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REVIEW ARTICLE

Community-Acquired Bacterial Pneumonia—Changing Epidemiology, Resistance Patterns, and Newer Antibiotics: Spotlight on Delafloxacin

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Abstract

Community-acquired pneumonia (CAP) is a major cause of morbidity and mortality both in the USA and globally. As the burden of CAP continues to increase due to several factors, the advances in its diagnosis, prevention, and treatment have taken on even greater interest and importance. The majority of CAP patients are treated empirically, and selection of appropriate antibiotic treatment is increasingly difficult because the epidemiology of CAP is changing, in part due to antimicrobial resistance, and the causative CAP pathogens differ between countries and regions. There is also an increasing prevalence of chronic co-morbid diseases among CAP patients. Treatment of CAP has become challenging because of these factors along with the varying safety profiles and efficacy of well-established antibiotics, as well as limited new therapeutic options. Recently, however, new antibiotics have been approved, which will expand the treatment options for CAP, particularly in those patients with underlying complications. Recently approved delafloxacin, an anionic fluoroquinolone, has a unique structure and distinct chemical characteristics; it demonstrated non-inferiority to moxifloxacin in a phase III clinical trial, but was shown to be superior to moxifloxacin at early clinical response in CAP patients who also have chronic obstructive pulmonary disease (COPD) or asthma as a co-morbidity, and in CAP patients who may have severe illness. Delafloxacin could offer an additional therapy against resistant isolates and among these difficult-to-treat patients. This review summarizes the development, latest research, and safety profile of the new antibiotic delafloxacin, and its potential future role in the treatment of CAP.

Key Points

Community-acquired pneumonia (CAP) is a major global health concern, accountable for considerable morbidity and mortality.

Changing etiology and increasing antimicrobial resistance have made CAP more challenging to treat empirically, particularly among patients with chronic co-morbid diseases.

Delafloxacin, a novel anionic fluoroquinolone, has demonstrated superior efficacy in CAP patients with COPD, asthma, and severe CAP, compared to moxifloxacin.

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1 Introduction

The fluoroquinolones (FQs) were introduced into clinical practice in the late 1980s. Ciprofloxacin was the first broadly used class member mainly due to its Gram-negative spectrum and its parenteral and oral administration. It was initially used in serious hospital infections but its utility spread into the community for treatment of pneumonia. However, its activity against *Streptococcus pneumoniae* precluded it being widely used in this infection. Subsequent class members such as levofloxacin and moxifloxacin were more active against *S. pneumoniae* and achieved more widespread use, especially levofloxacin. However, the class has been blighted with an array of safety issues including cardiotoxicity, phototoxicity, and CNS events. It is noteworthy that not all class members have the same spectrum of activity nor adverse event profile.

Delafloxacin, a recently approved anionic FQ, has a unique structure and possesses distinct chemical characteristics. As an anionic FQ, delafloxacin has increased intracellular penetration in bacteria allowing for enhanced bactericidal activity in acidic conditions [1]. Delafloxacin is has broad spectrum of activity against Gram-positive

pathogens, including *Staphylococcus aureus*, *S. pneumonia*, and most fluoroquinolone-resistant strains, except enterococci [2, 3].

Approved for use in adults for the treatment of community-acquired pneumonia (CAP) [4], delafloxacin was shown in a phase III clinical trial to be superior to moxifloxacin in patients with CAP who also have chronic obstructive pulmonary disease (COPD) or asthma as a co-morbidity, and in CAP patients who may have severe illness [5]. Additionally, delafloxacin appeared to be better tolerated compared to commonly used FQs; clinical data are limited, but showed a lack of corrected QT-interval (QTc) prolongation, phototoxicity, and major central nervous system (CNS) events [4, 6].

CAP is defined as an acute infection of the lower respiratory tract in a patient who has acquired the infection in the community and is without any associated healthcare contact [7–9]. Globally, CAP is a leading cause of hospitalization and death, presenting a significant health problem that is responsible for a substantial clinical and economic burden [10–16]. Globally, pneumonia is responsible for over 3 million deaths each year, surpassing all other infectious causes, including tuberculosis, malaria, and human immunodeficiency virus (HIV) infection [17]. Contributing to the escalating disease burden of CAP are antimicrobial resistance, a growing aging population, and increasing prevalence of co-morbidities.

Common antimicrobials used to treat CAP include macrolides (alone or in combination with β-lactams), amoxicillin (alone or in combination with a macrolide), fluoroquinolones, and third-generation cephalosporins combined with a macrolide [9, 18, 19]. Antimicrobial resistance is a global health threat that continues to develop and has contributed to the changing epidemiology of community-acquired bacterial pneumonia (CABP) [10, 20, 21], as well as rendering commonly used treatments ineffective. The etiology of CAP differs between countries and over time, but *S. pneumoniae* remains the most common causative bacterial pathogen regardless of setting, age, or co-morbidities [22, 23]. Additional causative pathogens include *Haemophilus influenza, S. aureus*, and the atypical pathogens *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*. Gram-negative pathogens such as *Klebsiella pneumoniae* cause a smaller proportion of CAP cases; however, their associated antibiotic resistance, especially multidrug resistance (MDR), extensive drug resistance (XDR), and pan drug resistance (PDR), make clinical management a challenge [24]. Atypical respiratory bacteria such as *M. pneumoniae* and *C. pneumoniae* have been isolated more frequently than before in recent studies and it has been hypothesized that these bacteria could supersede *S. pneumoniae* as the leading bacterial cause of CAP [15, 25–27]. Antimicrobial resistance to macrolides and other agents typically used to treat CAP has become increasing prevalent among *S. pneumoniae* and atypical pathogens such as *Mycoplasma pneumoniae* [7, 28].

While bacteria are the most common cause of CAP, advances in molecular diagnostics have shown a growing prevalence of respiratory viruses in CAP, especially in the USA [10, 29]. Their role as a sole causative agent for CAP, or as a factor in co-infection, suggests that viral pathogens may increase the risk of morbidity, as well as increase the risk of antibiotic failure [29]. Importantly, in two recent studies on CAP, one from the USA and one from Norway, two or more pathogens were identified in more than one-third of cases, typically a virus/bacteria combination [10, 30].

There is a significant need for the development of new antibiotics to treat CAP [31], which is driven by increasing macrolide resistance among the bacterial pathogens that cause CAP, and a lack of newly developed oral antimicrobial therapies [7]. The use of current macrolides has also been limited due to concerns over cardiac and gastrointestinal adverse events [7]. The FQs remain a treatment option for CAP; however, they do vary in their tolerability and safety profiles.

This article reviews CAP epidemiology and global resistance trends among CAP pathogens, CAP treatment guidelines, details the clinical development of delafloxacin, and describes the potential role for delafloxacin in treating CAP, focusing on populations with specific vulnerable co-morbidities.

2 Global and Regional Burden of Community-Acquired Pneumonia (CAP)

Worldwide, CAP affects 3–4 million people each year with high morbidity and mortality, particularly among elderly patients [32]. The WHO Global Burden of Disease study reported that lower respiratory tract infections (LRTIs), including CAP, cause approximately 429.2 million episodes of illness globally. The Global Point Prevalence Survey (Global-PPS) reported that worldwide pneumonia was the illness that antibiotics were most commonly prescribed for, accounting for 19% of all patients treated [33].

In the USA, CAP is the most common infectious cause of death, overall it is the eighth leading cause of death, accounting for more than 53,000 deaths per year [34], with approximately 85% of all pneumonia and influenza deaths occurring within the elderly (≥ 65 years old) population. A recent study estimated that in the USA, more than 1.5 million adult patients are hospitalized each year with CAP, and of these patients, 10,000 will die during hospitalization [21]. In the USA, the annual CAP incidence rate is estimated at 248 cases per 10,000 adults

[10]. In three Asian countries, a recent study reported that CAP is accountable for 1424.5, 420.5, and 98.8 episodes per 10,000 discharges in the Philippines, Indonesia, and Malaysia, respectively [35]. In India CAP accounts for 4 million cases annually, with 20% requiring hospitalization [36]. CAP hospital admissions in Vietnam are 8.1 per 10,000 adults [37], and in the UK 31.2 per 10,000 adults [38], but have risen in certain areas of the UK during the last 16 years [39]. In South Africa, in people age ≥ 15 years, the incidence of LRTI is estimated at 400 per 100,000 population, with the highest incidence in individuals aged 25–64 years, which is likely due to the high prevalence of HIV in this population [40]. In developing countries, pneumonia is the most common cause of emergency department (ED) visits and hospitalization [41]. Differences in the incidence of CAP between countries can reflect differences in study methods, case definitions, as well as healthcare systems, prevalence of co-morbidities and chronic disease, and population age [15].

The elderly are disproportionately affected by CAP, age > 65 years is one of the greatest risks of CAP-related morbidity and mortality [42], and older CAP patients have poorer health outcomes, higher rates of hospitalization, and longer length of hospital stay.

Jain et al. [10] reported that in the USA, the incidence of pneumonia increases with increased age; this has also been reported in Europe and South Africa [43]. The mortality rate of CAP is significantly higher in the elderly and immunocompromised, and can reach 20–40%, compared to 6–10% for the general population [44, 45].

Worldwide, the proportion of the population that is ≥ 65 years old is expected to increase in the coming years, and as this occurs the number of adult patients with CAP will also increase. The US population of those aged ≥ 65 years has increased by 33% since 2006, from 37.2 to 49.2 million in 2016 [46]. By 2040, individuals aged ≥ 65 years will represent 21.7% of the entire US population, and by 2060, this group is projected to more than double to 98 million [46]. In Europe, 25% of the population is over 60 years old and this is anticipated to reach 35% by 2050 [47]. Mortality rates for CAP vary widely depending on country and demographics; in Europe this ranges from < 1–48% [15], in the Philippines 2.5% [48], and 61% in Singapore [49], and stark differences in mortality rates were reported in a UK study where in patients aged < 65 years the mortality rate was 6% compared to 47% among patients aged > 85 years [15]. In Latin America adults ≥ 75 years account for > 50% of hospitalizations and almost 70% of deaths, even though they only represent 13% of the adults > 50 years of age [16]. This increased mortality with increased age trend is also observed in the USA, Portugal, Finland, and Asia [16]. Additionally, higher rates of multidrug-resistant pathogens are seen in people over 65 years due to their more frequent exposure to the healthcare system and cumulative exposure to previous antibiotics [50].

The combination of two factors are anticipated to impact CAP-related morbidity and mortality: the growing elderly population and the increasing incidence of co-morbidities among this population. Chronic co-morbidities are another risk factor for CAP. An increased risk of CAP is associated with a variety of medical conditions, including, but not limited to, chronic respiratory illness (e.g., chronic obstructive pulmonary disease (COPD), asthma), cardiovascular diseases, congestive heart failure (CHF), diabetes mellitus, chronic renal or liver disease, and cerebrovascular disease, which are all associated with poorer health outcomes in CAP, including increased morbidity, mortality, and excess costs [51].

Among elderly and co-morbid patients polypharmacy is commonly encountered, and medication side effects and drug–drug interactions can impact which antibiotics can be administered or how well they are tolerated [52].

Patients with these co-morbidities have a higher risk for CAP, which also increases the risk for complications and mortality during or following a CAP episode [53]. Higher rates of these co-morbidities are evident across the globe. For example, a recent US study of 2320 adult patients hospitalized with CAP found that more than one-third (35%) had co-morbid chronic heart disease. A European study assessing medical risk factors CAP in adults analyzed 40 studies and reported up to 47% of CAP patients had chronic heart disease, up to 46% had heart failure, and up to 33% had diabetes mellitus [42]. Empiric treatment of CAP is increasingly more challenging in patients aged > 65 years and/or those with co-morbidities because treatment options are limited.

3 Antimicrobial Resistance

Worldwide, increasing antimicrobial resistance remains a major problem with important implications for the treatment of CAP [7]. Increasing prevalence of resistant pathogens in CAP infections has been reported, especially in severe cases [54]. However, differences exist in prevalent pathogen and resistance rates between countries and regions throughout the world.

Globally, *S. pneumoniae* continues to be the most common bacterial CAP pathogen, but incidence rates vary per country, and have also been impacted by the introduction of the polysaccharide vaccines (e.g., PCV7 and PCV13) [10]. The incidence of *S. pneumoniae* in the USA and Canada has decreased in recent years, in part because of higher vaccination rates and a decrease in the rate of smoking [55]; in the USA, approximately 10–15% of CAP cases are caused by *S.*

pneumoniae [10]. However, this decrease has not been seen in Europe [22, 56–58], where *S. pneumoniae* is responsible for approximately 30% of the CAP cases [59]. In South Korea, 26.9–69.4% of CAP cases are caused by *S. pneumoniae* [60]. In the Asia Pacific region, *S. pneumoniae* is still the major bacterial pathogen causing CAP infections, but unique to this region is the higher incidence of *K. pneumoniae* and the presence of *Burkholderia pseudomallei* [14].

Causing approximately 15% of CAP, atypical pneumonias are not the most frequent; however, they have become increasingly important because it is difficult to differentiate between typical and atypical infections based on clinical features alone [61], and they are often non-responsive to recommended beta-lactam therapy [41, 62, 63].

The SENTRY Antimicrobial Surveillance Program reported global *S. pneumoniae* penicillin-susceptibility (≤0.06 mg/L) rates ranged from 55.6% in the Asia Pacific (APAC) to 71.8% in Europe in 2015–2016 (65.8% overall). The improvement from 2014 to 2016 in this susceptibility is potentially related to the introduction and widespread immunization with PCV13 [64]. Only 1.2–19% of bacterial CAP cases are caused by *H. influenza*; however, some studies have reported this has increased to around 50% [65].

Macrolides, specifically azithromycin, FQs in particular levofloxacin, amoxicillin-clavulanic acid, and third-generation cephalosporins, are the most frequently used antimicrobials for treating CAP. Widespread use of macrolides has contributed to the expansion of macrolide-resistant *S. pneumoniae*. Pneumococci and atypical pathogens of CAP have become increasingly resistant to these drugs [66].

The Center for Disease Dynamics, Economic and Policy resistance mapping demonstrates the geographic differences in the resistance rates of *S. pneumoniae* to macrolides in tested isolates: 94% in China (2017), 91% in Vietnam (2016), 34% in the USA (2012), 32% in India (2015), 23% in France (2017), 16% in Argentina (2017), and 7% in Germany (2017) [67].

S. pneumoniae has shown increasing resistance to penicillin, macrolides, and many cephalosporins, including ceftriaxone [68]. In pneumococci, two mechanisms of macrolide resistance have been reported. The efflux of the drug from the bacteria, conferring a low level of macrolide resistance, occurs most frequently in North America. Alterations at the level of the ribosomal target of antimicrobial action, which confers a high level of macrolide resistance, is the most common resistance mechanism seen in Europe, and will lead to macrolide treatment failure [69].

In the USA, the prevalence of high-level (≥25%) macrolide-resistant *S. pneumoniae* is over 30% and the overall prevalence of macrolide-resistant *S. pneumoniae* (high-level and low-level) is close to 50% [70]. There are also data suggesting that treatment failure, even in the presence of low-level macrolide resistance, may be more likely with macrolide monotherapy [71, 72].

FQ activity against *S. pneumoniae* is still very high; Europe has the highest rate of fluoroquinolone resistance at 5.2% compared to 1.2% in the USA and 2.4% in Asia [40–43, 69, 73]. Adults aged >64 years and those with COPD have higher rates of fluoroquinolone resistance [74].

Bacteria have been reported to be resistant to one or more clinically relevant antibiotics in approximately one-third of *S. pneumoniae* cases [70]. Macrolide resistance has not been limited to just pneumococcus [7, 75]—it is also evident among other CAP-causing bacterial pathogens, including *Mycoplasma pneumoniae* [76, 77].

Multidrug-resistant (MDR) pathogens, including methicillin-resistant *S. aureus* (MRSA), *P. aeruginosa*, *K. pneumoniae*, and *A. baumannii*, cause a small proportion (6%) of CAP infections, but are increasingly challenging to manage [54]. The SENTRY Antimicrobial Surveillance Program reported the incidence of MDR and XDR *S. pneumoniae* isolates from 2015–2016 was highest in the APAC (49.8% and 17.3% overall, respectively) and lowest in Latin America (10.8% and 1.9% overall, respectively). MDR rates were similar in North America, Europe, and Latin America (17.23–20.9%), but in the APAC region were a lot higher (39.2%) [64].

In a study ending in quarter 3 of 2019, 3,510 patients were cultured to determine the prevalence and rates of macrolide resistance in *S. pneumoniae* from the ambulatory and inpatient setting at 329 hospitals across nine US Census geographic regions [78]. Macrolide resistance was observed in 47.3% of *S. pneumoniae* obtained from respiratory cultures, and 29.6% from blood cultures. Higher rates of macrolide resistance were seen among ambulatory patients (45.3%) as compared with inpatients (37.8%). The overall rate of macrolide resistance was 39.5%; regional variation occurred, ranging from 13.9% in the mountain region to 54.2% in the West North Central region. These data demonstrate the importance of local epidemiology data to guide the choice of empiric therapy for patients with CABP.

4 Current Treatment Guidelines

Guidelines for the treatment and management of CAP are published by individual countries and professional societies, thus recommended first-line treatment recommendations can vary by region. The American Thoracic Society (ATS/Infectious Diseases Society of America (IDSA) guidelines [9] are often cited; however the British, Canadian [79], Spanish [80], Dutch [81], Chinese [82], and Japanese [83] guidelines are also widely used [84]. Differences in healthcare systems, payment processes, health policies, and purpose inform each

set of CAP treatment guidelines; some were developed as a tool for less experience clinicians while others such as the ATS/IDSA guidelines have progressed to include third-party payer rules and public reporting measures, which influences priorities and methods [9, 85–87].

Since 2013, little has changed in terms of treatment guidelines, however, in reality there is an increased recognition of pneumonia as a multisystem problem with adverse chronic health consequences, rather than solely an acute lung disease [9, 84].

Updated IDSA/ATS guidelines for the management of CAP recommends amoxicillin or doxycycline for first-line empiric treatment of outpatients with no comorbidities or risk factors for drug-resistant *S. pneumoniae* (DRSP), and suggest macrolide use only in areas where *S. pneumoniae* macrolide resistance is 25% [7]. In patients with co-morbidities such as COPD, diabetes, or renal disease, monotherapy with a respiratory FQ (levofloxacin or moxifloxacin) or combination therapy with a beta-lactam (e.g., amoxicillin-clavulanate) plus a macrolide is recommended, or for those with immunosuppressing conditions/taking immunosuppressing drugs; patients who used antimicrobials within the previous 3 months, or those who have other risks for DRSP infection [9]. Data from randomized controlled studies have demonstrated a relatively moderate reduction in treatment failure, adverse events, and treatment discontinuation with FQs compared with combination beta-lactam and macrolide antibiotics [88, 89].

Recently, there has been a shift in the concept of pneumonia, including CAP, from being just an acute lung disease to recognizing both the acute and the long-term cardiac complications and approaching it as a multisystem problem with adverse chronic health consequences [84]. Evidence on optimal CAP treatment has shifted, diagnostic methods are changing, and the causative pathogens are evolving, which inform what the optimal bundle of therapies contains.

5 New Therapeutic Options

Common bacterial pathogens associated with CAP continue to develop antibiotic resistance, especially staphylococci and *S. pneumoniae*, making empiric treatment increasingly difficult. Failure of initial empiric therapy for CAP is associated with worse clinical outcomes [90]. To improve the outcomes of initial empiric therapy in CAP, there is a clinical need for effective antimicrobial therapies that are active against a spectrum of CAP etiologies, especially resistant pathogens [54]. New antimicrobial agents provide an opportunity to enhance empiric treatment of resistant CAP pathogens.

Omadacycline, an aminomethylcycline, was recently approved for CABP as well as acute bacterial skin and skin-structure infections. Omadacycline has a spectrum of activity that includes methicillin-resistant MRSA, various resistant phenotypes of *S. pneumoniae*, as well as a range of Gram-negative and atypical pathogens [91]. For use in CABP treatment, omadacycline requires an intravenous (IV) loading dose prior to oral administration treatment. The OPTIC study [92] demonstrated omadacycline to be non-inferior to moxifloxacin but no benefit was observed in specific sub-groups such as COPD and asthma or diabetes, both of which are risk factors for poor outcomes. The safety of omadacycline was similar to older tetracyclines, with gastrointestinal events most frequently reported; nausea and vomiting were reported at incidences of 14.9% and 8.3%, respectively. However, these events did not lead to discontinuation of therapy. Although no QTc prolongation was observed, minor elevation in liver enzymes was seen but was similar to other tetracyclines [93]. In this trial there was an imbalance in mortality: eight deaths in the omadacycline group as compared with four in the moxifloxacin group. The reasons for this imbalance were not clear, but higher mortality was seen in patients with Pneumonia Severity Index risk class of IV [92, 93].

Lefamulin, a pleuromutilin antibiotic, is active against pathogens commonly causing CABP. In the LEAP double-blind study [94], adults with CABP of Pneumonia Outcomes Research Team (PORT) risk class ≥ III were randomized 1:1 to receive lefamulin 150 mg IV every 12 h or moxifloxacin 400 mg IV every 24 h. 551 patients were randomized ($n = 276$ lefamulin; $n = 275$ moxifloxacin), with lefamulin shown to be noninferior to moxifloxacin for Early Clinical Response (87.3% vs. 90.2%; difference −2.9% [95% confidence interval −8.5, 2.8]). Rates of study drug discontinuation due to treatment-emergent adverse events were 2.9% for lefamulin and 4.4% for moxifloxacin. Lefamulin showed a similar adverse event profile to that of moxifloxacin, including minor changes in QTc prolongation [94]. In August of 2019, lefamulin was approved by the US Food and Drug Administration (FDA) [95, 96].

Ceftaroline is a novel fifth-generation cephalosporin with bactericidal activity against most CAP pathogens, including *S. pneumoniae*, as well as multiple strains of resistant *S. pneumoniae* with enhanced activity towards penicillin-resistant *S. pneumoniae* [97]. Ceftaroline versus ceftriaxone was evaluated for treatment of CAP in two phase III randomized, double-blind, multicenter trials: Ceftaroline Community Acquired Pneumonia Trial versus Ceftriaxone in Hospitalized Patients (FOCUS) 1 and FOCUS 2 [98].

PORT risk class III or IV CAP patients were randomized by PORT class to either ceftaroline 600 mg IV every 12 h or ceftriaxone 1 g IV every 24 h for 5–7 days; this was the active comparator in both trials. To enable enrollment in North America, where adjunctive macrolide therapy is recommended, patients in FOCUS 1 received two doses of oral clarithromycin 500 mg every 12 h, but this was limited to day

1 only to minimize potential confounding of study drug treatment effect. In total, 591 and 562 patients were evaluated in the microbiological intent-to-treat (MITTE) populations for FOCUS 1 and FOCUS 2, respectively.

Within the integrated analysis of the CE and MITTE, the clinical cure rates were 6.7% (95% CI 1.6–11.8) and 6.0% (95% CI 1.4–10.7) higher for ceftaroline than for ceftriaxone in the CE and MITTE populations. The integrated clinical cure rate in the ME and mMITTE populations for ceftaroline were 85.1% (131 of 154 patients) and 83.6% (138 of 165 patients), respectively, compared with 75.5% (111 of 147 patients) and 75.0% (126 of 168 patients), respectively, for ceftriaxone. The only treatment-emergent AE considered related to the study drug was diarrhea, which occurred in > 3% of patients—3.1% with ceftaroline and 1.5% with ceftriaxone. Similar rates of serious adverse events occurred in the ceftaroline (11.3%) group and the ceftriaxone group (11.7%). Development of a QT interval occurred in a similar number of patients (six in the ceftaroline group and five in the ceftriaxone group). The results of these clinical trials demonstrated ceftaroline is efficacious, well tolerated, and is comparable to ceftriaxone for treatment of CAP [98].

MRSA is less common as a pathogen in out-patient CAP, < 5%, but in CAP patients who are hospitalized the incidence can rise to > 20% [99]. If MRSA is suspected in the admitted patient, ceftaroline may be a good option.

6 Delafloxacin

Delafloxacin is approved for use for treatment of CABP caused by *S. pneumoniae*, *S. aureus* (methicillin-susceptible [MSSA] isolates only), *K. pneumoniae, Escherichia coli, Pseudomonas aeruginosa*, *H. influenzae, Haemophilus parainfluenzae, C. pneumoniae, Legionella pneumophila*, and *M. pneumoniae* [4].

Delafloxacin, an anionic FQ, has a unique structure and possesses distinct chemical characteristics. Delafloxacin is an anionic FQ, which means that it has increased intracellular penetration in bacteria allowing for enhanced bactericidal activity in acidic conditions [1]. The increased potency in low pH is a special feature of delafloxacin as many infection sites such as the urinary tract, abscess fluid, decubitus ulcers, epithelial lining fluid, and phagolysosomes of infected cells have an acidic environment [100].

This is accompanied by increased activity against both extra- and intracellular pathogens, in particular *S. aureus*, and contrasts what has been observed for other agents (FQs, macrolides, aminoglycosides), which lose antibacterial potency under acidic conditions [100]. The increased intracellular accumulation of delafloxacin significantly decreased the MIC by four to five doubling dilutions. Delafloxacin has a broad spectrum that covers Gram-positive, Gram-negative, and atypical organisms [100]. Delafloxacin is currently the only oral antibiotic with in vitro activity against both MRSA and *P. aeruginosa*. In phase III studies delafloxacin exhibited a 64-fold lower MIC_{50} for MRSA isolates compared to levofloxacin and retained activity against levofloxacin non-susceptible isolates. This is thought to be influenced by delafloxacin's enhanced activity in acidic environments relative to other FQs [100].

A study [101] evaluating the activity of delafloxacin against bacterial surveillance isolates collected in the USA and Europe from 2014 to 2016 demonstrated that against *S. pneumoniae* using $MIC_{50/90}$, delafloxacin had lower MICs (0.015/0.03 mg/L) compared to tigecycline (0.03/0.06 mg/L). Considering activity against Gram-positive bacteria such as *S. pneumoniae,* levofloxacin's MIC (MIC_{90}) was 0.25 whereas delafloxacin was much lower with an MIC of 0.015. Delafloxacin has been shown to have an MIC_{90} at least eightfold more active than levofloxacin against MRSA isolates [101]. Delafloxacin has good activity against Gram-negative organisms that are susceptible to other FQs.

Using IV and oral delafloxacin pharmacokinetic–pharmacodynamic target attainment analyses were undertaken. Parameter estimates from a population pharmacokinetic model (three compartments; mixed linear plus saturable elimination; two parallel first-order absorption processes; creatinine clearance (CL_{cr}) was a predictor of clearance), free-drug plasma concentration–time profiles were generated for 5000 simulated patients with varying CL_{cr} following delafloxacin 300 mg IV every 12 h for 3 days followed by 450 mg orally every 12 h for 2 days.

Areas under the concentration–time curve up to 24 h ($AUC_{0–24}$) on days 1 and 4 were calculated. Percent probabilities of pharmacokinetic–pharmacodynamic target attainment by MIC and overall (i.e., weighted over the MIC distributions for *S. pneumoniae* from USA and Europe) were determined using median free-drug plasma AUC:MIC ratio targets associated with 1- and 2-log10 CFU reductions from baseline from a neutropenic lung infection model for *S. pneumoniae* (3.36 and 24.5, respectively). The results were stratified by renal function group [normal ($CL_{cr} \geq 90$ mL/min/1.73 m^2) and mild (CL_{cr} 60–89 mL/min/1.73 m^2) or moderate (CL_{cr} 30–59 mL/min/1.73 m^2) renal impairment]. Percent probabilities of attaining free-drug plasma AUC:MIC ratio targets associated with a 1-log10 CFU reduction from baseline by MIC on day 1 by renal group for *S. pneumoniae* (Fig. 1) were similar to those on day 4. Percent probabilities of pharmacokinetic–pharmacodynamic target attainment on either day across renal groups were ≥ 99.5% for *S. pneumoniae* at a MIC value of 1 mg/L. For free-drug plasma AUC: MIC ratio targets associated with a

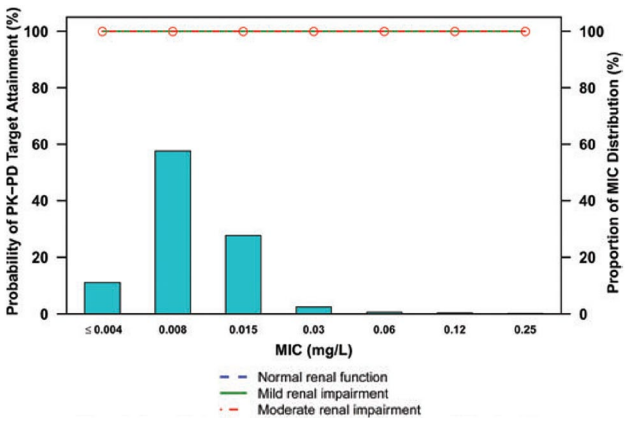

Fig. 1 Percent probabilities of pharmacokinetic–pharmacodynamic (PK–PD) target attainment by MIC on day 1 for delafloxacin 300 mg IV q12h for 3 days followed by 450 mg PO q12h for 2 days based on the evaluation of the free–drug plasma AUC:MIC ratio target associated with a $1-\log_{10}$ CFU reduction from baseline for *S. pneumoniae* among stimulated patients stratified by renal function group, overlaid upon the MIC distribution for *S. pneumoniae* [101]. *AUC* area under the concentration-time curve, *IV* intravenous, *MIC* minimum inhibitory concentration, *q12h* every 12 hours

2-log10 CFU reduction from baseline, percent probabilities of pharmacokinetic–pharmacodynamic target attainment at a MIC value of 0.12 mg/L was achieved on either day 1 or day 4 [102].

These in vitro and pharmacokinetic–pharmacodynamic findings were largely corroborated in the recent DEFINE-CABP study [103] in which delafloxacin was compared to moxifloxacin, another anti-pneumococcal fluoroquinolone. Of the 860 randomized patients, 520 had at least one pathogen at baseline. The most common pathogens were *S. pneumoniae* (226 (43.5%)) with penicillin-susceptible isolated in 102 (19.6%) patients, penicillin-intermediate in 25 (4.8%), penicillin-resistant in 19 (3.7%), multi-drug resistant in 12 (2.3%), and macrolide resistant in 35 (6.7%). Other frequently identified species include *H. parainfluenzae* (76 (14.6%)), *M. pneumoniae* (65 (12.5%)), and *L. pneumophila* (62 (11.9%)). Notably, *P. aeruginosa* was observed in 24 patients (4.6%), while MRSA was isolated in two (0.4%). Clinical success was evaluated in 488 patients with similar outcomes observed with both drugs. Documented persistence was reported in four delafloxacin- and three moxifloxacin-treated patients. Overall, *S. pneumoniae* success was reported in 93.6% and 94.9% delafloxacin- and moxifloxacin-treated patients, respectively. Additionally, similar responses were seen with *P. aeruginosa* 91.7% and 100% respectively for delafloxacin and moxifloxacin.

These results confirm the in vitro microbiological activity of delafloxacin is reflected in clinical practice.

6.1 Clinical Trials

In the phase I and II studies evaluating delafloxacin in complicated S. aureus/acute bacterial skin and skin structure infections, delafloxacin exhibited clinical and microbiological efficacy at dosages of 300 and 450 mg IV every 12 h, and these studies led to the phase III study for use in CABP. These studies have been described and critiqued in detail by others; here we summarize these results.

For use in acute bacterial skin and skin structure infections, delafloxacin was evaluated in four randomized, multicenter trials using tigecycline (TIG), linezolid, or vancomycin with or without aztreonam (AZ) as comparators.

A randomized, double-blind, multicenter phase II study compared the efficacy and tolerability of two different doses of delafloxacin with TIG in patients with complicated skin and skin structure infections [5] (NCT 0719810). Stratified by infection type, patients were randomized ($N=151$) 1:1:1 to receive delafloxacin 300 mg IV every 12 h ($n=49$), delafloxacin 450 mg IV every 12 h ($n=51$), or TIG 100 mg ×1 followed by 50 mg IV every 12 h ($n=50$). Duration of therapy was 5–14 days.

The primary efficacy analysis compared the clinical response rates in the delafloxacin and TIG groups, as well as between the two delafloxacin groups; this was conducted in the clinically evaluable (CE) population at the test of cure (TOC) visit (14–21 days post final dose of trial drug). At the TOC visit among the CE population, clinical cure rates were similar: 94.3% for delafloxacin 300 mg, 92.5% for delafloxacin 450 mg, and 91.2% for TIG. Both delafloxacin doses were comparable to TIG and achieved primary endpoints.

Delafloxacin 300 mg was the most well tolerated treatment. The most common adverse events reported in the study were gastrointestinal related—nausea and vomiting—and the incidence of these adverse events was lower in both delafloxacin groups than the TIG group. Infusion-site pain was reported in the 450 mg delafloxacin and tigercycline group, but not the 300 mg delafloxacin group. Five patients discontinued the study due to adverse events, two in the 450 mg delafloxacin group and three in the TIG group. Overall, delafloxacin was similarly effective to TIG for treatment of different complicated skin and skin-structure infections, and was well tolerated. Based on this trial, future trials planned to use a 300 mg dose of delafloxacin.

A second phase II trial evaluated the safety and efficacy of IV delafloxacin for the treatment of acute bacterial skin and skin structure infections, and IV linezolid or vancomycin were used as comparators (NCT01283581) [104]. This phase II trial was a multicenter, stratified, randomized, double-blind trial and took place at 23 US centers. In total, 256 patients were randomized (1:1:1) to 300 mg of delafloxacin ($n=81$), 600 mg of linezolid ($n=77$), or 15 mg/

kg vancomycin (actual body weight) ($n=98$), each administered IV twice daily for 5–14 days. Randomization was stratified by infection category.

Investigator's assessment of cure in the intent-to-treat (ITT) population, described as complete resolution of baseline signs and symptoms at follow-up, was the primary endpoint. Secondary endpoints were assessment of bacterial eradication, and reduction in total areas of erythema.

Overall, delafloxacin had the highest cure rate, which was not statistically significant compared to linezolid, but was a significant difference compared to vancomycin (mean difference: 216.3%; 95% CI 230.3–22.3; $P=0.031$). Interestingly, better results were seen among obese patients (BMI (body mass index) ≥ 30 kg/m^2) in the delafloxacin group; 78.8% delafloxacin versus 58.8% linezolid versus 48.8% vancomycin, $P<0.05$ (230.0%; 95% CI 250.7–29.3; $P=0.009$), but this has not been verified in larger cohorts. At follow-up, delafloxacin had a significantly greater percentage decrease in total erythema area compared to vancomycin (296.4% vs. 284.5%; $P=0.028$). Bacterial eradication was similar among treatment groups. Delafloxacin was well tolerated, nausea, diarrhoea, and vomiting were the most frequently reported treatment-emergent adverse effect (TEAE) from all groups [104].

Non-inferiority and safety of delafloxacin were evaluated in the first of the phase III trials, a multicenter, randomized, double-blind, active-controlled study; 660 patients were randomized to treatment with either delafloxacin 300 mg or vancomycin 15 mg/kg plus AZ 2 g, both administered IV twice daily for a period of 5–14 days.

In a phase II randomized, controlled trial of delafloxacin in CAP, 309 outpatients were treated with once-daily oral delafloxacin at different doses, 100 mg, 200 mg, or 400 mg, for 7 days; 87% of patients achieved clinical and bacteriologic cure rates [105].

The phase III CABP (DEFINE-CABP), was a randomized, double-blind, comparator-controlled, multicenter, global study in which patients received a minimum of six IV 300 mg delafloxacin doses (twice daily), with an option to switch to oral 450 mg delafloxacin (twice daily) for up to 20 total doses, or at least three IV moxifloxacin, 400 mg once daily, with an option to switch to oral moxifloxacin (400 mg once daily), for up to ten total doses [103]. The primary efficacy endpoint for the FDA was Early Clinical Response, defined as improvement at 96 h (±24 h) in at least two of the following: pleuritic chest pain, frequency/severity of cough, amount/quality of productive sputum, and dyspnea, without worsening of any other symptoms. Patient demographics are shown in Table 1; all characteristics were balanced across the two cohorts. Among patients, the average age was 60 years old, a larger proportion were men (58.7%), approximately 14% had COPD or asthma, and the majority of patients were classified as PORT Risk Class III (60.3%) and IV (25.4%).

Table 1 DEFINE-CABP study intent-to-treat population patient demographics and baseline characteristics for delafloxacin (DLX) and moxifloxacin (MOX) analysis groups

Characteristic	DLX ($N=431$)	MOX ($N=428$)	Total ($N=859$)
Age (years)			
Mean (SD)	60.7 (16.06)	59.3 (16.58)	60.0 (16.33)
Median (min, max)	63.0 (18, 89)	61.0 (18, 93)	62.0 (18, 93)
Sex, *n* (%)			
Male	251 (58.2)	253 (59.1)	504 (58.7)
Female	180 (41.8)	175 (40.9)	355 (41.3)
PORT class, *n* (%)			
II	54 (12.5)	57 (13.3)	111 (12.9)
III	258 (59.9)	260 (60.7)	518 (60.3)
IV	115 (26.7)	103 (24.1)	218 (25.4)
V	4 (0.9)	8 (1.9)	12 (1.4)
COPD/asthma	61 (14.2)	56 (13.1)	117 (13.6)

From Horcajada et al., with permission from Oxford University Press [103]

DEFINE-CABP compare delafloxacin to moxifloxacin for treatment of adults with community-acquired bacterial pneumonia, *PORT* pneumonia patient outcomes research team, *COPD* chronic obstructive pulmonary disease

Clinical response was measured at day 4 + 1 day in four different populations with non-inferiority demonstrated in the overall population. However, on examination of the pre-defined sub-groups, those with multi-lobar pneumonia showed a slightly better response with delafloxacin, while in the COPD/asthma cohort there was a significantly improved response in the delafloxacin arm—93.4% success compared with 76.8% in the moxifloxacin group (Table 2) [103].

Of 859 patients in the ITT population, 520 patients (60.5%) had at least one pathogen detected at baseline by any method (including culture, serology, PCR, and urinary antigen), and thus comprised the modified (M) ITT population. The most common pathogens isolated at baseline were *S. pneumoniae* (43.5%), *H. parainfluenzae* (14.6%), *M. pneumoniae* (12.5%), *Legionella pneumophila* (11.9%), *H. influenzae* (11.9%), and *S. aureus* (11.0%). The response rates were balanced across the two regimens, which, as no quinolone-resistant *S. pneumoniae* isolates were detected, is not surprising.

A detailed analysis of the microbiology from the phase III CABP study showed a high degree of favorable microbiological response at TOC (eradication or presumed eradication) for delafloxacin-treated patients. Delafloxacin retained potent activity against resistant phenotypes found in *S. pneumoniae* (PRSP, macrolide-resistant, MDR),

Table 2 DEFINE-CABP study early clinical response outcome by analysis set and subgroup of ITT population (from Horcajada et al. [103], with permission from Oxford University Press)

Patient population	Subgroup	*n/N* (%)		Difference (95% CI)
		Delafloxacin	Moxifloxacin	
Analysis set				
ITT	N/A	383/431 (88.8%)	381/428 (89%)	
MITT	N/A	236/257 (91.8%)	233/263 (88.5%)	3.2 (−1.9 to 8.5)
CE-ECR	N/A	381/418 (91%)	380/414 (91.7%)	−0.6 (−4.5 to 3.2)
ME-ECR	N/A	235/253 (92.8%)	233/256 (91%)	1.9 (−3.0 to 6.8)
Category				
History of asthma/COPD	Yes	57/61 (93.4%)	43/56 (76.7%)	16.7 (4.1 to 30.2)*
	No	326/370 (88%)	338/372 (90.8%)	−2.8 (−7.3 to 1.7)
Multilobar pneumonia	With at baseline	112/125 (89.6%)	104/120 (86.6%)	2.9 (−5.3 to 11.4)
	Without at baseline	271/306 (88.5%)	276/307 (89.9%)	−1.3 (−6.3 to 3.6)

Difference was the difference in early clinical response (ECR) rates (delafloxacin treatment group minus moxifloxacin treatment group). CIs were calculated using the Miettinen–Nurminen method without stratification

ITT intent-to-treat, *MITT* microbiological intent-to-treat, *CE-ECR* clinically evaluable early clinical response, *ME-ECR* microbiologically evaluable early clinical response, *N/A* not applicable

Difference in response rate (%): *significantly favors delafloxacin

Table 3 DEFINE-CABP study clinical outcome at test of cure by baseline pathogen (ME-TOC population) (from Horcajada et al. [103], with permission from Oxford University Press)

All pathogens	Clinical success *n/N* (%)[a]	
	Delafloxacin (*n* = 240)	Moxifloxacin (*n* = 248)
Streptococcus pneumoniae[b]	103/110 (93.6)	94/99 (94.9)
PSSP	47/49 (95.5)	44/47 (93.6)
PISP	16/17 (94.1)	6/7 (85.7)
PRSP	7/8 (87.5)	11/11 (100)
MDRSP	4/4 (100)	8/8 (100)
MRSP	16/17 (94.1)	17/18 (94.4)
Haemophilus parainfluenzae	32/35 (91.4)	34/37 (91.9)
Mycoplasma pneumoniae	29/30 (96.7)	29/29 (100)
Legionella pneumophila	27/29 (93.1)	32/32 (100)
Staphylococcus aureus[b]	25/27 (92.6)	28/30 (93.3)
MSSA	23/25 (92.0)	28/30 (93.3)
MRSA	2/2 (100)	0/0 (NA)
Chlamydia pneumoniae	24/24 (100)	15/15 (100)
Haemophilus influenzae	23/24 (95.8)	31/35 (88.6)
Klebsiella pneumoniae	14/17 (82.4)	16/16 (100)
Escherichia coli	13/13 (100)	9/9 (100)
Pseudomonas aeruginosa	11/12 (91.7)	11/11 (100)
Klebsiella oxytoca	6/6 (100)	3/4 (75.0)
Moraxella catarrhalis	6/6 (100)	6/6 (100)
Enterobacter cloacae complex	3/4 (75.0)	8/8 (100)

ME microbiologically evaluable, *TOC* test of cure, *MDRSP* multiple drug-resistant *Streptococcus pneumoniae, MRSA* macrolide-resistant *Staphylococcus aureus, MRSP* macrolide-resistant *Streptococcus pneumoniae*, *MSSA* methicillin-susceptible *Staphylococcus aureus, PISP* penicillin-intermediate *Streptococcus pneumoniae*, *PSSP* penicillin-susceptible *Streptococcus pneumoniae*, *PRSP* penicillin-resistant *Streptococcus pneumoniae*

[a]Microbiological success was defined as documented or presumed eradication

[b]Subjects with both MRSA and MSSA, or any combination of PSSP, PISP, or PRSP, were counted once in the overall category for that organism

Haemophilus species (macrolide-non-susceptible), and *S. aureus* (including MRSA and FQ-non-susceptible MSSA), and overall IV or oral delafloxacin monotherapy was efficacious for CAP [106] (Table 3).

Early clinical responders (ECRs) and clinical success were also analyzed in diabetic patients and the results for delafloxacin were comparable to moxifloxacin, regardless of diabetic status of patients, and were comparable to overall efficacy results [107]. Additionally, ECR responders and clinical success for delafloxacin were comparable to moxifloxacin, regardless of age or gender groups, and were comparable to overall efficacy results [103, 108].

Delafloxacin was safe and well tolerated in 431 patients in the phase III trial in CABP. In the delafloxacin group, 30.5% patients experienced a TEAE, while 26.2% in the moxifloxacin group experienced a TEAE. Of patients experiencing a TEAE, 15.2% ($n=65$) in the delafloxacin group and 12.6% in the moxifloxacin group were considered treatment related. The most common ($\geq 3\%$) TEAEs in both groups were diarrhea and elevation in transaminases. There were no significant differences in mortality at day 28 between treatment groups; 2.1% and 1.6% for delafloxacin and moxifloxacin, respectively [68].

Overall, delafloxacin demonstrated non-inferiority with moxifloxacin, and was effective and well tolerated; in addition, it provides coverage for Gram-positive, Gram-negative, and atypical pathogens. Delafloxacin is available in both parenteral and oral formulations, which distinguishes it from other available agents [109]. Delafloxacin is only approved in the USA for CABP [4].

In patients with co-morbidities, specifically COPD/asthma, which can be difficult to treat, delafloxacin could be a potential treatment option based on the improved response in these patients in the delafloxacin arm of the CABP DEFINE study.

6.2 Safety

Experience with the fluoroquinolones has increased, leading to an understanding of the adverse events associated with the class. These have been well defined and have become a prospective part of the development process of more current fluoroquinolones. Moreover, FQs have intraclass differences in their adverse event profile.

FQs (initially ciprofloxacin was approved in 1987) are considered a reasonably well-tolerated group of antibiotics, and have been widely used. Several class members have been approved, only to be withdrawn later due to unforeseen adverse events—drugs such temafloxacin, trovafloxacin, grepafloxacin, and gatifloxacin—while many other FQs have not passed clinical development due to various events, for example clinafloxacin and sitafloxacin. The labels of FQs all contain warnings of joint pathology, which was added to the norfloxacin and ciprofloxacin labels in 1987. A "boxed warning" was added to FQs by the FDA in July 2008 for increased risk of tendinitis and tendon rupture. Three years later in February 2011, the risk of worsening symptoms for those with myasthenia gravis was added to the boxed warning. August 2013 saw an update that described the potential for irreversible peripheral neuropathy. In July 2016, the FDA made changes to the label for all FQs, which included a boxed warning related to disabling and potentially permanent side effects involving the tendons, muscles, joints, nerves, and central nervous system. Additionally, the FDA concluded that for mild infections that do not require routine antibiotics (acute bacterial sinusitis, acute bacterial exacerbation of chronic bronchitis, and uncomplicated urinary tract infections), "fluoroquinolones should be reserved for use in patients who have no other treatment options." July 2018 saw new label changes directed by the FDA adding that hypoglycemia can lead to coma and making the mental health side effects (disorientation, agitation, nervousness, memory impairment, delirium) more prominent and more consistent across the systemic FQ drug class. Lastly, in 2019 the FDA updated the labels with warnings regarding potential for aortic rupture and dissection [110].

The FQ class is associated with an array of adverse events, including CNS toxicity, phototoxicity, hepatotoxicity, hypoglycemia, acute kidney injury, tendon rupture, cardiac issues including prolongation of the QT interval, torsade de pointes, and arrythmia in addition to the most recently recognized aortic rupture or dissection. Delafloxacin FDA labeling has the standard FQ class box warning of potential for tendinitis, tendon rupture, peripheral neuropathy, CNS effects, and exacerbation of myasthenia gravis. Occurrence of adverse events observed with delafloxacin were comparable between treatment groups in clinical studies. Gastrointestinal symptoms of diarrhea and nausea were the most common, mild CNS effects, endocrine abnormalities, and increased serum liver function tests were reported but appear to be dose dependent [54].

Delafloxacin did not cause cardiac repolarization using the QTcF interval, and in healthy volunteers no cases of clinically relevant prolongations of the QT/QTc interval have been reported [54, 111]. Peripheral neuropathies, tendinopathies, or CNS effects do not appear to be caused by delafloxacin in the clinical trial program that includes almost 3000 patients. Lodise et al. [6] conducted a detailed analysis of the clinical trial program for delafloxacin and concluded that the drug does not appear to be associated with the adverse events of special interest associated with fluoroquinolones. Finally, it is inappropriate to compare the package labels of other class members, but some drugs are more often associated with certain events.

Real-world case reports or studies on delafloxacin are not yet available as FDA and European Medicines Agency (EMA) approval was recent; however, as more people are exposed to delafloxacin in the post-approval phase, the emergence of adverse events such as liver toxicity, hypersensitivity, and FQ CNS effects may occur.

7 Conclusion

Despite advances in antimicrobial therapy, CAP continues to be a significant cause of morbidity and mortality in adults, resulting in more than 60,000 deaths annually. The risk of developing CAP is six to eight times higher in people with COPD compared to healthy individuals [11, 112]; these patients also have an increased risk for morbidity, mortality, and economic burden [112, 113]. CAP hospitalization is also more prevalent among the elderly and in patients with co-morbidities, which are a growing proportion of the population. Therefore, healthcare costs due to CAP are expected to increase alongside these populations.

CAP is caused by a wide variety of typical and atypical pathogens; however, *S. pneumoniae* remains the most commonly identified bacterial pathogen. The ability to effectively treat resistant *S. pneumoniae* is a growing concern as susceptibility to commonly used macrolides, tetracyclines, and some B-lactams has steadily declined. Macrolide resistance among *S. pneumoniae* isolates is reportedly between 20 and 40% [78]; however, prevalence of FQ resistance is low. The updated CAP guidelines recommend for patients with severe CAP and no risk factors for MRSA or *P. aeruginosa,* that a beta-lactam antibiotic plus a macrolide, or a beta-lactam plus a respiratory FQ, should be the treatment of choice. Delafloxacin, a novel anionic FQ, has a broader spectrum of activity compared to previously available FQs; additionally, its bactericidal activity and has been shown to be superior in patients with CAP who may have severe illness and in patients with COPD/asthma as a co-morbidity. Use of a new anionic FQ could be an optimal choice in an era of aging patients and complicating co-morbidities such as COPD or asthma. Delafloxacin appears to be well tolerated and compared with other FQs has an improved AE profile with minimal potential for QT prolongation and drug–drug interactions. However, the FDA and EMA cautions to avoid FQ use in cases where other agents could be utilized because the potential adverse events are still applicable to delafloxacin.

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Compliance with Ethical Standards

Conflict of Interest CS has served as a speaker for Allergan, Merck, Nabriva, and Paratek Pharmaceuticals, and has received consulting fees for working on clinical trials for Allergan, Shionogi, and Merck. Additionally, CS has received research grants from CMS, NIH and CDC, not for this manuscript but for work with Allergan, Shionogi, and Merck. RS, JM, and NT have no conflicts of interests.

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References

1. Mogle BT, Steele JM, Thomas SJ, Bohan KH, Kufel WD. Clinical review of delafloxacin: a novel anionic fluoroquinolone. J Antimicrob Chemother. 2018;73(6):1439–51.
2. Melinta Therapeutics Inc. Baxdela® (delafloxacin) product package insert. Lincolnshire: Melinta Therapeutics Inc; 2017.
3. Van Bambeke F. Delafloxacin, a non-zwitterionic fluoroquinolone in phase III of clinical development: evaluation of its pharmacology, pharmacokinetics, pharmacodynamics and clinical efficacy. Future Microbiol. 2015;10(7):1111–23.
4. Melinta Therapeutics Inc. BAXDELA® package insert Lincolnshire, Illinois; 2019. Available from: https://baxdela.com/docs/baxdela-prescribing-information.pdf. Accessed 12 Nov 2019.
5. O'Riordan W, Mehra P, Manos P, Kingsley J, Lawrence L, Cammarata S. A randomized phase 2 study comparing two doses of delafloxacin with tigecycline in adults with complicated skin and skin-structure infections. Int J Infect Dis. 2015;30:67–73.
6. Lodise T, Corey R, Hooper D, Cammarata S. Safety of delafloxacin: focus on adverse events of special interest. Open Forum Infect Dis. 2018;5(10):ofy220.
7. Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, et al. Diagnosis and treatment of adults with community-acquired pneumonia. An official clinical practice guideline of the American Thoracic Society and Infectious Diseases Society of America. Am J Respir Crit Care Med. 2019;200(7):e45–67.
8. File TM. Treatment of community-acquired pneumonia in adults who require hospitalization. UpToDate [Internet]. 2019. https://www.uptodate.com/contents/treatment-of-community-acquired-pneumonia-in-adults-who-require-hospitalization.
9. Mandell LA, Wunderink RG, Anzueto A, Bartlett JG, Campbell GD, Dean NC, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. Clin Infect Dis. 2007;44(Suppl 2):S27–72.

10. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM, et al. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med. 2015;373(5):415–27.
11. File TM Jr, Marrie TJ. Burden of community-acquired pneumonia in North American adults. Postgrad Med. 2010;122(2):130–41.
12. Griffin MR, Zhu Y, Moore MR, Whitney CG, Grijalva CG. U.S. hospitalizations for pneumonia after a decade of pneumococcal vaccination. N Engl J Med. 2013;369(2):155–63.
13. Rozenbaum MH, Mangen MJ, Huijts SM, van der Werf TS, Postma MJ. Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: a nationwide retrospective claims database analysis. Vaccine. 2015;33(28):3193–9.
14. Song JH, Huh K, Chung DR. Community-acquired pneumonia in the Asia-Pacific region. Semin Respir Crit Care Med. 2016;37(6):839–54.
15. Welte T, Torres A, Nathwani D. Clinical and economic burden of community-acquired pneumonia among adults in Europe. Thorax. 2012;67(1):71–9.
16. Buzzo AR, Roberts C, Mollinedo LG, Quevedo JM, Casas GL, Soldevilla JM. Morbidity and mortality of pneumonia in adults in six Latin American countries. Int J Infect Dis. 2013;17(9):e673–7.
17. World Health Organisation. The top 10 causes of death 2018. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
18. Lim WS, Baudouin SV, George RC, Hill AT, Jamieson C, Le Jeune I, et al. BTS guidelines for the management of community acquired pneumonia in adults: update 2009. Thorax. 2009;64(Suppl 3):iii1–55.
19. Woodhead M, Blasi F, Ewig S, Garau J, Huchon G, Ieven M, et al. Guidelines for the management of adult lower respiratory tract infections—full version. Clin Microbiol Infect. 2011;17(Suppl 6):E1–59.
20. Musher DM, Thorner AR. Community-acquired pneumonia. N Engl J Med. 2014;371(17):1619–28.
21. Ramirez JA, Wiemken TL, Peyrani P, Arnold FW, Kelley R, Mattingly WA, et al. Adults hospitalized with pneumonia in the United States: incidence, epidemiology, and mortality. Clin Infect Dis. 2017;65(11):1806–12.
22. Cilloniz C, Ewig S, Polverino E, Marcos MA, Esquinas C, Gabarrus A, et al. Microbial aetiology of community-acquired pneumonia and its relation to severity. Thorax. 2011;66(4):340–6.
23. Cilloniz C, Polverino E, Ewig S, Aliberti S, Gabarrus A, Menendez R, et al. Impact of age and comorbidity on cause and outcome in community-acquired pneumonia. Chest. 2013;144(3):999–1007.
24. Magiorakos AP, Srinivasan A, Carey RB, Carmeli Y, Falagas ME, Giske CG, et al. Multidrug-resistant, extensively drug-resistant and pandrug-resistant bacteria: an international expert proposal for interim standard definitions for acquired resistance. Clin Microbiol Infect. 2012;18(3):268–81.
25. Yu Y, Fei A. Atypical pathogen infection in community-acquired pneumonia. Biosci Trends. 2016;10(1):7–13.
26. Tong C, Chen H. Research development on the diagnosis of atypical pathogens in community-acquired pneumonia. Chin J Lung Dis (Electron Ed). 2014;7:59–62.
27. Isturiz RE, Luna CM, Ramirez J. Clinical and economic burden of pneumonia among adults in Latin America. Int J Infect Dis. 2010;14(10):e852–6.
28. Prina E, Ranzani OT, Torres A. Community-acquired pneumonia. Lancet. 2015;386(9998):1097–108.
29. Burk M, El-Kersh K, Saad M, Wiemken T, Ramirez J, Cavallazzi R. Viral infection in community-acquired pneumonia: a systematic review and meta-analysis. Eur Respir Rev. 2016;25(140):178–88.
30. Holter JC, Muller F, Bjorang O, Samdal HH, Marthinsen JB, Jenum PA, et al. Etiology of community-acquired pneumonia and diagnostic yields of microbiological methods: a 3-year prospective study in Norway. BMC Infect Dis. 2015;15:64.
31. Wongsurakiat P, Chitwarakorn N. Severe community-acquired pneumonia in general medical wards: outcomes and impact of initial antibiotic selection. BMC Pulm Med. 2019;19(1):179.
32. Cilloniz C, Dominedo C, Torres A. Multidrug resistant gram-negative bacteria in community-acquired pneumonia. Crit Care. 2019;23(1):79.
33. Versporten A, Zarb P, Caniaux I, Gros MF, Drapier N, Miller M, et al. Antimicrobial consumption and resistance in adult hospital inpatients in 53 countries: results of an internet-based global point prevalence survey. Lancet Glob Health. 2018;6(6):e619–29.
34. Xu J, Murphy SL, Kochanek KD, Bastian BA. Deaths: final data for 2013. Natl Vital Stat Rep. 2016;64(2):1–119.
35. Azmi S, Aljunid SM, Maimaiti N, Ali AA, Muhammad Nur A, De Rosas-Valera M, et al. Assessing the burden of pneumonia using administrative data from Malaysia, Indonesia, and the Philippines. Int J Infect Dis. 2016;49:87–93.
36. Shah BA, Singh G, Naik MA, Dhobi GN. Bacteriological and clinical profile of community acquired pneumonia in hospitalized patients. Lung India. 2010;27(2):54–7.
37. Takahashi K, Suzuki M, le Minh N, Anh NH, Huong LT, Son TV, et al. The incidence and aetiology of hospitalised community-acquired pneumonia among Vietnamese adults: a prospective surveillance in central Vietnam. BMC Infect Dis. 2013;13:296.
38. Zingone F, Abdul Sultan A, Crooks CJ, Tata LJ, Ciacci C, West J. The risk of community-acquired pneumonia among 9803 patients with coeliac disease compared to the general population: a cohort study. Aliment Pharmacol Ther. 2016;44(1):57–67.
39. Quan TP, Fawcett NJ, Wrightson JM, Finney J, Wyllie D, Jeffery K, et al. Increasing burden of community-acquired pneumonia leading to hospitalisation, 1998–2014. Thorax. 2016;71(6):535–42.
40. Cohen C, Walaza S, Moyes J, Groome M, Tempia S, Pretorius M, et al. Epidemiology of severe acute respiratory illness (SARI) among adults and children aged ≥ 5 years in a high HIV-prevalence setting, 2009–2012. PLoS ONE. 2015;10(2):e0117716.
41. Gupta D, Agarwal R, Aggarwal AN, Singh N, Mishra N, Khilnani GC, et al. Guidelines for diagnosis and management of community- and hospital-acquired pneumonia in adults: joint ICS/NCCP(I) recommendations. Lung India. 2012;29(Suppl 2):S27–62.
42. Torres A, Peetermans WE, Viegi G, Blasi F. Risk factors for community-acquired pneumonia in adults in Europe: a literature review. Thorax. 2013;68(11):1057–65.
43. Boyles TH, Brink A, Calligaro GL, Cohen C, Dheda K, Maartens G, et al. South African guideline for the management of community-acquired pneumonia in adults. J Thorac Dis. 2017;9(6):1469–502.
44. Eurich DT, Marrie TJ, Minhas-Sandhu JK, Majumdar SR. Ten-year mortality after community-acquired pneumonia. A prospective cohort. Am J Respir Crit Care Med. 2015;192(5):597–604.
45. Hayes BH, Haberling DL, Kennedy JL, Varma JK, Fry AM, Vora NM. Burden of pneumonia-associated hospitalizations: United States, 2001–2014. Chest. 2018;153(2):427–37.
46. Administration on Community Living. A Profile of Older Americans: 2017. Washington, DC: Administration for Community Living, Administration on Aging (AoA), U.S. Department of Health and Human Services; 2018.
47. United Nations Department of Economic and Social Affairs. World population prospects: the 2017 revision, key findings and advance tables. Working Paper No. ESA/P/WP/248. Population Division; 2017. Contract No.: Paper No. ESA/P/WP/248.

48. Tan CC, Ong-Mateo M. Management of community-acquired pneumonia in a university hospital: adherence to recommended practice guidelines. Santo Tomas J Med. 2006;53:37–44.
49. Tan CC, Ong-Mateo M. Management of community-acquired pneumonia in a university hospital: adherence to recommended practice guidelines. Santo Tomas J Med. 2006;53(2):37–44.
50. Faverio P, Aliberti S, Bellelli G, Suigo G, Lonni S, Pesci A, et al. The management of community-acquired pneumonia in the elderly. Eur J Intern Med. 2014;25(4):312–9.
51. Almirall J, Serra-Prat M, Bolibar I, Balasso V. Risk factors for community-acquired pneumonia in adults: a systematic review of observational studies. Respiration. 2017;94(3):299–311.
52. Faulkner CM, Cox HL, Williamson JC. Unique aspects of antimicrobial use in older adults. Clin Infect Dis. 2005;40(7):997–1004.
53. LaPensee K, Mistry R, Lodise T. Budget impact of omadacycline for the treatment of patients with community-acquired bacterial pneumonia in the United States from the hospital perspective. Am Health Drug Benefits. 2019;12(1-Supplement 1):S1–12.
54. Liapikou A, Cilloniz C, Palomeque A, Torres T. Emerging antibiotics for community-acquired pneumonia. Expert Opin Emerg Drugs. 2019;24(4):221–31.
55. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;(1):CD000422. https://doi.org/10.1002/14651858.CD000422.pub3.
56. Johansson N, Kalin M, Tiveljung-Lindell A, Giske CG, Hedlund J. Etiology of community-acquired pneumonia: increased microbiological yield with new diagnostic methods. Clin Infect Dis. 2010;50(2):202–9.
57. Rozenbaum MH, Pechlivanoglou P, van der Werf TS, Lo-Ten-Foe JR, Postma MJ, Hak E. The role of *Streptococcus pneumoniae* in community-acquired pneumonia among adults in Europe: a meta-analysis. Eur J Clin Microbiol Infect Dis. 2013;32(3):305–16.
58. Huijts SM, Pride MW, Vos JM, Jansen KU, Webber C, Gruber W, et al. Diagnostic accuracy of a serotype-specific antigen test in community-acquired pneumonia. Eur Respir J. 2013;42(5):1283–90.
59. Ramirez J. Overview of community-acquired pneumonia in adults. UpToDate [Internet]. 2019. https://www.uptodate.com/contents/overview-of-community-acquired-pneumonia-in-adults/print.
60. Lee MS, Oh JY, Kang CI, Kim ES, Park S, Rhee CK, et al. Guideline for antibiotic use in adults with community-acquired pneumonia. Infect Chemother. 2018;50(2):160–98.
61. Nagesh Kumar T, Rafiudeen R, Rashmi K. A study of clinical and etiological profile of community-acquired pneumonia with special reference to atypical pneumonia. Ann Niger Med. 2017;11(1):11–6.
62. Levy ML, Le Jeune I, Woodhead MA, Macfarlaned JT, Lim WS, British Thoracic Society Community Acquired Pneumonia in Adults Guideline G. Primary care summary of the British Thoracic Society Guidelines for the management of community acquired pneumonia in adults: 2009 update. Endorsed by the Royal College of General Practitioners and the Primary Care Respiratory Society UK. Prim Care Respir J. 2010;19(1):21–7.
63. Mandell L, Wunderink RG. "Pneumonia", Harrison's principles of internal medicine. 18th ed. New York: McGraw-Hill; 2008.
64. Sader HS, Mendes RE, Le J, Denys G, Flamm RK, Jones RN. Antimicrobial susceptibility of *Streptococcus pneumoniae* from North America, Europe, Latin America, and the Asia-Pacific Region: results from 20 years of the SENTRY Antimicrobial Surveillance Program (1997–2016). Open Forum Infect Dis. 2019;6(Suppl 1):S14–23.
65. Shindo Y, Ito R, Kobayashi D, Ando M, Ichikawa M, Shiraki A, et al. Risk factors for drug-resistant pathogens in community-acquired and healthcare-associated pneumonia. Am J Respir Crit Care Med. 2013;188(8):985–95.
66. Gramegna A, Sotgiu G, Di Pasquale M, Radovanovic D, Terraneo S, Reyes LF, et al. Atypical pathogens in hospitalized patients with community-acquired pneumonia: a worldwide perspective. BMC Infect Dis. 2018;18(1):677.
67. The Center for Disease Dynamics EP. ResistanceMap: resistance of *Streptococcus pneumoniae* to macrolides 2020. https://resistancemap.cddep.org/AntibioticResistance.php.
68. Musher DM, Abers MS, Bartlett JG. Evolving understanding of the causes of pneumonia in adults, with special attention to the role of pneumococcus. Clin Infect Dis. 2017;65(10):1736–44.
69. Cillóniz C, Cardozo C, García-Vidal C. Epidemiology, pathophysiology, and microbiology of community acquired pneumonia. Ann Res Hosp. 2018;2(1):1–11. https://doi.org/10.21037/arh.2017.12.03.
70. Keedy K, Nenninger A, Sheets A, et al., editors. Antibiotic susceptibility of *Streptococcus pneumoniae* in the US in 2014. Poster Presentation. ID Week. New Orleans: Infectious Diseases Society of America; 2016.
71. Nuermberger E, Bishai WR. The clinical significance of macrolide-resistant Streptococcus pneumoniae: it's all relative. Clin Infect Dis. 2004;38(1):99–103.
72. Rzeszutek M, Wierzbowski A, Hoban DJ, Conly J, Bishai W, Zhanel GG. A review of clinical failures associated with macrolide-resistant *Streptococcus pneumoniae*. Int J Antimicrob Agents. 2004;24(2):95–104.
73. Kim L, McGee L, Tomczyk S, Beall B. Biological and epidemiological features of antibiotic-resistant *Streptococcus pneumoniae* in pre- and post-conjugate vaccine eras: a United States perspective. Clin Microbiol Rev. 2016;29(3):525–52.
74. de la Campa AG, Ardanuy C, Balsalobre L, Perez-Trallero E, Marimon JM, Fenoll A, et al. Changes in fluoroquinolone-resistant Streptococcus pneumoniae after 7-valent conjugate vaccination, Spain. Emerg Infect Dis. 2009;15(6):905–11.
75. Arancibia F, Ewig S, Martinez JA, Ruiz M, Bauer T, Marcos MA, et al. Antimicrobial treatment failures in patients with community-acquired pneumonia: causes and prognostic implications. Am J Respir Crit Care Med. 2000;162(1):154–60.
76. Giske CG, Monnet DL, Cars O, Carmeli Y, ReAct-Action on Antibiotic R. Clinical and economic impact of common multidrug-resistant gram-negative bacilli. Antimicrob Agents Chemother. 2008;52(3):813–21.
77. Pendleton JN, Gorman SP, Gilmore BF. Clinical relevance of the ESKAPE pathogens. Expert Rev Anti Infect Ther. 2013;11(3):297–308.
78. Gupta V, Yu K, Jokinen-Gordon H, Gelone SP. A multi-centre evaluation of the US prevalence and regional variation in macrolide-resistant Streptococcus pneumoniae from blood or respiratory cultures among adult patients. Abstract #5523. Presented at 30th European congress on clinical microbiology and infectious diseases (ECCMID), Paris, France, April 18–21, 2020.
79. Mandell LA, Marrie TJ, Grossman RF, Chow AW, Hyland RH. Canadian guidelines for the initial management of community-acquired pneumonia: an evidence-based update by the Canadian Infectious Diseases Society and the Canadian Thoracic Society. The Canadian Community-Acquired Pneumonia Working Group. Clin Infect Dis. 2000;31(2):383–421.
80. Alfageme I, Aspa J, Bello S, Blanquer J, Blanquer R, Borderias L, et al. Guidelines for the diagnosis and management of community-acquired pneumonia. Spanish Society of Pulmonology and Thoracic Surgery (SEPAR). Arch Bronconeumol. 2005;41(5):272–89.
81. Wiersinga WJ, Bonten MJ, Boersma WG, Jonkers RE, Aleva RM, Kullberg BJ, et al. SWAB/NVALT (Dutch Working Party on Antibiotic Policy and Dutch Association of Chest Physicians)

guidelines on the management of community-acquired pneumonia in adults. Neth J Med. 2012;70(2):90–101.
82. Qu JM, Cao B. Guidelines for the diagnosis and treatment of adult community acquired pneumonia in China (2016 Edition). Zhonghua Jie He He Hu Xi Za Zhi. 2016;39(4):241–2.
83. Miyashita N, Matsushima T, Oka M, Japanese Respiratory S. The JRS guidelines for the management of community-acquired pneumonia in adults: an update and new recommendations. Intern Med. 2006;45(7):419–28.
84. Wunderink RG, Waterer G. Advances in the causes and management of community acquired pneumonia in adults. BMJ. 2017;358:j2471.
85. Eccles S, Pincus C, Higgins B, Woodhead M, Guideline Development G. Diagnosis and management of community and hospital acquired pneumonia in adults: summary of NICE guidance. BMJ. 2014;349:g6722.
86. Lilford R, Pronovost P. Using hospital mortality rates to judge hospital performance: a bad idea that just won't go away. BMJ. 2010;340:c2016.
87. Kupfer JM. The morality of using mortality as a financial incentive: unintended consequences and implications for acute hospital care. JAMA. 2013;309(21):2213–4.
88. Lee JS, Giesler DL, Gellad WF, Fine MJ. Antibiotic therapy for adults hospitalized with community-acquired pneumonia: a systematic review. JAMA. 2016;315(6):593–602.
89. Raz-Pasteur A, Shasha D, Paul M. Fluoroquinolones or macrolides alone versus combined with beta-lactams for adults with community-acquired pneumonia: systematic review and meta-analysis. Int J Antimicrob Agents. 2015;46(3):242–8.
90. Kollef MH, Betthauser KD. New antibiotics for community-acquired pneumonia. Curr Opin Infect Dis. 2019;32(2):169–75.
91. NUZYRA™ (omadacycline)) product package insert. Boston, MA.: Paratek Pharmaceuticals Inc.; 2018.
92. Stets R, Popescu M, Gonong JR, Mitha I, Nseir W, Madej A, et al. Omadacycline for community-acquired bacterial pneumonia. N Engl J Med. 2019;380(6):517–27.
93. Gallagher JC. Omadacycline: a modernized tetracycline. Clin Infect Dis. 2019;69(Supplement_1):S1–5.
94. File TM, Goldberg L, Das A, Sweeney C, Saviski J, Gelone SP, et al. Efficacy and safety of intravenous-to-oral lefamulin, a pleuromutilin antibiotic, for the treatment of community-acquired bacterial pneumonia: the phase III lefamulin evaluation against pneumonia (LEAP 1) trial. Clin Infect Dis. 2020;70(11):2459. https://doi.org/10.1093/cid/ciz710.
95. U.S. Food and Drug Administration. FDA approves new antibiotic to treat community-acquired bacterial pneumonia. [press release]. August 19, 2019. Available from: https://www.fda.gov/news-events/press-announcements/fda-approves-new-antibiotic-treat-community-acquired-bacterial-pneumonia. Accessed 10 Oct 2019.
96. Nabriva Therapeutics US, Inc. Nabriva Therapeutics receives U.S. FDA approval of XenletaTM (lefamulin) to treat community-acquired bacterial pneumonia (CABP) [press release]. Dublin: Nabriva Therapeutics US, Inc; 2019.
97. Koulenti D, Xu E, Mok IYS, Song A, Karageorgopoulos DE, Armaganidis A, et al. Novel antibiotics for multidrug-resistant gram-positive microorganisms. Microorganisms. 2019;7(8):270.
98. File TM Jr, Low DE, Eckburg PB, Talbot GH, Friedland HD, Lee J, et al. Integrated analysis of FOCUS 1 and FOCUS 2: randomized, doubled-blinded, multicenter phase 3 trials of the efficacy and safety of ceftaroline fosamil versus ceftriaxone in patients with community-acquired pneumonia. Clin Infect Dis. 2010;51(12):1395–405.
99. Sader HS, Flamm R, Streit JM, Mendes RE. Frequency of occurrence and antimicrobial susceptibility of bacteria isolated from patients hospitalised with community-acquired bacterial pneumonia: evaluation of ceftaroline potency and antimicrobial spectrum. #P1817. Poster session presented at 28th European congress on clinical microbiology and infectious diseases (ECCMID), Madrid, Spain, 21–24 April 2018.
100. Pfaller MA, Sader HS, Rhomberg PR, Flamm RK. In vitro activity of delafloxacin against contemporary bacterial pathogens from the United States and Europe, 2014. Antimicrob Agents Chemother. 2017;61(4):e02609-16.
101. Flamm RK, Shortridge D, Huband MD, McCurdy S, Pfaller MA. Activity of delafloxacin when tested against bacterial surveillance isolates collected in the US and Europe during 2014–2016 as part of a global surveillance program. Open Forum Infect Dis. 2017;4(Suppl 1):S373–4.
102. Bhavnani S, Zhang L, Rubino C, Bader J, Lepak A, Andes D, et al. Pharmacokinetic–pharmacodynamic (PK–PD) target attainment analyses for delafloxacin to provide dose selection support for the treatment of patients with community-acquired bacterial pneumonia (CABP). Open Forum Infect Dis. 2016;3(S1):1972.
103. Horcajada JP, Salata RA, Álvarez-Sala R, Nitu FM, Lawrence L, Quintas M, et al. A phase 3 study to compare delafloxacin with moxifloxacin for the treatment of adults with community-acquired bacterial pneumonia (DEFINE-CABP). Open Forum Infect Dis. 2019;7(1):ofz514.
104. Kingsley J, Mehra P, Lawrence LE, Henry E, Duffy E, Cammarata SK, et al. A randomized, double-blind, phase 2 study to evaluate subjective and objective outcomes in patients with acute bacterial skin and skin structure infections treated with delafloxacin, linezolid or vancomycin. J Antimicrob Chemother. 2016;71(3):821–9.
105. Longcor J, Hopkins S, Wikler M, Lawrence L. A phase 2 safety and efficacy study of oral delafloxacin (DLX) in subjects with acute bacterial exacerbation of chronic bronchitis (ABECB). Abstract 1071. Poster abstract session: lower respiratory tract infection. ID Week, San Diego, CA, October 17–21, 2012. https://idsa.confex.com/idsa/2012/webprogram/Paper37662.html.
106. McCurdy S, Keedy K, Lawrence L, et al., editors. Analysis of the microbiological data from the delafloxacin phase 3 community acquired bacterial pneumonia (CABP). Poster 2230. ID Week; 2–6 October 2019. Washington, D.C.: Infectious Disease Society of America; 2019.
107. Kaidashev I, Nitu F, Popescu M, editors. Treatment of community acquired bacterial pneumonia (CABP) in patients with diabetes: outcomes from a global phase 3 study of delafloxacin. Poster 2228. ID Week; 2–6 October 2019. Washington, D.C.: Infectious Diseases Society of America; 2019.
108. Madej A, Pullman J, Popescu M, editors. Outcomes by age and gender from a global phase 3 study of delafloxacin (DLX) in community acquired bacterial pneumonia (CABP). Poster 2234. ID Week; 2–6 October 2019; Washington, D.C.: Infectious Diseases Society of America; 2019.
109. Cho JC, Crotty MP, White BP, Worley MV. What is old is new again: delafloxacin, a modern fluoroquinolone. Pharmacotherapy. 2018;38(1):108–21.
110. Inc. BHP. CIPRO® (ciprofloxacin hydrochloride) Package Insert Whippany, NJ, USA. 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/019537s086lbl.pdf.
111. Bassetti M, Righi E, Pecori D, Tillotson G. Delafloxacin: an improved fluoroquinolone developed through advanced molecular engineering. Future Microbiol. 2018;13:1081–94.
112. Pasquale CB, Vietri J, Choate R, McDaniel A, Sato R, Ford KD, et al. Patient-reported consequences of community-acquired pneumonia in patients with chronic obstructive pulmonary disease. Chronic Obstr Pulm Dis. 2019;6(2):132–44.
113. Torres A, Blasi F, Dartois N, Akova M. Which individuals are at increased risk of pneumococcal disease and why? Impact of COPD, asthma, smoking, diabetes, and/or chronic heart disease on community-acquired pneumonia and invasive pneumococcal disease. Thorax. 2015;70(10):984–9.