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Review

Delafloxacin: what does a new fluoroquinolone offer?

Delafloxacino: ¿qué aporta una nueva fluoroquinolona?

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Abstract

Delafloxacin is a novel anionic fluoroquinolone with a different chemical structure from currently marketed fluoroquinolones, which gives it distinct physicochemical characteristics, being active in both acidic and neutral environments. Delafloxacin is also unique in showing a dual-targeted equipotent inhibition of the essential bacterial enzymes DNA gyrase and topoisomerase IV, which may explain the very low frequencies of spontaneous mutations *in vitro*. It shows potent *in vitro* activity against a broad spectrum of Gram-negative bacteria, including some fluoroquinolone-resistant strains, and increased efficiency against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*, although it is always necessary to determine the *in vitro* activity of delafloxacin against fluoroquinolone-resistant isolates. Delafloxacin exhibits linear pharmacokinetics, a wide volume of distribution, and a concentration-dependent pattern of antimicrobial killing, a property that allows the use of high doses for greater effectiveness in some difficult-to-treat infections. Delafloxacin is available for clinical use in oral and intravenous formulations and has been approved for the treatment of acute bacterial skin and skin-structure infections and community-acquired bacterial pneumonia based on the results from phase II and III clinical trials. Overall, delafloxacin has been well tolerated and has a low profile of drug-drug interactions. Its activity in local acidic environments and biofilms could play a role in the treatment of biofilm-related infections such as osteoarticular and medical device-associated infections, and due to its broad spectrum, it can also be useful in polymicrobial infections. Delafloxacin is an interesting new addition to the therapeutic arsenal against common and difficult-to-treat infections.

Keywords: Delafloxacin. Fluoroquinolones. Resistance. Topoisomerases. Acute bacterial skin and skin structure infections. Methicillin-resistant *Staphylococcus aureus*. Community-acquired bacterial pneumonia.

Resumen

Delafloxacino es una nueva fluoroquinolona aniónica con una estructura química diferente a otras fluoroquinolonas, lo que le confiere características fisicoquímicas distintivas, siendo activa tanto en ambientes ácidos como neutros. Además, presenta la singularidad de inhibir simultáneamente la ADN girasa y la topoisomerasa IV, lo que puede explicar la baja frecuencia de mutaciones espontáneas *in vitro*. Presenta una potente actividad *in vitro* frente a un amplio espectro de bacterias gramnegativas, incluidas algunas cepas resistentes a las fluoroquinolonas, y una mayor eficacia frente a grampositivas, incluyendo *Staphylococcus aureus* resistente a meticilina, aunque siempre es necesario determinar su actividad *in vitro* frente a aislados resistentes a otras fluoroquinolonas. Delafloxacino tiene una farmacocinética lineal, un amplio volumen de distribución y su farmacodinamia es concentración-dependiente, lo que permite el uso de dosis altas para obtener mayor eficacia en algunas infecciones difíciles de tratar. Delafloxacino está disponible para uso clínico

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por vía oral e intravenosa, y en base a ensayos clínicos en fase II y III, se ha aprobado para el tratamiento de infecciones bacterianas agudas de la piel y estructuras blandas y de la neumonía aguda bacteriana comunitaria. En general, delafloxacino se tolera bien y presenta escasas interacciones farmacológicas. Su actividad en medios ácidos y en biopelículas podría ser útil para el tratamiento de infecciones relacionadas con biopelículas, como las osteoarticulares y las asociadas a dispositivos médicos. Además, por su amplio espectro, también puede ser útil en infecciones polimicrobianas. Delafloxacino es una interesante incorporación para el tratamiento de infecciones habituales y difíciles de tratar.

Palabras clave: Delafloxacino. Fluoroquinolonas. Resistencia. Topoisomerasas. Infecciones bacterianas agudas de la piel y tejidos blandos. *Staphylococcus aureus* resistente a meticilina. Neumonía bacteriana adquirida en la comunidad.

Introduction

Antimicrobial resistance (AMR) to essential antibiotics poses a growing threat to global health. The Global Antimicrobial Resistance and Use Surveillance System (GLASS) established by the World Health Organization (WHO), has recently reported that resistance to essential antibiotics, particularly among Gram-negative bacteria, is widespread and increasing, although it is unevenly distributed [1]. Despite significant geographical differences, globally, *Escherichia coli* and *Klebsiella pneumoniae* are the leading antimicrobial-resistant Gram-negative bacteria, with more than 40% of *E. coli* resistant to third-generation cephalosporins and ciprofloxacin, and over 55% and 45% of *K. pneumoniae* resistant to third-generation cephalosporins and ciprofloxacin, respectively. Other essential life-saving antibiotics, such as carbapenems, are also losing effectiveness, with 15% of *K. pneumoniae* resistant to them. Among the Gram-positive bacteria, methicillin-resistant *Staphylococcus aureus* (MRSA) remains a problem, with a global level of resistance in bloodstream infections of 27.1%. In the case of *Streptococcus pneumoniae*, although the burden of infection has decreased with the introduction of pneumococcal conjugate vaccines, it remains an important cause of community-acquired bloodstream infections, often secondary to pneumonia, with variable levels of resistance to different antibiotics, while globally the level of resistance to penicillin remained low, at 5.2% [1].

In response to the AMR threat, the WHO launched its first Bacterial Priority Pathogens List (BPPL) in 2017, subsequently updated in 2024, with the aim of guiding and promoting the research and development of new antibacterials as part of efforts to address the growing global AMR threat [2,3]. In this context, a new compound from the fluoroquinolone family was developed with the aim of creating a broad-spectrum antibiotic to overcome the limitations and resistance associated with other fluoroquinolones. The novel anionic fluoroquinolone, delafloxacin, presented a different chemical structure, which confers distinct physicochemical characteristics. It is active in both acidic and neutral environments and shows dual-targeted equipotent inhibition of the essential bacterial enzymes DNA gyrase and topoisomerase IV. In addition, it shows potent *in vitro* activity against a broad spectrum of Gram-negative bacteria, including several fluoroquinolone-resistant strains, and increased efficiency against Gram-positive bacteria, including those carrying specific resistance mutations such as MRSA. This process culminated in 2017 with the authorization of delafloxacin (Baxdela®), in oral and intravenous formulations, by the Food and Drug Administration (FDA) for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI), when it is considered inappropriate to use other antibacterial agents that are commonly recommended for the initial treatment of these infections, and for the treatment of community-acquired bacterial pneumonia (CABP) [4]. The European Medicines Agency (EMA) approved delafloxacin (Quofenix®) in 2019 for the treatment of ABSSSI and later, in 2021, also authorised delafloxacin for the treatment of CABP [5].

ABSSSI are among the most common human bacterial infections and occur in both the community and hospital settings. These infections include cellulitis, erysipelas, wound infections (traumatic or post-surgical), and major abscesses. Cellulitis and abscesses are frequent in the community and also often result in hospitalisation. Other ABSSSI, such as surgical site infections and burn infections, are also seen in the hospital setting. The clinical manifestations of ABSSSI vary considerably and range from uncomplicated, superficial infections to life-threatening infections and represent a common indication for antibiotic use. Initial treatment of ABSSSI is usually empirical because culture results are not immediately available, and patients with ABSSSI benefit from the rapid initiation of appropriate therapy [6].

CABP is a global health problem with significant morbidity and mortality. It is the most common infectious cause of hospital admission in adults and poses a

high economic burden. The main management decisions should be guided by the severity of the disease. With the increasing availability of rapid molecular testing methods, antimicrobial therapy for hospitalised patients should be based on the results of diagnostic studies to allow pathogen-directed therapy. If rapid diagnostic tests are not available, patients can be treated empirically to cover the most likely bacterial pathogens [7].

This article aims to review the main differential characteristics of delafloxacin compared to other fluoroquinolones regarding its distinctive structural, chemical, and pharmacological characteristics and its *in vitro* activity, as well as its clinical use, including case reports and clinical trials that provide insights into the real-world application of delafloxacin.

Structure-activity relationships and mechanism of action of delafloxacin

Fluoroquinolones (FQs) are a family of broad-spectrum antibiotics that have been widely used in human medicine for many years. They are active against both Gram-positive and Gram-negative bacteria, including mycobacteria and anaerobes. Their mechanism of action is the inhibition of the bacterial nucleic acid synthesis through disruption of the enzymes topoisomerase IV and DNA gyrase, causing breakage of bacterial chromosomes. However, due to the overuse of FQs, bacteria have acquired resistance to these compounds, and FQs are currently facing increasing resistance and other challenges [8]. In this scenario, delafloxacin appears as a new quinolone with differential characteristics.

Delafloxacin (formerly known as ABT-492, RX-3341, and WQ-3034) is a novel fully synthetic anionic non-zwitterionic FQ with modifications to the quinolone structure that lead to increased efficiency in acidic conditions, an enhanced spectrum of antibacterial activity, and improved pharmacokinetic and toxicity profiles.

Delafloxacin is 1-(6-amino-3,5-difluoro-2-pyridinyl)-8-chloro-6-fluoro-7-(3-hydroxy-1-azetidinyl)-4-oxo-1,4-dihydro-3-quinolinecarboxylate (**Figure 1**). The molecule differs from previous FQs by three changes in the chemical structure of quinolones, namely: 1) the presence of a heteroaromatic substituent at position N-1, which enhances its antibacterial activity and steric hindrance, restoring its activity against bacterial strains resistant to other FQs; 2) the presence of chlorine at position C-8, which confers weak polarity, enhancing its activity against quinolone-resistant Gram-positive bacteria and anaerobes; and 3) the absence of a basic group at position C-7, resulting in a weak acidity and increased activity in acidic environments (such as in ABSSSIs, CABP, and biofilm) and preventing delafloxacin from existing under a zwitterionic form [9-11].

At neutral pH = 7.4, delafloxacin prevails under anionic form, but at acidic pH = 5.5 the dominant is the non-ionized delafloxacin which diffuses more easily

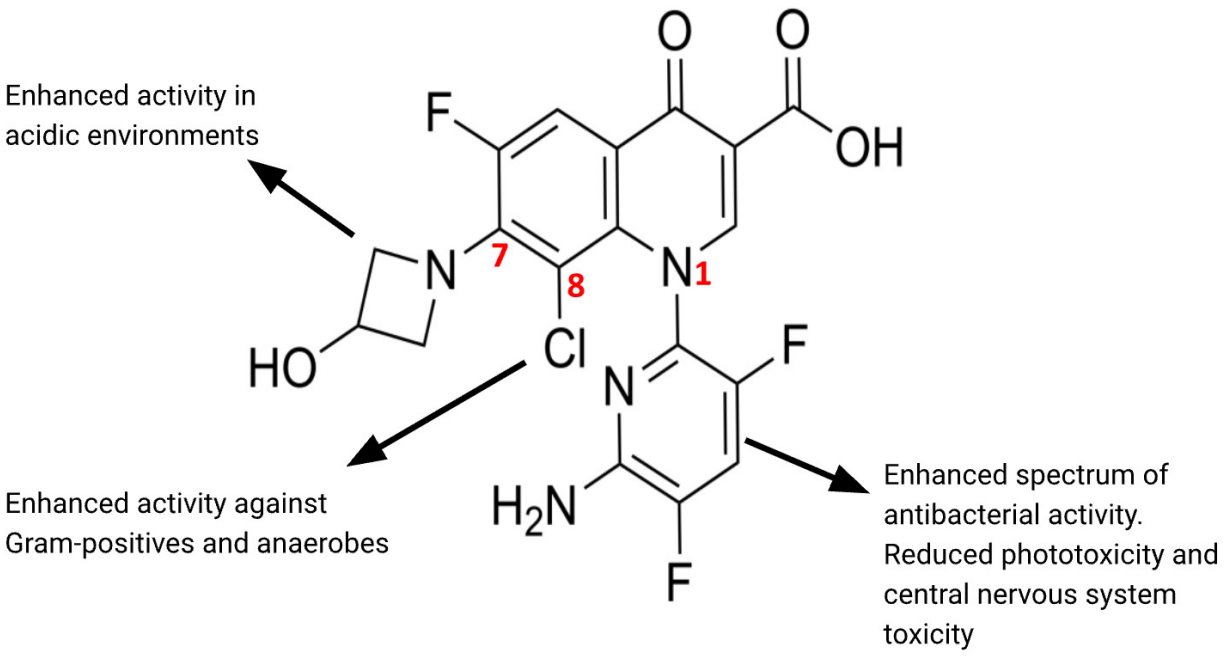


Figure 1. Structure-activity relationships of delafloxacin

through cell membranes and maintains an increased accumulation within bacterial cells. This property also translates into greater *in vitro* activity and a 4- to 5-fold decrease in MIC values from neutral to acidic conditions. The delafloxacin MIC decrease has been observed against *S. aureus*, *Escherichia coli, Klebsiella pneumoniae, Stenotrophomonas maltophilia,* and *Pseudomonas aeruginosa* under acidic conditions [12-17].

The chemical structure of delafloxacin also has an impact on its toxicity profile, since the large heterocycle at position N-1 decreases phototoxicity and reduces central nervous system toxicity compared with other FQs [18].

The antibacterial activity of delafloxacin is due to the dual inhibition with equal affinity of essential bacterial enzymes, DNA gyrase (topoisomerase II) and topoisomerase IV, in both Gram-negative and Gram-positive bacteria. This distinguishes it from other FQs (ciprofloxacin, levofloxacin) that exhibit greater inhibition of either DNA gyrase, preferably in Gram-negative bacteria, or topoisomerase IV in Gram-positive bacteria. As a consequence of this particularity, delafloxacin demonstrates excellent antibacterial potency against most clinically relevant microorganisms and a reduced the risk of the emergence of resistance, which would require multiple simultaneous mutations in both targets. In addition, delafloxacin is not a good substrate for efflux pumps, and the concentration of delafloxacin required to prevent the selection of resistant mutants is one and four times the MIC lower than those of comparator FQs [9,10, 19-25].

Delafloxacin breakpoints and susceptibility testing

To date, the European Committee on Antimicrobial Susceptibility Testing (EUCAST) has defined clinical breakpoints for delafloxacin for the following bacterial species: *S. aureus* (≤0.016 mg/L in community-acquired pneumonia and ≤0.25 mg/L in skin and skin-structure infections), *Streptococcus pyogenes*, *Streptococcus dysgalactiae, Streptococcus agalactiae,* and the *Streptococcus anginosus* group (≤0.03 mg/L), and *E. coli* (≤0.125 mg/L). It has also established an ECOFF of 0.06 mg/L for *S. pneumoniae* and 2 mg/L for *P. aeruginosa* [26-28]. The FDA has also defined clinical breakpoints for susceptible *S. aureus* and *S. haemolyticus* (≤0.25 mg/L*), S. pyogenes, S. agalactiae* and the *S. anginosus* group (≤0.06 mg/L), *E. faecalis* (≤0.12 mg/L), *E. coli, K. pneumoniae*, and *E. cloacae* (≤0.25 mg/L), and *P. aeruginosa* (≤0.5 mg/L) [29].

The EUCAST recommended method for susceptibility testing is broth microdilution [26]. Alternatively, gradient diffusion MIC test strips may be used for delafloxacin MIC testing, which generally perform similarly to the broth microdilution method [30]. In addition, the Gram-negative susceptibility cards VITEK®2 AST-XN38 and VITEK®2 AST-XN39 (Biomérieux, Marcy-l'Etoile, France), both including delafloxacin, have recently been introduced to the market and can be used for routine determination of delafloxacin MICs in clinical laboratories.

Activity of delafloxacin in biofilms and in acidic environments

A particularly important advantage of delafloxacin is its activity in biofilms due to its increased potency under acidic conditions. Biofilms consist of communities of bacteria encased in a matrix made of polysaccharides, proteins, and extracellular DNA that can develop on the surface of tissues or foreign bodies. In an *in vitro* model, Siala et al. compared delafloxacin to daptomycin and vancomycin using biofilms produced by seven clinical isolates of *S. aureus,* including methicillin-susceptible and MRSA, with a range of delafloxacin MIC values of 0.004-0.125 mg/L. Delafloxacin displayed potent activity at clinically achievable concentrations against five of the seven isolates tested, and the antibiotic penetration within the biofilms ranged from 0.6 to 52% for delafloxacin, 0.2 to 10% for daptomycin, and 0.2 to 1% for vancomycin. Acidic pH considerably increased the potency of delafloxacin when tested against planktonic forms of *S. aureus* by increasing its intrabacterial accumulation, but it did not substantially affect the potency of vancomycin or daptomycin [11]. The potency and efficacy of delafloxacin against biofilms are benefited by its penetration into the matrix and the local acidic microenvironmental pH [11,31]. In another study, delafloxacin showed greater activity against *S. maltophilia* under acidic conditions compared with levofloxacin. The MIC_{50} of delafloxacin decreased from 8 mg/L (in neutral pH conditions) to 0.25 mg/L (at pH = 6.5), whereas levofloxacin MIC values remained the same [15].

Delafloxacin has been shown to have excellent lung and biofilm penetration and enhanced activity in low-pH environments, such as those observed in the cystic fibrosis lung. Craddock et al. determined the MICs of delafloxacin, ciprofloxacin, and levofloxacin against six *P. aeruginosa* strains using standard culture media (pH 7.3), artificial sputum media (pH 6.9), and a cystic fibrosis sputum time-kill model.

Delafloxacin exhibited 2- to 4-fold MIC reductions at pH 6.9, which corresponded with significantly greater killing compared with ciprofloxacin and levofloxacin [16].

In a recent study, Alexandre et al. evaluated the pH-dependent antimicrobial activities of delafloxacin and ciprofloxacin against 81 isogenic *E. coli* strains carrying diverse fluoroquinolone resistance mechanisms and found that the ciprofloxacin MIC_{90} increased from 8 mg/L at pH 7.3 to 128 mg/L at pH 5.0, while the delafloxacin MIC_{90} decreased from 64 mg/L to 16 mg/L. At pH 5.0, the median MIC of delafloxacin was 2 mg/L *versus* 64 mg/L for ciprofloxacin ($P < 0.001$), demonstrating clinically relevant activity of delafloxacin in acidic environments [32].

In another study, Cortès-Tarragó et al. characterized in an *in vitro* infection model the intracellular activity of delafloxacin compared with levofloxacin against *Legionella* spp. in terms of culturability and viability and found that delafloxacin had higher intracellular activity than levofloxacin, decreasing the culturability of *Legionella* spp. from 5 to 10 times more than did levofloxacin, demonstrating the improved activity of delafloxacin in acidic environments [33].

In summary, the increased antibacterial efficacy of delafloxacin under acidic (inflammatory) environments may be a promising feature for the treatment of infections in acidic anatomical sites such as the urinary tract, skin, soft tissue, abscesses, respiratory tract, phagolysosomes, or biofilms [11,15,32,33].

In vitro antibacterial activity of delafloxacin

Delafloxacin has a broad spectrum of activity with improved potency compared with levofloxacin and moxifloxacin against Gram-positive pathogens (*S. aureus*, including MRSA; different species of coagulase-negative staphylococci (CoNS); *S. pneumoniae;* β-hemolytic streptococci; the *Streptococcus mitis* group; some *Enterococcus* spp.; and *Corynebacterium* spp.), Gram-negative bacteria (Enterobacterales, *Haemophilus influenzae, Moraxella catarrhalis, Neisseria meningitidis, Neisseria gonorrhoeae, Pseudomonas* spp., *S. maltophilia)*, anaerobes (*Bacteroides* spp., *Prevotella* spp., *Clostridioides difficile*, *Clostridium perfringens*, *Cutibacterium acnes*), and other microorganisms such as *Legionella pneumophila, Mycoplasma pneumoniae, Mycoplasma hominis, Ureaplasma* spp., *Chlamydia* spp. and *Mycobacterium tuberculosis* [9,10,15,34-46] (**Table 1**).

Activity against Gram-positive microorganisms

Delafloxacin shows potent *in vitro* activity against Gram-positive microorganisms. Several international multicenter studies have reported ranges of MIC_{50} and MIC_{90} values for *S. aureus* of ≤0.004 to 0.008 mg/L and 0.008 to 0.5 mg/L, respectively. Against MRSA, the MIC_{50} and MIC_{90} ranges were 0.06 to 0.5 mg/L, and 0.25 to 4 mg/L, respectively, which represents an activity at least 8-fold greater than that of levofloxacin or moxifloxacin [34,36,41,47,48]. Regarding CoNS, its

Table 1. ***In vitro*** **activity of delafloxacin against selected microorganisms (adapted from references [17,34-36,39, 41-45,47-67])**

Pathogens	Total no. of isolates	Delafloxacin MIC_{50} (mg/L)	Delafloxacin MIC_{90} (mg/L)	Delafloxacin MIC range (mg/L)	References
Gram-positive isolates					
Staphylococcus aureus	6,547	≤0.004 to 0.008	0.008 to 0.5	≤0.004 to 8	[34, 36, 41, 47]
MSSA	4,874	≤0.004 to 0.008	0.008 to 0.5	≤0.004 to 4	[34, 36, 47, 48]
MRSA	1,749	0.06 to 0.5	0.25 to 4	≤0.004 to 8	[34, 36, 47, 48]
MS CoNS	247	≤0.004	0.004 to 0.25	≤0.004 to 1	[34, 48, 50]
MR CoNS	577	0.06 to 0.25	0.5 to 2	≤0.004 to 4	[34, 48-50]
Enterococcus faecalis	465	0.06 to 0.12	1 to >32	≤0.004 to >32	[34, 48]
Enterococcus faecium	310	>32	>32	0.008 to >32	[34, 48]

...continuation table 1.

Pathogens	Total no. of isolates	Delafloxacin MIC_{50} (mg/L)	Delafloxacin MIC_{90} (mg/L)	Delafloxacin MIC range (mg/L)	References
Gram-positive isolates					
Streptococcus agalactiae	455	0.008 to 0.015	0.03 to 0.015	≤0.004 to 1	[34, 47]
Streptococcus dysgalactiae	415	0.008	0.015	≤0.004 to 0.12	[34, 47]
Streptococcus pyogenes	991	0.008	0.015 to 0.03	≤0.004 to 0.06	[34, 47, 51]
Streptococcus viridans group	367	0.015 to 0.06	0.03 to 0.06	≤0.004 to 2	[34, 48]
Streptococcus pneumoniae	842	0.008	0.015 to 0.12	≤0.004 to 0.25	[34, 35, 41, 48, 52]
S. pneumoniae LEV-R (MIC > 4 mg/L)	236	0.064 to 0.12	0.12 to 0.5	0.015 to 1	[35, 51, 39]
Corynebacterium spp.	136	0.008 to 4	0.5 to 8	≤0.002 to 16	[45, 48]
Bacillus spp.	20	0.06	0.06	≤0.03 to 0.12	[48]
Gram-negative isolates					
Enterobacterales	2,273	0.06 to 0.12	4	≤0.004 to >4	[34, 41]
Escherichia coli	1,802	0.03 to 0.06	4	≤0.004 to >4	[34, 47]
Klebsiella pneumoniae	409	0.06 to 0.12	1 to >4	0.015 to >4	[34, 48]
Klebsiella oxytoca	131	0.06 to 0.12	0.12 to 8	0.03 to 32	[34, 48]
Enterobacter spp.	424	0.06 to 0.12	0.25 to 1	≤0.004 to >4	[34, 48]
Proteus mirabilis	221	0.06	2 to 8	0.015 to >4	[34, 48]
Citrobacter spp.	198	0.06	0.25 to 2	0.008 to >4	[34, 48]
Serratia spp.	203	0.5 to 1	1 to 2	0.03 to >4	[34, 48]
Pseudomonas aeruginosa	680	0.25 to 32	0.25 to 32	0.094 to >32	[17, 34, 48, 53-56]
Acinetobacter spp.	200	2	>4	0.015 to >4	[34]
Stenotrophomonas maltophilia	19	1	2	0.12 to 16	[51]
Burkholderia spp.	12	4	16	0.25 to 16	[51]
Haemophilus influenzae	7,876	≤0.001	≤0.004	≤0.001 to 1	[35, 42, 51]
Moraxella catarrhalis	2,426	0.004 to 0.008	0.008 to 0.03	0.002 to 0.5	[35, 41, 42]
Anaerobes					
Bacteroides spp.	133	0.016 to 0.047	0.38 to 0.5	0.002 to >32	[57, 58]
Fusobacterium spp.	17	0.008	0.015	0.002 to 0.06	[41]
Prevotella spp.	65	0.002 to 0.004	0.032 to 0.5	0.002 to 1	[41, 57]
Clostridium spp.	55	0.004 to 0.032	0.38 to 0.75	0.002 to 0.75	[57, 58]

...continuation table 1.

Pathogens	Total no. of isolates	Delafloxacin MIC_{50} (mg/L)	Delafloxacin MIC_{90} (mg/L)	Delafloxacin MIC range (mg/L)	References
Anaerobes					
Gram-positive anaerobic cocci	105	0.004 to 0.008	0.008 to 0.5	≤0.001 to 1	[41, 57, 58]
Cutibacterium acnes	14	0.015	0.03	0.015 to 0.06	[41]
Veillonella spp.	16	0.03	1	0.002 to 2	[41]
Other microorganisms					
Legionella spp.	19	0.12	0.12	0.12	[59]
Chlamydia pneumoniae	13	ND	0.12	0.006 to 0.12	[43]
Mycoplasma pneumoniae	101	0.25	0.5	0.06 to 0.5	[44]
Mycoplasma hominis	39	0.016 to 0.5	0.016 to 1	0.008 to 1	[44, 61]
Ureaplasma spp.	89	0.06 to 2	0.25 to 4	≤0.008 to 4	[44, 61]
Neisseria gonorrhoeae	117	0.06	0.12	≤0.001 to 0.25	[60]
Helicobacter pylori	71	0.016	0.12	0.016 to 0.75	[64]
Bacillus anthracis	44	0.002	0.004	≤0.001 to 0.004	[62]
Burkholderia pseudomallei	30	0.5	1	0.12 to 2	[63]
Mycobacterium tuberculosis	225	0.39 to 1.5	0.78 to 8	0.06 to >16	[65, 66]
Mycobacterium avium complex	40	3.13 to 25	25	ND	[66]
Mycobacterium fortuitum	32	0.25	0.5	0.06 to 0.5	[67]

MSSA: methicillin-susceptible *S. aureus*; MRSA: methicillin-resistant *S. aureus*; MS CoNS: methicillin-susceptible coagulase-negative staphylococci; MR CoNS: methicillin-resistant coagulase-negative staphylococci; LEV-R: levofloxacin-resistant; MIC: minimum inhibitory concentration; ND: no data.

activity is similar, with MIC_{50} of ≤0.004 mg/L and MIC_{90} of 0.004 to 0.25 mg/L against methicillin-susceptible CoNS (MS-CoNS) and ranges of MIC_{50} and MIC_{90} of 0.06 to 0.25 mg/L, and 0.5 to 2 mg/L, respectively, against methicillin-resistant CoNS (MR-CoNS) [34,48-50]. In a large multicenter study including bacterial isolates from Europe and the United States, 99.5% of MSSA isolates (from both Europe and the United States), MRSA (95.3% and 91.2% of isolates from Europe and the United States, respectively), MS-CoNS (100% and 97.6%), and MR-CoNS (95.5% and 84.5%) isolates were inhibited by delafloxacin at an MIC of ≤ 0.5 mg/L. Notably, among fluoroquinolone-resistant *S. aureus* and CoNS isolates, 88.3% (484/548 isolates) were inhibited by ≤ 0.5 mg/L of delafloxacin [34]. In another multicenter study, delafloxacin also showed low MIC_{50} (0.06 mg/L) and MIC_{90} (0.50 mg/L) values against a series of linezolid-resistant *Staphylococcus epidermidis* involved in bone and joint infections [49]. In light of these results, it may be necessary to determine the susceptibility of staphylococcal isolates to delafloxacin regardless of their resistance pattern to other fluoroquinolones.

Against enterococci, the activity of delafloxacin is variable. While its activity against *Enterococcus*

faecalis is at least 8-fold greater than that of levofloxacin, with ranges of MIC_{50} and MIC_{90} of 0.06 to 0.12 mg/L and of 1 to >32 mg/L, respectively, it shows poor activity against *Enterococcus faecium* (MIC_{50} and MIC_{90} >32 mg/L), although it is active against isolates that are susceptible to levofloxacin [34,48].

Delafloxacin shows excellent *in vitro* activity against the *S. viridans* group (MIC_{50} and MIC_{90} at 0.015 and 0.06 mg/L, respectively) and against *S. pyogenes, S. agalactiae*, and *S. dysgalactiae* (MIC_{50} at 0.008 and MIC_{90} at 0.015 to 0.03 mg/L) [34,47,48,51]. In relation to its activity against *S. pneumoniae*, delafloxacin also displays an excellent activity (MIC_{50} at 0.008 and MIC_{90} at 0.015 to 0.12 mg/L), being 32- to 64-fold more active than levofloxacin [34,35,41,48,52]. It is also very active against levofloxacin-resistant *S. pneumoniae* isolates (MIC_{50} at 0.064 to 0.12 and MIC_{90} at 0.12 to 0.5 mg/L [35,51,39]. As indicated before, the characteristics of delafloxacin, as a dual-targeting fluoroquinolone against topoisomerase IV and DNA gyrase, decrease the selection of resistance by diminishing the likelihood of multiple mutational events in both enzymes. Thus, in one study, among 82 pneumococcal isolates resistant to levofloxacin, 71 (87%) were susceptible to delafloxacin despite the presence of mutations in *gyrA+parC* that lead to high level resistance to levofloxacin [23]. Finally, delafloxacin is also active against other Gram-positive bacteria such as *Corynebacterium* spp. and *Bacillus* spp. Against *Corynebacterium* spp. its activity varies depending on the species, with MIC values ranging from ≤0.002 to 16 mg/L [45,48] (**Table 1**).

Activity against Gram-negative microorganisms

Data from multicentre studies have shown that, in general, the activity of delafloxacin against Enterobacterales is similar to that of ciprofloxacin, presenting very good activity against *E. coli, K. pneumoniae, K. oxytoca,* and *Enterobacter* spp., among others, with MIC_{90} values ranging from ≤0.004 to >4 mg/L [34,41,47,48] (**Table 1**). However, as described above, it is important to note that in acidic infection sites such as abscesses, biofilms, and the urinary tract, while ciprofloxacin and other fluoroquinolones lose substantial activity, delafloxacin maintains and even enhances its antimicrobial potency [32]. Against *E. coli* and *K. pneumoniae* isolates producing extended-spectrum β-lactamases (ESBLs), its activity decreases, with MICs increasing up to 32-fold [34].

Against *P. aeruginosa*, the activity of delafloxacin (MIC_{50} and MIC_{90} range from 0.25 to >32 mg/L) is similar to that of ciprofloxacin (MIC_{50} and MIC_{90} at 0.25 and >4 mg/L, respectively) [17,34,48,53-56]. However, in one study, among 28 ciprofloxacin-resistant isolates, 10 were susceptible to delafloxacin (36%) [55]. In another study, among 101 *P. aeruginosa* isolates resistant to both ciprofloxacin and levofloxacin, 30 (29.7%) were susceptible to delafloxacin with an MIC <0.5 mg/L [54], demonstrating the diversity in antibacterial efficacy of delafloxacin against *P. aeruginosa*. This diversity makes it necessary to determine the susceptibility of *P. aeruginosa* isolates to delafloxacin in routine clinical laboratories, regardless of their ciprofloxacin and levofloxacin susceptibility results [53,56].

Against other non-fermentative Gram-negative bacilli, delafloxacin also shows variable activity, exhibiting $MIC_{50/90}$ values of 1/2 mg/L for *S. maltophilia*, 4/16 mg/L for *Burkholderia cepacia*, and 2/>4 mg/L for *Acinetobacter* spp. [34,51]. Delafloxacin is also very active against respiratory pathogens such as *H. influenzae* (MIC_{50} ≤0.001 mg/L; MIC_{90} ≤0.004 mg/L) and *M. catarrhalis* (MIC_{50} ≤0.008 mg/L; MIC_{90} ≤0.03 mg/L) [35,42,51].

Activity against other microorganisms

Delafloxacin exhibits high activity against Gram-positive and Gram-negative anaerobes, including *Clostridium* spp. (MIC_{50} ≤0.03 mg/L; MIC_{90} ≤0.75 mg/L), *Cutibacterium acnes* (MIC_{50} 0.015 mg/L; MIC_{90} 0.03 mg/L), Gram-positive anaerobic cocci (MIC_{50} ≤0.08 mg/L; MIC_{90} ≤0.5 mg/L), *Bacteroides* spp. (MIC_{50} ≤0.047 mg/L; MIC_{90} ≤0.5 mg/L), *Fusobacterium* spp. (MIC_{50} 0.08 mg/L; MIC_{90} 0.015 mg/L), *Prevotella* spp. (MIC_{50} ≤0.04 mg/L; MIC_{90} ≤0.5 mg/L), and *Veillonella* spp. (MIC_{50} 0.03 mg/L; MIC_{90} 1 mg/L). Overall, these values translate into an improvement in activity at least 32-fold higher than that of levofloxacin [41,57,58] (**Table 1**). The good activity of delafloxacin against anaerobes adds significant value as an alternative treatment option for polymicrobial skin and soft tissue infections.

Delafloxacin also has high *in vitro* activity against so-called atypical respiratory pathogens, including *Mycoplasma pneumoniae* (MIC_{50} 0.25 mg/L; MIC_{90} 0.5 mg/L), *Chlamydia pneumoniae* (MIC_{90} 0.12 mg/L), and *Legionella* spp. (MIC_{90} 0.12 mg/L). In all cases, its activity was 4-fold higher than that of levofloxacin [43,44,59].

It is also active against some organisms causing sexually transmitted diseases, including ciprofloxacin-resistant *Neisseria gonorrhoeae* (MIC_{50} 0.06 mg/L; MIC_{90} 0.125 mg/L) [60], *Mycoplasma hominis,*

Ureaplasma spp. and *Chlamydia trachomatis*, showing improved activity in levofloxacin-resistant strains [44,59,61] (**Table 1**). In addition, it is 16-fold more potent than ciprofloxacin against the biothreat pathogens *Bacillus anthracis* (MIC_{50} 0.002 mg/L; MIC_{90} 0.004 mg/L) and *Burkholderia pseudomallei* (MIC_{50} 0.5 mg/L; MIC_{90} 1 mg/L) [62,63].

Delafloxacin is also active *in vitro* against *Helicobacter pylori* (MIC_{50} 0.016 mg/L; MIC_{90} 0.125 mg/L). The enhanced antibacterial efficacy of delafloxacin in acidic environments enables it for therapeutic use against *H. pylori* infections [64]. Finally, regarding mycobacteria, the activity of delafloxacin is highly variable depending on the species. It shows moderate activity against *Mycobacterium tuberculosis* (MIC_{50} ≤0.5 mg/L; MIC_{90} ≤8 mg/L) [65, 66], lower activity than moxifloxacin or ciprofloxacin against *Mycobacterium avium* complex with MICs ranging from 4 to 25 mg/L [66], and similar activity to ciprofloxacin against *Mycobacterium fortuitum* (MIC_{50} 0.25 mg/L; MIC_{90} 0.5 mg/L) [67].

Activity of delafloxacin against fluoroquinolone-resistant *Staphylococcus aureus* and fluoroquinolone-resistant *Pseudomonas aeruginosa* in Spain

From 2019 to 2025, several studies have analyzed the activity of delafloxacin against fluoroquinolone-resistant *S. aureus* [20,68-83] and against fluoroquinolone-resistant *P. aeruginosa* [53,54,84-86] in different institutions across Spain. The institutions represented different geographical areas (**Figures 2 and 3**).

A total of 17 studies analyzed the activity of delafloxacin against *S. aureus*, and the percentages of susceptibility ranged from 53% to 95%. The 5 studies that analysed the activity of delafloxacin against fluoroquinolone-resistant *P. aeruginosa*, showed susceptibility ranges from 30% to 46% (**Figures 2 and 3**). Overall, these susceptibility data observed in Spain are lower than those found in other international multicentre studies [34]. However, it is important to note



Figure 2. Activity of delafloxacin (% susceptible) against fluoroquinolone-resistant *S. aureus* in Spain (2019-2025)

% Susceptible (No. isolates susceptible/No. isolates tested). EUCAST breakpoint ≤0.25 mg/L for *S. aureus*. Institutions: 1) Hospital Universitario de A Coruña; 2) Hospital Universitario Central de Asturias; 3) Hospital Universitario Donostia; 4) Hospital Universitario de Logroño; 5) Hospital Clínico Universitario de Valladolid; 6) Hospital Universitario Miguel Servet; 7) Hospital Universitario de la Santa Creu i San Pau (Barcelona); 8) Hospital Universitario Puerta de Hierro (Madrid); 9) Hospital Universitario de La Paz (Madrid); 10) Hospital Universitario Gregorio Marañón (Madrid); 11) Hospital Universitario de Toledo; 12) Hospital Universitario de Talavera de la Reina (Toledo); 13) Hospital Clínico Universitario de Valencia; 14) Hospital Universitario Nuestra Señora de Valme (Sevilla); 15) Hospital Universitario Virgen del Rocío (Sevilla); 16) Hospital Universitario Puerta del Mar (Cádiz); 17) Hospital Punta de Europa, Algeciras (Cádiz) (Adapted from references [20,68-83]).

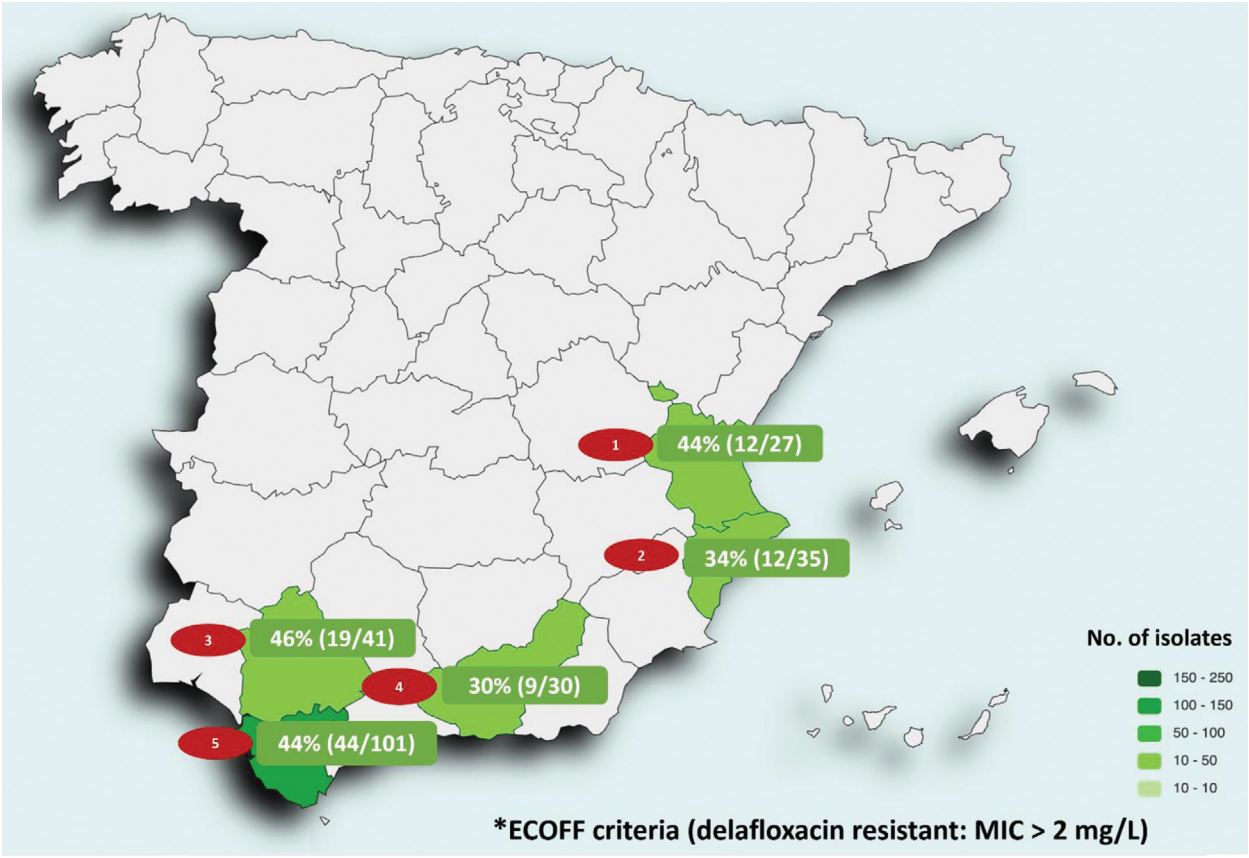


Figure 3. Activity of delafloxacin (% susceptible) against fluoroquinolone-resistant *P. aeruginosa* in Spain (2019-2025)

% Susceptible (No. isolates susceptible/No. isolates tested). EUCAST ECOFF breakpoint ≤2 mg/L for *P. aeruginosa*. Institutions: 1) Hospital Clínico Universitario La Fe (Valencia); 2) Hospital General Universitario Dr. Balmis (Alicante); 3) Hospital Universitario Virgen del Rocío (Sevilla); 4) Hospital Universitario San Cecilio (Granada); 5) Hospital Universitario de Puerto Real (Cádiz) (Adapted from references [53,54,84-86]).

that the isolates analysed were not collected consecutively, but were selected based on their fluoroquinolone resistance pattern or their multiresistance to other antimicrobials and where treatment options were limited. Moreover, despite being multidrug-resistant strains, a significant percentage are susceptible to delafloxacin.

Although most studies include limited numbers of isolates, the information is relevant because it indicates that even with resistance to other quinolones, some strains can still be rescued with delafloxacin. For this reason, it is important to determine the susceptibility of multiresistant *S. aureus* and *P. aeruginosa* to delafloxacin in difficult-to-treat infections, since it can be an alternative even in isolates resistant to other fluoroquinolones.

Pharmacokinetic/pharmacodynamic profile of delafloxacin

Pharmacokinetics

The pharmacokinetic profile of delafloxacin was initially evaluated in healthy volunteers using single and multiple ascending doses up to 1,200 mg and 1,600 mg of intravenous and oral drug, respectively [87-89]. Delafloxacin exhibits linear pharmacokinetics, in which ascending doses provide proportional increases in C_{max} and a little more proportional AUC values. The recommended intravenous dosage is 300 mg every 12 h, which allows a median C_{max} of 9-10 mg/L, and $AUC_{0\text{-inf}}$ 21-24 mg h/L.

The bioavailability of the oral formulation is 59%, which is lower than that of previous quinolones

levofloxacin or moxifloxacin; however, the oral dose of 450 mg is equivalent to 300 mg intravenously, and the AUC values are similar. In fact, switching between these equivalent intravenous and oral doses (300 mg q12h and 450 mg q12h, respectively) was approved by the FDA. Of note, the C_{max} after oral administration of delafloxacin is reduced by 20% when administered with food compared with the fasting state; however, no differences in AUC values were observed with or without food, suggesting no impact on clinical efficacy [88,90]. Delafloxacin possesses a large volume of distribution (35-48 L), which is almost equivalent to the total body water, and its protein binding is approximately 84%. High distribution in lung tissue has been reported [91], although information regarding its penetration into other tissues is still lacking. Recently, the penetration of delafloxacin into cerebrospinal fluid was evaluated in a murine model and showed a penetration ratio (cerebrospinal fluid/plasma) of 49% [92]. The mean half-life of delafloxacin is 3.7 h after a single intravenous 300 mg dose [89], and it increases to 4-8 h following multiple oral doses.

Delafloxacin is predominantly excreted via the kidney (65%), although additional clearance pathways have been identified, particularly fecal excretion of unchanged drug (30-50%). Delafloxacin is moderately metabolised via glucuronidation in humans with approximately 70% of the dose excreted unchanged [89].

The pharmacokinetic parameters of delafloxacin have been studied in patients with renal impairment [93,94]. In general, regardless of intravenous or oral administration, the total exposure of delafloxacin increased proportionally as the degree of renal impairment worsened. Thus, approximately 2-fold higher AUC values were observed in patients with severe renal impairment and end-stage renal disease undergoing hemodialysis compared with those with normal renal function, whereas this fact was not observed on the C_{max} values that did not differ significantly between groups. According to this information and supported by pharmacokinetic models and Monte Carlo simulations [95,96], the FDA recommends a dose adjustment of delafloxacin to 200 mg given intravenously every 12 hours in patients with severe renal impairment (eGFR, 15–29 mL/min/1.73 m^2); by contrast, no dose adjustment for oral delafloxacin is warranted in the same situation, although it could also be considered [96,97]. Since increases in drug exposure may cause more toxicity, more information regarding the requirement for dose adjustment in patients with renal impairment is needed; while waiting for more studies, we note that in the study of Hoover et al. there were no trends toward increased adverse events correlating with increased exposure in the group of renal impairment subjects following a single dose of intravenous or oral delafloxacin [93].

Regarding hepatic impairment, a study showed no changes in delafloxacin clearance; therefore, it is not recommended to adjust the dose in this situation, including the severe Child-Pugh class C group [98]. Of interest, the inhibitory effects of delafloxacin on cytochrome P450 have been evaluated both *in vitro* and *in vivo* using midazolam as a paradigm of cytochrome P450 substrate [96,99]; overall, the results of these studies showed no significant inhibitory impact of delafloxacin, and no drug-drug interaction in the case of midazolam. Finally, neither sex nor age had any significant effect on the pharmacokinetics of delafloxacin [88].

Pharmacodynamics

Delafloxacin, as well as other fluoroquinolones, shows a concentration-dependent pattern of antimicrobial killing, with the 24-h free-drug area under the curve/MIC value (*f*AUC/MIC) being the pharmacodynamic parameter that best correlates with efficacy [90]. Based on previous results, target AUC/MIC values differ between microorganisms.

Regarding *S. aureus* isolates, several studies have evaluated the pharmacodynamics against ciprofloxacin-susceptible and -resistant strains and compared the efficacy of delafloxacin with that of other fluoroquinolones. Initially, Firsov et al. used an *in vitro* pharmacodynamic model and mimicked several clinical achievable AUC/MIC ratios of delafloxacin and levofloxacin [100]; in this study, delafloxacin showed greater efficacy and prevention of the emergence of resistant strains. Of note, in this work the authors did not consider the protein binding of both drugs and thus acknowledged that the effects of delafloxacin might have been overestimated due to its high protein binding compared with levofloxacin. The pharmacodynamic targets for delafloxacin against *S. aureus* were also determined using the murine neutropenic thigh infection model [96]. Based on the results of this study, the median *f*AUC24/MIC ratios associated with net bacterial stasis and a 1-log10 CFU reduction were 9.3 and 14.3, respectively. Subsequently, two more studies evaluated the pharmacodynamics of delafloxacin in a murine lung model and observed high penetration into the lung compartment [91,101]. In these studies, the *f*AUC24/MIC ratios associated with a stasis effect and 1-log10 CFU reduction ranged from 0.4 to 1.4 for MSSA strains and were higher

for MRSA (24.7 to achieve 1-log CFU reduction). In any case, the authors noted that these *f*AUC24/MIC endpoints were >2-fold lower than those reported for other earlier fluoroquinolones. In the same studies, the authors also evaluated *S. pneumoniae* isolates and observed similar pharmacodynamic values.

Pharmacodynamic studies of delafloxacin have also been carried out against Gram-negative microorganisms, mainly *E. coli*, *K. pneumoniae* and *P. aeruginosa* isolates. Using the murine neutropenic thigh infection model and the murine lung infection model, the AUC/MIC ratio was confirmed as the best pharmacodynamic parameter to correlate with delafloxacin activity. Briefly, the median 24-h *f*AUC/MIC values associated with net stasis and 1-log kill for *E. coli*, *K. pneumoniae,* and *P. aeruginosa* were 14.5 and 26.2, 28.6 and 5.66, and 64.1 and 14.3, respectively [91,101,102].

Finally, population pharmacokinetic models and Monte Carlo simulations have been reported and have helped identify the most appropriate clinical dosages according to the probability of pharmacodynamic target attainment (PTA) [95,96,103,104]. According to the current clinical dosages of delafloxacin, for *S. aureus* isolates with MIC≤0.25 mg/L, the PTA associated with net stasis and a 1-log CFU reduction ranged from 91 to 100%, whereas for isolates with MIC=0.5 mg/L, the PTA was 90 and 86.8%, respectively. Similarly, the simulations for *P. aeruginosa* strains predicted a PTA of 97% for a stasis effect and 86% for a 1-log CFU reduction at MIC values of 1 mg/L.

Clinical efficacy

Delafloxacin is available for clinical use in oral and intravenous formulations. To date, clinical efficacy has been evaluated in phase II and phase III studies among patients with acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, uncomplicated gonorrhea, and surgical site infections.

Acute bacterial skin and skin structure infections (ABSSSI)

The first study was conducted by O'Riordan et al. and evaluated the clinical efficacy of delafloxacin (two different intravenous dosages) in comparison with tigecycline for different types of ABSSSI (cellulitis, wound infections, and abscesses) [105]. The study showed no differences between groups, with all groups achieving clinical cure rates >90%, and provided good results for an intravenous dose of 300 mg of delafloxacin, which was selected for further studies.

The study by Kingsley et al. compared the efficacy of delafloxacin (300 mg IV q12h), vancomycin (15 mg/kg IV q12h), and linezolid (600 mg IV q12h) [106]. Delafloxacin and linezolid achieved similar cure rates, whereas delafloxacin had a higher cure rate than vancomycin, particularly in the group of obese patients. Regarding microbiological eradication, there were no differences between groups; notably, *S. aureus* was the most frequently identified organism (90.9%), of which 67.2% were MRSA.

Two phase III studies were conducted; they included a total of 1,510 patients and compared the efficacy and safety of delafloxacin with vancomycin plus aztreonam. In the first study by Pullman et al. delafloxacin (300 mg IV q12h) demonstrated non-inferiority, achieving a cure rate of 78.2% compared with 80.9% of the comparator arm [107]. Bacterial eradication was similar between groups, and adverse events leading to discontinuation of therapy were lower in the delafloxacin group than in the vancomycin/aztreonam group (0.9% *vs*. 4.3%, respectively). The second study had a similar design but included the oral switch in the delafloxacin dose on day 3 of inclusion (300 mg IV q12h to 450 mg PO q12h), except for those cases with a creatinine clearance of 15-29 mL/min, which received delafloxacin 200 mg IV q12h throughout the entire treatment [108]. Delafloxacin showed non-inferiority to vancomycin/aztreonam (cure rate: 83.7% *vs*. 80.6%, respectively), was well tolerated, and presented a lower rate of discontinuation due to related adverse events than vancomycin/aztreonam (1.2% *vs.* 2.4%, respectively). Overall, when the data from both studies were analysed together, the most prevalent pathogen isolated from the infection site was *S. aureus*, and among all cases of ABSSSI caused by levofloxacin-resistant *S. aureus* (n=81), bacterial eradication was noticed in 80 cases.

Community-acquired bacterial pneumonia (CABP)

One phase III clinical trial was conducted to evaluate the comparative efficacy and safety of delafloxacin and moxifloxacin [109]. In this multicenter, randomized, double-blind trial, both drugs were administered initially intravenously, but the switch to oral treatment was allowed after 6 intravenous doses, and the total duration of treatment was 5-10 days. If MRSA was confirmed while on treatment with moxifloxacin, linezolid therapy was started in a blinded manner. Delafloxacin proved non-inferiority with similar early clinical response compared with moxifloxacin (88.9% *vs.* 89%, respectively), whereas the secondary

efficacy endpoint (early clinical response and improvement in vital signs) favored delafloxacin (52.7% *vs*. 43%, respectively). Of note, delafloxacin achieved better results than moxifloxacin, particularly in the subgroup of patients with chronic obstructive pulmonary disease or asthma.

Uncomplicated gonorrhea

A multicenter, randomized phase III clinical trial compared a single oral dose of delafloxacin (900 mg) with a single intramuscular dose (250 mg) of ceftriaxone in patients with uncomplicated gonorrhea [110]. Delafloxacin did not demonstrate non-inferiority to ceftriaxone, achieving cure rates of 85.1% and 91%, respectively. Failure rates were higher among *N. gonorrhoeae* isolates with delafloxacin MICs ≥0.008 mg/L. Moreover, adverse events related to delafloxacin dose were common, considered as mild in intensity, and mainly were gastrointestinal symptoms.

Surgical site infections

One recent phase III clinical trial evaluated the efficacy of delafloxacin compared with the best available therapy for the treatment of surgical site infections following a cardiothoracic or abdominal procedure [111]. Patients were randomized 1:1 to receive delafloxacin 300 mg IV q12h/450 mg PO q12h or the comparator (vancomycin or linezolid, and piperacillin/tazobactam or tigecycline for cardiothoracic and abdominal surgical site infections, respectively). Due to the COVID-19 pandemic, the study finally included only 266 patients, most of them with abdominal post-surgical infections (n=246), therefore the group of cardiothoracic infections was not well represented. Delafloxacin demonstrated non-inferiority to the comparators (clinical success 91.8% *vs.* 90.2%, respectively), and microbiological response was also comparable between the treatment groups. Whereas the eligibility for switching to the oral formulation was slightly in favor of delafloxacin, time to discharge was comparable between the two treatment arms.

Safety

The main adverse events reported of delafloxacin to date derive from clinical trials; most were considered mild to moderate in intensity, and the most frequent were gastrointestinal disorders (diarrhea and vomiting, around 8%) and headache [9,90,112,113]. Particularly, *Clostridioides difficile* infection has been reported in less than 1% in previous studies, this being like in the comparator arms. Among hepatic toxicity, the most frequent event reported is the transaminase increase; particularly, in the study by Horcajada et al. transaminase values up to 5-fold the upper limit of normal were observed in 1.4% of patients in the delafloxacin group [109].

Some class-related adverse events of fluoroquinolones have been particularly evaluated for delafloxacin. Phototoxicity was examined in a phase I study with healthy volunteers, in which delafloxacin showed results similar to placebo with no evidence of toxicity [114]. In addition, cardiac toxicity was assessed by evaluating QT interval prolongation; in this phase I study, delafloxacin did not induce significant QT interval modifications at therapeutic and supratherapeutic doses (300 mg-900 mg), whereas moxifloxacin showed significant changes compared with placebo [115].

Other adverse events related to fluoroquinolones, such as peripheral or central neuropathy and tendinopathies, have been reported at very low frequency in previous clinical trials. In particular, seizures occurred in one patient with a previous history of seizure disorder in the study by O'Riordan et al., and it was considered possibly related to delafloxacin [105].

Overall, delafloxacin has been well tolerated in all clinical trials, and the rate of adverse events did not differ from that of the comparators. As with other new antibiotics, additional information from a wider use of drugs in clinical practice is always needed, since safety data is initially limited due to the small number of healthy volunteers and patients recruited from trials, in which there are several exclusion criteria that limit the generalizability of the results to many real-world situations.

Place in clinical practice: potential benefits and limitations

Delafloxacin has been approved for the treatment of ABSSSI and CABP, and has also demonstrated efficacy against surgical site infections after abdominal surgeries. In the case of ABSSSI, notable advantages include the possibility of intravenous-oral switch during the treatment, its low profile of adverse events, and its activity against most of the Gram-positive microorganisms involved, including MRSA and other pathogens resistant to previous fluoroquinolones. Indeed, there are currently several therapeutic options for ABSSSI, including new drugs, so it will be important to evaluate which alternative is the most suitable for each patient based on the spectrum of activity (broad *versus* narrow), the possibility of adverse effects and drug-drug interactions, and treatment adherence. Another approved indication of delafloxacin is CABP, for which delafloxacin also exhibits an appropriate *in*

vitro spectrum of activity. In the same line, other respiratory tract infections could potentially be treated adequately with delafloxacin.

A potential and relevant advantage of delafloxacin is its activity in acidic local environments and biofilms. In this regard, delafloxacin appears to be a promising therapy for infections not only in some anatomical sites, such as urinary and respiratory tracts, but also in the presence of abscesses and intracellular bacteria. In addition, delafloxacin could play a role in the treatment of biofilm-related infections, such as osteoarticular infections and medical device-associated infections, in which effective therapies against persistent cells, intracellular, and biofilm-embedded bacteria are still needed. In this scenario, it should be of particular interest to study in depth the diffusion of delafloxacin into the bone tissue, and the potential benefits with the delafloxacin and rifampicin combination since staphylococcal infections are common and difficult to cure.

In relation to its broad coverage spectrum and the existence of intravenous and oral formulations, delafloxacin could be used for the treatment of polymicrobial infections, and may also be useful to complete an entire treatment course and facilitate early hospital discharge with oral therapy. In this regard, the activity of delafloxacin against levofloxacin-resistant isolates of methicillin-susceptible and -resistant staphylococci, as well as other fluoroquinolone-resistant Gram-negative bacilli, including *P. aeruginosa*, is of particular interest. While it is always necessary to determine the susceptibility to delafloxacin of these isolates resistant to previous fluoroquinolones, it may provide an additional chance to use quinolones in scenarios where they have proven benefits, such as osteoarticular and biofilm-associated infections [116,117].

The low profile of drug-drug interactions places delafloxacin favorably in the growing and common scenario of polypharmacy among patients. Delafloxacin demonstrated mild induction of cytochrome P450 isoenzymes *in vitro*, and it did not affect the C_{max} and AUC values for midazolam (a sensitive CYP3A4 substrate) when administered to healthy volunteers [99]. Finally, delafloxacin can also be an alternative therapy for patients with relevant drug allergies, such as those allergic to β-lactams.

Regarding the limitations of the current use of delafloxacin, they are mainly related to the approved indications derived from clinical trials, and therefore further clinical information from a wider use in other types of infections is needed. Furthermore, while delafloxacin can regain activity against Gram-positive and Gram-negative microorganisms resistant to previous fluoroquinolones, it is always advisable not to generalize its use as an empirical treatment in clinical situations with a high risk of multidrug-resistant bacteria as causative agents.

Future research and conclusions

Based on the distinctive properties of delafloxacin described so far, it seems of great interest to delineate further research that may allow clinicians to consider its use in other scenarios. Studies focusing on the diffusion of delafloxacin in specific tissues are needed, such as bone or prostatic tissues. Particularly, bone and joint infections, including prosthetic joint infections and osteosynthesis-associated infections, are a good niche for the use of delafloxacin, and therefore, data on its diffusion to bone tissue would be of potential relevance. Considering the main role of rifampicin against staphylococcal osteoarticular infections, it would be of great interest to study the combination of delafloxacin with rifampicin in terms of synergistic activity, lack of relevant drug-drug interaction, and appropriate tolerance in patients. Beyond this combination therapy, information on the effects of delafloxacin with other antibiotics would also be welcome, such as the combination with new beta-lactams and β-lactam/β-lactamase inhibitor associations.

In line with the recent growing interest in the human microbiome and the impact of antibiotic use, it seems appropriate to address future research with delafloxacin on this topic. Particularly, it would be desirable to study the impact of delafloxacin on the gut microbiota and the risk of *C. difficile* disease, especially considering what the outcome may be since delafloxacin is excreted unchanged in the feces in a non-negligible proportion, and that it has intrinsic activity against this species.

According to the concentration-dependent killing characteristic of fluoroquinolones, the use of high doses provides higher efficacy in some scenarios of difficult-to-treat microorganisms or infections. As an example, while the daily dosage of levofloxacin and ciprofloxacin may range from 500 mg to 1,000 mg, or 500 mg to 1,500-2,000 mg, respectively, there are no data on the use of delafloxacin at doses higher than those currently approved and during prolonged treatments. Information in this regard would be of great interest for the appropriate management of delafloxacin in difficult-to-treat scenarios according to the efficacy obtained, the safety for patients, and the protection against the emergence of resistant

strains. The latter appears to be crucial in some clinical situations, such as those caused by microorganisms resistant to the previous fluoroquinolones but still susceptible to delafloxacin. In this case, the isolates usually have relevant mutations in the quinolone targets, and this may lead to a narrower margin of protection against new mutations that could cause resistance to delafloxacin. However, the dual targeting activity and the demonstration of increased potency of delafloxacin at acidic pH may have an advantage in this regard, since delafloxacin levels will remain far above the actual mutant prevention concentration at the low-pH site, further impeding the selection of resistant mutants [24]. In a preliminary mouse renal abscess model, delafloxacin reduced bacterial load in abscesses with reduced pH [118]. This experimental model opens a new path for investigating delafloxacin's ability to reduce the emergence of drug-resistant mutants *in vivo*, and warrants further investigation for the potential treatment of drug-resistant infections.

It is noteworthy that when delafloxacin-resistant mutants are selected, a considerable fitness cost is observed, but resistance can also emerge through different mechanisms often acting in combination. In this regard, overexpression of efflux systems is a significant resistance mechanism, reducing intracellular drug concentrations and often acting synergistically with target site mutations, substantially increasing the risk of therapeutic failure. In addition, gene amplification can lead to rapid evolution of resistance against many classes of antibiotics, including those that have multiple targets in the cell. Future studies of combinatorial mutagenesis, genome-wide screens, and whole-genome sequencing may thus be critical for providing more comprehensive predictions of delafloxacin resistance.

In conclusion, delafloxacin is a novel anionic fluoroquinolone with unique properties. Its chemical structure, different from that of other quinolones, gives it distinct physicochemical characteristics, being active in both acidic and neutral environments, and showing a dual-targeted equipotent inhibition of the essential bacterial enzymes DNA gyrase and topoisomerase IV. As a consequence of dual targeting, delafloxacin shows a low risk of the emergence of resistance and potent *in vitro* activity against a broad spectrum of Gram-negative bacteria, including several fluoroquinolone-resistant isolates. Compared to levofloxacin and moxifloxacin, it shows increased efficiency against Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus*. Its increased antibacterial efficacy under acidic environments is an important potential advantage for the treatment of infections in acidic anatomic sites such as the urinary tract, skin, soft tissue, abscesses, and respiratory tract, but also in phagolysosomes, abscesses, and biofilm-related infections.

Currently, delafloxacin has been approved for the treatment of ABSSSI and community-acquired bacterial pneumonia based on the results from phase II and III clinical trials, in which delafloxacin showed non-inferiority compared to the standard-of-care therapy. Additionally, delafloxacin has been shown to be effective against surgical site infections after abdominal surgery, opening the possibility for its use in a new indication. The broad coverage spectrum and the existence of intravenous and oral formulations are also interesting aspects for its clinical use. Finally, delafloxacin appears to have a low profile of drug-drug interactions, and to date, it has been shown to be safe in all clinical trials with a rate of adverse effects similar to that of the comparators; however, it would always be desirable to continue accumulating more data on this topic through wider use of delafloxacin in clinical practice. Overall, the promising experimental and clinical data detailed here suggest an additional and interesting drug for the current pipeline against common and difficult-to-treat infections.

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Conflict of interest

E.C. and O.M. have received spoken support on behalf of Menarini.

AI statement

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