

Treatment of community-acquired pneumonia, with special emphasis on gemifloxacin

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Abstract: Community-acquired pneumonia (CAP) is the cause of substantial morbidity, mortality, and resource utilization worldwide. When choosing an antimicrobial, effective treatment depends on proper patient evaluation and the identification of numerous risk factors, such as recent antibiotic exposure or the presence of comorbidity. Patients without any risk factor should be treated effectively with a narrow spectrum β -lactam agent, like amoxicillin, or a macrolide. If a risk factor is present, agents with a broader spectrum of activity should be selected for the empirical therapy. The newer-generation quinolones are suitable agents with their excellent in vitro activity and pharmacodynamic–pharmacokinetic properties. They are not only active against susceptible CAP pathogens, but also against the resistant strains. Among the quinolones, gemifloxacin has the best in vitro activity. Its improved bioavailability, pharmacokinetic–pharmacodynamic properties, and safety profile make this agent an excellent option for the treatment of CAP.

Keywords: treatment, community-acquired pneumonia, gemifloxacin

Introduction

Community-acquired pneumonia (CAP) remains a frequent and important clinical entity. Each year, there are 2 to 3 million cases of CAP in the US, resulting in approximately 10 million physician visits (Bartlett et al 2000). Despite substantial progress in therapeutic options, CAP remains a significant cause of morbidity and death, and there continue to be major controversies concerning the antimicrobial management of this infection (Paganin et al 2004). The mixed etiology and the changing susceptibility of pathogens causing CAP, in particular that of *Streptococcus pneumoniae*, has created a challenge, in some circumstances, to clinicians as to which therapeutic approaches may be the most appropriate in terms of optimal patient outcome (Oncu et al 2005). Initial antimicrobial therapy is normally given empirically, before the bacterial cause of the infection can be determined in the laboratory, and in many cases treatment is empirical throughout due to the lack of reliable microbiological data. An understanding of the possible pathogens and resistance patterns is helpful in guiding antibiotic choice, and a detailed knowledge of the local susceptibility of the potential pathogens would ensure a more appropriate selection of the antimicrobial agent to be used (Appelbaum et al 2004). This review focuses on the treatment options of CAP with special emphasis on gemifloxacin.

Etiology of CAP

Although CAP may be caused by many possible pathogens, a limited number of common pathogens are responsible for most cases (Lim et al 2001). In fact, no etiologic agent is found in as many as 50% of cases, even when extensive diagnostic testing is performed (Niederman et al 2001). In those cases in which an etiologic agent is identified, *S. pneumoniae* accounts for the majority of bacterial pneumonia (Jokinen

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et al 2001). Relative to other pathogens, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Haemophilus influenzae*, *Legionella pneumophila*, and respiratory viruses are also common.

Staphylococcus aureus and Enterobacteriaceae pathogens are found in a selected group of patients such as those who have had influenza, have previously taken antimicrobial drugs, or have comorbidities (Arancibia et al 2002). Table 1 lists the most common pathogens associated with CAP based on the collective results of recent studies and based on the severity of illness as judged by the site of care (outpatient versus inpatient) (File 2003; File and Niederman 2004).

Of the respiratory pathogens, penicillin-resistant *S. pneumoniae* (PRSP) has attracted the greatest interest. PRSP is a widespread problem, with rates of resistance ranging from 5% to 80% in various parts of the world (Forward 1999; Öncü et al 2005). Risk factors for infection with PRSP strains include young age, day-care center attendance, prior administration of antimicrobial agents, and severe underlying diseases (Clavo-Sanchez et al 1997). As the use of non-penicillin antimicrobials has increased, so has the development of resistance to these agents among *S. pneumoniae*. Worldwide rate of macrolide resistance has risen dramatically in recent years. The prevalence of resistance is highly variable between countries, ranging from <3% to >70% (Cizman et al 1999; Oster et al 1999). Emergence of *S. pneumoniae* with reduced susceptibility to quinolones has also been reported in England and the US (Brueggemann et al 2002; Johnson et al 2003). Fortunately, the incidence of quinolone resistance is currently low worldwide (<1%) (Garcia-Rodriguez and Munoz Bellido 2000).

Outpatient vs inpatient treatment

A clinical prediction rule has been tested based upon the likelihood of mortality from CAP (Fine et al 1997; Lim et al 2003). It is especially useful to predict the severity of CAP,

to identify patients who can be safely treated as outpatients (Figure 1) (Lim et al 2003). Prediction of the severity of CAP is also used to estimate the possible etiology of CAP and guides the selection of empirical therapy. The approach to empirical antimicrobial drug selection in CAP is presented in Figure 2.

Antimicrobial therapy

Ideally, the choice of antibacterial therapy for the empirical treatment of CAP will be one that is highly effective against the common respiratory pathogens, in particular *S. pneumoniae*, has a good safety profile with few adverse effects, and is formulated to achieve adequate dosing to eradicate the infecting pathogen.

β -lactam antibiotics

The relationship between the inappropriate use of antimicrobials and resistance might suggest that β -lactams would have reduced effectiveness in CAP caused by *S. pneumoniae*. Although this is the case for meningeal infections, the clinical relevance of resistance in the treatment of pneumonia remains controversial. Several studies have shown no difference in outcomes, including mortality, between patients with penicillin-susceptible and those with penicillin-resistant *S. pneumoniae* as the cause of CAP (Friedland 1995; Pallares et al 1995; Choi and Lee 1998; Deeks et al 1999). It is likely that, in cases in which isolates have intermediate or low-level resistance to penicillin, the drug concentrations achieved in serum and in the lungs are adequate to eradicate these strains. However, strains for which the minimum inhibitory concentrations (MICs) of penicillin are higher (≥ 4 mg/L) may affect outcomes, and therapeutic failures are more likely to be seen as more strains with high-level penicillin resistance emerge (Pallares et al 2003). Although the impact of PRSP in CAP has been evaluated in several studies, the impact of cephalosporin resistance is less well studied. Several studies reported that cephalosporin resistance negatively affected the clinical outcomes of patients with CAP (Ailani et al 2002; Yu et al 2003; Garau 2005). In pneumonia caused by other respiratory pathogens, such as *H. influenzae* and *Moraxella catarrhalis*, the impact of resistance caused by β -lactamase production can be overcome by the use of a β -lactam/ β -lactamase inhibitor combination or a β -lactamase-stable cephalosporin (Garau 2005).

Macrolides

Although the global increase in macrolide resistance in isolates of *S. pneumoniae* is disturbing, the clinical impact

Table 1 Microbiological etiology in CAP by site of care

CAP in primary care	CAP requiring hospitalization
<i>S. pneumoniae</i>	<i>S. pneumoniae</i>
<i>M. pneumoniae</i>	<i>H. influenzae</i>
<i>C. pneumoniae</i>	<i>M. pneumoniae</i>
<i>H. influenzae</i>	<i>C. pneumoniae</i>
<i>M. catarrhalis</i>	<i>M. catarrhalis</i>
Respiratory viruses	<i>Legionella</i> spp.
	<i>S. aureus</i>
	Enterobacteriaceae species
	Respiratory viruses

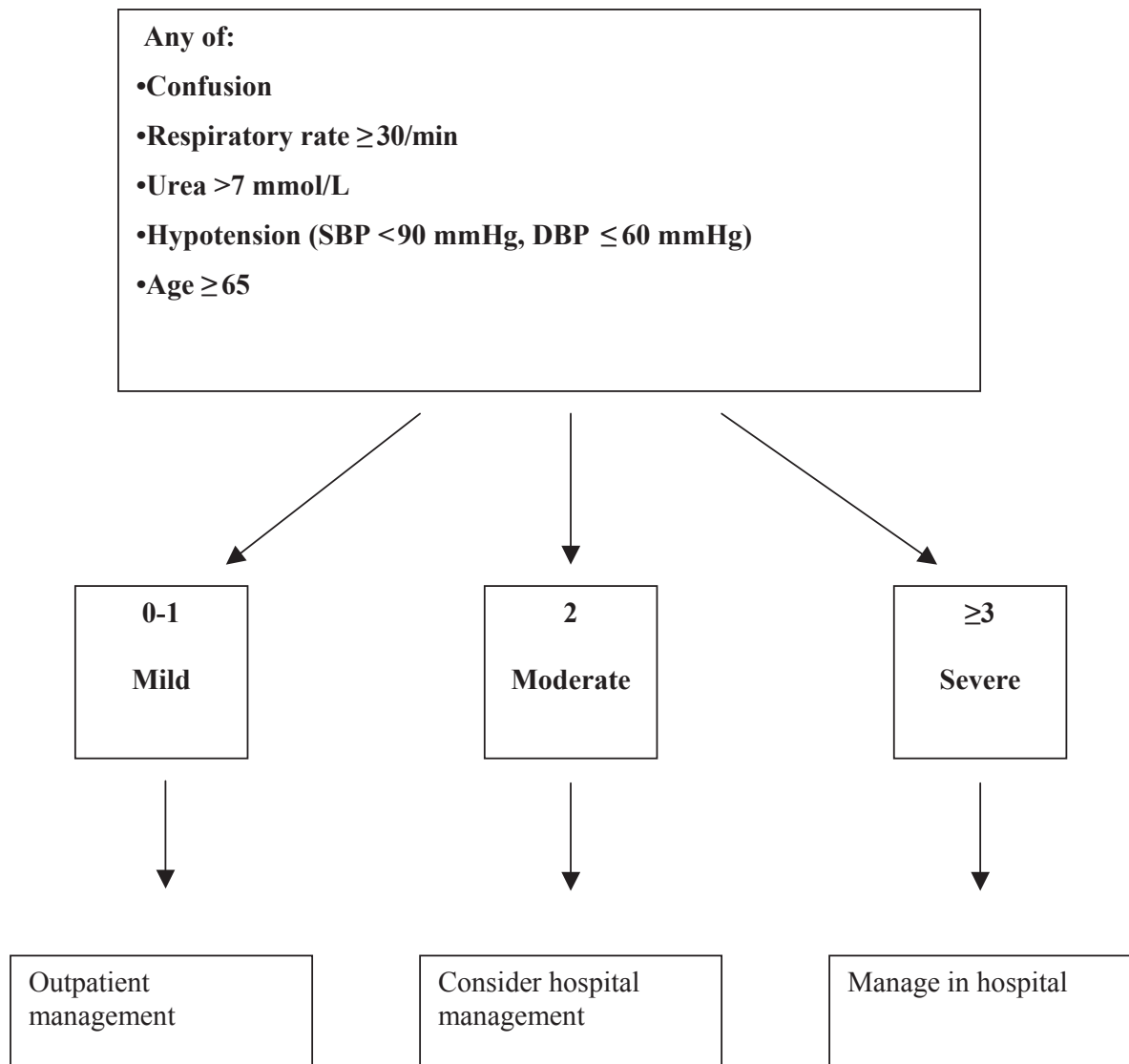


Figure 1 Prediction of the severity of CAP and recommendation for patient site of management.

of these in vitro results has not been determined (Gotfried 2000). In vitro macrolide resistance may not translate into therapeutic failure if high tissue concentrations are achieved at the site of infection. This may be the case for infections caused by strains of *S. pneumoniae* with low-level macrolide resistance (MIC <8 µg/mL) through increased active efflux of antimicrobials (Shortridge et al 1999). On the other hand, the majority of pneumococci harboring the ermB gene exhibit high levels of resistance that cannot be overcome by clinical use of macrolides; therefore, failure is predictable if a macrolide is used in infections caused by strains harboring the ermB gene (Oster et al 1999). Several studies have examined macrolides in the treatment of CAP in outpatients who were subsequently hospitalized (Kelley et al 2000; Lonks et al 2002; Van Kerkhoven et al 2003). The results of

these studies suggest that breakthrough bacteremia is likely to occur during macrolide therapy for pneumonia due to the presence of macrolide-resistant *S. pneumoniae* strains. In addition, there have been several case reports and case series concerning macrolide failures in patients with pneumonia caused by macrolide-resistant strains (Fogarty et al 2000; Kelley et al 2000; Musher et al 2002).

Based on current rates and level of macrolide resistance, continued use of this drug class is warranted for most patients with CAP. A macrolide alone should be an adequate treatment option for mild-to-moderate CAP in patients who have been healthy and are without risk factors for antibiotic resistance (recent macrolide use, age <5 or >65 years, daycare attendance, recent hospitalization, residence in a high prevalence area). Given the inability

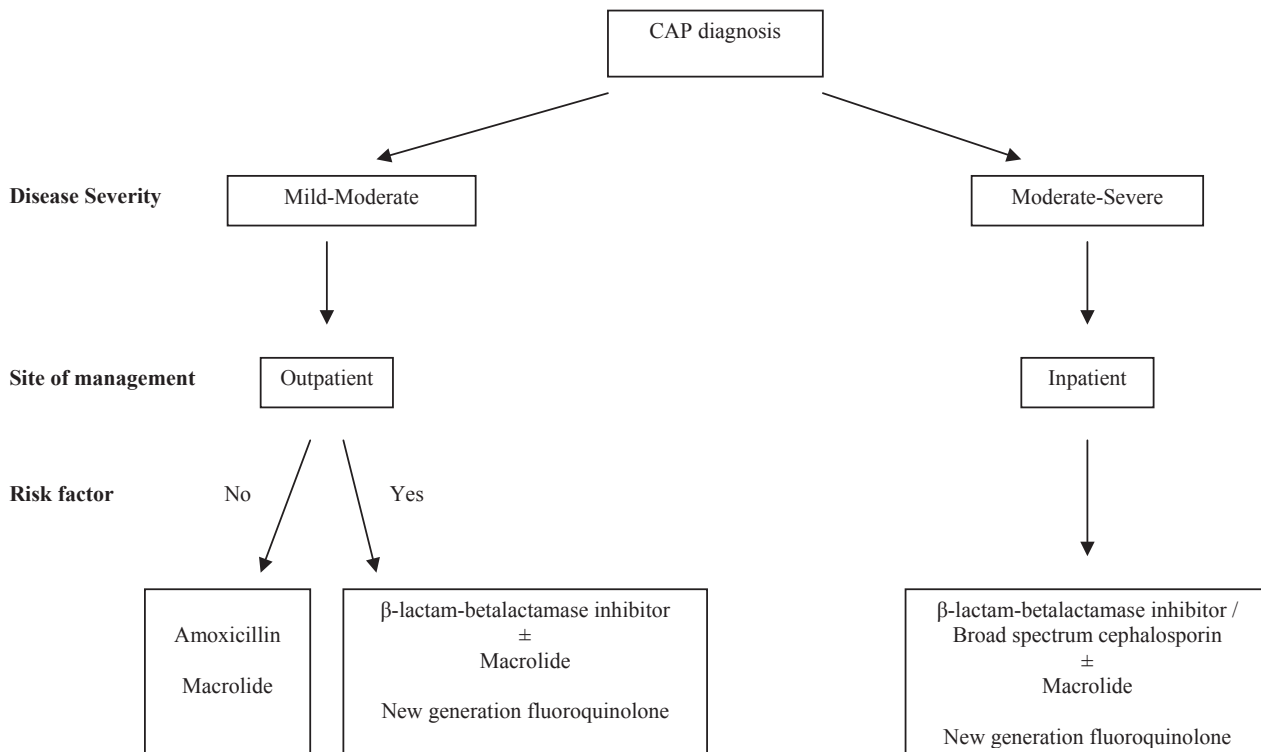


Figure 2 Algorithm for the selection of empirical antimicrobial agent in CAP.

to predict antibiotic resistance, however, macrolides are not recommended for the treatment of complicated or life-threatening severe CAP.

Quinolones

Quinolones inhibit bacterial DNA gyrase and topoisomerase IV, thereby causing bacterial cell death (Lewis et al 1996; O'Donnell and Gelone 2000). Topoisomerase IV is a key target for quinolones that have activity against Gram-positive organisms (O'Donnell and Gelone 2000). The early quinolones, ciprofloxacin and ofloxacin, are not considered suitable for the treatment of CAP because of their low activity against Gram-positive bacteria (O'Donnell and Gelone 2000). Recent years have seen the development of newer quinolones such as levofloxacin, gatifloxacin, moxifloxacin, and gemifloxacin, which have significantly improved activity against Gram-positive organisms (including PRSP) and macrolide-resistant strains (Garcia-Rodriguez and Munoz Bellido 2000). These agents have enhanced activity against topoisomerase IV. They have rapid bactericidal activity and desirable pharmacokinetic and pharmacodynamic features (Garcia-Rodriguez and Munoz Bellido 2000). These newer quinolones are also active against bacteria causing atypical pneumonia and against β -lactamase producing and

non-producing *H. influenzae* and *M. catarrhalis*. Moreover, they have a good activity against other other Gram-negative bacilli, similar or even higher, in some cases, to ciprofloxacin. Current resistance is very low in these agents and so, from a theoretical point of view, their spectrum and intrinsic activity are suitable for the treatment of CAP.

Gemifloxacin

Gemifloxacin was approved by the FDA in 2003 to treat mild-to-moderate CAP caused by a range of pathogens. It is a fluoronaphthyridone possessing a C-7 pyrrolidine substitution. The commercially available product is gemifloxacin mesylate salt in the sesquihydrate form. Gemifloxacin is available in tablet formulation, with each tablet containing gemifloxacin mesylate equivalent to 320 mg of gemifloxacin (Hong 2001).

Mechanism of action and resistance

Gemifloxacin possesses a strong affinity for topoisomerase IV, which is likely to be responsible for its potent in vitro activity against *S. pneumoniae* (Morrissey and George 2000). It is a dual targeting quinolone and retains activity against mutations in either or both targets (Heaton et al 2000; Gillespie et al 2002; Yague et al 2002). The high affinity for

gemifloxacin for both targets accounts for its high potency and continued activity.

Organisms with a single mutation in the ParC subunit usually remain susceptible to these agents. *S. pneumoniae* becomes resistant to gemifloxacin through mutations in *gyrA*. Because mutations in *parC* arise at a much higher rate than in *gyrA* in *S. pneumoniae*, resistance to gemifloxacin may be expected to emerge at a slower rate than for quinolones that become resistant through mutations in *parC* (Gillespie et al 2003). In fact, despite a variety of resistance mechanisms, quinolone-resistant strains of *S. pneumoniae* remain susceptible to gemifloxacin (Heaton et al 1999; Broskey et al 2000).

Gemifloxacin was also shown to have a significant in vitro post-antibiotic effect against strains of *S. pneumoniae* and *H. influenzae* (Davies et al 2000a). In another study, the PAE at 4 x MIC was greater than 6 hours for *H. influenzae*, *Pseudomonas aeruginosa*, and *Proteus vulgaris* and 0.1–2.5 hours for the other Gram-positive and Gram-negative organisms tested (Davies et al 2000b).

In vitro activity

Compared with other quinolones, it possesses enhanced in vitro activity against *S. pneumoniae*, including isolates resistant to β -lactams, macrolides, and quinolones, while retaining activity against Gram-negative and atypical pathogens. The in vitro activity of gemifloxacin, compared to other quinolones, against commonly isolated respiratory pathogens is shown in Table 2 (Deshpande and Jones 2000; Marchese et al 2000; McCloskey et al 2000; File and Tillotson 2004; Oncu et al 2004; Bhavnani and Andes 2005).

Pharmacokinetic and pharmacodynamic properties

Gemifloxacin given orally is rapidly absorbed, with the peak concentration being observed in 30–120 minutes, and it is widely distributed throughout the body (2004). Compared with other quinolones, gemifloxacin achieves higher concentrations in bronchial mucosa, epithelial lining fluid, and bronchoalveolar macrophages than in plasma (Appelbaum

et al 2004; Bhavnani and Andes 2005). It has also the highest area-under-the-curve (AUC)/MIC and C_{max} /MIC values among quinolones (Firsov et al 2000).

Gemifloxacin and its metabolites are dually excreted via urine and feces. Approximately 20%–30% of the administered dose is excreted unchanged in the urine, and the plasma half-life is approximately 6–8 hours (Allen et al 2001; Zhanel and Noreddin 2001). Dosage adjustments are not necessary in patients with mild renal or any level of hepatic insufficiency, nor in the elderly.

Drug–drug interactions

Gemifloxacin has been investigated for interactions with various other substances (File and Tillotson 2004). Gemifloxacin can be taken with or without food, should be taken either 2 hours before sucralfate or ferrous sulfate, or at least 3 hours after ferrous sulfate, and should be administered 2 hours or more prior to or 3 hours or more after cation-containing compounds (Allen et al 1999, 2000a, b).

Adverse effects

The most frequently reported adverse effects in the clinical trials were diarrhea, nausea, and rash (File et al 2001; File and Tillotson 2004). The potential of phototoxicity caused by gemifloxacin is similar to that of ciprofloxacin (Allen et al 1999). Gemifloxacin has been reported to demonstrate small, non-significant QTs interval prolongation (Yoo et al 2004). Liver failure does not appear to be associated with gemifloxacin, but mild and reversible elevations of liver enzymes may occur (Lode et al 2002).

On the whole, the following advantages are more prominent in gemifloxacin compared with other drugs usable in CAP (Ball 2000; File and Tillotson 2004):

- Enhanced activity against *S. pneumoniae* (including PRSP)
- Improved activity against atypical pathogens
- Active against Gram-negative pathogens except *P. aeruginosa*

Table 2 The MIC₉₀ (μ g/mL) values of gemifloxacin and other quinolones against common CAP pathogens

Microorganism	Gemifloxacin	Levofloxacin	Gatifloxacin	Moxifloxacin	Ciprofloxacin
<i>S. pneumoniae</i>	0.015–0.06	1–2	0.50	0.12–0.25	1–4
<i>H. influenzae</i>	<0.004–0.06	0.015–0.12	0.015–0.03	<0.03–0.06	0.008–0.03
<i>M. catarrhalis</i>	0.008–0.03	<0.03–0.06	<0.03–0.03	0.03–0.125	<0.016–<0.5
<i>M. pneumoniae</i>	0.125	0.5	0.125	0.125	2
<i>C. pneumoniae</i>	0.25	1	0.25	1	2
<i>L. pneumophila</i>	0.016	0.016	0.016	0.016	0.03

Table 3 Clinical and bacteriological efficacy of gemifloxacin and comparator antibiotics in CAP

Compared antibiotic regimen	Clinical success (%)		Bacteriological success (%)	
	Gemifloxacin	Comparator	Gemifloxacin	Comparator
Trovafloxacin	94	89.9	87.9	89.3
Sequential iv ceftriaxone/oral cefuroxime	92.2	93.4	90.6	87.3
Amoxicillin/clavulanate	88.7	87.6	87.2	89.1
Oral cefuroxime + clarithromycin	87.6	92.6	89.9	88.9
Non-comparative	91.7	–	87.3	–
Non-comparative	89.8	–	90.0	–

- Favorable pharmacokinetics, once-daily dosing, balanced elimination requiring very little dosage modifications
- Based on pharmacokinetics, highly effective in respiratory infections
- Few drug–drug interaction
- Few adverse drug reactions

Clinical experience of gemifloxacin in CAP

Six clinical trials of gemifloxacin have been performed in CAP (Ball et al 2001; File et al 2001; Lode et al 2002; Appelbaum et al 2004; Leophonte et al 2004). The clinical success rates were all close to or above 90% for gemifloxacin (87.6%–94.0%) and were similar to the comparators (87.6%–93.4%). Also, bacteriological success rate with gemifloxacin was good in all six studies (87.2%–90.6%) and comparable with that recorded by the comparators in the four comparative studies (88.9%–89.3%). Table 3 summarizes the clinical and bacteriological efficacy of gemifloxacin and comparator agents.

Conclusion

CAP remains a frequent and important clinical entity. Nearly 80% of the treatment for this condition is provided in the outpatient setting. Antimicrobial treatment of CAP must cover *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* and in many circumstances should also cover the intracellular atypical pathogens. The β -lactams have been considered standard therapy for the treatment of CAP. However, rising resistance rates among CAP pathogens are now a primary concern. Recent antibiotic usage and the presence of comorbidities are among the accepted risk factors for CAP caused by resistant pathogens. Patients without any risk factor should be treated effectively with a narrow spectrum β -lactam agent, like amoxicillin, or a macrolide. For patients with risk factors broader-spectrum β -lactam agents and a macrolide or a new generation of quinolones should be started empirically. Quinolones are broad-spectrum antibiotics that exhibit high levels of penetration into the lungs and low levels of resistance. Gemifloxacin is a new quinolone antibiotic

that targets pneumococcal DNA gyrase and topoisomerase IV and is highly active against *S. pneumoniae* including penicillin-, macrolide-, and quinolone-resistant strains, as well as *H. influenzae* and the atypical pathogens. Among the quinolones, it has the best in vitro activity. In clinical trials in CAP, gemifloxacin has been shown to be as effective as the comparators and demonstrates an adverse event profile that is in line with comparator agents. Its improved bioavailability, pharmacokinetic–pharmacodynamic properties, and safety profile make this agent an excellent option for the treatment of CAP. But it should be kept in mind that unnecessary use of these agents will facilitate the emergence of resistant strains.

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