015	>32	>32	0.12	0.03	32	0.06	2	4	0.25	2
	MIC_{90}	>2	8	>8	>4	>32	>32	16	4	>64	0.12	32	>128	1	8
Serratia marcescens (n = 61)	MIC_{50}	1	0.12	0.25	0.06	>32	>32	0.25	0.25	>64	0.03	1	4	2	2
	MIC_{90}	>2	2	2	1	>32	>32	4	>32	>64	0.06	2	128	32	4

AMC: Amoxicillin/Clavulanate; AMP: Ampicillin; CAZ: Ceftazidime; CIP: Ciprofloxacin; CRO: Ceftriaxone; CXM: Cefuroxime; LVX: Levofloxacin; MEM: Meropenem; MIC: Minimum inhibitory concentration; MXF: Moxifloxacin; NEO: Neomycin; OZN: Ozenoxacin; PIP: Piperacillin; TGC: Tigecycline; TZP: Piperacillin/tazobactam.

All quinolones were less active against *H. parainfluenzae* than *H. influenzae*. Ceftriaxone (MIC_{90} of 0.008 mg/l) was the most active antibacterial agent against this species, followed by ceftazidime and meropenem (0.06 mg/l), levofloxacin (0.12 mg/l), then ozenoxacin, moxifloxacin and piperacillin/tazobactam (0.25 mg/l); all other antibacterial agents had MIC_{90} values of 1–16 mg/l.

Ozenoxacin and meropenem were the most active agents against *M. catarrhalis* (MIC_{90} of ≤0.008 mg/l), followed by piperacillin/tazobactam (≤0.03 mg/l), levofloxacin and moxifloxacin (0.06 mg/l), and clarithromycin (0.12 mg/l); all other agents had MIC_{90} values of 0.25–16 mg/l.

Discussion

A previously published study that compared the antimicrobial activity of ozenoxacin versus 17 antibacterial agents in more than 2000 Gram-positive clinical isolates from SSTIs showed that ozenoxacin is a potent antimicrobial agent against both staphylococci and streptococci, irrespective of levofloxacin susceptibility status [14]. The current comparative study examined the antibacterial activity of ozenoxacin in Gram-positive and Gram-negative clinical isolates derived mainly from SSTIs, RTIs and UTIs, which were stratified according to their methicillin and levofloxacin susceptibility status. The antibacterial activity of ozenoxacin was compared with that of 22 other antibacterial agents against approximately 4500 Gram-positive SSTI isolates, and with that of 13 other antibacterial agents against approximately 900 Gram-negative SSTIs isolates and Gram-negative isolates from other sources (e.g., RTIs, UTIs, etc).

Against Gram-positive isolates from SSTIs, ozenoxacin was highly active against staphylococci and streptococci, confirming the results of previously published comparative studies [14]. Ozenoxacin had a lower MIC_{90} than mupirocin and fusidic acid against the CNS isolates *S. capitis*, *S. epidermidis*, *S. hominis* and *S. lugdunensis*, and against combined β-haemolytic streptococci, combined viridans streptococci, all other subspecies of streptococci, and enterococci. Ozenoxacin was equally active as mupirocin (as measured by MIC_{90}) against *S. haemolyticus* and *S. aureus*. These results confirm and extend the previously reported results showing higher activity of ozenoxacin compared with mupirocin and fusidic acid against staphylococci and streptococci [14].

Clinical breakpoints of antibiotics are calculated based on MIC distributions, and pharmacokinetic and pharmacodynamic data (area under the curve of plasma concentrations). Because topical antibiotics are minimally absorbed, clinical breakpoints cannot be determined. Instead, combined MIC distributions from multiple sources and time periods are used to define epidemiological cutoffs that provide an indication of MICs for organisms with acquired or mutational resistance mechanisms. The inferred breakpoint for mupirocin is 1/256 mg/l and applies to topical nasal administration three-times daily. It is based on microbiological data (epidemiological cutoffs) and clinical experience [20]. In the case of fusidic acid, breakpoints for *Staphylococcus* spp. are S ≤1 mg/l and R >1 mg/l for an oral or IV dosage of 500 mg two- to three-times daily. The breakpoints are based on pharmacokinetic data, microbiological data and clinical experience [21]. In the current study, BSAC disk diffusion breakpoints that are harmonized with the European Committee on Antimicrobial Testing were used for susceptibility testing of mupirocin and fusidic acid [18]. Disk diffusion tests with ozenoxacin have yet to be conducted but are planned. According to the BSAC breakpoints in this study, the resistance rate of *S. aureus* to mupirocin and fusidic acid was higher in MRSA isolates than in MSSA isolates (9.0 and 1.6% for mupirocin and 8.5 and 5.1% for fusidic acid, respectively).

Fusidic acid, mupirocin or retapamulin are the main topical treatments recommended in Europe for treatment of impetigo [22], although resistance of staphylococcal strains to these agents is becoming a concern. Resistance to fusidic acid [23–27] and mupirocin [28–30] has been reported in Europe and may be increasing. Investigators in Greece reported a sevenfold increase from 2013 to 2016 in the rate of mupirocin-resistant *S. aureus* strains among community-associated staphylococcal infections (mainly impetigo cases), concurrent with a 1.9-fold increase in resistance rates to fusidic acid [31], highlighting the need for alternatives. Ozenoxacin's dual inhibitory activity against DNA gyrase and topoisomerase IV, in addition to other characteristics such as a mutant prevention concentration below that in skin, appear to protect it from the development of resistance [10].

Elsewhere, a Japanese comparative study of ozenoxacin with other antibacterial agents against cutaneous bacterial isolates from pediatric patients reported MIC_{90} values for ozenoxacin of 0.12, ≤0.06 and ≤0.06 mg/l against MRSA, MSSA and *S. pyogenes* isolates, respectively [32]. Respective MIC_{90} values for gentamicin against MRSA, MSSA and *S. pyogenes* isolates in this same Japanese study were more than 128, 64 and 4 mg/l for SSTIs from adults and 128, 16 and 4 mg/l for SSTIs from children. Gentamicin is used topically to treat SSTIs in some countries

but was not included in the present study. The Japanese results highlight that ozenoxacin is markedly more active than gentamicin against the most common Gram-positive bacteria found in SSTIs.

Another Japanese study showed that MICs of ozenoxacin against three levofloxacin-susceptible *Propionibacterium acnes* strains (MIC of levofloxacin; ≤4 μg/ml) and three levofloxacin-resistant *P. acnes* strains (MIC of levofloxacin; ≥8 μg/ml) ranged from 0.03 to 0.06 μg/ml and from 0.25 to 0.5 μg/ml, respectively [33]. These results suggest that ozenoxacin has a potent bactericidal activity against both levofloxacin-susceptible and levofloxacin-resistant *P. acnes*, a microorganism not included in the present study. A 2% lotion formulation of ozenoxacin has been approved since 2015 in Japan for treatment of inflamed acne.

In this study, the quinolones (ozenoxacin, ciprofloxacin, levofloxacin and moxifloxacin) exhibited comparable activity against Enterobacteriaceae, whereas ozenoxacin was the most active quinolone against *E. cloacae, E. coli, K. pneumoniae* and *M. morganii*. Ozenoxacin had lower activity than other quinolones against *C. freundii, C. koseri, K. aerogenes, K. oxytoca* and *S. marcescens*, although the differences were relatively small.

As SSTIs are caused mainly by Gram-positive cocci (especially *S. aureus* and *S. pyogenes*), the numbers of Gram-negative isolates derived exclusively from SSTIs were insufficient to compare ozenoxacin with other antibacterial agents. Moreover, other commonly used topical antibiotics such as mupirocin [34] and fusidic acid [35] have no or limited activity against Gram-negative isolates. The vast majority of *Haemophilus* spp. and *M. catarrhalis* isolates were derived from RTIs. Nevertheless, irrespective of the source, ozenoxacin was highly active against all *Haemophilus* spp. (0.03 mg/l), *H. influenzae* (0.015 mg/l) and *M. catarrhalis* (MIC_{90} of 0.008 mg/l), and was somewhat less active against *H. parainfluenzae* (0.25 mg/l).

Conclusion

In conclusion, ozenoxacin was shown to be a potent antibacterial agent against Gram-positive (staphylococci and streptococci) isolates and showed activity against some Gram-negative isolates. The high activity of ozenoxacin in staphylococcal and streptococcal spp. including methicillin and quinolone-resistant strains most commonly associated with childhood impetigo suggests that ozenoxacin may be a valuable alternative to other topical antibiotics in the eradication of these same bacterial species derived from SSTIs.

Summary points

- Ozenoxacin, a novel nonfluorinated quinolone with bactericidal activity, is approved in the USA, Canada and 12 EU countries as a 1% cream formulation for treatment of impetigo and in Japan as a 2% lotion formulation for treatment of superficial skin infections and acne.
- During development of ozenoxacin, surveillance studies compared its *in vitro* antibacterial activity with that of other topical and systemic antibacterial agents.
- In 2010, a total of 10,054 Gram-positive and Gram-negative isolates were collected from 128 centers worldwide; isolates were derived mainly from skin and soft tissue infections (SSTIs; 44.8%) and respiratory tract infections (38.1%).
- Minimum inhibitory concentrations were determined for 23 and 13 antimicrobial agents, respectively, using standard broth microdilution methods.
- Ozenoxacin exhibited high *in vitro* activity against susceptible, and methicillin- or levofloxacin-resistant, Gram-positive bacteria (*Staphylococcus aureus*, coagulase-negative staphylococci, β-haemolytic streptococci, viridans streptococci, enterococci and *Streptococcus pneumoniae* isolates).
- In the case of Gram-positive SSTI isolates, ozenoxacin was generally more active than mupirocin or fusidic acid and other quinolones.
- Ozenoxacin showed one or two dilutions less activity against Enterobacteriaceae isolates, except for *Escherichia coli*, than other quinolones tested.
- In the case of Gram-negative SSTI isolates, no comparisons of ozenoxacin were made with mupirocin and fusidic acid as these antibiotics are not active against these bacteria.
- Ozenoxacin is a potent antimicrobial agent mainly against susceptible and resistant strains of Gram-positive isolates (staphylococci and streptococci), and shows activity against some Gram-negative isolates.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations.

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Papers of special note have been highlighted as: • of interest; •• of considerable interest

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