Review

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Community-acquired pneumonia: Trends in and research on drug resistance and advances in new antibiotics

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SUMMARY Community-acquired pneumonia (CAP) refers to infectious inflammation of the lung parenchyma developing outside of a hospital. CAP has quite a high mortality and morbidity rate worldwide, and especially among elderly patients. The increasing burden of CAP is due to antibiotic resistance, the growth of the elderly population, and underlying comorbidities. *Streptococcus pneumoniae* remains the most common bacterial pathogen causing CAP, but multi-drug resistance bacteria and potential pathogens have increased the difficulty and challenges of managing CAP. Although preventive measures, diagnostic techniques, and treatment strategies are constantly advancing and improving, the susceptibility of multi-drug resistant pathogens, such as including Methicillin-Resistant *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*, has not improved significantly in recent decades, thus highlighting the importance and necessity of developing new antibiotics for the treatment of CAP. New antimicrobials have been approved over the past few years that will expand treatment options for CAP, and especially for patients with potential comorbidities. This situation also offers the chance to reduce the abuse of antibiotics, their toxicities, and their adverse reactions and to provide effective personalized antibiotic treatment.

Keywords Community-acquired pneumonia (CAP), antimicrobial resistance, epidemiology, treatment guidelines

1. Introduction

Community-acquired pneumonia (CAP) refers to lower respiratory tract infections acquired outside of hospitals or local medical facilities. Clinical diagnosis is based on a set of signs and symptoms associated with lower respiratory tract infections, which may present as a fever, cough, expectoration, chest pain, dyspnea, and signs of infiltration of alveolar spaces (*1-3*). Worldwide, CAP is a major health issue and it imposes a massive clinical and economic burden. CAP results in a high rate of hospitalization, which is 63% in Dutch patients with CAP and 68% among U.S. adult patients with CAP (*4-6*). Despite progress in preventive measures, microbiological diagnostic tests, and antimicrobial therapy, the emergence of an increasing number of multidrug-resistant (MDR) bacteria, refractory microorganisms, and new pathogens has resulted in pneumonia still being the leading cause of mortality from infectious diseases worldwide (*7-9*). Another major reason for the continued increase in CAP is the growth of the elderly population and its underlying comorbidities (*10,11*). The current review will summarize advances in research and the medical status of CAP in terms of its epidemiology, global trends in antibiotic resistance, treatment guidelines and advances in research on new antibiotics.

2. Epidemiology of CAP

Lower respiratory tract infections, most of which are CAP, are one of the major health issues facing the world. Lower respiratory tract infections are the most common communicable disease that causes death (*12*), and the global death toll in 2019 was 2.6 million (*13*). Despite decades of efforts to control the morbidity and mortality of CAP through advances in preventive measures, diagnostic techniques, and treatment

strategies, CAP still imposes a very heavy burden, particularly in developing countries, and worldwide efforts are seeking to prevent CAP (*14*).

2.1. Etiology

The etiology of CAP varies in different countries and periods, but *Streptococcus pneumoniae* (*S. pneumoniae*) remains the most common bacterium responsible (*15-17*). Other pathogens include *Staphylococcus aureus* (*S. aureus*), *Haemophilus influenzae* (*H. influenzae*), and atypical pathogens such as *Chlamydia pneumoniae* (*C. pneumoniae*) and *Mycoplasma pneumoniae* (*M. pneumoniae*) (*18,19*). Although the proportion of CAP cases caused by Gram-negative pathogens such as *Klebsiella pneumoniae* (*K. pneumoniae*)is small, its related antimicrobial resistance causes difficulties with clinical treatment (*20*). In recent studies, atypical pathogens such as *C. pneumoniae* and *M. pneumoniae* have been detected at a higher rate than before (*21-23*), A statistical analysis of 4,300 patients from 35 countries in 2012 indicated that the rate of detection of pneumonia caused by atypical pathogens can be as high as 20% (*24*). A study has reported that the rate of infection with *M. pneumoniae* in Chinese adults exceeded that of *S. pneumoniae*, so *M. pneumoniae* is now the most common pathogen responsible for adult CAP (*25*). These findings suggest that these atypical bacteria may replace *S. pneumoniae* as the main bacteria causing CAP.

Although bacteria are the most common cause of CAP, CAP caused by respiratory viruses is increasingly detected as a result of advances in molecular diagnostic technology (*26,27*). As a single pathogen causing CAP, or a factor for co-infection, viruses both increase the risk of morbidity and antibiotic inefficacy (*26*). Importantly, recent studies have reported that two or more pathogens, usually a combination of bacteria and viruses, were found in more than one-third of CAP cases (*4,28)*. Over the last 20 years, there have been outbreaks of severe acute respiratory syndrome (SARS), influenza H1N1, influenza H7N9, and Middle East respiratory syndrome (MERS), as well as the current global epidemic of coronavirus disease 2019 (COVID-19). These facts continue to signal the severity of CAP caused by viruses. Monitoring current and emerging viruses that cause CAP and taking rapid and timely measures to combat them are necessary for public health.

2.2. Risk factors

The age over 65 years is one of the greatest risk factors for CAP. Elderly patients with CAP have a poor health status and more comorbidities, which means a higher rate and a longer duration of hospitalization (*11*). The morbidity of CAP increases with age in the United States, South Africa, and Europe (*4,29*). In Japan, the total number of adult CAP cases is approximately 1.88 million per year, 69.4% of which involve patients over the age of 65 (*30*). A study in the Netherlands indicated that about 45% of CAP cases involved people over the age of 65, and about 64% of CAP cases involved people over the age of 50 (*6*). In China, however, the highest morbidity of CAP is among children though the morbidity among the elderly is relatively high as well (Figure 1). The annual morbidity of CAP among children under the age of 5 in China is estimated to be 65.8% (*31*), which is much higher than that in other countries such as the United States (6.22%, age < 2 years) and the annual morbidity of CAP among adults over the age of 60 in China is 34.68% (*32*). Consistent with the overall etiology, *S. pneumoniae* is still the predominant pathogen causing CAP among the elderly (Figure 2), and the incidence of viral infection is higher than that of atypical bacteria in the elderly (*33*). The differences in morbidity and etiology of CAP in different countries may reflect the diversity in methodologies, systems of diagnosis and treatment, age groups, and population distribution (*22,34*).

Chronic comorbidities are another risk factor for CAP. Chronic obstructive pulmonary disease (COPD) is the highest risk for morbidity and hospitalization due to CAP, and the annual incidence of CAP in patients with COPD is 5,832 per 100,000 adults in the United States (*35*). Other chronic comorbidities associated with the increased morbidity of CAP include asthma, bronchiectasis, coronary heart disease, cardiac failure, chronic liver disease, diabetes mellitus, cerebrovascular diseases, immune deficiency, and malnutrition, all of which are related to poor outcomes of CAP (*36,37*). People with comorbidities have an increased risk of other complications and death while suffering from CAP (*38*). The morbidity of CAP with these comorbidities remains high across the globe. For example, a European study reported that up to 33% of patients with CAP had diabetes mellitus and up to 47% of patients with CAP had chronic heart disease (*39*). Elderly patients with CAP and patients with CAP and comorbidities are often treated with a combination of multiple antibiotics. Moreover, frequent exposure to healthcare settings and cumulative exposure to multiple antibiotics lead to a higher rate of infection with MDR pathogens in patients over the age of 65 (*33*). Adverse reactions to agents and interactions between agents impact therapeutic efficacy and antimicrobial resistance (*40*). The empirical treatment of CAP is becoming increasing challenging in patients over the age of 65 and patients with chronic comorbidities due to the limited treatment options.

2.3. Mortality

Elderly patients are the main population susceptible to CAP. The number of adult patients with CAP in the future will increase in conjunction with the increasing

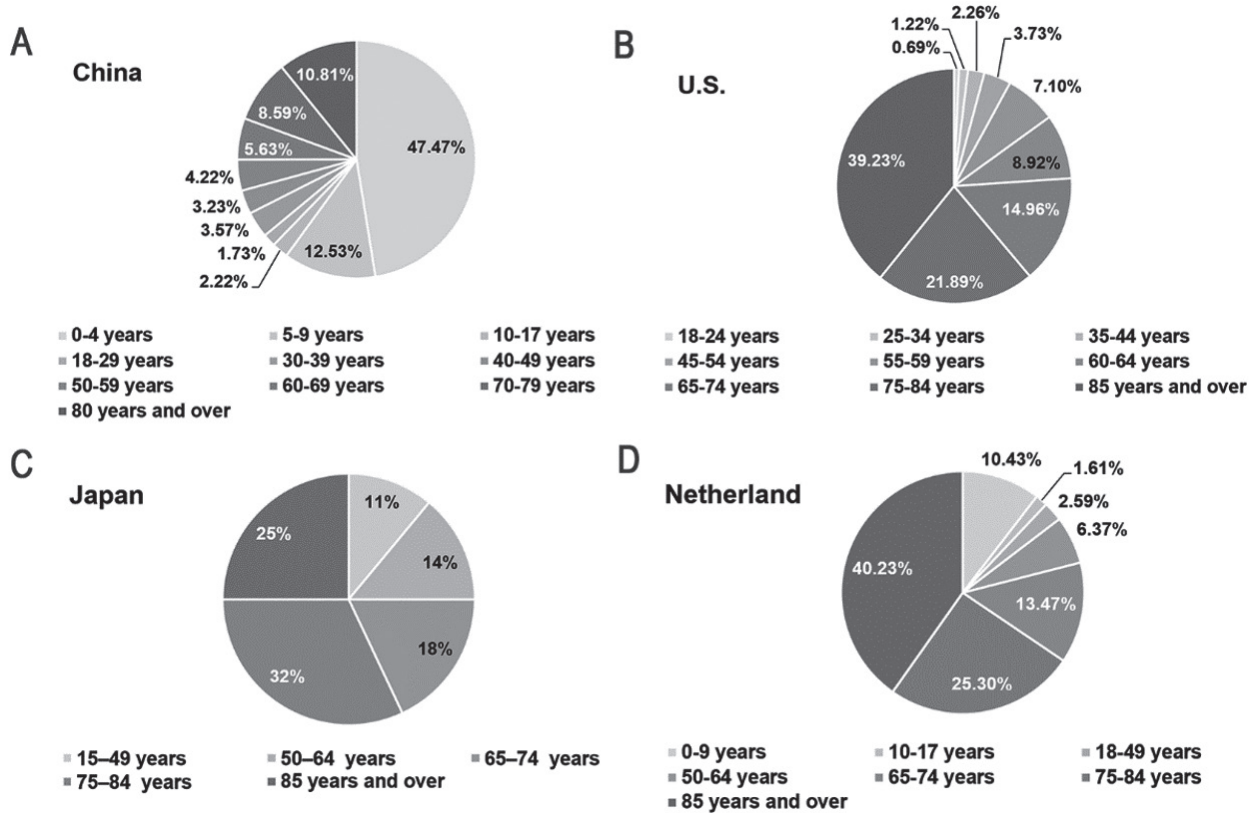

Figure 1. Proportion of CAP incidence in different age groups. The proportion of CAP incidence in China **(A)** (*31*) and the Netherlands **(D)** (*6*) for all age groups and the proportion of CAP incidence in the US **(B)** (*35*) and Japan **(C)** (*30*) in adults in different age groups.

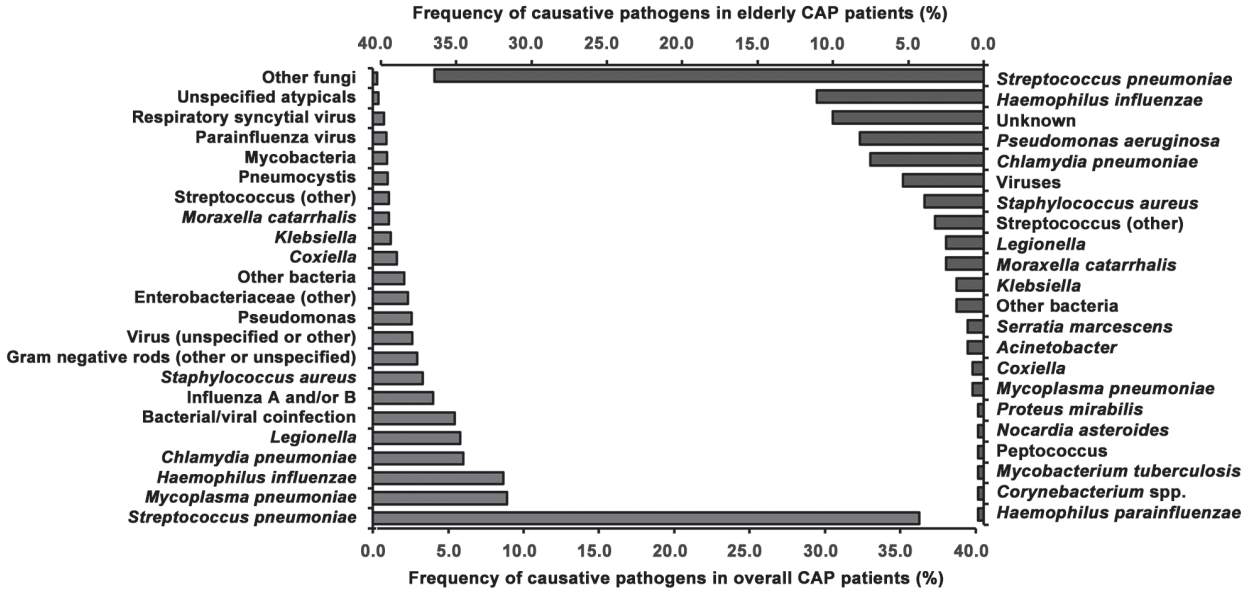

Figure 2. The characteristics of CAP etiology. Frequency of causative pathogens in patients with CAP as a whole (*19*) and in elderly patients with CAP (*93,94*).

proportion of the population over the age of 65, and the mortality of CAP is expected to fluctuate accordingly. The mortality rate of CAP varies greatly by country and demographic composition. The mortality rate in Europe ranges from less than 1% to 48% while that in the United Kingdom is 6% among patients under the age of 65 and 47% among patients over the age of 85 (*22*). In the United States, CAP is the sixth leading cause of death among the elderly (*41*), accounting for more than 50% of hospitalized patients over the age of 75 and resulting in a mortality rate of nearly 70% (*42*). An increasing rate of hospitalization and an increasing

mortality rate with age have also been noted in Asia (*42*). A Chinese study involving 5,828 adult patients with CAP indicated that the 30-day mortality rate of hospitalized patients with CAP was 4.2% and the in-hospital mortality rate increased significantly in the population over the age of 65 (*43*). The mortality rate of CAP has declined as the public healthcare system has improved and the use and availability of antibiotics, but the aging population and antibiotic resistance (detailed later) are still the main obstacles and challenges that need to be studied further.

3. Antimicrobial resistance

Antimicrobials frequently used to treat CAP include macrolides (*e.g.*, azithromycin), β-lactams (*e.g.*, amoxicillin/clavulanic acid), fluoroquinolones (*e.g.*, levofloxacin), and third-generation cephalosporins (*44*). Antibiotic treatment of CAP is usually empirical because it is generally impossible to ascertain the exact pathogenesis of CAP given the potential factors mentioned earlier. Although antibiotic treatment of CAP needs to target typical bacteria, there is no clinical consensus as to whether it needs to target atypical bacteria. A study has found that the adequacy of initial antimicrobial therapy is a critical factor affecting the course of treatment and the prognosis of pneumonia (*45*). However, increasing resistance to antibiotics remains a major issue for poor outcomes of CAP treatment (*46-48*). This is due to a growing number of MDR bacteria, intractable microorganisms, and the emergence of new pathogens (*49,50*).

Globally, *S. pneumoniae* remains the most common bacterium responsible for CAP. In approximately one-third of streptococcal pneumonia cases, bacteria are reported to be resistant to one or more antibiotics during clinical treatment (*51*). The frequency with which drug-resistant *S. pneumoniae* is isolated varies from regions. The frequency with which MDR and extensively resistant *S. pneumoniae* is isolated is highest in the Asia-Pacific region (39.2% and 10.9%, respectively) and lowest in Latin America (19.1% and 4.0%, respectively) (*52*). MDR *S. pneumoniae* has displayed resistance to macrolides (such as azithromycin and erythromycin), tetracycline, and penicillin (Table 1). The SENTRY Antimicrobial Surveillance Program reported that the global average susceptibility of MDR *S. pneumoniae* to azithromycin (> 4 mg/L) is 3.4%, its susceptibility to erythromycin (> 2 mg/L) is 1.9%, its susceptibility to tetracycline (> 4 mg/L) is 8.8%, and its susceptibility to penicillin (2 mg/L) is 15.7% (*52*). According to that Program, MDR *S. pneumoniae* is susceptible to vancomycin (≤ 1 mg/L, 100%), ceftaroline (0.12 mg/L, 99.9%), and levofloxacin (1 mg/L, 97.1%). The introduction of 7-valent and 13-valent pneumococcal conjugate vaccines (PCV-7 and PCV-13) has reduced the morbidity of macrolide-resistant invasive pneumococcal disease (*53,54*), but serotype substitution and the emergence of macrolide resistance are still major issues that urgently need to be addressed (*55,56)*.

Resistance to macrolides and other antibiotics is not limited to Pneumococcus, and other bacteria that cause CAP have also displayed drug resistance (*52,57*). The ESKAPE pathogens (*Enterococcus faecium*, *S. aureus*, *K. pneumoniae Acinetobacter baumannii*, *Pseudomonas aeruginosa* (*P. aeruginosa*), and *Enterobacter* spp.)

Table 1. Antimicrobial susceptibility of several pathogenic bacteria causing CAP

Items	Susceptibility in %				
	Streptococcus pneumoniae (*52*)	MDR *Streptococcus pneumoniae* (*52*)	MSSA (*86,87*)	MRSA (*86,87*)	*Haemophilus influenzae* (*87,88*)
Ampicillin	100	100	100	100	
Amoxicillin-clavulanate	93.9	68.5			99.9
Azithromycin	63.1	3.4			99.5
Ceftaroline	99.9	99.7	97.4	88.6	99.8
Ceftriaxone	87.1	42.8	77.5		100
Ciprofloxacin			90	28	99.9
Clarithromycin					81.1
Clindamycin	83.1	24.3	26	70	
Doxycycline			99	96	
Erythromycin	63.1	1.9	74	18	
Gentamicin			98	89	
Levofloxacin	98.6	96.6	92.1	23.4	100
Meropenem	83.1	45.2			99.9
Penicillin	65.8	15.7	26		
Tetracycline	77.2	8.8	95	90	99.2
TMP-SMX	71.9	25.2	99	97	
Trimethoprim/sulfamethoxazole	68.5				78.6
Vancomycin	100	100	100	100	100

CAP, community-acquired pneumonia; MDR, multidrug-resistant; MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

cause a small proportion of CAP cases but have been highlighted as a faction of antibiotic-resistant bacteria that have become increasingly difficult to manage over the past few years (*49,57*). Studies have found that the ESKAPE pathogens have varying degrees of resistance to macrolides, fluoroquinolones, β-lactams, and third- and fourth-generation cephalosporins (*57,58*). Methicillin-Resistant *S. aureus* (MRSA), a typical ESKAPE pathogen, is highly resistant to macrolides and fluoroquinolones; its susceptibility to erythromycin is 18%, its susceptibility to ciprofloxacin is 28%, and its susceptibility to levofloxacin is 23.4%. The susceptibility of MRSA to antibiotics has improved over the past 20 years, *e.g.* its susceptibility to erythromycin has increased from 7% to 18%, but its susceptibility did not improve significantly from 2009 to 2016 (only increasing from 15% to 18%).

Atypical bacteria account for about 15% of CAP cases, so they are less common. However, atypical bacteria have received increasing attention in clinical practice because distinguishing pneumonia caused by atypical bacteria from pneumonia caused by typical bacteria based on clinical characteristics alone is difficult (*44*). Atypical pathogens as typified by *M. pneumoniae* have a high level of resistance to macrolides (*21*). β-lactam drugs as are recommended in guidelines are usually ineffective in treating pneumonia caused by atypical bacteria (*52,59*). Fluoroquinolones or tetracyclines should be considered as alternative therapy (*21*).

Increasing and intractable antibiotic resistance is mainly caused by bacterial gene mutations or the acquisition of drug resistance genes due to antibiotic overuse (*60*). Macrolides are one example. Macrolides are bacteriostats with bacteriostatic action as a result of binding with the 50S ribosomal subunit to inhibit protein synthesis (*61*). In *S. pneumoniae*, macrolide resistance is mainly due to the dimethylation of ribosomes by proteases encoded by erm(B) (*62*), the efflux of the efflux pump encoded by mef(E)/mel(msr (D)) (*63*), and ribosomal target site mutations (*64*). The agent efflux mechanism can lead to a low level of macrolide resistance, which is the most common mechanism of resistance in North America, and alteration of the ribosomes targeted by antimicrobials can induce a high level of resistance to macrolides, which is the mechanism of resistance commonly found in Europe (*65*). The distribution of macrolide resistance genotypes in China is mainly erm(B) (62.9%) and erm(B)+mef(E) (27.1%) (*66*). Antimicrobial resistance is a continuously developing global health threat, leading to alterations in the epidemiology of community-acquired bacterial pneumonia (CABP) (*4,35,67*), which makes empirical CAP therapy more challenging. Thus, understanding the genetic basis of different pathogens in the etiology of pneumonia is pivotal for the management and effective guidance of appropriate antimicrobial therapy.

4. Current treatment guidelines

Guidelines for the treatment and management of CAP have been issued in various countries and by various professional associations, so the recommended first-line treatment strategies vary by region (*68*). The Infectious Diseases Society of America/American Thoracic Society (IDSA/ATS) guidelines (*1*) are frequently cited. Guidelines from China (*69*), Europe (*70*), and the UK (*71*) are also widely used (Table 2). The guidelines for the treatment and management of CAP suggest that stratified empirical antibiotic treatment be based on the presence or absence of underlying disease and the severity of CAP. The CAP management guidelines updated by IDSA/ATS recommend amoxicillin or doxycycline as the first-line empirical treatment for drug-resistant *S. pneumoniae* in outpatients without comorbidities or risk factors. For patients with other chronic diseases such as COPD, diabetes mellitus, or liver disease, monotherapy with fluoroquinolones (levofloxacin or moxifloxacin) or combination therapy with β-lactams (such as amoxicillin) and macrolides is recommended. These treatment strategies also apply to patients with suppressed immunity/taking immunosuppressive drugs, patients who have received antibiotics within the past 3 months, or patients at risk of some other infection with drug-resistant *S. pneumoniae* (*1,2*).

Unlike in the West, the preferred therapeutic strategy for CAP in China involves cephalosporins. Chinese guidelines recommend aminopenicillin and first- or second-generation cephalosporins as the treatment of choice for outpatients without comorbidities. For outpatients who have comorbidities, a combination of penicillin and a β-lactamase inhibitor or monotherapy with second- or third-generation cephalosporins is recommended (*69*). For non-ICU inpatients, penicillin combined with a β-lactamase inhibitor or carbapenems (such as cephamycins, oxacephems, or ertapenem) is the treatment of choice. For hospitalized ICU patients with comorbidities such as severe COPD, penicillin combined with a β-lactamase-inhibitor is recommended as the preferred treatment (*69*).

The selection of empirical treatments requires a comprehensive assessment of the patient's condition, possible pathogens, and antibacterials. Thus, adverse reactions to antibiotics will limit the treatment options of clinicians. The use of macrolides is currently restricted due to adverse cardiac and gastrointestinal events, whereas fluoroquinolones remain a treatment option for CAP (*1,72*). Randomized controlled trials have indicated that the incidence of adverse events such as treatment failure and discontinuation of fluoroquinolones was relatively low compared to a combination of a β-lactam and macrolide (*73,74*). Therefore, new antibiotics for CAP treatment need to be developed to facilitate closely tailored and effective

Table 2. Empirical antibiotics suggested for CAP

Populations	US (IDSA/ATS) (*1*)		China (*69*)		Europe (*70*)		Britain (NICE/BTS) (*71*)	
	Preferred	Alternative	Preferred	Alternative	Preferred	Alternative	Preferred	Alternative
Outpatients without comorbidities; low severity	Amoxicillin	Doxycycline	Aminopenicillins, 1st or 2nd generation cephalosporins	Respiratory Fluoroquinolone[c], doxycycline and macrolide	Amoxicillin or tetracycline	Macrolide	Amoxicillin	Macrolide or tetracycline
Outpatients with comorbidities or a high rate of bacterial resistance	β-lactam with macrolide	Respiratory fluoroquinolone	Penicillins with β-lactamase inhibitor,	2nd or 3rd generation cephalosporins, Respiratory fluoroquinolone	Respiratory fluoroquinolone			
Inpatients not in the ICU; moderate severity	β-lactam[a] with macrolide	Respiratory fluoroquinolone	Penicillins with lactamase inhibitor, carbapenems[b]	Preferred drugs with macrolide, respiratory fluoroquinolone	Aminopenicillin with or without macrolide	Respiratory fluoroquinolone	Amoxicillin with macrolide	Respiratory fluoroquinolone
Inpatients in the ICU; high severity	β-lactam with macrolide	β-lactam with respiratory fluoroquinolone	Penicillins or 3rd generation cephalosporins with β-lactamase-inhibitor	Carbapenems with respiratory fluoroquinolone	3rd generation cephalosporin with macrolide	Respiratory fluoroquinolone with or without 3rd generation cephalosporin	β-lactamase stable β-lactams[d] with macrolide	Respiratory fluoroquinolone

CAP, community-acquired pneumonia; IDS: Infectious Diseases Society of America, ATS: American Thoracic Society, NICE: National Institute for Health and Care Excellence, BTS: British Thoracic Society, ICU: intensive care unit. [a] Preferred β-lactam drugs include cefotaxime, ceftriaxone, and ampicillin. [b] Preferred carbapenem drugs include cephamycins, oxacephems, and ertapenem. [c] Alternative respiratory fluoroquinolone drugs include levofloxacin, moxifloxacin, and gemifloxacin. [d] β-lactamase-stable β-lactams include co-amoxiclav, cefotaxime, ceftaroline fosamil, ceftriaxone, cefuroxime, and piperacillin-tazobactam.

treatment plans.

Recently, the concept of pneumonia, including CAP, has changed from just an acute lung disease to a multi-system disease with chronic adverse effects on health (*68*). The basis for the best therapeutic strategy against CAP has changed, diagnostic methods are being optimized, and pathogens are evolving. These events will determine the direction of future research.

5. New therapeutic agents

The constant emergence of antibiotic resistance is common in bacteria associated with CAP, and especially Staphylococcus and *S. pneumoniae*, making empirical treatment increasingly difficult (*75*). To improve the efficacy of initial empirical treatment of CAP, effective clinically antimicrobial therapy needs to combat a range of CAP etiologies, and particularly antibiotic-resistant pathogens (*49*). New antimicrobials offer an opportunity to improve the empirical treatment of CAP caused by drug-resistant pathogens (Table 3).

Lefamulin is a pleuromutilin antibiotic with antimicrobial activity against common pathogens that cause CABP (*76*). Lefamulin can be used to treat atypical pathogens, such as *M. pneumoniae*, *C. pneumoniae*, *H. influenzae*, and *Legionella*, as well as MDR *Neisseria gonorrhoeae* and *Mycoplasma genitalium* (*76*).

Omadacycline, a novel tetracycline, was recently approved for treatment of CABP and acute bacterial skin and skin structure infections (*77*). The therapeutic scope of omadacycline includes MRSA, various resistant *S. pneumoniae*, and a range of Gram-negative and atypical pathogens (*78*). Studies have confirmed that the efficacy of omadacycline is on par with that of moxifloxacin for the treatment of CABP in adults (*79*).

Ceftaroline, a fifth-generation cephalosporin, displays bactericidal action by interfering with the cell wall of bacteria and it displays bactericidal activity against most pathogens that cause CAP, including *S. pneumoniae* (*80*). The incidence of MRSA in outpatients with CAP is low but it can increase to more than 20% in inpatients with CAP (*81*). If an inpatient is suspected of having MRSA, ceftaroline may be the antibiotic of choice.

Delafloxacin, an anionic fluoroquinolone, has been approved for treatment of CABP caused by *S. pneumoniae*, *Escherichia coli*, *S. aureus*, *K. pneumoniae*, *P. aeruginosa*, *H. influenzae*, *Legionella pneumophila*, *Haemophilus parainfluenzae* (*H. parainfluenzae*), and *M. pneumoniae* (*82*). Delafloxacin is currently the only oral antibiotic with activity against MRSA and *P. aeruginosa* (*83*). Compared to moxifloxacin, delafloxacin has demonstrated excellent efficacy in patients with CAP and COPD or asthma and in patients with severe CAP (*65*). New anionic fluoroquinolones may be the best choice for elderly patients with comorbidities such as COPD or asthma.

Table 3. New antibiotics for community-acquired pneumonia (*75*)

Items	Antibiotic Classification	Mechanism	Route of Administration	Targeted Pathogens	Toxicity
Lefamulin (*89*)	pleuromutilin antibiotic	inhibits bacterial growth by binding to the peptidyl transferase center of the 50S ribosomal subunit	Intravenous and Oral	Haemophilus influenzae and Legionella, multidrug-resistant Neisseria gonorrhoeae, MRSA, MRSP, atypical pathogens	Diarrhea, vomiting
Omadacycline (*90*)	tetracycline	inhibits protein synthesis by binding to the 30S ribosomal subunit	Intravenous and Oral	MRSA, MRSP, Gram-negative and atypical pathogens	Nausea, headache
Ceftaroline (*91*)	fifth-generation cephalosporin	N-phosphonoamino water-soluble prodrug cephalosporin with broad-spectrum in-vitro antimicrobial activity	Intravenous	typical bacteria, MRSA, MRSP	Nausea
Delafloxacin (*92*)	anionic fluoroquinolones	targets both topoisomerase IV and DNA gyrase with a high level of affinity to inhibit bacterial DNA replication	Intravenous and Oral	MRSA, MRSP, S. pneumoniae, Staphylococcus aureus, Gram-negative and atypical pathogens	Diarrhea, nausea

MRSA: methicillin-resistant *Staphylococcus aureus*, MRSP: macrolide-resistant *Streptococcus pneumonia*.

6. Conclusion

Despite advances in antimicrobial therapy, CAP remains a major cause of mortality due to infectious diseases (*84*). The risk of CAP in patients with COPD is 6 to 8 times that in healthy individuals (*85*), and those patients also have increased morbidity and mortality (*37*). The proportion of the elderly and patients with comorbidities in the general population is increasing, and those groups are more likely to be hospitalized for CAP. Thus, the medical costs caused by CAP are expected to increase as well.

CAP is caused by a variety of typical and atypical pathogens, but *S. pneumoniae* remains the most common bacterium responsible. Due to its reduced sensitivity to macrolides, tetracyclines, and β-lactams that are frequently used, increasing attention has been paid to the efficacy of other antibiotics. New antibiotics that have recently been approved may represent more possibilities to expand the treatment options for CAP, and especially for patients with comorbidities. Several multi-center research and surveillance networks on pneumonia have been established worldwide, and they are coordinating large-scale longitudinal studies on the epidemiology, diagnosis, and treatment of pneumonia. In order to cope with the public health challenges posed by population trends and limited public healthcare resources, the CAP-China clinical research network (*31*) has been established to mitigate the research gap in surveillance, rapid diagnosis, and optimal treatment and to also ardently support the development of new antibiotics.

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