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Emerging antibiotics for Community-Acquired Pneumonia

Liapikou Adamantia[1,*], Cilloniz Catia[2], Palomepue Andrea[2], Torres Toni[2]

1. Sotiria Hospital, 6st Respiratory Department, Mesogeion 152, Athens, Greece, GR 11527

2. Hospital Clinic de Barcelona, Respiratory Institute, CIBERES- IDIBAPS C, Villarroel 170 , Barcelona, Catalunya, Spain, ES 08036

***Correspondence**

Liapikou Adamantia

Email: mliapikou@yahoo.com

Abstract

Introduction: Community-acquired pneumonia is the most common infection leading to hospitalization and death in all age groups, especially in elderly populations. Increasing antibiotic resistance among the common bacterial pathogens associated with community-acquired pneumonia, especially Streptococcus pneumoniae and staphylococci, has made its empirical treatment increasingly problematic, highlighting the need for effective antibiotic therapy.

Areas covered: We searched PubMed and ClinicalTrials.gov for English-language reports of phase III clinical trials conducted between 2000 and 2019 concerning the antibiotic treatment of community-acquired pneumonia. We provide a summary of the latest approved drugs for this indication and highlight emerging drugs with a potential indication.

Expert opinion: Ceftaroline (a new cephalosporine) and omadacycline (a cycline alternative), either parenterally or orally, are the only two new antibiotics to have been approved by the FDA for the treatment of community-acquired pneumonia in the last five years. Among the antimicrobials in development, Lefamulin (the first pleuromutilin), is currently in phase III development. Among the known antibiotic classes, solithromycin (a macrolide), nemonoxacin (a quinolone), and delafloxacin and zabofloxacin (both fluoroquinolones), have been studied in phase II and III in clinical trials. The availability of these new antibiotics may offer opportunities to improve the empirical treatment for community-acquired pneumonia.

Keywords: Community acquired pneumonia, emerging, antibiotics, omadacycline, lefamulin, solythromycin

1. Background

Community-acquired pneumonia (CAP) remains an important worldwide health problem. It is responsible for hospitalization, re-admissions, pulmonary and extra-pulmonary complications, and short- and long-term mortality [1, 2, 3]. The clinical presentation of CAP ranges from mild or localized to severe or systemic disease, which may be associated with complications such as sepsis, septic shock, and respiratory failure, even leading to multiple organ dysfunction and death. CAP is especially dangerous in elderly and immunocompromised patients, in whom the mortality rate can reach 20%–40%, which is significantly higher than the 6%–10% reported for the general population [4, 5].

Recently, investigations have focused on the increasing prevalence of antibiotic-resistant pathogens causing CAP, especially in severe cases [6, 7, 8], and on the relation between cell-mediated immunity and the inflammatory response to pneumonia [9, 10]. *Streptococcus pneumoniae* remains the main causative pathogen in CAP [11], despite studies indicating that respiratory viruses play an important role [12, 13]. However, a small proportion (6%) are caused by multidrug-resistant (MDR) pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae,* and *Acinetobacter baumannii.* The antibiotic resistance of these pathogens makes them a challenge for clinical management and a key global public health concern.

The development of molecular diagnostic techniques over the last three decades has led to the importance of respiratory viruses being emphasized as causes of CAP and its associated mortality worldwide. Indeed, approximately 20%–30% of patients hospitalized with viral CAP are estimated to need intensive care unit admission. Recently, our group [11] reported that viral sepsis was present in 19% of patients admitted to intensive care with CAP, with influenza viruses being most common, and males and older patients being at greatest risk. An interesting recent study by Zhou et al. [12] that investigated non-influenza viruses causing CAP showed that 63%, 26%, and 10% of cases were caused by influenza viruses, non-influenza viruses,

and mixed viral infections, respectively. The authors found that complications were common in patients with non-influenza CAP, but that outcomes were similar to those in patients with influenza. Together, these data support the importance of respiratory viruses as causes of CAP.

There is an urgent clinical need for effective antimicrobial therapy to treat the range of etiologies of CAP, especially in terms of improving the initial therapy given to patients with MDR pathogens. In this review, new antibiotics belonging to both old and new antibiotic classes will be analyzed and discussed with these considerations in mind.

2. Methods

The PubMed database was searched using the following search string: “Pneumonia” AND English AND (“Community-acquired” OR “Community acquired” OR “CAP” OR “Hospitalized” OR “Hospitalized”) AND (“Antibiotics” OR “Antimicrobial” OR “Resistance” OR “Anti-Bacterial Agents” OR “Antiviral Agents”). Search results were restricted to clinical trials, meta-analyses, observational studies, and systematic reviews. Titles and abstracts were initially screened to identify relevant citations, and these were then reviewed in full by two authors. We included all publications presenting data on CAP, and reviewed the study setting, methodology, and characteristics of the study population. All authors confirmed that the inclusion of the identified publications was appropriate.

3. Existing Treatment Options and Needs

3.1 Antibiotics

Antibiotic resistance in *S. pneumoniae* (pneumococcus), the main pathogen responsible for CAP, is a major global concern. The emergence of MDR pneumococcus due to overuse of antibiotics is a global concern that affects the main anti-pneumococcus drugs, β-lactams, macrolides, and fluoroquinolones. Last year a study about the burden of pneumococcal CAP in adults across Europe [1] showed that the overall incidence was 68–7000 per 100,000 and the incidence in hospitalized CAP cases was 16–3581 per 100,000. The authors reported that the

incidence increased with age, and that the greatest impact was observed in patients with more comorbidities. Interestingly, a study published by our group. [14] about the 20-year trend in mortality due to pneumococcal CAP in 1120 hospitalized adults in Spain failed to show any decrease in mortality over time. The recent report by the SENTRY Antimicrobial Surveillance Program [15] evaluated antimicrobial susceptibility for *S. pneumoniae* isolates worldwide over a 20-year period (1997–2016) indicated that MDR and extensively drug resistant isolates varied by region. The Asia–Pacific region showed the highest rates (41% in 1997–1998; 53% in 2007–2008; 39% in 2015–2016), whereas Latin America presented the lowest rates (10% overall). In North America, the data showed an increase from 9% in 1997–1998 to 24% in 2009–2010, followed by a decrease to 17% in 2015–2016. An increase was also seen in Europe from 17% in 1997–1998 to 24% in 2007–2008, but this also decreased in the last period (19% in 2015–2016).

The PES pathogen group (i.e., *P. aeruginosa*, extended-spectrum β-lactamase *Enterobacteriaceae*, and methicillin-resistant *S. aureus*) cause approximately 6% of cases of CAP [16]. Among them, *P. aeruginosa* and MRSA are the most frequently reported, and they require different antimicrobial therapy compared with typical pathogens. A recent multinational point-prevalence study [17] presented data from 3193 patients with CAP in 222 hospitals from 54 countries and reported the burden and risk factors associated with *P. aeruginosa* infection. The study showed that there was a low prevalence of CAP caused by *P. aeruginosa* (4%), corresponding to only 11% of patients with culture-positive pneumonia. The prevalence rates of antibiotic-resistant and MDR *P. aeruginosa* were also low at 2% and 1% respectively. By continent, the prevalence of *P. aeruginosa* in CAP was as follows: 3.8% in Europe, 4.3% in North America, 5.2% in Asia, 4.9% in South America, 5.5% in Africa, and 3.1% in Oceania. The corresponding prevalence of antibiotic-resistant *P. aeruginosa* was 1.6% (MDR, 0.9%) in Europe, 2.5% (MDR, 1.2%) in North America, 2.2% (MDR, 0.5%) in Asia, 3.0% (MDR, 2%) in South America, and 3.9% (MDR, 2.3%) in Africa, with no reported cases of *P. aeruginosa* antibiotic resistance in Oceania. Similarly, a Spanish prospective cohort study [18] into the clinical outcomes and risk factors for MDR and non-MDR *P. aeruginosa* reported a prevalence of 1.1% for MDR *P. aeruginosa* among 2023 culture-positive patients. CAP due to *P. aeruginosa* was shown to be an individual risk factor for mortality in that study population.

In two independent European studies of patients hospitalized with CAP, it was reported that MDR pathogens were causative in 3.3% (a Spanish cohort) and 7.6% (an Italian cohort), with MRSA pathogens being most common [8, 19]. The Global initiative for MRSA pneumonia (GLIMP) analyzed data for 3191 patients receiving microbiological tests within 24 h of admission for CAP and reported a 3% global incidence for MRSA as a cause. Risk factors for MRSA in CAP were prior MRSA infection or colonization, recurrent skin infection, and severe pneumonia. Other studies in the USA have reported incidence rates of 0.7%–2.4% [20, 21].

A. baumannii has been considered a rare cause of CAP, but one that retains clinical relevance. The great majority of CAP cases caused by *A. baumannii* are reported in tropical or sub-tropical countries, principally in Asia-Pacific regions, with the highest prevalence in Hong Kong, Singapore, Taiwan, South Korea, and Australia [22, 23]. In Europe and North America, however, *A. baumannii* is exceedingly rare. A recent USA report found that only 19 cases of severe CAP were caused by this pathogen [24]. Interestingly, in a case-control study in the USA that aimed to characterize the epidemiology of MDR *A. baumannii* colonization in high-risk nursing home residents, 15% (n = 25) of residents were noted to be colonized, with all isolates being resistant to cephalosporins, monobactam (aztreonam), and quinolones. They reported the main risk factors for MDR *A. baumannii* as functional disability, *Proteus mirabilis* colonization, and diabetes mellitus [25].

CAP caused by *K. pneumoniae* is reported in approximately 1%–7% of cases [8], with MDR strains accounting for only 5%–36%. In Asian countries, such as Taiwan, Cambodia, and Shanghai, *K. pneumoniae* has been described as a frequent cause of bacteremia [26, 27]. By contrast, CAP caused by *K. pneumoniae* is generally rare in Europe and USA, despite there being an increasing incidence in these regions over recent years [28, 29].

Empirical antibiotic therapy for severe CAP remains based on international guidelines that recommend a macrolide or a respiratory fluoroquinolone in combination with a β-lactam, with coverage for PES pathogens only given when certain risk factors are present. The research and development of new antibiotics is scientifically and economically challenging, yet this must remain a key goal given current global needs and the spread of antimicrobial resistance. Given that antibiotic therapies for MRSA and *P. aeruginosa* differ from typical empirical therapy, we must

recognize the risk factors and local epidemiology relevant to these resistant microorganisms in clinical contexts. Early recognition and prompt initiation of broad-spectrum empirical antibiotic therapy is mandatory to limit the negative effects of these pathogens, but this is limited by a decline in the production of new antibiotics and a failure to keep pace with epidemiological changes over recent decades. Arguably the most important consideration with these new antimicrobials is that they should be broad spectrum to allow clinicians to treat CAP in the era of increasing resistance.

3.2 Antivirals

Currently, neuraminidase inhibitors (e. g., oseltamivir, zanamivir, peramivir) are well established in clinical practice for use in patients with influenza infection, but no randomized-controlled trial (RCT) of has been completed to confirm the efficacy of these antivirals in hospitalized patients. The data of several prospective observational studies and meta-analysis indicate that neuraminidase inhibitor therapy at the time of hospitalization reduces both the length of hospitalization and the related mortality [30, 31]. The main problem with neuraminidase inhibitors like oseltamivir, however, is the need for early treatment. Other antivirals approved by the Food and Drug Administration (FDA) include adamantanes (e.g., amantadine and rimantadine) are not recommended because of widespread resistance. The polymerase inhibitors baloxavir marboxil and favipiravir have shown efficacy against influenza A and B, and against strains resistant to neuraminidase inhibitors, but is known about their resistance profiles.

During influenza seasons, respiratory syncytial virus (RSV) is a major cause of moderate-to-severe respiratory infection, especially in immunocompromised patients. Ribavirin is the only approved treatment option for RSV, but this antiviral suffers from its limited efficacy and propensity for genotoxicity.

4. Market review and current research goals

The increase in antimicrobial resistance has led to the development of new antibiotics in recent years, with may being approved for the treatment of pneumonia. Unfortunately, the development of new resistant bacterial strains has outstripped this

development because of high costs, long drug development times, and difficulties in designing and performing adequate trials. A current estimate is that fewer than 10 of the 50 leading pharmaceutical companies have active antimicrobial drug development programs [32].

Omadacycline, is a modernized tetracycline that was specifically designed to overcome tetracycline resistance. It received FDA approval in October 2018 for the treatment of bacterial CAP and acute bacterial skin and skin structure infections (ABSSSIs). Most agents detailed in this text have primarily been designed to treat infections caused by MRSA, but these have only proven secondarily to be active against MDR *S. Pneumoniae*. New lipoglycopeptides (e.g., dalbavancin, oritavancin, and telavancin) and oxazolidinones (e.g., tedizolid) are therefore attractive options for treating infections due to gram-positive MDR bacteria [33,34].

Unlike MRSA, research and development into novel drug candidates for gram-negative resistant bacteria, especially extended spectrum beta-lactamase inhibitors or carbapenem-resistant Enterobacteriaceae, will take longer and incur higher costs. Despite this clear need for novel antibiotics without the potential cross-resistance, no new drug classes are close to market entry. Two new cephalosporins with or without a β-lactamase inhibitor have been approved for such infection, just not for CAP: ceftolozane with tazobactam and ceftazidime with avibactam.

This situation is by no means new. Indeed, nearly all antibiotic classes in use today were discovered during the Golden Age of antibiotic innovation in the 1940s and 1960s [32]. Efforts to modify the chemical structures then focused on circumventing emerging class-specific target or drug-modifying resistance mechanisms, or to lower the affinity for efflux pumps, as well as on improving the pharmacokinetics and extending the spectrum of activity. The holy grail of antibiotic progress—a truly novel class of antibiotics—has not been achieved since 1987, and current economic incentives will likely continue this trend. A major hope lies with several biological agents, mainly monoclonal antibodies, which are in phase I or II development for use as adjunctive therapy in staphylococcal infections (e.g., 514G3, AR-301, DSTA-46375, suvratoxumab, SAL-200, ASN-100, and CF-301).

Numerous agencies and professional societies have tried to draw attention to the lack of new antibiotics, especially for the treatment of MDR gram-negative

pathogens. Since January 2012, when the Generating Antibiotic Incentives Now (GAIN) act came into effect in the USA, development of a new antibiotic agent that is active against one or several pathogens on a central list allows a Qualified Infectious Disease Product (QIDP) designation to be obtained [35]. Consequently, the overall USA budget to fight antimicrobial resistance almost doubled to about 1.2 billion dollars by 2016, with more antibacterial molecules clearly being approved in recent years.

5. Newly approved antibiotics and drugs in development

Newly approved and phase III drugs against gram-positive and gram-negative bacteria are described in Table 1. There are also a number of promising antibiotics in development that should be able to widen the therapeutic armament against difficult-to-treat gram-positive infections. Solithromycin, delafloxacin, zabofloxacin, and nemonoxacin have each demonstrated broad-spectrum antibacterial activity, together with other beneficial features such as intracellular accumulation, anti-inflammatory effects, and inhibition of biofilm production. A new drug, lefamulin, is a pleuromutilin antibiotic that is currently in phase III of development.

In this section we look at the main drugs showing potential in each of the main drug classes.

5.1. Cephalosporins: the potential of ceftaroline

The cephalosporins are known for their broad spectrum of activity, proven efficiency, and favorable safety profile, making them among the most commonly prescribed antimicrobials. Ceftobiprole and ceftaroline are particularly noted for their activity against MRSA and MDR S. *Pneumoniae*, but only ceftaroline is approved by the FDA in the treatment of CAP [36].

Ceftaroline (Teflaro® in the USA and Zinforo® in Europe) is a fifth-generation cephalosporin with an in vitro spectrum of activity that includes most of the common bacterial pathogens associated with CAP. It has bactericidal activity against MDR *S. pneumoniae,* non-extended-spectrum β-lactamase producing *K. pneumoniae*, and *Escherichia coli*, and its high affinity for PBP2a grants coverage against MRSA [37].

In vitro and in vivo animal models: The effect of ceftaroline in both combination therapy and monotherapy has been examined in multiple in vitro pharmacokinetic models. It has been used in combination with daptomycin, vancomycin, and rifampin. Ceftaroline and daptomycin both provide activity against MRSA, and ceftaroline increases the binding of daptomycin. B-lactams are used in combination with vancomycin due to the seesaw effect, an in vitro phenomenon where, as daptomycin and vancomycin minimum inhibitory concentations (MICs) increase in MRSA, the MICs of β-lactams, including ceftaroline, decrease [38].

However, both low-level and high-level resistance to ceftaroline have been observed in MRSA strains; particularly concerning are recent reports of resistance discovered in clinical MRSA isolates from patients in geographic regions never exposed to the drug [39]. Little is known of ceftaroline's ecological impact, though it is expected to be minor, as the drug is not excreted in the faeces.

The approval of ceftaroline for the treatment of CAP was based on two phase III multinational RCTs conducted in hospitalized patients: FOCUS 1 (NCT00621504) and FOCUS 2 (NCT00509106). In these, 600 mg ceftaroline fosamil was given every 12 h and demonstrated noninferiority to 1 g ceftriaxone every 24 h, but with differences in clinical cure rates at the test-of-cure visit favoring ceftaroline fosamil in each trial [40,41]. With ceftaroline, clinical cure was achieved in up to 80% of cases and the agent was well tolerated, with only mild adverse events (e.g., diarrhea, headache, and insomnia). However, neither study included patients admitted to intensive care or who had comorbidities, and there were few MDR S. *pneumoniae* (n ≤ 10) and MRSA (n = 1) isolates. Analysis of data from the FOCUS trials showed that ceftaroline was still associated with a shorter time to clinical response than ceftriaxone [42]. Although there are no data from RCTs supporting the use of ceftaroline fosamil for MRSA pneumonia, some research supports its efficacy in cases of MRSA bacteremia, MRSA endocarditis, and CAP [43,44].

Ceftaroline appeared to be well tolerated in these trials, but several post-marketing reports of severe myelotoxicity associated with prolonged exposure (>7 days) to ceftaroline have emerged [45]. At present, it is approved by the FDA and the European Medicines Agency (EMA) for the treatment of both CAP and complicated skin and skin structure infections [46].

5.2. Tetracyclines: the potential of omadacycline

Tetracyclines are a group of broad-spectrum antibiotics whose general usefulness has reduced with the onset of bacterial resistance. Despite this, they remain the treatment of choice for CAP due to their effectiveness against atypical bacteria.

Omadacycline is the lead compound of the novel aminomethylcycline subclass of tetracyclines. Similar to tetracyclines, omadacycline acts by inhibiting protein synthesis, but binds to 70 S ribosomes with greater affinity than tetracycline. The modification in the C-9 position arose from the finding that tigecycline, a C-9 substituted semisynthetic derivative of minocycline, was not affected by the most common resistance mechanisms, namely efflux and ribosomal protection, despite retaining clinical activity [47]. It is a broad-spectrum antibiotic with improved activity against tetracycline-resistant pathogens, including methicillin-susceptible *S. aureus* and MRSA, as well as various *streptococci* and *enterococci*. It is also more active than doxycycline and minocycline against Enterobacteriaceae and *A. baumannii*, with MICs of <4 μg/mL for 90% of strains [48]. Omadacycline is also active against many clinically important *Enterobacteriaceae* and a wide range of anaerobes [49], including the atypical organisms *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*.

Of clinical importance, omadacycline has also shown promise against fast-growing mycobacteria in a comparison with tigecycline and doxycycline, where it was demonstrated that omadacycline and tigecycline had similar activities against *M. abscessus*, (MIC_{50} of 1 μg/mL and MIC_{90} of 2 μg/mL. Against *M. chelonae*, the MIC_{50} values for omadacycline and tigecycline were 0.125 μg/mL and 0.06 μg/mL, respectively, indicating that the latter was superior; however, both drugs had the same MIC_{90} of 0.25μg/mL [50]. This notwithstanding, omadacycline has pharmacokinetic advantages of higher and more sustained concentrations in the plasma and epithelial lining fluid (ELF)compared with tigecycline, suggesting that it may be a promising antibacterial agent for the treatment of CAP caused by susceptible pathogens [51].

In the US, omadacycline was approved in October 2018 for the treatment of bacterial CAP and ABSSSIs . It is taken once daily, which offers an advantage over

minocycline and doxycycline, and is available in both oral and intravenous forms as a tosylate salt. However, its oral bioavailability is only 35%, with food reducing the oral bioavailability. It should therefore be administered in the fasted state. It is 20% protein bound in the serum and has a biologic half-life of 17 h [52].

The use of omadacycline was based on the results of a 750-patient phase III RCT (OPTIC Trial) that compared oral or intravenous omadacycline to oral or intravenous moxifloxacin for the treatment of mild, moderate, and severe bacterial CAP from November 2015 [53]. Patients were given 100 mg intravenous omadacycline twice a day (two doses), followed by 100 mg daily, intravenously, or 400 mg intravenous moxifloxacin once a day for three days. In both cases, there was an option to switch to oral administration. Omadacycline was statistically non-inferior to moxifloxacin for early clinical response, with rates of 81.1% and 82.7%, respectively [54]. Even though omadacycline had slightly lower success rates with *S. aureus*, it was still considered non-inferior to moxifloxacin [55]. Unfortunately, patients with severe CAP (graded class V in the Fine score) or those who presented in septic shock were excluded. Gastrointestinal side effects were also greater with omadacycline [56].

5.3. The ketolides: solithromycin, a next-generation macrolide

Solithromycin is the first next-generation macrolide of the fluoroketolide class [57]. Drug-binding studies indicate that it interacts with the 50S ribosomal site that either coincides or overlaps with that of other macrolides and ketolide [58]. Solithromycin binds to three distinct sites on the ribosome, whereas telithromycin binds to two sites. In terms of resistance selection, solithromycin has demonstrated a low tendency to select for resistant mutants, with little or no yields being detected in single-step studies [59]. In addition, it has potent in vitro activity against the most common bacterial pathogens in CAP, including macrolide-, penicillin-, and fluoroquinolone- resistant *S. pneumoniae* isolates, as well as *Haemophilus influenzae* and atypical bacteria.

Pharmacodynamically, solithromycin is 16-times more potent than either azithromycin, clarithromycin, or telithromycin against gram-positive aerobes and both atypical and gram-negative CAP pathogens [58]. It has good oral bioavailability (67%) when given orally and is not influenced by concomitant food intake, it serum

protein binding is 81%, and its biologic half-life of 8.5 h, allowing once daily dosing [60]. The major metabolic pathway appears to involve cytochrome P450 (CYP) 3A4, with most of the metabolite undergoing biliary excretion[61].

A phase II trial evaluated the safety and efficacy of solithromycin in the treatment of bacterial CAP (ClinicalTrials.gov registration no. NCT01168713) for the treatment of uncomplicated urogenital gonorrhea [62]. Recently, two phase III RCTs were completed for the treatment of mild-to-moderate bacterial CAP (NCT01968733 and NCT01756339). Solithromycin demonstrated noninferiority to moxifloxacin within 72 h, meeting the FDAs primary endpoint, but was inferior at 5–10 days, as required by the EMA. The efficacy and safety of oral solithromycin versus oral moxifloxacin in the treatment of bacterial CAP was also assessed in a global noninferiority RCT [63]. In the separate SOLITAIRE-IV phase III trial, the efficacy and safety of intravenous-to-oral solithromycin was assessed against intravenous-to-oral moxifloxacin for the treatment of bacterial CAP [64]. All patients began treatment with 400 mg intravenous solithromycin or moxifloxacin before switching to oral dosing when clinically indicated for a total treatment duration of 7 days. Oral dosing was 800 mg daily then 400 mg daily for solithromycin, or 400 mg daily for moxifloxacin. In this, 79.3% of patients who received solithromycin showed early clinical response compared with 79.7% of patients who received moxifloxacin. Finally, solithromycin is being tested in a phase II/III pivotal trial for bacterial CAP in a pediatric cohort (age 2 months to 17 years) (NCT02605122).

It appears that solithromycin does cause more adverse events (34%; mainly at the infusion site) compared with moxifloxacin (13%), though it does not prolong the cardiac QT interval. Solithromycin is chemically and biologically differentiated from telithromycin by its side chain, which does not significantly block nicotinic acetylcholine receptors. This could potentially reduce blurry vision, exacerbations of myasthenia gravis, loss of consciousness, and idiosyncratic hepatic failure reported with ketolides [65]. Nevertheless, hepatic safety remains a concern, with 5%–10% of patients experiencing mild transaminase elevations. Given the relatively small sample sizes in which solithromycin was studied, the FDA believes this may underestimate this particular safety risk. For this reason, on December 29th, 2016, the FDA recommended further studies, increasing the number of exposed patients from 924 to approximately 12,000 in an effort to evaluate the risk of hepatic toxicity

before formally granting approval [66, 67].

5.4. Quinolones: nemonoxacin, zabofloxacin, and delafloxacin

The quinolones levofloxacin and moxifloxacin have both been applied in the treatment of CAP, with each having antibacterial efficacy against major gram-positive and gram-negative respiratory tract pathogens. Novel quinolones therefore hold promise for the treatment of CAP even though fluoroquinolone resistant gram-negative and gram-positive respiratory tract pathogens are detected worldwide [68].

5.4.1 Nemonoxacin

Nemonoxacin is a novel C-8-methoxy non-fluorinated quinolone that targets DNA gyrase and topoisomerase IV, having a broader profile of activity and reduced resistance profile compared with other fluoroquinolones. TaiGen in-licensed nemonoxacin from Procter & Gamble Healthcare in 2011, when it obtained worldwide rights [69]. The drug benefits from a broad spectrum of activity against gram-positive, gram-negative, and atypical pathogens, including activity against MRSA (MIC_{90} = 1 μg/mL) and vancomycin-resistant pathogens, with similar activity to levofloxacin and moxifloxacin against most gram-negative bacteria [70]. It has also been shown to exhibit the best in vitro activity against *Nocardia spp*. among all tested antibiotics, including fluoroquinolones, carbapenems, tigecycline, and linezolid [71]. However, it exhibits poor activity against both MDR and non-MDR strains of *Mycobacterium tuberculosis*.

According to pharmacokinetic studies, the oral absorption of 500 mg nemonoxacin is rapid [70]. It has a mean time to maximum plasma concentration of 1–2 h, a half-life of 12.83–18.56 h, and a near 100% bioavailability. Moreover, it has low serum protein binding (16%) and no known interaction with cytochrome P450 isoenzymes, giving it minimal potential drug-drug interactions. Food significantly decreases both the maximum serum concentration (by 34%–46%) and the area under the curve (by 18%–27%) but increases the time to maximum serum concentration (by two- to three-fold). It is available in both oral and intravenous forms.

To date, phase II and III trials have compared oral formulations of nemonoxacin with

levofloxacin, but only a phase II trial has compared intravenous formulations of nemonoxacin with moxifloxacin. Despite these being complete, only one phase II trial of oral nemonoxacin has been published [72,73]. In a recent phase III noninferiority RCT in Taiwan, the efficacy and safety of nemonoxacin was compared with levofloxacin in 532 adults (≥ 70 years old) with mildly to moderately severe CAP (PORT scores II-IV) [74]. This showed nemonoxacin to be non-inferior to levofloxacin, with clinical cure rates of 94% in both groups and a favorable safety profile for nemonoxacin (adverse events of the gastrointestinal and nervous systems were most common). A second phase III multicenter, noninferiority RCT has completed enrollment and publication is anticipated (NCT02205112) [75].

In Taiwan, an oral formulation of nemonoxacin was approved in March 2014 for the treatment of bacterial CAP, and it had reached market in Taiwan, Russia, the Commonwealth of Independent States, Turkey, mainland China, and Latin America (brand name Taigexyn) by the end of 2016 [76]. It has already received priority review status by the FDA as a QIDP once further phase III studies are available documenting its safety and efficacy.

5.4.2 Zabofloxacin

Zabofloxacin is a broad-spectrum fluoroquinolone manufactured by Dong Wha Pharm. Co., Ltd. (Seoul, Republic of Korea). It has proven bactericidal efficacy both in vitro and in vivo against major gram-positive and gram-negative community-acquired pathogens of the respiratory tract, including *S. pneumoniae*, *S. aureus, H. influenzae, and M. catarrhalis*. By contrast, zabofloxacin has no activity against major pathogens associated with nosocomial pneumonia, such as *P. aeruginosa* and *A. baumannii* [77, 78]. The support for zabofloxacin's antibacterial efficacy and information about its pharmacokinetic profile have been gathered from three clinical trials. In a phase III, noninferiority RCT efficacy of 367 mg oral zabofloxacin once daily for 5 days was comparable to 400 mg moxifloxacin once daily for 7 days [79]. In a phase II RCT of the safety and efficacy of 400 mg oral zabofloxacin for 5 days compared to 500 mg oral levofloxacin for 7 days in CAP was terminated in 2012.

5.4.3 Delafloxacin

Delafloxacin, currently marketed as Baxdela in the US, is a fluoroquinolone with activity against a variety of gram-positive bacteria, including methicillin- and quinolone-resistant *S. aureus*, as well as quinolone-resistant strains of *P. aeruginosa* or *K. pneumonia* 80,81].

Its unique chemical structure facilitates improved cellular transmembrane penetration and potency in acidic environments common to most infectious sites. It has a novel mechanism of action that inhibits bacterial DNA replication by binding concurrently to both topoisomerase IV and DNA gyrase, in contrast to older fluoroquinolones that only inhibit either enzyme. The dual targeting of gyrase and topoisomerase IV decreases likelihood of resistance, which requires the accumulation of multiple mutations affecting both enzymes. This feature may contribute to the activity of delafloxacin against MRSA isolates, including those harboring mutations in the quinolone resistance determining region (QRDR) and to the low levels of resistance to delafloxacin among these MRSA isolates [82].

It also has greater affinity for DNA gyrase that older fluoroquinolones [83], which contributes to it having MICs that are consistently three- to five-fold lower. These features mean that delafloxacin not only exhibits a broader spectrum of activity but also confers less resistance compared to other fluoroquinolones.

Indeed, a 2014 surveillance study revealed that all European and 98% of USA isolates of *S. pneumoniae* were inhibited at <0.03 mg/L [84], with susceptibility rates among USA *E. coli and K. pneumoniae* isolates of 65% and 78%, respectively. Delafloxacin is also active against *P. aeruginosa* ($MIC_{50/90}$ 0.25/4 mg/l; 65% susceptible; comparable to other anti-pseudomonal fluoroquinolones) [85] as well as anaerobes, atypical respiratory tract pathogens (e.g., *Legionella*, *Chlamydia*, and *Mycoplasma*), and even against *M. tuberculosis*. Moreover, the biofilm penetration capacity of has been reported to vary between 0.6% and 52%, with an acidic environment favoring antibiotic entry [86].

The bioavailability of delafloxacin is 58% when given orally and it can be dosed without regard to food. It is only 16% protein bound and has a half-life of 3.7 h following a single 300 mg intravenous dose, which ranged from 4.2 to 8.5 h following multiple oral doses per day. Delafloxacin shares the class characteristic of high pulmonary distribution with a 13:1 mean penetration ratio into the pulmonary ELF compared with the free plasma concentration [87].

The role of delafloxacin for the treatment of CAP has shown promise in two phase II studies. In a phase II RCT, 309 outpatients affected by CAP were treated with once daily oral administration of delafloxacin at different dosages (100 mg, 200 mg, or 400 mg) for 7 days, with overall clinical and bacteriologic cure rates achieved in up to 87% of patients. A phase III RCT (DEFINE-BCAP) has also compared delafloxacin with either moxifloxacin or linezolid for the treatment of adults with bacterial CAP, including MRSA [88]. To date, the incidence of adverse effects appears to be dose dependent, with diarrhea and nausea being most common; others include mild central nervous system effects, endocrine abnormalities, and increased serum liver function tests. However, no cases of clinically relevant prolongations of the QT/QTc interval have been reported in healthy volunteers [78]. It is also worth noting that delafloxacin is currently in phase III clinical development for the treatment of uncomplicated gonorrhea (as a single 900 mg oral dose) [89], and that phase III trials have determined that it is non-inferior to vancomycin or aztreonam for the treatment of ABSSSI [90,91].

In 2017, delafloxacin received FDA approval for the treatment of ABSSSIs caused by gram-positive and gram-negative bacteria, including MRSA, and is available in intravenous and oral formulations. The recommended dosage is 300 mg administered intravenously over 60 minutes or 450 mg administered orally every 12 h for a maximum of 14 days [92]. Delafloxacin has been designated a QIDP by the FDA and has been granted fast track status for CAP once phase III trials are complete.

5.5. The pleuromutilins: Lefamulin

Pleuromutilin antibiotics are semisynthetic derivatives of pleuromutilin, a natural product of the fungi *Pleurotus mutilus* (now called *Clitopilus scyphoides*). These function by inhibiting bacterial protein synthesis through binding to the peptidyl transferase site on 23S RNA of the 50S ribosome. Retapamulin was the first agent to be approved by the FDA in 2006, but this was only for topical use in impetigo. Another pleuromutilin, tiamulin, has been used with success as a veterinary drug in Europe and Canada [33]. However, lefamulin is the first pleuromutilin to be developed for oral or intravenous use in humans.

Lefamulin works by binding to the 50S subunit of the bacterial ribosome at four distinctive binding sites in a highly conserved core of the ribosomal peptidyl transferase center. This unique mechanism of action also results in a lack of cross-resistance to most currently marketed antibiotics and has inspired the development of analogs in an attempt to find clinically desirable derivatives [93]. Indeed, the drug has potent in vitro activity against organisms resistant to β-lactam antibiotics, fluoroquinolones, macrolides, tetracyclines, and vancomycin.

Lefamulin achieves extensive penetration and accumulation in pulmonary epithelial lining fluid, with epithelial lining fluid exposure to lefamulin being 5.7-fold higher than the unbound fraction in plasma [94]. It is 80% protein bound in the serum, has a biologic half-life of 12 hours, and is largely excreted unchanged via the gastrointestinal tract (86%), with the remainder eliminated via the kidneys (14%) [95]. Intravenous dosing is only required once per day, but the oral route requires dosing twice per day. Pharmacodynamically, it is highly potent with an MIC_{90} that is four-times lower than either oxacillin, vancomycin, linezolid, or ceftaroline for *S. aureus* species (including MRSA) and many other common CAP-associated pathogens [96,97]. In addition, it has displayed potency against Neisseria spp., including MDR and extensively drug resistant N. gonorrhea isolates, supporting its potential use against gonorrhea [98].

Two phase III, noninferiority RCTs have compared the efficacy and safety of lefamulin with moxifloxacin for adult patients with mildly to moderately severe CAP, associated with PORT scores of II–IV (ClinicalTrials.gov identifier: NCT02559310 & NCT02813694) [99,100]. In LEAP 2, lefamulin met the primary endpoint for noninferiority (within 10%) set by the EMA based on investigator assessment of clinical response rates at 5–10 days following therapy completion in modified intent-to-treat and clinically evaluable at test-of-cure populations [101]. The reported side effects mainly consist of headaches (7%), nausea (7%), and diarrhea/vomiting (4%) [102]. Intravenous and oral formulations of lefamulin are currently undergoing FDA review for use in the treatment of CAP.

6. Antiviral options

6.1. Favipiravir

Favipiravir is a selective and potent inhibitor of influenza viral RNA polymerase [103] with efficacy against all subtypes and strains of influenza (A, B and C), including those that are sensitive or resistant to neuraminidase and M2 inhibitors. Interestingly, favipiravir has antiviral activity against other RNA viruses, including Bunyaviridae, Arenaviridae, Filoviridae, Flaviviridae, and Picornaviridae [104-108]. In 2010, Sleeman et al. evaluated the in vitro ability of favipiravir to block the proliferation of representative influenza viruses: 2009 A(H1N1) strains, A(H1N1) and A(H1N2) viruses of swine origin which were isolated from humans during 2007 and 2008, A(H2N2), A(H4N2), and A(H7N2), A(H5N1). This included strains that were resistant to either oseltamivir, zanamivir, or both, yet favipiravir retained antiviral activity against a wide range of influenza viruses, including the resistant ones. Currently, favipiravir is approved in Japan, where its use is restricted to patients infected with influenza virus resistant to neuraminidase inhibitors or in the event of a pandemic. Unfortunately, favipiravir is associated with a risk for teratogenicity and embryotoxicity.

6.2 Pimodivir

Pimodivir inhibits the protein basic 2 (PB2) subunit of the influenza A virus polymerase complex, thereby inhibiting viral replication[109]. It has in vitro activity against influenza A virus, including influenza pandemic 2009 H1N1, H7N9, H5N1, and strains resistant to neuraminidase and amantadine. Although it lacks activity against influenza virus B, in vitro studies have demonstrated synergy between pimodivir and oseltamivir.

In a phase IIa study [110] of 104 healthy volunteers infected with an influenza virus A (H3N2), 72 received pimodivir and 32 received placebo. The pimodivir was given once daily for 5 days from 24 h after viral inoculation at doses of 100 mg, 400 mg, 900/600 mg (as a loading dose), or 1,200/600 mg (as a loading dose). The authors significantly reduced viral shedding, influenza-like symptoms, and clinical symptoms in all dose groups compared with placebo, and that these doses were generally safe and well tolerated. In the subsequent phase IIb study [111], adults with acute uncomplicated influenza A infection were given one of the following treatments twice daily for 5 days: placebo, pimodivir 300 mg, pimodivir 600 mg, or pimodivir 600 mg

plus oseltamivir 75 mg. Pimodivir produced significant virologic improvements over placebo, with or without oseltamivir, showing a trend in clinical improvement and not serious adverse events. Currently, a phase III test among patients hospitalized with influenza A virus infection is ongoing.

6.3. Presatovir

Presatovir is an antiviral that inhibits the fusion of RSV with host cell membranes. Its efficacy has been demonstrated in preclinical and clinical studies [112–114], with in vitro activity against both major RSV strains (A and B). Studies have specifically reported lower viral loads after healthy volunteers infected with RSV received presatovir [113, 115]. Moreover, these studies have reported a favorable safety profile.

6.4. Other agents

Ziresovir is a fusion protein inhibitor with purported activity against RSV and is currently undergoing phase II clinical trials. Lumicitabine, a nucleoside analog prodrug, is also in clinical development. However, there is limited data on either of these new drugs.

7. Conclusion

CAP management requires prompt and adequate antibiotic therapy. Newly approved and investigational agents for the treatment of CAP hold promise that we can enhance our antibiotic armamentarium. However, we must first ensure that these new antibiotics are not only effective and well tolerated in patients but also that their use is kept appropriate so that we can avoid the emergence of resistance.

8. Expert opinion

Although the specific of antimicrobial therapy for CAP vary between countries, β-lactams, fluoroquinolones, and macrolides are among the most commonly recommended agents. Ceftaroline, a new cephalosporine, may be considered a reasonable future option for empirical therapy in areas with a high prevalence of

MRSA or drug-resistant pathogens, rather than being kept as a reserved drug. Hope exists with the development of novel agents from known antibiotic classes, such as solithromycin (a ketolide) and zabofloxacin and delafloxacin (fluoroquinolones).

Solithromycin benefits from having multiple binding sites in the 50S ribosome, making it more potent than other macrolides. Its oral formulation appears to be clinically effective, well tolerated, and to be suitable for once daily dosing over 5 days. We anticipate that its development will be pursued to treat infections in children and pregnancy given its desirable antibacterial activities and safety profile in preclinical studies. Omadacycline (a newly approved cycline) offers a single-agent parenteral or oral alternative to traditional empirical therapy in bacterial CAP. Additionally, it is significantly more active than doxycycline or minocycline against Enterobacteriaceae and *A. baumannii*, and meets the FDA criterion for susceptibility of *K. pneumoniae*. Unfortunately, patients with severe CAP (Fine class V) or those who presented in septic shock were excluded from the RCTs of solithromycin and omadacycline, so we lack clinical data for their use in those patients.

Importantly, delafloxacin could represent a highly promising option for the treatment of CAP based on broad-spectrum activity (including MRSA), oral formulation, diminished risk of resistance selection, and a favorable tolerability profile. The chemical structure of delafloxacin (lack of basic group in position C7) also makes it a non-zwitterion agent that facilitates it's in vivo activity in acidic mediums. Together with its in vitro sensitivity against anaerobes, lipid solubility, and pulmonary diffusion, this could make it a viable empirical treatment in cases of aspiration pneumonia or bacterial pulmonary abscesses. However, fluoroquinolones have increasingly fallen from favor because of rare adverse events, including tendinopathies, neuropathies, and aortic dissection. On this basis, omadacycline probably represents the most appropriate first-choice empirical treatment for CAP.

A major limitation of the antimicrobials described in this review is a lack of potency against pathogens responsible for nosocomial pneumonia. Infections caused by MDR *P. aeruginosa, A. baumannii*, and *Stenotrophomonas maltophilia* will therefore continue to pose clinical challenges because of the limited availability of potent antimicrobials against these gram-negative pathogens. Although there are several promising antibiotics in development, regulatory approval over the next five years will be key to any return to the availability of a more comprehensive antimicrobial

armamentarium that can cope with the broad spectrum of bacterial disease presenting in CAP.

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TABLES 1: Antibacterial agents in the pipeline for CAP

Drug Class	Drug Name	Spectrum	Dose	Development phase for CAP	Indications
Fluoroquinolone	Nemonoxacin	*MRSA, VRE, A. baumannii*	500mg /24h	Phase III recruiting for i.v. formulation under US IND; phase III oral formulation complete	ABSSI, BCAP,diabetic foot ulcer infections
	Delafloxacin Baxdela	Gram+ and –, including MRSA	Dosage for IV use is 300 mg / 12 h, and 450 mg /12h p.o.	Phase III for VAP	Approved in 2017 for Acute bacterial skin and skin structure infection
	Zabofloxacin	Gram+ and –,	367mg/24h p.o. for 5 days	Phase II for CAP	AECOPD BCAP
Macrolide	Solithromycin	Gram(+), including macrolide resistant strains	800mg loading dose and 400mg once a day for five days	Phase III for CABP and uncomplicated gonorrhoea, in phase II for paediatric use	ABSSSI; Prophylaxis for *N. meningitidis*; potential for urethritis and other urogenital infections
Tetracycline	Omadacycline	Broad spectrum incl MDR	100mg/24h (i.v.) 150mg/24h p.o.	Phase II complete; phase III planned under FDA SPA	**FDA ACCEPTED FOR**: ABSSSI AND BCAP
Pleuromutilin	Lefamulin	Broad spectrum	600mg/12h p.o.	Phase III	BCAP
Cephalosporine	Ceftaroline Teflaro	Gram (+), gram (-), and	600mg/12h for 10 days		**FDA ACCEPTED**

		MRSA			**FOR** :BCAP

ABSSI: Acute bacterial skin and skin structure infection, BCAP: Bacterial community-acquired pneumonia