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# Community-acquired pneumonia

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Community-acquired pneumonia causes great mortality and morbidity and high costs worldwide. Empirical selection of antibiotic treatment is the cornerstone of management of patients with pneumonia. To reduce the misuse of antibiotics, antibiotic resistance, and side-effects, an empirical, effective, and individualised antibiotic treatment is needed. Follow-up after the start of antibiotic treatment is also important, and management should include early shifts to oral antibiotics, stewardship according to the microbiological results, and short-duration antibiotic treatment that accounts for the clinical stability criteria. New approaches for fast clinical (lung ultrasound) and microbiological (molecular biology) diagnoses are promising. Community-acquired pneumonia is associated with early and late mortality and increased rates of cardiovascular events. Studies are needed that focus on the long-term management of pneumonia.

## Clinical presentation

Community-acquired pneumonia is responsible for great mortality and morbidity and high costs. Community-acquired pneumonia was featured in Seminars in *The Lancet* in 1998<sup>1</sup> and 2003.<sup>2</sup> In this updated Seminar, we address important topics related to community-acquired pneumonia in immunocompetent adults.

Suspected community-acquired pneumonia is defined by acute symptoms and presence of signs of lower respiratory tract infection (LRTI) without other obvious cause, whereas new pulmonary infiltrate on chest radiograph is needed for definite diagnosis.<sup>3-6</sup> The most common signs and symptoms are dyspnoea, cough, fever, and new focal chest signs (appendix). In subgroups of patients (eg, elderly people), clinical presentation can have less evident symptoms (eg, an altered state of consciousness, gastrointestinal discomfort, and fever can be absent) and diagnosis is frequently delayed. A prolonged time between the onset of symptoms and a medical visit has been described for less severe pneumonia, individuals with alcoholism, and for patients receiving drugs such as corticosteroids, non-steroidal anti-inflammatory drugs, and antibiotics.<sup>7</sup> For some pathogens, unusual clinical presentations that involve the gradual onset of symptoms such as dry cough, the

absence of fever, and extrapulmonary manifestations are frequent. For example, patients with pneumonia due to *Legionella* spp can present with headache, confusion, diarrhoea, and clinical manifestations of hyponatraemia.<sup>8</sup> *Mycoplasma pneumoniae* can be associated with upper respiratory involvement (otitis, pharyngitis), skin changes (Stevens-Johnson-like syndrome), and haemolytic anaemia.<sup>9</sup> Investigators have clearly shown that differentiation between typical and atypical pneumonia on the basis of patient history and chest radiograph is not reliable in guidance of antibiotic treatment.<sup>3,10</sup> By contrast, the use of validated scores for antibiotic decisions is promising. A 2014 study<sup>11</sup> proposed a score that can rule out *Legionella* spp pneumonia with a negative predictive value of 99%.

## Differential diagnosis

Many diseases and syndromes have clinical signs and symptoms that can mimic pneumonia (appendix). When the probability of a differential diagnosis is high, careful assessment is needed because delays in correct diagnoses increase the risks of poor outcomes.<sup>12</sup> In patients with not-severe community-acquired pneumonia, the main differential diagnosis is upper respiratory infection. In these cases, clinicians should rely on clinical evaluations (including manifestations of LRTI, focal chest sounds, exclusion of other possible diagnosis) and point-of-care tests (eg, C-reactive protein [CRP]).<sup>6</sup>

Patients with severe community-acquired pneumonia should be monitored for other life-threatening disorders. Because differentiation of pneumonia from non-infectious disorders such as acute heart failure is occasionally difficult, prompt start of antibiotic treatment is recommended. Biomarkers (eg, procalcitonin [PCT]) can help in the early differentiation from heart failure decompensation, avoiding antibiotic misuse.<sup>13</sup> When the diagnosis of pneumonia is excluded, antibiotic treatment must be stopped. Dynamic evaluation of the patient also helps the clinician in terms of management (eg, pulmonary infiltrates that resolve completely after positive pressure ventilation are probably due to heart failure or atelectasis). In patients with recurrent pneumonia, underlying diseases should be suspected

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See Online for appendix

## Search strategy and selection criteria

We searched Medline, Embase, and the Cochrane Library for papers published from inception to Jan 31, 2015. We used the search terms "community-acquired pneumonia" or "lower respiratory tract infection", in combination with the terms "epidemiology", "diagnosis", "aetiology", "pathophysiology", "risk factors", "management", "treatment", "outcomes", "long-term", and their variations. We restricted the search strategy to adults. We largely selected publications in the past 5 years and also searched the reference lists of articles identified by this search strategy. We gave more weight to randomised controlled trials and meta-analyses, as suggested by *The Lancet*. Review articles and book chapters are cited to provide readers with more details and more references. The reference list was modified on the basis of peer-review process.

such as lung cancer, metastasis, tuberculosis, foreign bodies, hypersensitivity pneumonitis, and unknown immunosuppressed status.

## Epidemiology

### Worldwide incidence

The Global Burden of Disease Study<sup>14</sup> reported that LRTI remains the second biggest cause of deaths and years of life lost in 2013. The age-standardised death rate was 41.7 (95% CI 37.1–44.1) per 100 000 population for LRTI.<sup>14</sup> The incidence of pneumonia is estimated to be between 1.5 and 14.0 cases per 1000 person-years.<sup>15–17</sup> This rate varies according to the region, season, and population characteristics. In terms of age, incidence of community-acquired pneumonia is U-shaped—it is common in children younger than 5 years and adults older than 65 years. The incidence is also higher in men and boys than in women and girls. Patients who do not need admission into hospital have a mortality rate of lower than 1%.<sup>18,19</sup> Short-term mortality (in-hospital and 30 day mortality) for hospitalised patients ranges from 4.0% to 18.0%,<sup>17,20,21</sup> however, for patients in intensive care, this rate can reach 50%.<sup>22</sup> Costs related to community-acquired pneumonia are high,<sup>23</sup> and few approaches (such as reducing the length-of-stay, adequate use of antibiotics, and the introduction of vaccines) have reduced these costs so far.<sup>24,25</sup>

### Causative pathogens

*Streptococcus pneumoniae* is the main pathogen that causes community-acquired pneumonia worldwide, independent of age.<sup>23,26,27</sup> In Europe, nearly 35% (12–68%)<sup>23</sup> of cases are caused by pneumococcal disease; worldwide it is about 27.3% (95% CI 23.9–31.1).<sup>28</sup> Other frequent causes include *Haemophilus influenzae*, which accounts for 12% (2.4–44.9%) of cases<sup>23</sup> and the so-called atypical bacteria (including *Mycoplasma*, *Chlamydia*, and *Legionella* spp), which caused 22% of cases in a large worldwide cohort.<sup>29</sup>

In recent years, the availability of molecular microbiological tests and clinical suspicion has increased isolation of respiratory viruses in community-acquired pneumonia.<sup>30</sup> In adults, viruses, particularly influenza, rhinovirus, and coronaviruses, cause a third of cases of pneumonia.<sup>30</sup> However, the attribution of the aetiology to respiratory viruses is debatable because it is difficult to define the virus as the causative agent of pneumonia.

Resistance of *S pneumoniae* to penicillin and macrolides has been nearly stable in recent years.<sup>2–4</sup> The introduction of the conjugated pneumococcal vaccine in children has decreased the incidence of the invasive penicillin-resistant cases; however, infections with serotypes not affected by the vaccine have increased.<sup>31</sup> The incidence of *Mycoplasma pneumoniae* resistant to macrolides varies greatly with geography (eg, with peak of about 69% in China).<sup>32,33</sup>

Although the proportion of patients infected with pathogens not covered by standard empirical treatment is low, these pathogens are associated with high mortality and

costs. In immunocompetent patients with community-acquired pneumonia, these pathogens are more frequently *Pseudomonas aeruginosa*, *Enterobacteriaceae* extended-spectrum  $\beta$ -lactamase (ESBL+), and *meticillin-resistant Staphylococcus aureus* (MRSA).<sup>34,35</sup>

## Pathophysiology

In healthy individuals, many microorganisms colonise the nasopharynx and oropharynx. Microaspiration of contaminated secretions can cause infections in the lower airways. The glottal reflexes, the presence of complement proteins and immunoglobulins, the secretion of peptides with antimicrobial activities, and the inhibition of bacteria binding all protect the lower airways.<sup>36</sup> The healthy microbiota of the upper airway also exert protection effects by competing with pathogens for nutritional resources and interacting with cellular receptors. The use of broad-spectrum antibiotics can modify the microbiota and predispose to infection.<sup>37</sup> The interactions between the virulence of the pathogens, the amount of inoculum, and the innate and adaptive immune responses determine the development of pneumonia.<sup>36</sup>

## Risk factors and genetics

All individuals are at risk for development of pneumonia. However, some individuals are more prone to pneumonia than are others due to intrinsic and extrinsic factors (appendix).<sup>38</sup> New findings have revealed individual genetic variability in the predisposition to the development of pneumonia and its clinical presentation.<sup>39</sup> For example, specific variants of the *FER* gene are associated with a reduced risk of death in patients with sepsis due to pneumonia. Thereby, the *FER* gene might be a potential target for new therapies.<sup>40</sup> Misch and colleagues<sup>41</sup> showed that TLR6 polymorphism is associated with increased risk of Legionnaires' disease (odds ratio [OR] 5.83, 95% CI 2.21–16.39).

## Diagnostic investigations

### Laboratory evaluation

In patients who clinicians suspect to have community-acquired pneumonia, blood tests can provide information about the inflammatory state (ie, leucocyte cell number and characteristics [neutrophilia] and CRP), the associated organ damage (ie, acute renal failure), and the severity of the disease. Biomarkers can support clinicians in the differentiation of bacterial pneumonia from other disorders (eg, upper respiratory tract disorders). A meta-analysis suggested that antibiotic exposure can be reduced in suspected LRTI via the use of CRP measurements in primary care (risk ratio [RR] 0.78 [95% CI 0.66–0.92]).<sup>42</sup> The 2014 NICE guidelines<sup>6</sup> recommend not to offer antibiotics when CRP is lower than 20 mg/L in primary care for patients without a convincing clinical diagnosis of community-acquired pneumonia.

PCT had high sensitivity but moderate specificity to differentiate bacterial and viral infections. For outpatients, patients in emergency departments, and inpatients, an antibiotic is encouraged when PCT concentrations are higher than 0.25 µg/L and is strongly encouraged when PCT concentrations are higher than 0.5 µg/L; whereas they are discouraged when concentrations are lower than 0.10 µg/L.<sup>43</sup> In patients admitted to intensive care, antibiotic treatment is always strongly encouraged with PCT concentrations higher than 0.25 µg/L. A meta-analysis reported that the use of PCT to guide antibiotic treatment in pneumonia resulted in a reduction in the exposure to antibiotics from median 8 days [IQR 5–12] to 4 days [0–8], with an adjusted difference of –3.34 days (95% CI –3.79 to –2.88) without increases in mortality or treatment failure.<sup>44</sup> Moreover the use of PCT to guide antibiotic treatment reduced costs of treatment.<sup>45</sup>

### Microbiological evaluation

Despite many improvements, the pathogen is not detected in nearly half of pneumonia episodes.<sup>3</sup> Microbiological tests are recommended in patients in whom the probability of changing the empirical antibiotic is high: reducing treatment failure and preventing antibiotic overuse. Microbiological evaluations (figure 1) are recommended for higher-risk patients such as those with severe community-acquired pneumonia, special disorders (eg, asplenia, immunosuppression, HIV infection, and alcohol abuse), severe sepsis or septic shock, a risk of resistant pathogens, and failure of the initial empirical treatment.<sup>3–5</sup> By contrast, recommendations for microbiological testing remain controversial in less severe pneumonia because such tests are expected to have little effect on antibiotic management due to good responses to empirical treatment.<sup>46–48</sup> However, microbiological evaluations could be valuable for surveillance.

Although a positive blood (or pleural fluid) culture test definitively identifies the pathogen responsible for pneumonia, a positive respiratory tract sample needs clinical interpretation because the microorganism can be present due to colonisation or be part of the healthy flora. The main difficulties are related to the need for a high-quality sample.<sup>3</sup> Furthermore, the collection of any sample after the administration of antibiotics increases the rate of false-negative results. Despite these limitations, in patients in hospital with purulent sputum, a sample collection for Gram stain and culture is recommended.<sup>5,6</sup>

Urinary antigens are useful for the detection of all serotypes of *S pneumoniae* and for serogroup 1 of *Legionella pneumophila* (responsible for about 90% of legionella cases of community-acquired pneumonia). Advantages of these tests are promptness (<15 min), reasonable accuracy, and the ability to detect the infection while the patient is receiving antibiotic therapy.<sup>6</sup> The main drawback is the absence of information about

resistance. The urinary antigen for *S pneumoniae* has a sensitivity of 74.0% (95% CI 66.6–82.3) and a specificity of 97.2% (92.7–99.8).<sup>49</sup> For *L pneumophila*, sensitivity is 74.0% (68.0–81.0) and specificity is 99.1% (98.4–99.7).<sup>50</sup> Two randomised controlled trials have tested empirical versus pathogen-directed antibiotic treatment through urinary antigen tests in patients in hospital with stable pneumonia<sup>51,52</sup> and shown no differences in major outcomes, although their conclusions were hampered by methodological issues.

For atypical pathogens, blood serology tests are available for *Chlamydia pneumoniae*, *M pneumoniae*, and *Legionella* spp; however, their clinical usefulness is limited by the delay in the results and difficulty in interpretation. PCR tests are available for bacterial causes related to *Mycoplasma*, *Chlamydia*, *Streptococcus*, and *Legionella* spp, which have to be done on bronchoalveolar lavage fluid or nasopharyngeal swabs. Real-time and multiplex-panel PCR aim to provide results in a few hours and are promising methods for fast bacterial aetiological diagnoses of community-acquired pneumonia.<sup>53</sup> However, their cost-effectiveness is unclear, and there are no data about resistance. PCR tests are available for several respiratory viruses.<sup>30</sup> In view of the controversies about the use of antiviral therapy, difficulties related to the diagnosis of viral pneumonia, and cost-effectiveness, clinicians should reserve testing for viruses for special groups of patients and within influenza season.

### Imaging

Thoracic images are essential for several aspects of pneumonia management. Chest radiograph has diagnostic accuracies of 75% for alveolar consolidation and 47% for pleural effusion, considering CT as the gold standard technique.<sup>54</sup> Performing both posteroanterior and laterolateral projections increases its accuracy. By contrast, chest radiograph has less accuracy in bedridden, obese, and severely immunosuppressed patients and in patients with previous alterations on chest radiograph.

	Outpatient	Inpatient, low severity	Inpatient, no ICU, moderate severity	Inpatient, ICU, high severity
Sputum culture	None routinely	Yes	Yes	Yes
Blood culture	None routinely	None routinely	Yes	Yes
Legionella urinary antigen	None routinely	None routinely	Yes	Yes
Pneumococcal urinary antigen	None routinely	None routinely	Yes	Yes
Invasive respiratory tract sample culture	None routinely	None routinely	None routinely	Yes
Others	None routinely	None routinely	None routinely	Yes*

**Figure 1: Microbiological investigations**

ICU=intensive care unit. \*Others indicates fungal, tuberculosis cultures, PCR, specific serology, lung biopsy.

CT is the most accurate imaging technique for the diagnosis of lung condensation<sup>54</sup> and provides detailed information about the lung parenchyma and mediastinum and can also reveal alternative diagnoses. However, CT has limitations that include increased cost, radiation exposure, and the impossibility of doing CT at the bedside.<sup>54,55</sup> For these reasons, CT is reserved for specific situations such as excluding the presence of other diagnoses (eg, pulmonary embolism), when the suspicion of a fungal lung infection is present, in patients with unclear chest radiograph (eg, occult pneumonia in chronic obstructive pulmonary disease), and in non-responding pneumonia for the detection of complications (eg, lung abscesses).

Lung ultrasound is a useful method for evaluating respiratory diseases including pneumonia.<sup>56</sup> A recent meta-analysis showed a sensitivity of 94.0% (95% CI 92.0–96.0) and a specificity of 96.0% (94.0–97.0) in the diagnosis of pneumonia in adults.<sup>57</sup> Compared with previous methods, lung ultrasound has some advantages; it is radiation-free, can be done at the bedside and on pregnant woman, allows for dynamic evaluations, has increased accuracy in the detection of consolidation and pleural effusion compared with chest radiograph, and takes less time.<sup>56–58</sup> Lung ultrasound is limited by its learning curve, repeatability, and operator dependency.<sup>59</sup>

## Acute management

### Site of care

Early in the evaluation of patients with community-acquired pneumonia, two questions need to be answered: does the patient need to be admitted in the hospital and

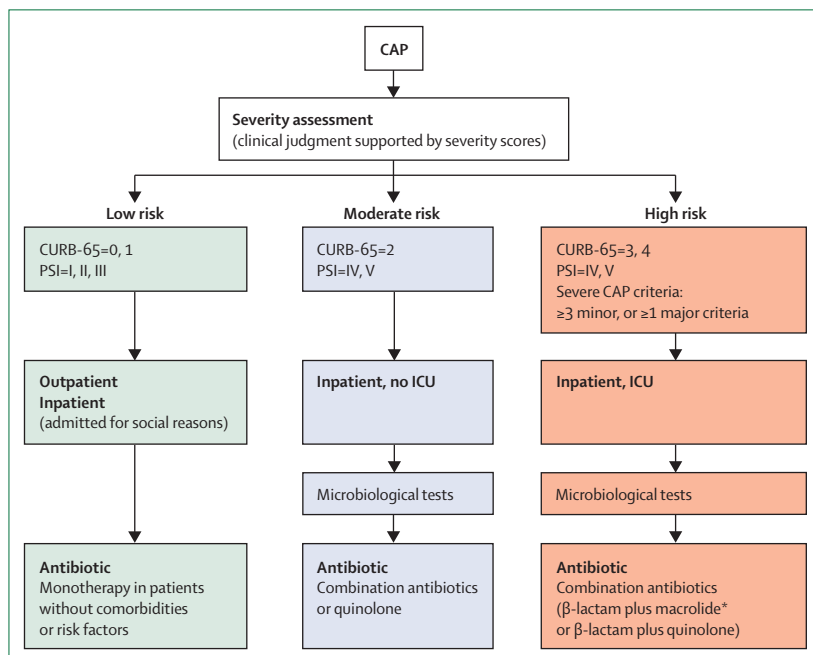
should they be treated in intensive care? These decisions need to be made early because it has been widely shown that late admission into intensive care is associated with increased mortality.<sup>60</sup> By contrast, the admission of patients who can be treated outside the hospital is associated with increased costs and risk of the development of nosocomial infections.<sup>61</sup>

Clinical judgment is the main determinant of the site-of-care decision.<sup>6</sup> Oxygen saturation (SpO<sub>2</sub>) and arterial gas analysis can give important information about severity (eg, SpO<sub>2</sub> <92% can be considered a safer cutoff than can SpO<sub>2</sub> <90% for hospital admission).<sup>62</sup> Furthermore, scores and biomarkers can assist the clinical judgment. The Pneumonia Severity Index (PSI)<sup>18</sup> and CURB-65<sup>63</sup> are the most frequently used scores. PSI is composed of 20 items and classifies patients into five categories of severity that are associated with the risk of mortality. Age and comorbidities are highly weighted in the PSI, and for these reasons, PSI can underestimate the severity of pneumonia in young patients and in those without previous diseases. CURB-65 uses five items and is practical for calculations, although it does not account for comorbidities. Important considerations not included in either score are socioeconomic status and social support, both of which can affect outcomes.<sup>64</sup> Both PSI and CURB-65 were not developed to predict complications associated with community-acquired pneumonia; clinical research is needed to develop specific scores to predict these events.

Patients should be admitted to intensive care when they require mechanical ventilation or vasopressors (both of which are major criteria for severe pneumonia in the American Thoracic Society and Infectious Diseases Society of America guidelines).<sup>3</sup> In addition to the major criteria, nine minor criteria are included to predict admission into intensive care.<sup>3</sup> A meta-analysis proposed a simplification of the American Thoracic Society and Infectious Diseases Society of America minor criteria through removal of three variables (thrombocytopenia, hypothermia, and leucopenia), which had a similar accuracy.<sup>65</sup> Other useful scores that are used to predict admission into intensive care are the SMART-COP<sup>66</sup> and the REA-ICU for late admission.<sup>67</sup> Some biomarkers can increase the performance of some scores to predict ICU admission (eg, proadrenomedullin)<sup>68</sup> and can identify severe community-acquired pneumonia (eg, CRP).<sup>69</sup> Biomarkers can also identify patients who are first admitted to the ward who might need an admission into intensive care later.<sup>70</sup>

### Selection of antibiotics

Antibiotic treatment is typically chosen empirically because of the absence of microbiological results upon diagnosis. The choice of the empirical antibiotic depends on the most likely pathogen, individual risk factors, comorbidities, allergies, and cost-effectiveness (appendix). Figure 2 and the table describe the management and antibiotic treatment proposed by community-acquired



**Figure 2: Acute management of the community-acquired pneumonia**

CAP=community-acquired pneumonia. CURB-65=Confusion Urea Respiratory rate Blood pressure and age  $\geq 65$  year old score. PSI=Pneumonia Severity Index. ICU=intensive care unit. \*Combination with macrolide is preferred.

pneumonia guidelines.<sup>3-6</sup> Several studies have shown reductions in mortality when these guidelines are followed.<sup>7,72</sup> Guidelines suggest the coverage of *S pneumoniae* and atypical pathogens (eg, combination of a  $\beta$ -lactam plus macrolide or respiratory fluoroquinolone).<sup>3,6</sup> However, dual coverage is still debated,<sup>6,73</sup> and three meta-analyses reported different results about mortality.<sup>74-76</sup> Furthermore, concerns exist about side-effects (such as an increased risk of cardiovascular events in patients who receive macrolides)<sup>77,78</sup> and selective pressure for resistance to macrolides and fluoroquinolone.

Two recent randomised controlled trials provided important results about antibiotic treatment for people admitted into hospital with non-severe community-acquired pneumonia. A cluster-crossover trial assessed the non-inferiority of  $\beta$ -lactam versus  $\beta$ -lactam plus macrolide versus fluoroquinolone regimens with 90 day mortality as the primary outcome. Including 2283 patients with clinically suspected pneumonia treated in non-intensive-care-unit wards, monotherapy with  $\beta$ -lactam was not inferior to the other antibiotic regimens.<sup>79</sup> Another non-inferiority, open-label trial randomly assigned 580 patients with moderately severe community-acquired pneumonia to receive  $\beta$ -lactam or  $\beta$ -lactam plus macrolide.<sup>80</sup> The study was unable to show non-inferiority for clinical stability after 7 days of treatment. Nevertheless, a non-significant trend for superiority was shown in favour of dual therapy (between-group difference 7.6%, two-sided 95% CI -0.8% to 16.0%). For severe community-acquired pneumonia, coverage of typical and atypical pathogens seems to be protective of mortality and is recommended by major guidelines.<sup>3-5</sup> Macrolides seem to have additional benefits due to their immunomodulatory effects in severe community-acquired pneumonia.<sup>81,82</sup>

A small proportion of patients with specific pathogens require a different treatment because they do not

respond to the standard empirical treatment.<sup>34</sup> For this reason, the 2005 American Thoracic Society and Infectious Diseases Society of America nosocomial pneumonia guidelines introduced a new category of pneumonia called health-care-associated pneumonia to help clinicians to select patients who need an extended-spectrum antibiotic due to a high probability of resistant pathogens.<sup>83</sup> This definition has been widely criticised because it has many limitations, and studies have shown it not to be accurate in the detection of at-risk patients.<sup>84,85</sup> Other scores have been developed and have better accuracies; however, they also have some limitations and still need strong external validation.<sup>34,86-88</sup> A summary of risk factors for resistant pathogens is contained in the appendix. Because resistant pathogens have different treatments, scores based on specific risk factors for each pathogen might be more useful methods compared with general definitions.<sup>34,35,89</sup> Another concern is related to the treatment of patients who are at risk for resistant pneumococcus, such as elderly patients (age >65 years), those who have received recent therapy with  $\beta$ -lactams, macrolides, or fluoroquinolones; alcohol consumption; and immunosuppression (appendix).<sup>3,90</sup>

New antibiotics are urgently needed for infections because of the spread of resistance in some settings. A recent phase 3 trial showed promising results for ceftaroline fosamil, a fifth-generation cephalosporin with activity against MRSA, in the treatment of community-acquired pneumonia with PSI III-IV in Asian patients.<sup>91</sup> Among macrolides, solithromycin is a potential new antibiotic with activity against macrolide-resistant bacteria.<sup>92</sup>

The efficacy of neuraminidase inhibitors to prevent and treat influenza pneumonia is still controversial.<sup>93</sup> For patients with influenza A H1N1, a recent meta-analysis

	American (IDSA/ATS) <sup>3</sup>		British (NICE/BTS) <sup>4,6</sup>		European <sup>5</sup>	
	Preferred	Alternative	Preferred	Alternative	Preferred	Alternative
Outpatient without comorbidities; low severity	Macrolide	Doxycycline	Amoxicillin	Macrolide or tetracycline	Amoxicillin or tetracycline	Macrolide
Outpatient with comorbidities or high rate bacterial resistance	$\beta$ -lactam plus macrolide	Respiratory fluoroquinolone			Respiratory fluoroquinolone	
Inpatient not in ICU; moderate severity	$\beta$ -lactam* plus macrolide	Respiratory fluoroquinolone	Amoxicillin plus macrolide	Respiratory fluoroquinolone†	Aminopenicillin with or without macrolide	Respiratory fluoroquinolone
Inpatient in ICU; high severity	$\beta$ -lactam‡ plus macrolide	$\beta$ -lactam‡ plus respiratory fluoroquinolone	$\beta$ -lactamase stable $\beta$ -lactams¶ plus macrolide	Respiratory fluoroquinolone‡	Third-generation cephalosporin§ plus macrolide	Respiratory fluoroquinolone with or without a third-generation cephalosporin§

Local or adapted guidelines should be used to adapt for different epidemiology. 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. \*Preferred  $\beta$ -lactam drugs include cefotaxime, ceftriaxone, and ampicillin. †Respiratory fluoroquinolone limited to situations in which other options cannot be prescribed or are ineffective (eg, hepatotoxicity, skin reactions, cardiac arrhythmias, and tendon rupture). ‡Preferred  $\beta$ -lactam drugs include cefotaxime, ceftriaxone, or ampicillin-sulbactam. ¶ $\beta$ -lactamase-stable  $\beta$ -lactams include co-amoxiclav, cefotaxime, ceftaroline fosamil, ceftriaxone, cefuroxime, and piperacillin-tazobactam. §Third-generation cephalosporin (eg, cefotaxime, ceftriaxone).

**Table: Empirical antibiotics suggested for community-acquired pneumonia**

showed a reduction in mortality in hospitalised patients who received neuraminidase inhibitors.<sup>94</sup>

#### Timing of antibiotic treatment

The first dose of antibiotics should be given as soon as possible after diagnosis of community-acquired pneumonia. The antibiotics should be started preferably within the first 4–8 h of hospital arrival and a shorter time to the first dose of antibiotic can be a marker of quality of care.<sup>95</sup> However, a meta-analysis of stable patients with community-acquired pneumonia revealed that administration within 4 h was not associated with lower mortality (OR 0.95, 95% CI 0.73–1.23)<sup>96</sup> and the pressure for rapid antibiotic administration was associated with an increased risk of misdiagnosis and an increased risk of adverse effects.<sup>97</sup> In unstable patients with severe sepsis or septic shock, the time to the first dose is strongly associated with a reduction in mortality, and administration in the first hour after diagnosis is recommended.<sup>82,98</sup>

#### Care of pneumonia-related sepsis

Pneumonia is the main cause of sepsis worldwide, and for severe sepsis or septic shock, the previous aspects of care are the priority (ie, assessment of pathogens, antibiotics, and whether early intensive care unit admission is needed).<sup>82,98</sup> The Surviving Sepsis Campaign also advocates the measure of lactate concentration at diagnosis and prompt initial expansion with 30 mL/kg of crystalloid for hypotension or lactate concentrations of 4 mmol/L or higher.<sup>82</sup> Results related to recommendation of early goal-directed therapy are controversial mainly because of insufficient benefits reported in well designed multicentre randomised controlled trials.<sup>99–101</sup> A major concern about patients with sepsis due to pneumonia are the risks associated with cumulative fluid balance and blood transfusion because of worsening in respiratory function.<sup>102,103</sup>

#### Respiratory support

Patients with acute respiratory failure due to pneumonia must be assessed early for a need for respiratory support, and oxygen saturation is an important marker for outcome.<sup>62</sup> Patients with severe pneumonia are candidates for invasive mechanical ventilation, and a delay can lead to an increased mortality.<sup>104</sup> Patients with moderately severe disease can be cautiously managed with the use of non-invasive ventilation by trained staff.<sup>105</sup> A meta-analysis suggested that the appropriate use of non-invasive ventilation in pneumonia can reduce the need for endotracheal intubation (OR 0.28, 95% CI 0.09–0.88), intensive care unit mortality (0.26, 0.11–0.61), and the length-of-stay in intensive care units (mean –1.00, 95% CI –2.05 to –0.05). However, this meta-analysis included only 151 patients in three randomised trials, and benefits were particularly evident in patients with chronic obstructive pulmonary disease or

immunosuppression.<sup>106</sup> Non-invasive ventilation can also be considered a palliative treatment in patients with terminal illness.<sup>107</sup> For mechanically ventilated patients, protective ventilation is strongly recommended on diagnosis of acute respiratory distress syndrome. For less severe pneumonia, protective ventilation also seems to prevent the progression of lung injury.<sup>3,108</sup>

#### Adjunctive therapy

The use of corticosteroids for community-acquired pneumonia is debated, especially how it affects mortality.<sup>109</sup> Meta-analyses<sup>110,111</sup> have reported reduced hospital length-of-stay (mean –1.21 days, 95% CI –2.12 to –0.29) with use of corticosteroids. A multicentre randomised controlled trial<sup>112</sup> showed a shorter time to reach clinical stability in patients with pneumonia receiving oral prednisone (50 mg a day for 7 days) in relation to the placebo group (3.0 days vs 4.4 days, hazard ratio 1.33, 95% CI 1.15–1.50). Another multicentre randomised controlled trial<sup>113</sup> showed that methylprednisolone (0.5 mg/kg per 12 h for 5 days) reduced risk for treatment failure compared with placebo (OR 0.34, 95% CI 0.14–0.87) in patients with severe community-acquired pneumonia with high baseline concentrations of CRP. For mortality, updated meta-analyses<sup>110,111,114–116</sup> report no conclusive results for hospitalised patients, although corticosteroids were associated with better survival in the subgroup with severe community-acquired pneumonia.<sup>114–117</sup> However, trials included in the meta-analyses were small, have high heterogeneity, and insufficient power to assess mortality. No definitive data are available for the best type and dose of corticosteroids for patients with community-acquired pneumonia, nor those for whether they should be given continuously or to intermittent and tapering schemes.<sup>6</sup> The clinician should be aware of possible steroid-induced side-effects in patients. In controlled settings (eg, randomised controlled trials), only hyperglycaemia was more frequently reported for patients with community-acquired pneumonia receiving a corticosteroid. However, large trials including patients with severe sepsis or septic shock with community-acquired pneumonia as the main source of infection, showed other steroid side-effects such as superinfection.<sup>6,118</sup>

Investigators have proposed statins as an adjunctive therapy in pneumonia due to their anti-inflammatory activities and ability to reduce cardiovascular events, but their effects are controversial.<sup>119</sup>

#### Long-term management

##### Evaluation of clinical stability

After the initial management of community-acquired pneumonia, the subsequent days are fundamental for good outcomes and high-quality management needs a multidimensional approach (figure 3). The evaluation of clinical stability (appendix) is a fundamental aspect of community-acquired pneumonia care.<sup>120,121</sup> Stability

criteria offer information about antibiotic treatment (eg, the appropriateness of such treatment, switching to oral medication, and short antibiotic treatment durations) and indications for hospital discharge that reduce hospital length-of-stay.<sup>122-124</sup>

### Stewardship

When microbiological tests become available, it is important to re-evaluate antibiotic treatment. Antibiotics should be adapted according to antibiogram results, narrowed according to the identified pathogen, and discontinued when a diagnosis of pneumonia is unlikely.<sup>25</sup> Stewardship is fundamental to avoid the continuation of unnecessary treatment, increasing the selective pressure for resistance, and reducing the risks of unnecessary complications (eg, *Clostridium difficile* infection).<sup>125</sup>

### Switch to oral therapy

Most patients in hospital with community-acquired pneumonia began treatment with an intravenous antibiotic. A switch to oral therapy should be considered for patients who reach clinical stability. Two randomised controlled trials<sup>25,126</sup> have shown no difference in mortality, but important reductions in the length-of-stay and adverse drug reactions, in patients who switch to oral therapy early.

### Duration of therapy

5 days of treatment should be given for low-severity pneumonia with clinical stability after 3 days of treatment, and 7 days should be given for severe pneumonia, which should be adapted depending on the improvements in symptoms and stability.<sup>3,4,6,122,127</sup> Indeed, two meta-analyses reported similar efficacies for short-course ( $\leq 7$  days) and long-course ( $> 7$  days) treatments when patients with severe pneumonia were excluded.<sup>127,128</sup> Additionally, an observational study with robust analyses reported similar outcomes for short-course and long-course antibiotic treatments for patients with severe community-acquired pneumonia.<sup>123</sup> Patients with extrapulmonary complications or empyema and pneumonia due to specific pathogens (eg, *Legionella* spp and MRSA) seem to have benefits from prolonged treatments.

Biomarkers can be used to guide antibiotic duration. One-time PCT values lower than 0.25  $\mu\text{g}/\text{mL}$  or a decrease from the peak by 80–90% are a strong indication that antibiotics should be discontinued.<sup>43-45</sup> A randomised controlled trial<sup>129</sup> to compare PCT and CRP for antibiotic guidance in patients with severe sepsis and septic shock showed similar outcomes; however, more studies are needed to compare cost-effectiveness among biomarkers.<sup>6</sup>

### Clinical failure

Patients with community-acquired pneumonia can present with deterioration, known as clinical failure, which predicts mortality.<sup>130</sup> Therefore, definition of the causes of failure is essential. Early failure ( $< 72$  h) seems to be related to the severity of the primary infection (eg, the

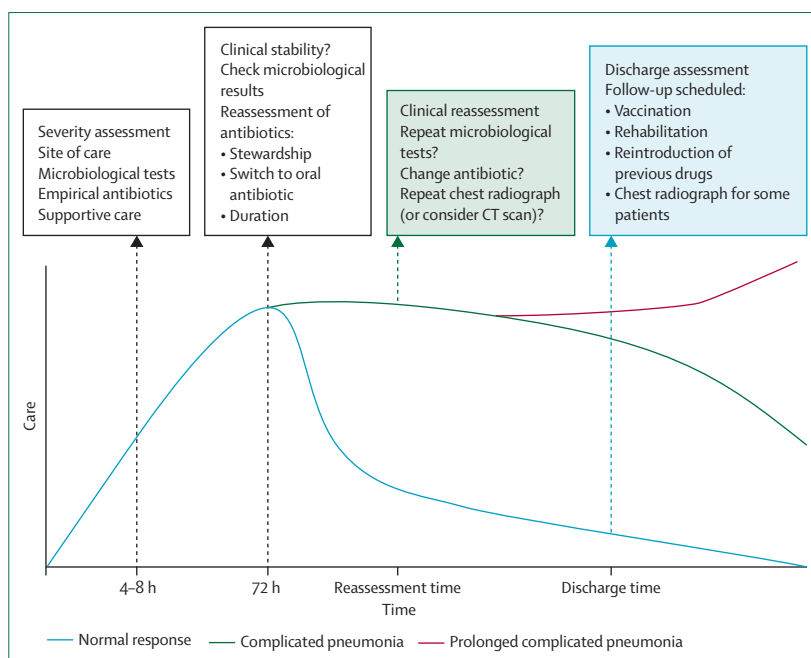


Figure 3: Acute and long-term assessment of community-acquired pneumonia

development of septic shock), whereas the late failures ( $> 72$  h) tend to be due to secondary events (eg, nosocomial superinfection, exacerbation of comorbidities). The development of severe sepsis is the primary reason for failure.<sup>131</sup> Outpatients also need an early follow-up (after 72 h) to detect development of failure.<sup>132</sup> Non-responding pneumonia is a different disorder that comprises the persistence of pulmonary infiltrates 1 month after symptom onset and can be due to many causes, such as the presence of lung cancer or an underlying lung disease.<sup>3</sup>

### Early rehabilitation

Patients in hospital seem to benefit from early mobilisation and rehabilitation.<sup>133,134</sup>

### Follow-up and outcomes

#### Readmission rate

Between 7% and 12% of patients who are admitted into hospital for community-acquired pneumonia are readmitted within 30 days.<sup>135,136</sup> In more than half of cases, comorbidities are the cause of readmission (mainly cardiovascular, pulmonary, or neurological diseases), whereas in other patients, a new episode of pneumonia is the cause of readmission. The main risk factors for readmission are initial treatment failure, clinical instability at hospital discharge, older age, comorbidities, and impaired functional status.<sup>135,136</sup>

#### Long-term mortality

Pneumonia causes much short-term and long-term mortality. Mortality for patients with community-acquired pneumonia is higher than for those with other infections



**Panel 1: Controversies and uncertainties**

- 1 The implementation of rapid diagnostic testing using PCR techniques for viruses and bacteria might increase the number of microbiological diagnoses and consequently the number of initial appropriate treatments; although some devices are able to provide rapid diagnoses, well designed studies are needed to investigate major outcomes and cost-effectiveness<sup>4,53</sup>
- 2 The real rates of different to treat pathogens in community-acquired pneumonia, such as *Pseudomonas aeruginosa*, *Enterobacteriaceae extended-spectrum β-lactamase*, and *meticillin-resistant Staphylococcus aureus*, differ between continents and countries (eg, the USA and Japan vs Europe); the concept of health-care-associated pneumonia is not accurate and has resulted in the excessive administration of broad-spectrum antibiotics;<sup>84</sup> risk factors for these microorganisms have been described recently, but implementation in clinical practice is still lacking<sup>34,35</sup>
- 3 Combination antibacterial therapy is a matter of debate; such therapy is recommended for patients with community-acquired pneumonia who are admitted to the intensive care unit,<sup>3,4</sup> and in patients with bacteraemic *Streptococcus pneumoniae*;<sup>82</sup> furthermore, patients with high mortality admitted to the ward might benefit from this treatment strategy<sup>80</sup>
- 4 Recent data from randomised controlled trials<sup>112,113</sup> showed a reduction of time to clinical stability and of treatment failure in patients with community-acquired pneumonia receiving corticosteroids; however, data are controversial for effect on mortality; a prematurely halted trial of severe community-acquired pneumonia revealed an important decrease in mortality (39% vs 0%)<sup>117</sup>
- 5 The long-term cardiovascular complications of patients with community-acquired pneumonia are not completely understood; but it seems that residual inflammation might have an important role in triggering procoagulation pathways and leading to cardiovascular complications<sup>37,138</sup>

**Panel 2: Outstanding research questions**

- 1 Interventional studies are needed of microbiological testing techniques to increase the rate of initial appropriate treatments, which would result in improved outcomes and reduced overuse of antibiotics
- 2 Validation studies that use risk factors for different-to-treat microorganisms to confirm the accuracies of these risk factors for their implementation in clinical practice are also needed
- 3 Interventional studies should be done to assess cost-effectiveness for C-reactive protein and procalcitonin in low-income and middle-income countries and specific settings
- 4 A randomised controlled trial is needed in patients with severe community-acquired pneumonia who are not admitted to the intensive care unit that compares monotherapy with respiratory quinolones and combination therapy (β-lactam plus macrolide)
- 5 Investigators should do a large randomised controlled trial in patients with community-acquired pneumonia who are admitted to intensive care units that assesses the administration of corticosteroids versus placebo powered to address mortality and quality-of-life outcomes
- 6 Studies of severe community-acquired pneumonia are needed, both in animal models and in human beings, to test new adjuvant treatments, such as enriched immunoglobulin M, monoclonal antibodies, and molecules that can block the endotoxins and exotoxins of the microbes
- 7 Prospective observational follow-up studies in patients with community-acquired pneumonia are needed to better describe the clinical and biological risk factors for cardiovascular complications to design a pharmacological randomised controlled trial

and patients who are admitted into hospital for other reasons after adjusting for important variables.<sup>137</sup> Several predictors of long-term mortality have been described and include age, comorbidities, frailty, cardiovascular complications, inflammation and the severity of the initial insult.<sup>137</sup>

**Cardiovascular events**

Community-acquired pneumonia is associated with an increased risk of cardiovascular complications.<sup>138</sup> Some explanatory reasons for this include hypoxaemia, inflammation, prothrombotic status, pathogen-specific factors, and host characteristics.<sup>137,139</sup> A meta-analysis for the incidence of cardiac events within 30 days of hospital admission for community-acquired pneumonia reported a cumulative rate of heart failure of 14% (range 7–33%), an arrhythmia rate of 5% (range 1–11%), and an acute coronary syndrome rate of 5% (range 1–11%).<sup>140</sup>

**Prevention and vaccines**

Clinicians should pay attention regarding modifying factors available to decrease the risk of a new episode of community-acquired pneumonia (appendix). Influenza vaccines are robustly associated with a reduced rate of pneumonia and better outcomes.<sup>34</sup> A study of 286 000 individuals older than 65 years reported a 30% reduction in the rate of pneumonia and influenza infection that was followed by a reduction in all-cause mortality.<sup>141</sup>

Two vaccines are available for *S pneumoniae*: the pneumococcal polysaccharide vaccine and the pneumococcal conjugate vaccine. The pneumococcal polysaccharide vaccine contains polysaccharides for 23 pneumococcal serotypes and the most recent version of pneumococcal conjugate vaccine contains 13 serotypes. By comparison with pneumococcal polysaccharide vaccine, the pneumococcal conjugate vaccine seems to induce a stronger and longer-lasting secondary immune response with booster effect.<sup>142</sup> Results from a recent meta-analysis showed strong evidence for the recommendation for pneumococcal polysaccharide vaccine-23 vaccination to prevent invasive pneumococcal disease in adults.<sup>143</sup> Nevertheless, there is less clear evidence for its efficacy in the prevention of non-bacteraemic pneumonia,<sup>143</sup> in patients with chronic illnesses, and for the reduction of all-cause pneumonia and mortality.<sup>143</sup> The pneumococcal conjugate vaccine-13 was approved for clinical use in adults by the US and European agencies. The CAPiTA study<sup>144</sup> (a double-blind, randomised, placebo-controlled clinical trial involving nearly 85 000 adults older than 65 years) showed clinical efficacy of pneumococcal conjugate vaccine-13 in the prevention of the first episode of vaccine-serotype pneumococcal community-acquired pneumonia (including non-bacteraemic pneumonia and invasive pneumococcal disease);<sup>144</sup> however, the trial excluded immunosuppressed patients and previously vaccinated person. Because a substantial number of cases of pneumonia is caused by serotypes not included in the

pneumococcal conjugate vaccine-13 (38% of invasive pneumococcal disease in the US in 2013), the US Centers for Disease Control and Prevention recommended the administration of both pneumococcal conjugate vaccine-13 and pneumococcal polysaccharide vaccine-23 in series to all adults aged 65 years and older (panel 1).<sup>142</sup> Outstanding research questions remain, which should be addressed in future large trials (panel 2).

#### Contributors

All authors equally contributed in the literature search and data interpretation, conceived, wrote, and approved the final version of the manuscript.

#### Declaration of interests

AT participated in advisory boards for Merck, Pfizer (vaccines), and Ceptra. EP and OTR declare no competing interests.

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