REVIEW

Managing community-acquired pneumonia: A European perspective

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Summary
Community-acquired pneumonia (CAP) is a common disease and a frequent cause of morbidity and mortality worldwide. It puts an enormous burden on medical and economic resources, particularly if hospitalization is required. Initial antibacterial therapy for CAP is usually empirical, as culture and antibacterial sensitivity test results are rarely available at initial diagnosis. Any agent selected for empirical therapy should have good activity against the pathogens commonly associated with CAP, a favorable tolerability profile, and be administered in a simple dosage regimen for good compliance. Streptococcus pneumoniae remains the most common causative pathogen, although the incidence of this organism varies widely. Streptococcus pneumoniae strains with decreased susceptibility to penicillin have become increasingly prevalent over the past 30 years and are now a serious problem worldwide. In addition, an increase in the prevalence of pneumococci resistant to macrolides has been observed in Europe over recent years. Mycoplasma pneumoniae and Chlamydia pneumoniae are among the most common atypical pathogens isolated from patients with CAP. Haemophilus influenzae, Staphylococcus aureus and Moraxella catarrhalis are less commonly identified as causative organisms. The emergence and spread of resistance to commonly used antibiotics has challenged the management of CAP. Multiple sets of CAP guidelines have been published to address the continued changes in this complex disease.

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Introduction

The management of adults with community-acquired pneumonia (CAP) remains a considerable challenge.1 CAP continues to be an important disease because of its frequency, which is highest among the very young and the very old, and its associated significant morbidity and mortality. CAP puts an enormous strain on health-care resources, for example, in the United Kingdom the annual cost has been calculated to be > 400 million [pounds sterling],2 and in Spain, the cost of hospitalizations alone due to CAP was estimated at $137 million (in US dollars) per annum in 2001.3 Depending on the severity of illness, CAP may be managed in either the ambulatory or hospital setting. In a recent ISOCAP study in Italy, the majority of 737 patients presenting to GPs with CAP, were managed as outpatients, with only 8.5% requiring hospitalization, due to age, co-morbidities or severity of CAP.4 Similarly, in France, only 13 of 130 patients (10%) were hospitalized initially, although a further 9 patients were subsequently hospitalized due to treatment failure [diagnostic error (6) and antibiotic failure (3)].5

A number of factors influence a patient’s susceptibility to specific pathogens in CAP, including age, disease severity at presentation, co-morbidities (including immune status), site of care (inpatient or outpatient), geographic location, and local susceptibility patterns, including local trends with respect to the incidence of drug-resistant Streptococcus pneumoniae (DRSP), or other unusual pathogens.1

A variety of pathogens are known to cause CAP, yet, in most patients with CAP (about 98% of those treated as outpatients and 50–60% of those treated as inpatients), the causative organism is not known.6 Even in studies at academic centers where every effort is made to culture samples, the success rate in determining the microbiological cause is usually about 50%.6 Given this diagnostic limitation, clinicians must rely heavily on empiric antibiotic therapy.1

The prompt initiation of appropriate antibiotic therapy has been shown to be essential for a favorable outcome.7

Causative pathogens

Streptococcus pneumoniae is the most frequently isolated organism from the outpatient, hospitalized and ICU setting (see Table 1).8,9 Of the other causative agents, Staphylococcus aureus, Legionella spp. and Gram-negative enteric bacteria are uncommon in CAP that is managed outside the hospital setting. These organisms appear with greater frequency among patients with more severe disease and rarely in those with mild illness, such as is generally managed in the community. For Mycoplasma pneumoniae the converse is true, with rising frequency as illness severity decreases.10 M. pneumoniae, Legionella spp., Chlamydia pneumoniae and respiratory viruses constitute the “atypical” pneumonia pathogens and with the exception of Legionella spp. are causes of CAP, especially in outpatients. Legionella spp. appears to vary in importance in different countries.11,12 It appears to be more prevalent in Mediterranean countries,12 and is uncommon in Northern European countries.

Some patients with CAP may have a mixed infection involving both “typical” and “atypical” pathogens,1 although the incidence of such co-infection is particularly difficult to ascertain because the identification of atypical pathogens in patients with CAP is usually made by serologic testing, which only indicates whether there has been

<table>
<thead>
<tr>
<th>Organism</th>
<th>Community (%)</th>
<th>Hospital (%)</th>
<th>ICU (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No pathogen identified</td>
<td>49.8</td>
<td>43.8</td>
<td>41.5</td>
</tr>
<tr>
<td>Streptococcus pneumoniae</td>
<td>19.3</td>
<td>25.9</td>
<td>21.7</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>3.3</td>
<td>4.0</td>
<td>5.1</td>
</tr>
<tr>
<td>Legionella spp.</td>
<td>1.9</td>
<td>4.9</td>
<td>7.9</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>0.2</td>
<td>1.4</td>
<td>7.6</td>
</tr>
<tr>
<td>Moraxella catarrhalis</td>
<td>0.5</td>
<td>2.5</td>
<td>–</td>
</tr>
<tr>
<td>Gram-negative enteric bacteria</td>
<td>0.4</td>
<td>2.7</td>
<td>7.5</td>
</tr>
<tr>
<td>Mycoplasma pneumoniae</td>
<td>11.1</td>
<td>7.5</td>
<td>2</td>
</tr>
<tr>
<td>Chlamydiophila (Chlamydia) pneumoniae</td>
<td>8</td>
<td>7</td>
<td>–</td>
</tr>
<tr>
<td>Chlamydiophila (Chlamydia) psittaci</td>
<td>1.5</td>
<td>1.9</td>
<td>1.3</td>
</tr>
<tr>
<td>Coxiella burnetii</td>
<td>0.9</td>
<td>0.8</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Adapted from Woodhead.10
exposure to these organisms and an immunologic response; it does not necessarily establish that they are causative agents of the pneumonia. 17,6,13

Risks for CAP infection from other bacterial causes include non-typeable Haemophilus influenzae and Moraxella catarrhalis (underlying bronchopulmonary disease), Enterobacteriaceae and Pseudomonas aeruginosa (chronic steroid administration, severe underlying bronchopulmonary disease, carcinoma, diabetes mellitus, alcoholism, frequent previous antimicrobial therapy), and anaerobes (aspiration pneumonia, concomitant gingival disease, esophageal motility disorder). 1 Risk factors for infection with drug resistant strains of Streptococcus pneumoniae which have emerged include age > 65 years, previous β-lactam therapy (in last 3 months) and fluoroquinolone therapy, alcoholism, co-morbidities and immunosuppressive illness or therapy. Staphylococcus aureus CAP is associated with periods of high influenza activity, and in communities with a high prevalence, MRSA may be causative of severe pneumonia. 14 Staphylococcus aureus CAP is otherwise most often seen in ICU patients, with risk factors including end stage renal failure, injection drug abuse and prior antibiotic therapy, especially with fluoroquinolones and post viral influenza. Severe pneumonia with necrotizing features has been documented in Europe caused by Panton Valentine leukocidin -producing CA-MRSA. 15,16

Other less common causes of CAP include Mycobacterium tuberculosis, Francisella tularensis, Bordetella pertussis, Streptococcus pyogenes, Neisseria meningitidis, Pasteurella multocida, Chlamydia psittaci, H. influenzae type b and endemic fungi. Coxiella burnetii is a rare cause of CAP; however, there appears to be some geographic variation in the frequency with which this organism is isolated. It is virtually non-existent in some parts of Scandinavia, 11 yet it is the second leading cause of CAP, second only to Streptococcus pneumoniae, in northwest Spain. 17

Antibiotic resistance and CAP

The relatively recent development of resistance among CAP pathogens to antibiotics once routinely effective against these organisms has prompted modifications in the management of CAP. Further, because infections caused by resistant pathogens are associated with higher morbidity and mortality than those caused by susceptible pathogens, the global impact of increasing resistance is a major concern. 18,19 The frequency of resistance varies markedly between European countries. Because Streptococcus pneumoniae predominates as the causative CAP pathogen, considerable effort has been put into tracking the emergence of resistant pneumococcal isolates.

Data for isolates collected over a five-year period (1999–2004) by the European Antimicrobial Resistance Surveillance System (EARSS) show levels of penicillin nonsusceptibility amongst Streptococcus pneumoniae ranging from < 5% to > 40% (Fig. 1). 20 It is encouraging to note that the data show a decrease in penicillin non-susceptibility in four countries (from 13% to 9% in Belgium, from 19% to 10% in Ireland, from 7% to 3% in the UK and from 33% in 2000 to 29% in Spain), which may be attributable to the uptake of pneumococcal vaccination programmes. 21

Similar resistance problems have surfaced with respect to macrolide resistance. The EARSS data indicate that Spain and Belgium have the highest rates of macrolide-resistant Streptococcus pneumoniae isolates. However, other surveillance studies suggest that macrolide resistance is also an increasing problem in France. 22 The development and widespread availability of the "respiratory" fluoroquinolone antibiotics with enhanced activity against Streptococcus pneumoniae, compared to ciprofloxacin and ofloxacin, has, predictably, been followed by reports of resistance to these agents also. 23 This emergence of drug-resistant pneumococcal infections has caused considerable concern among physicians treating these infections. 24 Because the resistance to β-lactam agents and macrolides in many pneumococcal strains is low level, with MICs only slightly above Clinical Laboratory Standards Institute (CLSI, formerly NCCLS: http://www.nccls.org) breakpoints, the clinical importance of this resistance has been questioned. 25–27 Indeed, at least one study of the molecular epidemiology of Streptococcus pneumoniae has shown that penicillin resistance is not a risk factor for fatal disease. 28 Because resistance was not a risk factor, the authors concluded that resistance in pneumococcal strains may actually reduce virulence, perhaps by causing the bacteria to grow more slowly relative to the wild type and thus reducing the ability of the resistant strain to survive and cause disease.

The clinical relevance of macrolide resistance in Streptococcus pneumoniae isolates has similarly been questioned. 29 Treatment failures for macrolide therapy of pneumococcal infections have been rare despite the increasing resistance to these agents. The level of resistance to date has been relatively low, which may explain the success of macrolide therapy despite the presence of resistance. Another explanation may be that these resistant strains are more easily treated due to a loss of virulence, as has been shown experimentally with penicillin-resistant strains. However, an increase in the level of macrolide resistance in pneumococci together with mutations that restore virulence are likely to evolve and create clinically troubling resistant pneumococcal strains. Yu et al. 30 performed a prospective study of 844 hospitalized patients with blood cultures positive for Streptococcus pneumoniae and found that 15% of these
isolates had in vitro intermediate susceptibility to penicillin (minimum inhibitory concentration [MIC], 0.12–1 μg/mL), and 9.6% were resistant (MIC, $\geq 2$ μg/mL). They further found that while age, severity of illness, and underlying disease with immunosuppression were significantly associated with mortality; penicillin resistance was not a risk factor for mortality. Assessment of the impact of concordant antibiotic therapy (i.e., receipt of a single antibiotic with in vitro activity against *Streptococcus pneumoniae*) versus discordant therapy (inactive in vitro) on mortality showed that discordant therapy with penicillins, cefotaxime, and ceftriaxone (but not cefuroxime) did not result in a higher mortality rate. Similarly, time required for defervescence and frequency of suppurative complications were not associated with concordance of β-lactam antibiotic therapy. The authors concluded that β-lactam antibiotics should be used to treat pneumococcal infections that do not involve cerebrospinal fluid, regardless of in vitro susceptibility.

Antibiotic resistance impacts each country to a different degree, but there does appear to be a consensus that resistance is an inevitable consequence of inappropriate antibiotic use. Thus, until prescribing habits are modified in those regions where antibiotic resistance is growing, it will continue to be a problem. Physicians should make use of local susceptibility data to make informed decisions with respect to their antibiotic prescribing and use.

### Guidelines

Guidelines help physicians to stratify patients according to specific risk factors, and provide diagnostic and treatment options for patients in the community, hospital or intensive care units. Several studies have shown that implementation of CAP guidelines results in a significant reduction in morbidity and mortality. Moreover, a study by Marrie et al. showed that following CAP guidelines allowed physicians to safely identify patients that could be treated as outpatients, resulting in decreased hospitalization rates, which in turn would lead to a decreased length of hospital stay, with a concomitant decrease in the cost of care.

The most recent European CAP guidelines (2005) recommend that a patient should be suspected of having pneumonia when acute cough, and one of the following signs/symptoms are present: new focal chest signs, dyspnea, tachypnea, fever lasting $> 4$ days with diagnosis confirmed by chest radiograph. CAP is often managed in the outpatient setting. However, many patients are hospitalized who could be treated as outpatients, increasing hospital costs and the patient’s risk of death, thromboembolic events and superinfection with resistant nosocomial bacteria. Both US (2007) and European guidelines recommend that an initial assessment of CAP severity is carried out using objective criteria [CURB (Europe) and CURB-65 (US) criteria and/or the Pneumonia Severity Index (PSI)] which, together with other factors, including patient ability to reliably take oral therapy and the availability of outpatient support, may aid the identification of patients appropriate for outpatient or inpatient care.

The main advantages of the PSI are increasing age; co-morbidity; vital sign, laboratory and radiographic abnormalities; oxygenation parameters and nursing home residency. Patients are stratified into 5 mortality risk classes; I–III (mortality risk up to 3%), IV (8%) and V (35%). European guidelines suggest that patients in class IV and V should be seriously considered for hospitalization. US guidelines suggest treatment as an outpatient for classes I and II; in an observation unit or with short hospitalization (class III); or as inpatients (classes IV–V). The CURB index, in European guidelines, is an acronym for 4 variables: mental confusion, blood urea nitrogen (BUN) level $> 7$ mmol/L, Respiratory rate $\geq 30$ min$^{-1}$, and diastolic blood pressure of 60 mmHg. The presence of each criteria scores 1 point. Patients with a CURB score 0 have a risk mortality of 1%, 1–2 (8%), 3–4 (30%). Patients with a CURB score of $\geq 2$ should be seriously considered for hospitalization. In US guidelines, the CURB-65 criteria has been extended to include age $\geq 65$ years. Patients with CURB-65 scores of 0–1 are treated as outpatients, $\geq 2$, hospitalization or intensive in home health care, and $\geq 3$, ICU care is often required.

Both European and US guidelines suggest that it is unsafe to rely on PSI or CURB score alone for determination of hospitalization. Studies have shown that some patients with low PSI or CURB-65 scores require hospital admission, even to ICU. Other factors for hospitalization of low-mortality risk patients include supplemental oxygen requirement, pleural effusion drainage, CAP complications, underlying disease exacerbation, inability to reliably take oral medication or receive outpatient care, and/or multiple risk factors falling just above/below score thresholds. Increasing age as a major determinant in the PSI, may lead to underestimation of pneumonia in younger patients. The CURB criteria based on pneumonia severity, avoids this problem and potential bias from co-morbidities. It is also easier to calculate the score for CURB, as opposed to the PSI with 20 variables and complex scoring.

European guidelines suggest that once a decision has been made to treat as an outpatient, clinical reassessment should be carried out in 24–48 h, as deterioration is most likely to occur during this time. Hospitalization of patients initially treated as outpatients is infrequent (7.5%) within 10 days, but they are at a greater risk of death, and longer recovery time. European guidelines suggest that if there is any doubt, hospitalize.

Criteria for admission to ICU describe patients at increased risk of death. In European guidelines, PSI and CURB criteria have not been used to predict severe pneumonia in individual patients and may be of limited value. In US guidelines, direct admission to ICU is required for patients with 2 major criteria of septic shock requiring vasopressors and acute respiratory failure requiring intubation and mechanical ventilation. Direct admission to ICU or high-level monitoring unit is recommended for patients with 3 minor criteria including respiratory rate ($\geq 30$ breaths/min), PaO$_2$/FiO$_2$ ratio $< 250$, multilobar infiltrates, confusion/disorientation, uremia, leukopenia, thrombocytopenia, hypothermia or hypotension requiring aggressive fluid resuscitation. In European guidelines, referral to ICU in all unstable patients should be guided by the presence of $\geq 2$ indicators of severe pneumonia; systolic blood pressure $< 90$ mmHg, severe respiratory failure (PaO$_2$/FiO$_2$ ratio $< 250$), multilobar involvement or a requirement for either mechanical ventilation or vasopressors $> 4$ h (septic shock).
Key differences exist, mainly for outpatient care, between those issued in North America and those released in Europe. The two approaches differ primarily because of the greater emphasis in North America to routinely treat the atypical pathogens and the fact that macrolide-resistance to **Streptococcus pneumoniae** is of a higher level in Europe than in North America because of the difference in resistance mechanisms between North America (**mef**) and Europe (**erm**). The risk of pneumococcal infections increases linearly with age, disability and hospitalization. A higher frequency of gram-negative enteric bacteria (GNEB), *Staphylococcus aureus*, *P . aeruginosa* and anaerobic pathogens is also reported in elderly and institutionalized patients.36

The North American approach is to use broad initial coverage, whereas Europeans focus on providing pneumococcal coverage with less emphasis on covering atypical pathogens. While the role of atypical pathogens in CAP appears to be established among North American investigators, their importance in Europe continues to be debated, partly due to diagnostic difficulties. Disease caused by *M. pneumoniae* or *C. pneumoniae* is thought to be self-limiting, and many investigators feel that initial empirical coverage against these pathogens is unnecessary. However, in patients hospitalized with CAP, current guidelines recommend empiric therapy which includes atypical coverage.37

Current US guidelines recommend macrolides, doxycycline, a respiratory fluoroquinolone or the combination of a β-lactam plus macrolide as treatment options for individuals who can be treated as outpatients. In general, the North American guidelines recommend a macrolide as first-line treatment for outpatients with no co-morbidity or risk factors for drug-resistant *Streptococcus pneumoniae*. Macrolides are considered in North America to provide effective therapy for *Streptococcus pneumoniae* and for the atypical organisms, such as *M. pneumoniae* and *C. pneumoniae*, which are relatively common in outpatients. In contrast, the British Thoracic Society guidelines recommended β-lactams, primarily penicillins as first-line therapy. The rationale here is that these agents are effective against *Streptococcus pneumoniae*, even strains with decreased sensitivity to penicillin if the antibiotics are given at a high enough dose. The guidelines suggest that because *M. pneumoniae* exhibits epidemic periodicity every 4–5 years and largely affects younger patients, initial empirical therapy that aims to cover this pathogen is unnecessary. The British guidelines thus place less significance than their North American counterparts on the need to treat empirically outpatients who are infected with atypical pathogens. In hospitalized patients, a recently published systematic review of CAP admissions covering an eight year period reported that empirical antibiotic coverage of atypical pathogens did not reduce mortality or improve clinical efficacy.40

Current European guidelines provide recommendations for the diagnosis and treatment of the three most common lower respiratory tract infections: CAP, acute exacerbations of chronic obstructive pulmonary disease (COPD; AECB) and exacerbations of bronchiectasis. Unlike previous guidelines, ERS/ESCMID guidelines are presented in a question and answer format. They ask the following key questions: how do I diagnose or identify CAP?; how should I treat my patient with CAP?; and how should I prevent CAP? They do not recommend outpatient testing for the etiologic cause of the infection; rather, their recommendations for antimicrobial therapy are based on the severity of illness; the frequency of specific pathogens; local patterns of microbial resistance; and drug safety profiles (see Table 2). These guidelines also emphasize the probability of a viral cause for the pneumonia, and in so doing remind physicians of the importance of withholding antibiotics to reduce costs and simultaneously minimize the emergence of antibiotic-resistant bacterial strains in the community.

Initial treatment should be empiric according to risk of mortality related to pneumonia severity distinguishing low risk patients treated as outpatients (mild pneumonia); patients at increased risk and hospitalized (moderate pneumonia) and patients with a high risk admitted to ICU (severe pneumonia.). Antimicrobial therapy should be rapid (within first 2h of hospitalization or within first hour after ICU admission) and appropriate to the general pattern of expected pathogens according to pneumonia severity and additional risks factors. (In hospitalized patients, *Streptococcus pneumoniae* is the most frequent pathogen, and thus

### Table 2  Summary of antibiotic recommendations for CAP from the European CAP guidelines by Woodhead et al.35

<table>
<thead>
<tr>
<th>Setting</th>
<th>Severity/subtype</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outpatient</strong></td>
<td>All</td>
<td>Amoxicillin or tetracycline.</td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td>Nonsevere</td>
<td>Penicillin G + macrolide; Aminopenicillin + macrolide; Co-amoxiclav + macrolide; 2nd or 3rd cephalosporin + macrolide</td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td>Severe</td>
<td>3rd Cephalosporin + macrolide</td>
</tr>
<tr>
<td><strong>Hospital</strong></td>
<td>Severe and risk factors for <em>Pseudomonas aeruginosa</em></td>
<td>Anti-pseudomonal cephalosporin+ ciprofloxacin</td>
</tr>
</tbody>
</table>
the treatment regimen should have high activity.) The frequency of others is dependent on population, age/region, season but are most commonly *H. influenzae*, *M. pneumoniae*, *C. pneumoniae*. In ICU there is the potential for higher frequency of *Legionella* spp., GNEB, *P. aeruginosa* but not so much *H. influenzae* and *M. pneumoniae*. For GNEB/ *P. aeruginosa* there is considerable variability in incidence across Europe with regional and local patterns of microbial resistance [penicillin resistance is 50% in France and Spain, Germany (5%)].

Recommended preferred treatment options for hospitalized patients with CAP in regions with low resistance rates include; either penicillin G, aminopenicillin, aminopenicillin/β-lactamase inhibitor or non-antipseudomonal cephalosporin II or III; each + a macrolide (new macrolide preferred to erythromycin). In regions with increased resistance rates or intolerance to preferred drugs, levofloxacin or moxifloxacin may be alternatives. When oral treatment is adequate, ketolides may offer an alternative. In patients with severe CAP, and no risk factors for *P. aeruginosa*, guidelines recommend a non-antipseudomonal cephalosporin III+ a macrolide or moxifloxacin or levofloxacin and with risk factors for *P. aeruginosa*, either an antipseudomonal cephalosporin, aclyureidopenicillin/β-lactamase inhibitor or a carbapenem; each with ciprofloxacin. Guidelines also list recommended treatment for specific pathogens, including intermediate and highly resistant *Streptococcus pneumoniae*, MSSA, MRSA.

Oral therapy is appropriate for hospitalized, mild CAP and for all patients treated in the community. In hospitalized patients not requiring ICU admission, European guidelines support the consideration of sequential treatment unless there are contraindications (impaired gastrointestinal absorption, inability to swallow oral medication due to impaired consciousness). Resolution of the most prominent clinical feature at admission may be used as the signal to switch from IV to oral therapy. Intravenous therapy needs only be instituted in patients with severe CAP. For patients treated in the community, antibiotic monotherapy is directed against *Streptococcus pneumoniae*. Empirical antibiotic therapy for hospitalized patients varies according to the severity of the pneumonia. In non-severe cases, where pneumonia is the cause of admission, combination oral therapy is recommended because of the greater incidence of atypical pathogens. In severe CAP, combination intravenous therapy using a broad-spectrum β-lactam antibiotic plus a macrolide should be commenced immediately. The guidelines recommend the use of a fluoroquinolone with gram-positive coverage for patients intolerant of penicillins and macrolides.

US CAP guidelines suggest that there is substantial overlap among patients with CAP and patients with healthcare-associated pneumonia (HCAP) for whom separate guidelines have been published. However, it is suggested that some patients with HCAP with specific pathogens may be better managed under CAP guidelines. HCAP is associated with patients who have close association with acute care hospitals or reside in chronic care settings (nursing home and other long term care facilities) that increase their risk of pneumonia caused by MDR bacteria such as MRSA, Gram-negative bacilli (*P. aeruginosa*, ESBL Klebsiella pneumoniae and *Acinetobacter* spp.). European guidelines do not mention HCAP. However, in a recent Spanish study investigators concluded that healthcare-associated pneumonia should be regarded as a separate entity to CAP with a distinct approach to antimicrobial therapy. Of 389 patients admitted to hospital with CAP, 20% were HCAP. Patients with HCAP were older, had more co-morbid conditions, and were more commonly assessed as high severity risk classes than CAP patients. Aspiration and Gram-negative pneumonia were more frequent, whereas *Legionella* spp. and atypical bacteria were rarely identified. Mortality was higher in HCAP patients (8%) compared to CAP (3%).

**Prevention of CAP**

Vaccines targeting pneumococcal disease and influenza are important in the prevention of CAP. In a recent worldwide meta-analysis, in homes for the elderly, well matched IM inactivated influenza vaccine prevented pneumonia with a vaccine efficacy of 46%, but in the elderly living in the community, it was not significantly effective (Relative risk, RR, 0.88, 0.64–1.20). However, influenza vaccination has been shown to be effective (adjusted odds ratio 0.21 and 33%, respectively) in reducing hospital admissions due to pneumonia in non-institutionalized older adults ≥65 years in Spain and in Italy. European guidelines suggest inactivated influenza vaccine should be given annually to persons with increased risk of complications due to influenza including immunocompromised adults aged ≥65 years; institutionalized, or with chronic cardiac, pulmonary or renal disease, diabetes mellitus, and/or hemoglobinopathies; females who will be in the 2nd or 3rd trimester of pregnancy in the influenza season; health care personnel or persons in contact with high risk patients. US guidelines recommend inactivated influenza vaccine for all persons >50 years, younger persons (6 months–49 years) in high risk groups, household contacts of high risk persons and health workers. The inactivated rather than the intranasal spray live attenuated vaccine, is recommended in adults in the European guidelines, however, in US guidelines the live vaccine is recommended for healthy persons 5–49 years, including health care workers.

The evidence for the effectiveness of IM 23-valent pneumococcal polysaccharide vaccine (PPV) in prevention of pneumonia is not as strong as for influenza vaccination. However, in a recent Spanish study (EVAN-65), the 23-valent PPV was significantly effective (45%) in preventing pneumococcal pneumonia and was associated with a significant reduction in the risk of hospitalization for pneumonia (hazard ratio, HR 0.74), the overall pneumonia rate (HR 0.79) and in the risk of death (59%) in vaccinated individuals of mortality due to pneumonia in older non-institutionalized adults (≥65 years). European guidelines recommend that PPV is given to all adults at risk from pneumococcal disease including ≥65 years, institutionalized, with dementia, seizure disorders, congestive heart failure, cerebrovascular disease, COPD, history of previous pneumonia, chronic liver disease, diabetes mellitus, asplenia, chronic cerebrospinal leakage. In US guidelines, IM pneumococcal polysaccharide vaccine (PPV) is recommended for all older persons (≥65 years) and high-risk younger persons (2–64 years). Smokers are included in US, but not European guidelines.
The cost of treating patients with CAP

As previously stated, CAP is associated with significant morbidity, mortality and utilization of health care resources. Strategies for decreasing the cost of treating CAP include identifying low-risk patients who can safely be treated as outpatients, decreasing lengths of hospital stay, decreasing the use of emergency departments as sites for initial evaluation, and promoting the use of lower cost antibiotic therapy. Stratification of CAP severity is mostly based on the CURB-65 criteria in Europe.48,49

In the US, hospitalization costs resulting from CAP have been estimated to be between US$7000 and US$8000 per admission or US$4 million per 100,000 individuals. In Europe, hospitalization costs are significant (representing about 90% of the total costs), but are much lower than in the US (one-third to one-ninth of the US estimates in the UK and Spain, respectively). A review of US and European economic studies of the treatment of CAP by De Graeve and Beutels50 suggests that, in general, these studies are in line with clinical evidence. A drug with proven clinical effectiveness appears to be supported from an economic standpoint. Economic data also support an early switch from an intravenous to an oral antibacterial, the use of fluoroquinolones for inpatients with CAP, and the use of guidelines built on clinical evidence. However, Barlow et al recently evaluated the effect of implementing the British Thoracic Society CAP guidelines on antibiotic prescribing and costs in a UK teaching hospital and found an increase in antibiotic use and, therefore costs.51 Overall, broad-spectrum antibiotic prescribing increased from 42.5% to 77.5% at the intervention site, but decreased from 45% to 41.5% at the control site. There were no significant differences or trends towards improvement in length of hospital stay or 30-day mortality rates. Before implementation, the mean cost of the first dose of antibiotic(s) prescribed was £6.34 (Euro 8.9) at the intervention site and £4.83 (Euro 6.8) at the control site. Post-implementation, costs increased at both sites to £9.01 (Euro 12.6) at the intervention site and £6.42 (Euro 9.0) at the control site.51

The results of the cost-effectiveness studies of influenza vaccination in healthy adults have varied. One study demonstrated a net cost of US$68.00 per vaccinated subject in a year with a poor match between vaccine and infecting strains compared to US$11.00 during the following year with a good vaccine match.44 Other studies have found cost savings with vaccination, particularly in long-term healthcare facilities. In elderly persons, vaccination is probably cost-effective relative to providing anti-viral treatment with neuraminidase inhibitors.

The pneumococcal polysaccharide vaccine appears to be relatively cost effective (and potentially cost saving) for those between 65 and 75 years of age, for military recruits and for HIV positive patients with a sufficiently high CD4 cell count.50 Evaluations of the pneumococcal conjugate vaccine (PCV) indicate that the price of the vaccine is the main determinant of cost effectiveness, but this vaccine has an impressive impact on the frequency of pneumococcal pneumonia, pneumococcal colonization, and resistance development.52

New antibiotic options for the treatment of CAP

Ceftobiprole medacori is a broad spectrum IV cephalosporin with excellent activity against penicillin-resistant pneumococci and MRSA, VRSa, ampicillin-sensitive enterococci, β-lactamase positive H. influenzae and M. catarrhalis.53 It has a favorable pharmacokinetic and safety profile and may be a promising antimicrobial for the treatment of CAP in patients requiring hospitalization. However, it has not demonstrated any activity against ESBL-producing Enterobacteriaceae which may limit its clinical usefulness.

Quinupristin-dalfopristin is a IV semi-synthetic streptogramin, and has activity against serious Gram-positive pathogens including penicillin resistant Streptococcus pneumoniae, MRSA and ERSA.54 However, it should not be used in the treatment of nosocomial MRSA as it has been shown to be inferior in clinical trials.55 It also is not active against the majority of Gram-negative bacilli or Pseudomonas aerugiosa.

The lipopeptide, daptomycin failed to meet statistical noninferiority criteria in an in vitro modeling trial.56 It was shown to interact with pulmonary surfactant, resulting in inhibition of antibacterial activity; it was efficacious to Staphylococcus aureus heamatogenous pneumonia, but demonstrated no activity against Streptococcus pneumoniae in simple bronchial alveolar pneumonia.

The oxazalidinone linezolid shows activity against Gram-positive CA-MRSA, GISA, and multidrug-resistant Streptococcus pneumoniae. It can be administered i.v. in serious infections or orally in less serious conditions. In pooled clinical studies of CAP due to MDRSP, clinical efficacy was 73%.57 Recent data suggest that linezolid may also be considered in the treatment of MRSA nosocomial pneumonia in patients with vancomycin-induced nephrotoxicity or documented lack of response to vancomycin.55 Adverse events with prolonged linezolid use include thrombocytopenia and serotonin syndrome.

Telithromycin, is a first in class oral ketolide. Its main advantage is its enhanced activity against macrolide-sensitive and resistant Streptococcus pneumoniae. Against atypical bacteria, it has similar or slightly greater activity than macrolides. It has been shown to be an effective new option in the treatment of CAP.58 However, Enterobacteriaceae are intrinsically resistant to macrolides and ketolides. There have been several reports of serious liver toxicity, loss of consciousness and visual disturbances following telithromycin administration and contraindications in myasthenia gravis leading to a change of label in the United States restricting its use to the treatment of CAP.59

One of the newest respiratory fluoroquinolones, oral gemifloxacin has enhanced activity against Gram-positive cocci, and is the most potent fluoroquinolone against drug resistant Streptococcus pneumoniae including penicillin-, macrolide- and many ciprofloxacin-resistant strains.60 It is the least likely of the fluoroquinolones to be affected by resistance, and has the most impressive pharmacokinetic profile. A frequent adverse event of mild rash has been recorded in younger women, which may limit its clinical utility. Current evidence supports the use of respiratory fluoroquinolones as first choice agents in CAP, however increasing resistance may threaten the class.
The recently approved novel antibiotic tigecycline is currently undergoing clinical evaluation as a therapeutic option for the treatment of CAP, especially in countries with high rates of multi-drug resistant *Streptococcus pneumoniae*. The in vitro activity of tigecycline has been shown to cover many community-acquired pathogens. *Streptococcus pneumoniae* may provide clinicians with an expanded spectrum antibiotic option that can be used at the onset of treatment when the specific bacteria present are not yet known. In a recent Phase III study it was demonstrated that tigecycline was slightly more clinically effective (88.9%) than levofloxacin (85.3%) in the treatment of hospitalized patients with CAP. For patients with a Fine score of < 3 or 3/4, clinical efficacy for tigecycline was 89.6% and 88.0%, respectively, and for levofloxacin was 87.3% and 83.3%, respectively. Adverse events of nausea (26.9% tigecycline vs. 8.5% levofloxacin), vomiting (16.7% vs. 6.6%), and leukocytosis (6.9% vs. 0.9%) were more common in tigecycline-treated patients, whereas hypokalemia was more common in levofloxacin treated patients (0.5% tigecycline vs. 3.8% levofloxacin, *P* = 0.019). Further studies will provide more information on the clinical utility of tigecycline, which may be of therapeutic significance to treat multi-drug resistant pneumococci.

**Conclusion**

Community-acquired pneumonia (CAP) is a major global public health problem, affecting millions of people annually. Up to a third of patients are hospitalized with CAP, and this infection contributes considerably to morbidity and mortality. Despite continuous advances in the diagnosis and treatment of CAP, this infection remains a significant socioeconomic burden, and its management presents a challenge to physicians. The predominant pathogen associated with CAP is *Streptococcus pneumoniae*; other commonly identified pathogens include *H. influenzae*, and atypical organisms, such as *M. pneumoniae*, *C. pneumoniae* and *Legionella* spp. For years, *Streptococcus pneumoniae* was sensitive to penicillin, and β-lactams were an effective treatment option for *Streptococcus pneumoniae* infections. However, over the past 20 years, drug-resistant pneumococci have spread rapidly over a wide geographic area, such that today drug-resistant *Streptococcus pneumoniae* is recognized worldwide. Surveillance programs developed to track resistance to *Streptococcus pneumoniae* and other organisms are currently reporting the prevalence of *Streptococcus pneumoniae* non-susceptibility to penicillin to be as high as 50% and the prevalence of resistance to macrolides to be similarly on the rise. Of particular concern is the increasing prevalence of resistance to fluoroquinolones. Although fluoroquinolone-resistance has been slow to emerge, there are now more and more geographic regions reporting resistance. As resistance to commonly prescribed antibiotics for CAP has increased, the need for safe and effective new antimicrobials has grown, as has the call for more judicious use of antibiotics. Updated guidelines are of immense value to physicians trying to help their patients overcome this still common, yet serious infection.

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**References**


