



# Outpatient management of community-acquired pneumonia

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## Purpose of review

Although most patients with community-acquired pneumonia (CAP) are treated as outpatients, the majority of data regarding CAP management is provided by hospitals, either from emergency department or inpatients. This was already noted in the first CAP guidelines, published in 1993, and the challenges regarding the outpatient management of CAP persist nowadays. These include the uncertainty of the initial diagnosis and risk stratification, the empirical choice of antibiotics, the overgrowing of antibiotic resistance bacteria and the relative scarcity of novel antibiotics.

## Recent findings

New molecular biology methods have changed the etiologic perspective of CAP, unveiling the role of virus. Diagnostic uncertainty may lead to antibiotic overuse and bacteria resistance. Novel antibiotics along with diagnostic improvement, related to the use of lung ultrasound and point-of-care biomarkers testing, may help to improve CAP treatment. Prevention, especially the use of antipneumococcal vaccine, is instrumental in reducing the burden of disease.

## Summary

Most of CAP cases are managed in the outpatient setting. However, most research is focused on hospitalized severe patients. New and awaited advances might contribute to aid diagnosis, cause and assessment of patients with CAP in the community. This knowledge might prove decisive in improving outcomes, as well as to the execution of stewardship programs that maintain current antibiotics, safeguard future ones and reinforce prevention.

## Keywords

ambulatory, antibiotic therapy, community-acquired pneumonia, outpatient, pneumonia

## INTRODUCTION

In 2018, the first published international guidelines assessing community-acquired pneumonia (CAP) celebrate its 25 years [1]. This document, published in 1993 by the American Thoracic Society (ATS), was at the same time pioneer and visionary, and deeply changed the management of CAP.

CAP is a frequent entity and its history follows the history of humankind. In 1881, Pasteur [2] and Sternberg [3] independently described a microorganism, named *Pneumococcus* by Fraenkel because it caused pulmonary disease [4]. Two decades later, William Osler identified the clinical entity of pneumonia as the ‘Captain of the men of death’ [5]. The introduction of serum therapy, and particularly vaccines and antibiotics, had a major impact in the treatment and prevention of pneumonia during the 20th century. However, in the last 50–60 years, no significant novel treatment has been introduced. Simultaneously new pathogens are increasingly described (e.g. SARS, MERS-CoV) and multidrug-resistant pathogens are

a cause of concern. As a result, pneumonia remains a major public health problem, with enormous morbidity and mortality [6].

Despite many advances, some challenges persist since 1993. These include the difficulty in establishing the initial clinical diagnosis, risk stratification, empirical choice of antibiotics, the relative scarcity of novel antibiotics and the importance of knowing

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**Curr Opin Pulm Med** 2018, 24:000–000

DOI:10.1097/MCP.0000000000000558

## KEY POINTS

- The majority of patients with CAP are treated as outpatients, although most of the research on CAP originates from inpatients.
- The main challenges in the outpatient management of CAP persist. These include the initial clinical diagnosis, its risk stratification and the empirical choice of antibiotics.
- Despite the growing acknowledgment of viral agents, all patients with CAP should receive antibiotic treatment. These should be adapted from current guidelines and must take into account local microbiological susceptibility patterns.
- The worrying problem of antibiotic resistance increases the need for stewardship programs along with improvements in diagnostic accuracy, which maintains current antibiotics, safeguards future ones and reinforces prevention.

local microbiological susceptibility patterns. The uncertainty in CAP diagnosis also leads to antibiotic overuse and growing bacteria resistance.

It is expected that the next Infectious Disease Society of America (IDSA)/ATS guidelines actualization due in 2019, will clarify some of these challenges [7<sup>•</sup>].

## EPIDEMIOLOGY

Respiratory tract infections (RTI) remain the most common infectious disease in the ambulatory setting [8]. Calculating the true incidence of CAP, however, remains a challenge. Patients with mild systemic and respiratory symptoms rarely seek their general practitioners; this is evident in incidence studies from France with less than seven CAP per year per family physician [9]. The use of confirmatory diagnostic tests varies widely, namely for the availability of chest X-ray and point-of-care testing (POCT). With these limitations, the estimated annual incidence of CAP is 5–11 cases per 1000 adults [10]. CAP incidence presents a marked seasonal variation (more in winter), a U-shaped age distribution (more frequent in children and the elderly), a sex asymmetry (more in men) and is more frequent in the presence of known risk factors (alcohol, tobacco consumption, chronic pulmonary disease, renal failure and malnutrition) or medications (inhaled corticosteroids, proton pump inhibitors, antipsychotic drugs, oral antidiabetic drugs, namely DPP-4 inhibitors) [11<sup>•</sup>, 12<sup>•</sup>].

The percentage of CAP patients admitted to hospital varies from country to country ranging

between 1.1 and 4.0 per 1000 inhabitants [13]. This means that roughly two-thirds of patients are treated as outpatients. The annual incidence of hospitalized CAP seems to have decreased slightly in the United States (2.67 to 2.48/1000 inhabitants/year in 2000 and 2010–2012) [14,15], whereas it is increasing in several European countries, such as the UK (1.48–1.98/1000 inhabitants/year between 1997–1998 and 2004–2005) [13], Germany (2.75–2.96/1000 inhabitants/year in 2005 and 2006) [16] and Portugal (3.02–4.70/1000 inhabitants/year in 2000 and 2009) [17]. These differences could reflect different studied populations and healthcare organizations.

A global study found that lower RTI, including pneumonia, ranks fifth as the most common cause of death worldwide, behind Alzheimer disease and other dementias, and shows a slight decrease to 36.8/100 000 inhabitants [18]. But even in higher income countries, pneumonia remains the leading cause of death by infectious diseases [7<sup>•</sup>] and ranks eighth amongst the causes of death in the United States in 2014 [19].

The decrease in hospital admissions and CAP mortality observed in some countries [20,21] may be the result of widespread immunization of high-risk groups with pneumococcal and influenza vaccines together with improvement of care process [7<sup>•</sup>].

## CAUSE

Although more than 100 microorganisms can cause CAP, a limited number account for the majority of cases. Nowadays, the use of molecular diagnostic techniques can yield a microbiological diagnosis in 75% of cases [22]; however, outside research settings, this figure drops to 10–20% [23].

In a review of 46 European outpatient studies [24], there was microbiological isolation in half the patients. Pneumococcus was the most common organism accounting for 38% of isolates. The pneumococcal incidence is higher in countries with lower use of pneumococcal vaccines and higher tobacco use [25]. In Norway, a study of 267 inpatients [26], isolated an aetiological agent in 63% of cases, mostly pneumococcus (30%), influenza (15%) and rhinovirus (12%). Viral–bacterial co-detections were established in one-third of patients. In another US study, cause was established in 38% of 2320 patients, particularly rhinovirus (9%), influenza virus (6%) and pneumococcus (5%) [14]. Despite the frequent identification of viruses, their role as colonizers, predisposing to secondary bacterial infection or as microorganisms responsible for pneumonia is not well established, particularly for noninfluenza viruses.

In the previously mentioned review [24], community-managed CAP was attributed to atypical microorganisms in 30% of patients. In a study from four Dutch hospitals, atypical microorganisms were isolated in 20.7% of patients [27]. Risk factors for atypical agents were: noninfluenza season, age less than 60 years, male sex and absence of COPD.

CAP because of *Legionella* spp. is more frequent in specific geographic locations. Since 2014, several *Legionella* outbreaks have been reported [28–31]. In the second largest outbreak in the world, with 430 cases, occurred the first documented case of probable person-to-person transmission of Legionnaires' disease [32<sup>¶</sup>].

## DIAGNOSIS AND RISK STRATIFICATION

The definite diagnosis of pneumonia requires systemic manifestations, signs and symptoms of lower RTI, a new or progressive pulmonary infiltrate in chest X-ray and, finally, microbiologic documentation. However, even in severe CAP, microbiologic documentation is obtained in only 50% of patients.

Radiologic evaluation is rarely available in the primary care setting; hence, family physicians frequently will rely solely on clinical evaluation for CAP diagnosis. Clinical criteria are overly sensitive and poorly specific and, if used indiscriminately, could result in antibiotics overuse.

Older patients, however, often present with atypical symptoms, such as falls, fatigue, lethargy, delirium, anorexia [33]. This is particularly worrying as the elderly are at higher risk of resistant microorganisms and death [34].

Several scoring systems have been developed to stratify severity of pneumonia like the PSI, CURB-65, IDSA/ATS 2007, SMART-COP, SCAP. Although these severity scores performed well in the identification of high-risk patients, they have not been designed to be applied to outpatients. There are three scores that do not require laboratory testing. The NEWS (National Early Warning Score) includes seven items: respiratory rate, peripheral oxygen saturation, oxygen supplementation, temperature, SBP, heart rate and level of consciousness. It has a moderate association with mortality but performed better than PSI and CURB-65 to identify patients needing ICU admission [35]. The other two scores are even simpler and both use the same three clinical items: level of consciousness, respiratory rate and blood pressure. One is an 'old' CAP score, the CRB/CRB-65 [36,37], the other is a data-driven score using big data, the qSOFA [38,39]. The performance of qSOFA for mortality prediction was similar to CRB, but better for ICU admission.

In the near future, POCT will become more available in the primary care setting [40]. Currently, POCT exists for several laboratory variables, such as CRP and PCT, but the array of possibilities is wide and could include microbiologic identification. The challenge is how to use this technology and its additional information. Currently, there are three RCTs performed in primary care settings using a biomarker decision tree algorithm in patients with suspicion of lower RTI [41–43]. In two RCTs, both with less than 500 patients, one using PCT and the other CRP, the authors found a significant decrease in antibiotic prescription without any adverse events. In a Cochrane review published in 2014, CPR in primary care can reduce antibiotic use; however, with a possible increase in hospitalizations [44]. The larger RCT ( $N=1656$ ) that evaluated a PCT-guided use of antibiotics for suspected lower RTI, was performed in 14 US hospitals with a high adherence to quality measures. The study showed no impact on the rate of antibiotic prescription and consumption [45<sup>¶</sup>].

The combination of a severity scoring system and a biomarker has also been tested. The additional value of CRP combined with PSI and CURB-65 was evaluated but produced conflicting results [46,47]. Probably, more important that any single value of CRP would be its kinetics after 12–24 h, which could contribute to the clinical decision-making process [48]. Other biomarkers, like PCT and proadrenomedullin, have also been tested with similar results [49,50].

Lack of chest imaging in the primary care setting is a major limitation in pneumonia diagnosis. The development of portable ultrasound devices and training of primary care physicians could change the paradigm of pneumonia diagnosis [51].

## TREATMENT

Antibiotic treatment is recommended for all patients with CAP, including outpatients [1,10,52–56]. Treatment success relies on prompt delivery of antibiotics, adapted to the likely causative organisms and clinical severity. Antibiotic selection should take into consideration up-to-date local guidelines adapted to the microorganism prevalence and susceptibility pattern (Table 1). The antibiotic management of CAP was the subject of a recently published comprehensive review [57<sup>¶</sup>].

Proposed first-line therapy in the outpatient includes monotherapy with a  $\beta$ -lactam, a macrolide or a tetracycline. These choices exclude those with significant comorbidities or at risk of antibiotic resistance. Fluoroquinolone use is ubiquitous but, from an antibiotic stewardship perspective, a

**Table 1.** Guidelines for outpatient treatment of CAP in several countries between 1993 and 2018

Organization (country)	ATS (US) [1]	IDSA/ATS (US) [53]	NICE (UK) [60]	Chinese Thoracic Society, Chinese Medical Association (China) [53]	South African Thoracic Society, Federation of Infectious Diseases Societies of Southern Africa [54]	Brazilian Thoracic Association (Brazil) [56]
Year	1993	2007	2014	2016	2017	2018
Outpatient treatment	60 years or less of age AND without comorbidity: Macrolide OR Tetracycline At least 60 years of age AND/OR comorbidity: second-generation cephalosporin OR TMP/SMX OR Beta-lactam/beta-lactamase inhibitor ± Macrolide	Previously healthy and no risk factors for DRSP infection: Macrolide OR Doxycycline Presence of comorbidities (e.g. chronic heart, lung, liver, or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs); use of antimicrobials within the previous 3 months; or other risks for DRSP infection: Fluoroquinolone OR β-lactam and macrolide (doxycycline is an alternative to the macrolide)	Amoxicillin. Macrolide or tetracycline for patients allergic to penicillin.	Young adults without underlying disease (s): Aminopenicillins, penicillins-β-lactamase inhibitor; First or second generation cephalosporins; Doxycycline or minocycline (suspected <i>Mycoplasma</i> or <i>Chlamydia</i> infection); fluoroquinolone (in regions with higher resistance rates to macrolides or in patients hypersensitive or intolerant to the drugs mentioned above); macrolides (only in regions with lower resistance rates). Patients with underlying disease(s) or elderly patients (age >65 years): Penicillins-β-lactamase inhib.; Second or third generation cephalosporin.; fluoroquinolones; Penicillins-β-lactamase inhibitor or Second or third generation cephalosporins plus doxycycline or minocycline or macrolides	<65 years old, without antibiotic exposure in the past 90 days or comorbidities: amoxicillin (macrolide in the presence of severe β-lactam allergy) ≥65 years old, have received antibiotics within the previous 90 days, or who have comorbidities: Amoxicillin-clavulanate OR second generation cephalosporin	No comorbidities, no recent use of antibiotics, no risk factors for resistance, and no contraindication or history of allergy: β-lactam OR Macrolide Use of antimicrobials within the previous 3 months, regions where the rate of resistance to macrolides is >25%, concomitant diseases (COPD, liver or kidney disease, cancer, diabetes, congestive heart failure, alcoholism, or immunosuppression): Macrolide combined with β-lactam OR Fluoroquinolone

ATS, American Thoracic Society; COPD, Chronic obstructive pulmonary disease; DRSP, drug-resistant *S. pneumoniae*; IDSA, Infectious Diseases Society of America; NICE, The National Institute for Health and Care Excellence; TMP/SMX, Trimethoprim/sulfamethoxazole.

narrower coverage is preferable, particularly in countries with high tuberculosis prevalence [54].

In a retrospective US analysis from 2011 to 2015, and involving 251 947 adult patients, the most commonly prescribed antibiotics to outpatients were macrolides (43.6%), fluoroquinolones (43%),  $\beta$ -lactam compounds (6.5%) and tetracyclines (5.5%) [58].

In the United Kingdom [10,59], atypical microorganism coverage is not routinely recommended. However, both *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* can cause severe CAP, and adequate antibiotic treatment even in mild disease can reduce morbidity and symptom duration [60].

A recent Dutch study compared monotherapy with a  $\beta$ -lactam, a fluoroquinolone or a combination of a  $\beta$ -lactam combined with a macrolide in inpatients [61]. There was no significant difference in 90-day mortality between the three groups. However, this study had several limitations. In 25% of patients, there was no radiographic confirmation of pneumonia, atypical organisms were identified in only 2% of patients, 39% of patients randomized to the monotherapy  $\beta$ -lactam group had atypical coverage and 12% of patients to the  $\beta$ -lactam combined with macrolide did not receive a macrolide [7<sup>a</sup>,57<sup>a</sup>].

Antimicrobial resistance is a growing problem. The current level of  $\beta$ -lactam pneumococcal resistance in the community is not generally associated with treatment failure when appropriate agents (e.g. amoxicillin, ceftriaxone, cefotaxime) and adequate doses are used [62]. The incidence of pneumococcal and mycoplasma macrolide resistance reaches 55–

60% in China [53] and is now more than 25% across the whole USA [63], which can limit its use as monotherapy [64]. The use of clinical scores may help identify patients infected with resistant microorganisms [65], and lead to better antibiotic accuracy.

Strategies to reduce the overuse of antibiotics in outpatients, especially for acute RTI (easily mistaken for CAP), are needed, as almost 50% of these patients receive antibiotics [66<sup>a</sup>,67].

The development of new antibiotics is crucial and new drugs will be available soon. For outpatient management, the most promising seem to be omadacycline and lefamulin (Table 2). Omadacycline is a new, once-daily, intravenous and oral, broad-spectrum antibiotic of the tetracycline family that was approved by the Food and Drug Administration (FDA) in October 2018 for the treatment of bacterial CAP. Omadacycline will probably be available in 2019. Also, in 2018, the results of Lefamulin Evaluation Against Pneumonia (LEAP 2) study were presented, showing noninferiority of a 5-day oral lefamulin treatment compared with a standard 7-day oral moxifloxacin treatment [68].

## REASSESSMENT

Effective clinical response to therapy is commonly defined as resolution of fever, normalization of heart and respiratory rate, normal blood pressure and normal oxygen saturation [53]. Among outpatients, treatment failure is usually defined as the need for hospitalization or change in antibiotic therapy.

**Table 2.** Antibiotics being developed with possible use for outpatient management of community-acquired pneumonia

Antibiotic	Class	Spectrum of activity	Route	Comments
Omadacycline	Tetracycline	DRSP, atypicals, <i>Staphylococcus aureus</i> (including MRSA), some Gram-negatives and bacteria resistant to older tetracyclines, like doxycycline	Oral and intravenous	Approved by the FDA in October 2018 for the treatment of acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia
Lefamulin	Pleuromutilin	DRSP, atypicals, <i>S. aureus</i> (including MRSA), some Gram-negatives	Oral and intravenous	In Lefamulin Evaluation Against Pneumonia (LEAP 2) study presented in October 2018, 5-day oral lefamulin demonstrated noninferiority for both FDA and EMA efficacy endpoints versus 7-day oral moxifloxacin
Solithromycin	Ketolide (fourth generation macrolide)	DRSP (including macrolide-resistant), atypicals (including macrolide-resistant <i>Mycoplasma pneumoniae</i> ), <i>Moraxella catarrhalis</i> , <i>S. aureus</i> (including community-acquired MRSA)	Oral and intravenous	No developments since December 2016, after FDA request for further safety investigations

DRSP, drug-resistant *Streptococcus pneumoniae*; EMA, European Medicines Agency; FDA, Food and Drug Administration; MRSA, methicillin-resistant *S. aureus*.

Therapeutic failure in outpatients seems to be unusual, ranging from 2.3–8% [69–71]. Moreover, mortality is low, less than 2.5% [70], both in patients discharged from the emergency department [69,72] or assessed in the primary care setting. Yet a note of caution is warranted, as mortality in the small group of patients who has late hospital admission may be high [72].

NICE guidelines [59] recommend that low-severity CAP patients be advised to seek further medical consultation if their symptoms do not begin to improve in a short period of time or if they feel that their condition is deteriorating. This approach seems to be quite intuitive, although there is scarce data to support it. A clinical reevaluation, either in person or by phone, may be a useful approach.

Recommendations should be provided for the ambulatory patient. Treatment failure may also be associated with increased costs. In a large cohort ( $N=9446$ ) from the United States, authors identified a 58% increase in costs when treatment failure occurred, with either antibiotic retreatment (89.4%) or hospitalization (10.6%) [73].

Follow-up chest X-ray has been recommended, especially for patients at increased risk of underlying neoplastic disease [74]. Delay in the complete resolution of chest infiltrates is common, especially in patients who are aged at least 50 years or with multiple comorbidities [55].

An increase in cardiovascular disease risk after an episode of CAP is increasingly recognized [75<sup>■</sup>]. It is not known if outpatients with less severe CAP share the same risk.

## PREVENTION

In 2015, the results of the CAPITA trial lead to a significant increase in recommendations for immunization in adults [76]. In the United States, the Advisory Committee on Immunization Practices (ACIP) recommends that all adults aged at least 65 years have the 13-valent pneumococcal conjugate vaccine (PCV13) [77] and at least 1 year later the 23-valent pneumococcal polysaccharide vaccine (PPSV23) [78]. Yet, the uptake of PCV13 in the United States is low among adults aged 65 and older. Centers for Disease Control and Prevention (CDC) researchers found that by 2016, 43% of beneficiaries had received at least one dose of PPSV23, 32% one dose of PCV13 and 18% had received both. The highest vaccination cover was seen among patients who were older, white, or had chronic medical conditions [79]. A review of ACIP recommendations is due on 2019.

In other developed countries, pneumococcal vaccination is widely recommended. France now recommends the scheme PCV13->PPSV23 to all immunocompromised or immunocompetent adults at risk because of a predisposing condition for pneumococcal disease [80]. Both South Africa 2017 and South Korea 2018 CAP guidelines recommend pneumococcal and influenza vaccination as a key pillar of antibiotic stewardship [54,55].

In a real-world study with 2034 CAP inpatients, aged at least 65 years, the PCV13 showed an adjusted effectiveness of 71.1–73.3% for prevention of CAP caused by the vaccine serotypes [81<sup>■</sup>]. Several studies [11<sup>■</sup>,82] investigated the association between CAP and lifestyle factors. The association lead to a bundle of lifestyle interventions that include responsible alcohol consumption, smoking cessation, dental hygiene, dietary advice to ensure good nutritional status, the avoidance of children with lower RTI and vaccination against influenza and pneumococcus [82,83].

## CONCLUSION

Even though most patients with CAP are treated in the community, the majority of research comes from inpatients. Since the publication of CAP guidelines in 1993 the main challenges persist. These include the difficulty in establishing the initial diagnosis, its risk stratification, the empirical choice of antibiotics and the importance of local microbiological susceptibility patterns. New molecular biology methods have changed the etiologic perspective of CAP, particularly the role of viruses. These methods, along with lung ultrasound and biomarkers might improve diagnosis accuracy and severity stratification. Antibiotic resistance is a growing problem that reinforces the importance of novel antibiotics and disease prevention.

## Acknowledgements

*We would like to thank Dr Ana Cysneiros for her assistance with the manuscript.*

## Financial support and sponsorship

*None.*

## Conflicts of interest

*F.F. reports personal fees or nonfinancial support from Pfizer, MSD, TEVA, Sanofi, Novartis, Bial, Angelini, outside the submitted work; J.G.P. reports personal fees or nonfinancial support from MSD, Angelini, Pfizer outside the submitted work; P.P. reports personal fees or nonfinancial support from Pfizer, Fresenius Kabi, outside the submitted work.*

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