Community-acquired pneumonia

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Community-acquired pneumonia is not usually considered a high-priority problem by the public, although it is responsible for substantial mortality, with a third of patients dying within 1 year after being discharged from hospital for pneumoniae. Although up to 18% of patients with community-acquired pneumonia who were hospitalised (admitted to hospital and treated there) have at least one risk factor for immunosuppression worldwide, strong evidence on community-acquired pneumonia management in this population is scarce. Several features of clinical management for community-acquired pneumonia should be addressed to reduce mortality, morbidity, and complications related to community-acquired pneumonia in patients who are immunocompetent and patients who are immunocompromised. These features include rapid diagnosis, microbiological investigation, prevention and management of complications (eg, respiratory failure, sepsis, and multiorgan failure), empirical antibiotic therapy in accordance with patient's risk factors and local microbiological epidemiology, individualised antibiotic therapy according to microbiological data, appropriate outcomes for therapeutic switch from parenteral to oral antibiotics, discharge planning, and long-term follow-up. This Seminar offers an updated view on community-acquired pneumonia in adults, with suggestions for clinical and translational research.

Introduction

Community-acquired pneumonia is an acute disease caused by an infection of the lung parenchyma acquired outside of a hospital setting. It is one of the leading global causes of morbidity and mortality in patients who are immunocompetent and patients who are immunocompromised.[1] Unfortunately, community-acquired pneumonia is a neglected, but common, medical event; the lack of a sense of emergency within the general public, little economic investment at a public and private level, and absence of advocacy and disease awareness are worrisome.[2]

In this Seminar, evidence on community-acquired pneumonia in adults, especially those admitted to hospital, will be reviewed. The clinical presentation and management of COVID-19 will not be discussed, nor will the definition of health-care-associated pneumonia be considered, in line with the published guideline change.[1,3] Although the definition of health-care-associated pneumonia was initially developed to identify patients with risk factors for multidrug-resistant organisms or resistance to standard community-acquired pneumonia therapy, subsequent evidence showed that health-care-associated pneumonia risk factors were neither sensitive nor specific to detect at-risk patients. Poor clinical outcomes were also associated with age and comorbidities, rather than with multidrug-resistant organisms.[4] Single risk factors, such as residency in nursing homes or long-term care facilities, should be carefully considered given their association with high mortality rate and other specific conditions (eg, malnutrition and acute mental changes).[5]

Search strategy and selection criteria

We searched PubMed for articles published from Jan 1, 1990, to Sept 1, 2020, using the terms "pneumonia" or "community-acquired pneumonia" or "CAP", "diagnosis", "therapy" or "antibiotics", and "prevention" or "vaccines". We did not adopt any language or time restrictions. We evaluated the reference lists of narrative and systematic reviews on community-acquired pneumonia to retrieve key documents. WHO and other international scientific websites were accessed to retrieve relevant information not included in the PubMed list.

Epidemiology

The Global Burden of Diseases, Injuries, and Risk Factors Study[6] showed that 336·5 million lower respiratory tract infections occurred in 2016, resulting in 32·2 per 100 000 people worldwide. In the USA, community-acquired pneumonia accounted for more than 4·2 million ambulatory care visits in 2016, and 1 286 000 emergency department visits in 2017.[6–9] In a 2-year study done in the USA, the annual age-adjusted incidence was 649 patients hospitalised (admitted to hospital and treated there) with community-acquired pneumonia per 100 000 adults, corresponding to more than 1·5 million annual adult community-acquired pneumonia hospitalisations in the USA.[10] Mortality during hospitalisation was 6·5%; its rate at 30 days was 13·0%, 6 months was 23·4%, and 1 year was 30·6%.[10] In low-income countries, epidemiological data on pneumonia at the population-based level are scarce and are mainly based on hospital registries, with pneumonia one of the most common reasons for hospitalisation in adults.[11] Incidence of community-acquired pneumonia in three cities in South America ranged from 1·76 per 1000 person-years to 7·03 per 1000 person-years.[12] A large portion of mortality related to community-acquired pneumonia might be attributed to an existing comorbidity. It might be the final step to mortality, especially in patients with low performance status and severe underlying diseases. Thus, a proportion of the deaths related to community-acquired pneumonia might not be preventable.[13] Patients for community-acquired pneumonia incurred a substantial annual economic burden with high cost of hospitalisation.[14] An

episode of community-acquired pneumonia managed in the hospital is associated with a mean all-cause total health-care cost of US$11 148 in uncomplicated cases and $51 219 in complicated cases.[15]

Risk factors

Over the past two decades, different risk factors for community-acquired pneumonia have been recognised. Clinical conditions associated with an increased risk of community-acquired pneumonia include history of pneumonia (odds ratio [OR] ≤6·25); chronic cardiovascular diseases (OR ≤3·20); cerebrovascular disease, stroke, and dementia (OR ≤2·68); neurological or psychiatric conditions (OR ≤3·20); chronic respiratory diseases, including chronic obstructive pulmonary disorder (COPD), bronchitis, or asthma (OR ≤2·17); dysphagia (adjusted OR [aOR] from 2·10 to 11·90); diabetes (aOR ≤1·33); cancer (aOR ≤1·42); and chronic liver disease (aOR ≤1·87) or renal disease (aOR ≤1·78).[16,17] Several lifestyle factors are associated with an increased risk of community-acquired pneumonia, namely history of alcohol abuse or alcoholism (OR ≤2·91), being underweight (OR ≤2·20), living with more than ten people (OR ≤2·20), current smoking status (aOR ≤2·00), former smoking status (aOR ≤1·04), and regular contact with children (OR ≤1·48).[16–19] Finally, clinical conditions and therapies leading to an immunocompromised state are crucial determinants for community-acquired pneumonia.[20]

Clinical presentation

Clinical presentation of community-acquired pneumonia varies widely, ranging from mild pneumonia characterised by fever and cough, to severe pneumonia with sepsis and respiratory failure, and depends on the interaction between the patient's immune system, patient's characteristics, and pathogen's virulence. The suspicion of community-acquired pneumonia is based on the acute onset of signs or symptoms suggestive of a lower respiratory tract infection (eg, cough, fever, sputum production, dyspnoea, chest pain, and new focal chest signs), whereas the definitive diagnosis of community-acquired pneumonia requires the evidence of a new pulmonary infiltrate on a chest x-ray, chest CT, or lung ultrasonography.[21] A large observational study identified, among different clinical symptoms and examination findings at presentation, significant independent predictors of pneumonia in those patients receiving a chest radiograph within 1 week of consultation: temperature 37·8°C or higher, crackles on auscultation, oxygen saturation less than 95%, and pulse of 100 beats per min or more (appendix p 1).[22] Diagnosis of community-acquired pneumonia might be challenging in particular populations, including older (65 years or older) patients and patients who are immunocompromised, with atypical signs or symptoms. Lethargy and change in mental status, including delirium, can be signs of community-acquired pneumonia, especially in older patients, and also in the absence of fever.[23] The clinical presentation of community-acquired pneumonia can also depend on the pathogen causing the infection, with community-acquired pneumonia caused by *Legionella* frequently associated with hyponatraemia, dry cough, or elevated lactate dehydrogenase, whereas community-acquired pneumonia caused by *Mycoplasma* is associated with extrapulmonary manifestations such as encephalitis, acute psychosis, or stroke.[24] Two earlier studies investigated how to discriminate *Legionella* and *Mycoplasma* from other causes of community-acquired pneumonia on the basis of clinical parameters and laboratory findings (including the C-reactive protein to procalcitonin ratio on admission); a specific clinical prediction rule for *Legionella* spp was also derived.[25,26] A prospective cohort study identified cough, dyspnoea, and pleuritic pain as the most prevalent respiratory symptoms in patients with pneumococcal pneumonia, whereas haemoptysis occurs in up to 22% of the cases, with numerous non-respiratory symptoms.[27]

No group of symptoms is adequate for diagnosis of community-acquired pneumonia without chest imaging; the positive predictive value of the combination of fever, tachycardia, crackles or rales, and hypoxia among patients with respiratory complaints was shown to be less than 60% when chest radiograph was used as a reference standard.[28]

Imaging

The diagnosis of community-acquired pneumonia requires evidence of an infiltrate on chest x-ray, chest CT, lung ultrasonography, or all three, in a patient with a clinically compatible syndrome.[22] A posteroanterior and lateral chest x-ray is the most commonly used imaging technique for a definitive diagnosis of community-acquired pneumonia, with signs of focal non-segmental or lobar pneumonia, multifocal bronchopneumonia or lobular pneumonia, or focal or diffuse interstitial pneumonia, in the presence or absence of possible complications, such as pleural effusion. The radiological appearance of pneumonia alone cannot make the causal diagnosis of community-acquired pneumonia, although this information could contribute to the clinician's investigation. Several diseases might mimic community-acquired pneumonia, and infiltrates that might be absent at the initial chest x-ray evaluation might become apparent after 24–72 h. Chest CT is usually required when a discrepancy exists between the clinical suspicion of pneumonia and a negative chest x-ray (eg, in patients who are immunocompromised), if complications are suspected (eg, lung abscess), or in the presence of new or decompensated comorbidities (eg, pulmonary embolism or cancer). A multicentre, prospective study showed that hospitalised patients with community-acquired pneumonia who have radiographic evidence of pneumonia

See Online for appendix

	Strengths	Limitations
Chest radiograph	Lower radiation dose compared with chest CT; accessibility; excellent cost–benefit ratio; timesaving	Performance distorted by coexisting comorbidities; not sufficiently sensitive to rule out pneumonia; infiltrates might be absent at the initial evaluation, but might become apparent later; performance affected by patient's condition (eg, confined to bed or acute confusion)
Chest CT	High sensitivity to rule out pneumonia; ensures early diagnosis and assessment of complications in particular populations (eg, immunocompromised patients); identification of signs compatible with specific causes (eg, *Mycoplasma pneumonia*, *Staphylococcus aureus*, *Pneumocystis jirovecii*); assess the presence of new or decompensated comorbidities (eg, pulmonary embolism or cancer)	Time consuming; high-dose radiation exposure; cost-effectiveness; performance not affected by patient's conditions
Lung ultrasound	Radiation-free; can be done at bedside; can be done in particular populations (eg, children and pregnant women); allows for dynamic evaluation; accurate in the detection of parapneumonic pleural diseases (eg, pleural effusion); timesaving	Not sufficiently sensitive to rule out pneumonia; operator dependent; unable to detect pneumonia in cases with normally aerated lung between the consolidation and the pleural line

Table 1: **Strengths and limitations of chest radiograph, chest CT, and lung ultrasound in diagnosing pneumonia**

on CT scan, but not on concurrent chest x-ray, have similar pathogens, disease severity, and outcomes to patients with chest x-ray signs of pneumonia.[29] Up to 30% of patients with a chest x-ray diagnosis of pneumonia do not show CT findings, whereas a third of patients with a negative chest x-ray might have CT changes consistent with pneumonia.[30] Deep learning-based algorithms have been developed and tested over the past 10 years to discriminate between chest radiographs with major thoracic diseases, including pneumonia, and those without disease, and show their potential role in improving their quality and efficiency in clinical practice.[31,32] Over the past two decades, lung ultrasonography has been shown to have a substantial role in diagnosing community-acquired pneumonia, with one meta-analysis showing an area under the summary receiver operating characteristic curve of 0·95.[21] For the diagnosis of pneumonia with lung ultrasonography, pooled sensitivity is 94% (95% CI 92–96) and pooled specificity is 96% (94–97).[33] Strengths and limitations of chest x-ray, chest CT, and lung ultrasonography in diagnosing pneumonia are reported in table 1. The use of these techniques should continue to evolve to better integrate the patient's symptomatology with objective involvement of the lower respiratory tract in the diagnosis and management of community-acquired pneumonia.

Cause of community-acquired pneumonia

Different laboratory methods are available to assess the cause of pneumonia, including microscopy and culture of respiratory tract samples, blood cultures, antigens in urine, antibodies in blood, and nucleic acid detection, such as PCR. However, despite extensive laboratory testing, the cause of community-acquired pneumonia can be identified in only a third of patients.[34] *Streptococcus pneumoniae* and respiratory viruses are among the most frequently identified pathogens in patients with community-acquired pneumonia.[34–36] Other common bacteria causing community-acquired pneumonia are *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, and atypical organisms such as *Legionella* spp, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*. At least one atypical pathogen can be isolated in 4·7% of hospitalised patients with community-acquired pneumonia. Patients with community-acquired pneumonia due to atypical pathogens were significantly younger, with fewer comorbidities, than patients with community-acquired pneumonia from non-atypical pathogens.[37] Among respiratory viruses, influenza and rhinovirus seem to be the most common cause of viral community-acquired pneumonia.[35,38] Other respiratory viruses reported as relevant to community-acquired pneumonia include parainfluenza viruses, adenoviruses, respiratory syncytial virus, human metapneumovirus, and coronaviruses. The extent to which respiratory viruses serve as single pathogens or cofactors in the development of bacterial community-acquired pneumonia has not been established. The prevalence and effect of each single pathogen as a cause of community-acquired pneumonia are heterogeneous at a global level, varying according to geography, health-care systems, vaccination rates, and specific host risk factors.

In community-acquired pneumonia microbiology, one of the most relevant challenges is the management of drug-resistant organisms—ie, organisms resistant to one or more antibiotics usually prescribed in patients with pneumonia, including non-community-acquired bacteria (*Acinetobacter baumanii*, vancomycin-resistant *Enterococcus* spp, and Nocardia spp), mycobacteria, fungi (*Aspergillus fumigatus*, *Coccidioides immitis*, *Cryptococcus neoformans*, and *Pneumocystis jirovecii*), and viruses other than influenza.[20] For cases of community-acquired pneumonia caused by *S pneumoniae*, the global prevalence of drug-resistant cases is 1·3%, multidrug-resistant cases is 0·2%, and extremely drug-resistant cases is 0·03%, and vary worldwide with relevant differences between continents and countries.[39] The prevalence of confirmed methicillin-resistant *S aureus* (MRSA) pneumonia is around 3% worldwide, and the three independent risk factors associated with MRSA community-acquired pneumonia are previous MRSA infection or colonisation,

	Risk factors
Drug-resistant *Streptococcus pneumoniae*	Asthma (for penicillin and macrolide resistance); liver disease (for tetracycline resistance); bronchiectasis (for penicillin resistance)[1]
Legionella pneumophila	Advanced age; alcoholism; cigarette smoking; chronic disease; immunosuppression; organ transplantation; predisposing environmental factors include overnight stay away from home and changes in domestic plumbing
Mycoplasma pneumonia and *Chlamydophila pneumoniae*	Younger age; female sex; having no or few comorbidities (eg, cardiovascular disease or chronic renal failure)*
Enterobacteriacae	Male sex; severe community-acquired pneumonia; underweight (body-mass index <18·5 kg/m²); previous extended-spectrum β-lactamase infection
Multidrug-resistant *Enterobacteriacae*	Cardiovascular diseases; hospitalisation in the past 12 months for multidrug-resistant *Enterobacteriacae*†
Pseudomonas aeruginosa	Previous *Pseudomonas* infection or colonisation; previous tracheostomy; bronchiectasis; invasive respiratory or vasopressor support; very severe COPD
Antibiotic-resistant *P aeruginosa*	Previous *Pseudomonas* infection or colonisation; tracheostomy; invasive respiratory or vasopressor support
Multidrug-resistant *P aeruginosa*	Previous *Pseudomonas* infection or colonisation; invasive respiratory or vasopressor support; COPD
MRSA	Previous MRSA infections or colonisation; recurrent skin infections; severe pneumonia

COPD=chronic obstructive pulmonary disease. MRSA=methicillin-resistant *Staphylococcus aureus*. *Having no or few comorbidities might be a function of age, because patients with atypical pneumonia are young. †The presence of specific risk factors, such as previous extended-spectrum β-lactamase infection and being underweight, should raise the clinical suspicion for *Enterobacteriacae* and multidrug-resistant *Enterobacteriacae* in patients admitted to hospital with community-acquired pneumonia.

Table 2: **Risk factors for specific pathogens in community-acquired pneumonia**

recurrent skin infections, and severe pneumonia.[40] The worldwide prevalence of *Pseudomonas aeruginosa*-caused community-acquired pneumonia is around 4%, antibiotic-resistant *P aeruginosa*-caused community-acquired pneumonia is around 2%, and multidrug-resistant *P aeruginosa*-caused community-acquired pneumonia is around 1%.[41] A history of *Pseudomonas* infection or colonisation or the coexistence of chronic lung diseases significantly increase the risk for antibiotic-resistant *P* aeruginosa-caused community-acquired pneumonia.[41] Finally, *Enterobacteriaceae*, including *Klebsiella pneumoniae* and *Escherichia coli*, have been detected in up to 6% of patients with community-acquired pneumonia, and in 1·2% of all patients with community-acquired pneumonia there were multidrug-resistant *Enterobacteriaceae*.[42] Risk factors for specific pathogens are reported in table 2.

Community-acquired pneumonia pathogenesis has been based on the concept of a sterile alveolar space and the acquisition of a new pathogen.[43] Over the past decade, the use of next-generation sequencing has offered new insights into the microbiome of the lower airways, with microbes forming complex metacommunities where microbe–host and microbe–microbe interactions have important roles in the host's susceptibility to pathogens. Many pathogens causing community-acquired pneumonia can be part of the normal lung microbiota, and changes in local conditions could lead to an overgrowth of one of these bacteria. On the basis of studies on culture-independent techniques and the lung microbiome, a new framework can be described that moves away from the concept of a unique pathogen causing pneumonia to that of a disrupted community of microorganisms, which might enhance the pathogenic potential of each other.[44]

Diagnostic and microbiological investigations

Among the most common blood tests ordered after the diagnosis of community-acquired pneumonia are those for white blood cells, C-reactive protein, and procalcitonin, all of which measure the systemic inflammatory state. Other tests, such as lactate or renal, liver, or coagulation tests, are useful in evaluating the associated organ damage, as seen in severe sepsis and multiorgan failure, and help guide the clinician in the evaluation of disease severity and site-of-care decision. Much discussion over the past 20 years has focused on the use of procalcitonin as a biomarker to initiate empiric antibiotic therapy in patients with community-acquired pneumonia, with a threshold of 0·25 µg/L or more as an indication of bacterial pneumonia and 0·1 µg/L or less as likelihood of viral infection.[45] The controversy is also documented by a study showing an inability of procalcitonin to discriminate between viral and bacterial infection.[46]

At least one microbiological test is done in most hospitalised patients with community-acquired pneumonia, with geographical area and disease severity influencing testing frequency and the diagnostic yield of the tests.[34] Most of the microbiological tests are usually recommended by international guidelines for hospitalised patients with severe community-acquired pneumonia, with severe sepsis or septic shock, patients with special conditions (eg, immunosuppression), patients at risk of resistant pathogens, and patients who do not respond to the initial empirical treatment (figure).[1,47,48] The latest guidelines from the American Thoracic Society and the Infectious Diseases Society of America (ATS and IDSA)[1] neither recommend nor discourage routinely obtaining sputum Gram stain and culture in all adults with community-acquired pneumonia managed in the hospital setting.[49] Whether to

Figure: **Tests required for community-acquired pneumonia cause according to disease severity across different guidelines**

MRSA=methicillin-resistant *Staphylococcus aureus*. *Clinical suspect or outbreak. †Clinical suspect. ‡MRSA or *Pseudomonas aeruginosa* risk. §*Legionella* outbreak or clinical suspect. ¶In case of clinical suspect in combination with other diagnostic test (eg, PCR). ||Only for Mycoplasma pneumoniae during mycoplasma years. **During periods of high influenza activity. ††During outbreaks, when clinical suspect and when needed for the purposes of surveillance.

culture patients or not should be established by the individual clinician on the basis of clinical presentation, local causal considerations, and local antimicrobial stewardship processes.[1] A crucial point would be to obtain sputum for Gram stain and culture in patients with risk factors for MRSA or *P aeruginosa* caused community-acquired pneumonia and in patients being considered for coverage for MRSA or *Pseudomonas*. The 2019 ATS and IDSA guidelines[1] identified previous infection and hospitalisation and treatment with parenteral antibiotics in the past 90 days as the two most important risk factors for MRSA or *Pseudomonas* leading physicians to order sputum culture.

The effect of blood cultures on the outcomes of hospitalised patients with community-acquired pneumonia has not been fully evaluated, with studies showing mixed results.[50–53] Experts suggest that blood culture should be obtained before treatment in hospitalised patients with severe community-acquired pneumonia (because a delay in targeting less common pathogens might harm patients), and in hospitalised patients undergoing empiric antibiotic therapy against MRSA or *P aeruginosa*, or patients previously infected with MRSA or *P aeruginosa*, or who were hospitalised and received parenteral antibiotics, in the past 90 days.[1]

Urinary antigen testing for *S pneumoniae* and *Legionella pneumophila* are rapid and readily available; they are included in most community-acquired pneumonia algorithms. However, despite a high specificity, the low sensitivity does not rule out a pneumonia caused by *S pneumoniae* and *L pneumophila*. No benefit of a pathogen-directed treatment based on these tests versus guideline-based treatment has been identified in terms of clinical outcomes or length of antibiotic treatment.[54] Both tests are recommended for severe community-acquired pneumonia, and a *Legionella* test is also recommended for epidemiological reasons (eg, outbreaks).[1]

Although serology is currently available for *Chlamydophila*, *Mycoplasma*, and *Legionella*, its clinical usefulness is controversial, especially given the delay in results. The specificity of the serology for *M pneumoniae* is not sufficiently high; furthermore, the test typically becomes positive about 7 days after the onset of the disease.[55] Real-time and multiplex panel PCR, currently available for bacteria and viruses, can provide results in a few hours, and are promising methods for fast causal diagnosis of community-acquired pneumonia.[1] Testing for influenza with a rapid molecular assay is recommended during influenza season, although no studies evaluating the effect of influenza testing on outcomes of patients with community-acquired pneumonia have been published.[1] Finally, the sensitivity of both influenza rapid antigen tests and viral culture is low when the tests are done in older hospitalised adults.[56]

Disease severity and site-of-care decision

Different severity assessment tools have been developed to predict mortality and other clinical events (eg, intensive care unit [ICU] admission and bacteraemia), and to support physicians in their clinical decisions, including the site of care.[1,57–65] The Pneumonia Severity Index (PSI) and CURB-65 are the most frequently used severity scores (appendix pp 2–3).[59,60] The PSI guides the initial site-of-care decision and identifies patients who could be managed outside of the hospital setting as low risk. CURB-65 is simpler to use than PSI, but is less effective in guiding the site-of-care decision.[66,67] International guidelines suggest the use of validated clinical prediction rules for prognostication in addition to clinical judgment.[1,47,48] The latest ATS and IDSA guidelines[1] state a preference for the use of PSI over CURB-65 to decide the site of care. Notably, site of care is decided not only by the risk of death, but also by several other medical and social factors.[68,69] Admission to the ICU is a crucial decision in the management of patients with community-acquired pneumonia, and hypotension requiring vasopressors or respiratory failure requiring mechanical ventilation are major indications used to define severe pneumonia by the ATS and IDSA guidelines,[1] along with other minor criteria.[70–72] Other scores have been used to predict ICU admission (eg, the so-called SMART-COP score and REA-ICU index), and biomarkers (eg, proadrenomedullin)

have also been tested to evaluate their performance in predicting ICU admission.[61,72–74]

Empiric antibiotic treatment

Empiric antibiotic treatment should be started as soon as possible once the diagnosis of community-acquired pneumonia has been made, according to the most likely pathogen, local microbiology, patient's risk factors for specific pathogens, pneumonia severity, patient's preference and potential antibiotic allergies, and cost-effectiveness evaluation. Guideline recommendations on the choice of the empiric antibiotic therapy in patients with community-acquired pneumonia should be critically interpreted and individualised on the basis of local epidemiological data and health-care system characteristics (appendix pp 4–6).

The ATS and IDSA guidelines[1] suggest amoxicillin, doxycycline, or a macrolide (only in areas with <25% of pneumococcal resistant to macrolide) for healthy outpatients without comorbidities or risk factors for resistant microorganisms. For outpatients with comorbidities, community-acquired pneumonia treatment options include either a monotherapy with a respiratory fluoroquinolone, or a combination therapy of amoxicillin–clavulanic acid or a cephalosporin and a macrolide or doxycycline.[1] Disease severity, risk factors for MRSA, and risk factors for *P aeruginosa* are three crucial factors to be investigated when ordering empiric antibiotic therapy for hospitalised patients with community-acquired pneumonia. According to evidence on fluoroquinolone, β-lactams, and macrolide treatment, a combination therapy with a β-lactam plus macrolide or monotherapy with a respiratory fluoroquinolone are recommended for inpatient adults with non-severe community-acquired pneumonia, and with no risk factors for MRSA or *P aeruginosa*.[1,75–78] No randomised controlled trials have evaluated empiric antibiotic therapy in patients with severe community-acquired pneumonia, and the 2019 ATS and IDSA guidelines[1] suggest a β-lactam plus macrolide or β-lactam plus a respiratory fluoroquinolone for those patients without risk factors for MRSA or *P aeruginosa*.[79] The addition of an empiric anti-MRSA coverage or anti-*Pseudomonas* is recommended if risk factors for MRSA or *P aeruginosa* are present and supported by local microbiological data.[1,40,41] The use of the health-care-associated pneumonia classification to identify patients with potential risk for multidrug-resistant bacteria has been abandoned in light of many studies showing its low performance and potential risk to overtreat with broad spectrum antibiotics.[4,80,81]

Once a causative pathogen has been identified in patients with community-acquired pneumonia, antibiotic therapy could be tailored to target the identified pathogen.[82] For the first time in almost 15 years, three new antibiotics have been approved by the US Food and Drug Administration (FDA) for community-acquired pneumonia: delafloxacin (October, 2019), omadacycline (October, 2018), and lefamulin (August, 2019).[83–87] Delafloxacin is an anionic fluoroquinolone, which showed its non-inferiority to moxifloxacin in a phase 3 clinical trial, and its superiority at early clinical response in patients who have COPD or asthma and in patients who have severe illness.[88] Omadacycline is an aminomethylcycline showing non-inferiority to moxifloxacin in terms of clinical response, with high clinical success across pathogen types and patient subgroups.[84,89] Lefamulin is a novel pleuromutilin antibiotic with a broad activity against Gram-positive and atypical organisms, showing similar efficacy to moxifloxacin, with or without linezolid, in patients with community-acquired pneumonia in two phase 3 clinical trials.[90]

Anti-influenza treatment

Influenza therapy is recommended for inpatients and outpatients with community-acquired pneumonia and a positive influenza test, independent from the duration of signs and symptoms before the diagnosis of pneumonia.[1,91] Several drugs were approved for treatment and prevention of influenza, although yearly vaccination remains the basis for both prevention and control of influenza. Uncomplicated influenza usually improves with or without antiviral treatment. However, antivirals reduce the time from symptoms to clinical improvement. Complications of influenza are bacterial infections, viral pneumonia, and cardiac events.[92] There are four US FDA-approved influenza antiviral drugs recommended by the US Centers for Disease Control and Prevention (CDC): peramivir, zanamivir, oseltamivir phosphate, and baloxavir marboxil.[93] Two older drugs, amantadine and rimantadine, were approved for the treatment and prevention of influenza A virus infection, but many strains, including the 2009 H1N1 influenza virus, are now resistant. The US CDC has not recommended amantadine and rimantadine for the treatment of current circulating influenza viruses.

Recognition and management of sepsis and respiratory failure

Sepsis, respiratory failure, and acute respiratory distress syndrome are the most severe complications of community-acquired pneumonia.[94–96] Moreover, the mortality rate can be up to 50% in patients with community-acquired pneumonia who require admission to the ICU after developing septic shock or require mechanical ventilation for respiratory failure. Therefore, early recognition and management of community-acquired pneumonia and its acute complications are needed. These measures include correct diagnosis and treatment of infections, fluid management, vasopressor use, respiratory support, and other ICU-supportive care such as nutrition, early mobilisation, and prevention of secondary infections such as ventilator-associated pneumonias.[97] Acute respiratory failure in patients with

community-acquired pneumonia might require both ventilatory and non-ventilatory management. Although the past two decades have seen progressive use of continuous positive airway pressure and non-invasive ventilation as first-line ventilatory support of community-acquired pneumonia-related respiratory failure in clinical practice, a systematic review revealed a paucity of studies evaluating the use of both techniques.[96,98,99] The use of helmet and high-flow nasal cannula oxygen therapy appear to be promising tools, but their role needs to be confirmed by future research.[99]

Panel 1: **Criteria for clinical stability suggested by international guidelines**

American Thoracic Society 2001[108]
- Improvement of cough and dyspnoea
- Temperature <37·8°C on two occasions, 8 h apart
- White blood cell count decreasing

American Thoracic Society and the Infectious Diseases Society of America 2007[109]
- Temperature ≤37·8°C
- Heart rate ≤100 beats per min
- Respiratory rate ≤24 beats per min
- Systolic blood pressure ≥90 mm Hg
- Arterial oxygen saturation ≥90% or PaO_2 ≥60 mm Hg on room air
- Normal mental status

European Respiratory Society 2005[110]
- Body temperature
- Parameters of respiration (preferably respiratory rate and partial oxygen tension or oxygen saturation)
- Haemodynamics (arterial blood pressure and heart rate)
- Mental state

British Thoracic Society 2009[48]
- Resolution of fever for >24 h
- Pulse rate <100 beats per min
- Resolution of tachypnoea
- Clinically hydrated and taking oral fluids
- Resolution of hypotension
- Absence of hypoxia
- Improving white cell count
- Non-bacteraemic infection
- No microbiological evidence of *Legionella*, *Staphylococcal,* or Gram-negative enteric bacilli infection

European Respiratory Society 2011[47]
- Body temperature
- Respiratory and haemodynamic parameters

National Institute for Health and Care Excellence 2014[111]
- Temperature ≤37·8°C
- Heart rate ≤100 beats per min
- Respiratory rate ≤24 beats per min
- Systolic blood pressure ≥90 mm Hg
- Arterial oxygen saturation ≥90% or PaO_2 ≥60 mm Hg on room air
- Normal mental status

PaO_2=partial pressure of oxygen.

Adjunctive therapy

Controlling excessive systemic inflammatory response is an objective in the management of community-acquired pneumonia, especially in the early hours after diagnosis, to prevent systemic complications and worse outcomes. Despite clinical recovery, several patients with community-acquired pneumonia are discharged with a subclinical inflammation, which could be associated with an increased risk of death.[100] Promising data have been published over the past two decades on the administration of corticosteroids as coadjuvant treatment in hospitalised patients with community-acquired pneumonia.[101] One study on 1506 patients recruited in six trials showed that corticosteroids prescribed to hospitalised patients with community-acquired pneumonia can reduce time to clinical stability and length of hospital stay, without a statistically significant effect on overall mortality.[102] Only some meta-analyses suggest benefits of steroids in reducing mortality in cases of severe community-acquired pneumonia but with notable potential risks (eg, increase of hyperglycaemia, higher secondary infection rate and mortality in the case of influenza, and complications up to 90 days).[103,104] In view of the fact that the evidence thus far is underwhelming and the risks might be understated and understudied, both the 2011 European Respiratory Society[47] and 2019 ATS and IDSA guidelines[1] do not recommend routine use of steroids in non-severe community-acquired pneumonia, severe community-acquired pneumonia, or severe influenza pneumonia.[105] Results from a completed trial (NCT01283009) might further inform clinicians on this topic. Mixed results have been published on the use of corticosteroids in patients with acute respiratory distress syndrome. A short course of hydrocortisone is currently recommended by the Surviving Sepsis Campaign[97] for all patients with refractory septic shock.

Early and late clinical outcomes

After empirical antibiotic therapy is started, outcomes of patients with community-acquired pneumonia depend on the interaction among host characteristics (eg, immune system, comorbidities, and performance status); pathogen characteristics (eg, virulence, susceptibility, and resistance to antimicrobials); and antibiotic characteristics, such as timing, adequacy of therapy, and pharmacokinetic factors. Patients might have either a clinical improvement (early, within the first 3 or 4 days after antibiotic initiation; or late, after 4 days) or a clinical deterioration (early or late), or can remain at the same degree of severity in comparison with baseline (non-resolving pneumonia), and clinical improvement might not occur.[106] In a US study on 7449 patients admitted to hospital with community-acquired pneumonia, clinical improvement was documented in 77% of patients, clinical failure in 20%, and non-resolving community-acquired pneumonia in 3%.[107] Mortality at 30 days was 6% for patients who improved, 34% for patients who had clinical failure, and 34% for patients with non-resolving pneumonia. Mortality at 1 year

was 23% for patients who improved, 52% for patients who did not improve, and 51% for patients with non-resolving pneumonia.

Clinical stability and switch to oral therapy

The identification of clinical stability is a crucial step for physicians once patients have started antibiotic therapy for community-acquired pneumonia. Different criteria for clinical stability have been suggested by international guidelines (panel 1), with a tentative effort to include biomarkers (eg, C-reactive protein or procalcitonin) to improve the criteria performance.[112,113] No set of criteria seems to be superior in identifying clinical improvement.[112] In patients with community-acquired pneumonia who are immunocompetent and respond to treatment, clinical improvement is usually expected to be reached around day 3 or 4 after the initiation of antibiotic therapy.[114] Several factors might be implicated in a delay in reaching clinical stability, including patient's characteristics, local or systemic complications, specific pathogen's characteristics, and adherence to treatment. Time to clinical stability is the most important early outcome in community-acquired pneumonia and has been widely accepted as a tool to guide the switch from intravenous to oral antibiotic therapy during hospitalisation, as well as to establish duration of antibiotic therapy and to judge appropriateness for hospital discharge.[115] No difference in mortality and important reductions in length of stay and adverse drug reactions have been shown in patients with community-acquired pneumonia who switch to oral therapy within the first 4 days.[116]

Duration of therapy

The appropriate duration of antibiotic therapy has been subject to expert opinions due to the lack of strong evidence. To date, patients with community-acquired pneumonia have been treated with relatively standard, prolonged antibiotic courses from 7 days to 14 days.[117] The appropriate duration of antibiotic therapy should balance the risks of illness, progression, or complications because of short treatment, with the risks of antibiotic resistance and adverse drug events associated with prolonged antibiotic treatment. Several studies have investigated the effects of a shorter duration of antibiotic treatment. A 2018 meta-analysis evaluated 21 clinical trials to compare the effectiveness and safety of antibiotic treatments for 6 days or less with 7 days or more, and showed similar clinical cure irrespective of patient setting or severity of pneumonia.[118] Short-course treatment was associated with fewer serious adverse events and lower mortality than long-course treatment. A 2016 multicentre, non-inferiority, randomised, clinical trial showed that the 2007 ATS and IDSA recommendations for duration of antibiotic treatment, based on clinical stability criteria, can be safely implemented in hospitalised patients with community-acquired pneumonia.[119] Patients with extrapulmonary complications, or empyema and pneumonia due to specific pathogens (eg, *Legionella* and MRSA), might benefit from prolonged treatment. Individualising duration of antibiotic therapy in community-acquired pneumonia with clinical stability criteria, biomarkers, or pharmacological properties of antibiotics is supported by several observations. Current scientific evidence shows that procalcitonin-guided antimicrobial stewardship reduces the antibiotic exposure without increasing mortality in patients with pneumonia.[120] A 2018 patient-data meta-analysis, which recruited 6708 patients from 26 trials in 12 countries, showed that procalcitonin can help guide antibiotic treatment in patients with acute respiratory infections, reducing antibiotic exposure and the risk of adverse events, and improving survival.[121]

Non-resolving pneumonia and clinical failure

There is a deficiency of studies evaluating the definition and cause of non-resolving pneumonia.[122] Usually, non-resolving pneumonia is considered to be a clinical syndrome characterised by signs and symptoms compatible with respiratory infection and infiltrates on chest x-ray, which persist after antibiotic initiation, with a patient's clinical status that neither improves nor deteriorates.[106]

***Panel 2*: Controversies and uncertainties**

1. Although up to 18% of patients with community-acquired pneumonia admitted to hospital worldwide are immunosuppressed, recommendations for clinicians on how to manage these patients are scarce; existing recommendations have been based on expert opinions and do not target prevalent populations, such as people receiving chronic steroids or biological drugs
2. Scarce evidence on the use of steroids in reducing treatment failure in patients with community-acquired pneumonia with high C-reactive protein, there are no definitive data on whether these patients would benefit from steroid treatment; if steroids are to be used, there is no information on the optimal drug, dosage, and time and system of administration to support physicians' decisions and use
3. Although data have offered some suggestions on the causal investigations in hospitalised patients with severe community-acquired pneumonia, most of the recommendations worldwide on non-severe community-acquired pneumonia are based on expert opinions
4. Guidance to treat outpatients with community-acquired pneumonia with macrolide monotherapy, according to a threshold of 25% antibiotic resistance (based on expert opinion), is not supported by substantial peer-reviewed evidence and several regions (eg, Europe and Japan) have higher prevalence of macrolide-resistant *Streptococcus pneumoniae*
5. Although the 2019 American Thoracic Society and Infectious Diseases Society of America guidelines[1] suggest the use of β-lactam–macrolide combination in all hospitalised patients with community-acquired pneumonia, evidence in patients with mild to moderate disease is scarce, which might lead to an increase in costs and development of adverse events
6. The use of fluoroquinolone for patients with community-acquired pneumonia, outpatients should be supported by evidence against the potential adverse events this class of antibiotics might have and the risk of future antibiotic resistance
7. The use of procalcitonin to support the diagnosis of primary viral cause is not supported by substantial peer-reviewed evidence

More evidence has been generated on clinical failure in patients with community-acquired pneumonia whose incidence ranges from 6% to 31%. Furthermore, when clinical failure occurs, it substantially increases the risk of complications, length of stay, and mortality, especially in patients with severe community-acquired pneumonia.[107,119] Clinical failure has been defined according to different parameters, including symptoms (eg, dyspnoea and altered mental status), vital signs (ie, fever, respiratory rate, and oxygen saturation), laboratory (ie, white blood cells and partial oxygen pressure in arterial blood) and radiological findings, and the need for invasive procedures or treatment changes. According to one study, clinical failure occurs when one or both of the following criteria are met during the first week of hospitalisation: acute pulmonary deterioration with the need for mechanical ventilation or acute haemodynamic deterioration with the need for vasopressors.[107] Early clinical failure is defined as failure that developed between days 1 and 3 from hospital admission, whereas late clinical failure is defined as failure that developed between days 4 and 7 of hospitalisation.[107] Identifying the cause of clinical failure is a crucial step to improve patient outcomes. It could be investigated according to host-related, drug-related, and pathogen-related causes, and include the initial disease severity, older age, new or decompensated comorbidities, presence of complications such as pleural effusion or empyema, pathogen characteristics (eg, resistance patterns), and antibiotic therapy given, but not in compliance with guidelines.[106,120]

***Panel 3*: Outstanding research questions**

1. Do the most common pneumonia severity scores also work in supporting site-of-care decisions for immunocompromised patients with community-acquired pneumonia?
2. What is the most common microbiology profile of patients with community-acquired pneumonia undergoing chronic steroid treatment, and of patients with other risk factors for immunodeficiencies?
3. Can corticosteroids be used in patients with community-acquired pneumonia and, if so, which population groups would benefit from corticosteroids, and which is the best drug, dosage, and time and system of administration to prescribe?
4. Should duration of antibiotic therapy be tailored on time to clinical stability in both immunocompetent and immunosuppressed patients with community-acquired pneumonia?
5. Can non-invasive ventilation and high-flow nasal cannula treatment improve outcomes in patients with community-acquired pneumonia with acute respiratory failure?
6. What is the best combination of interventions during the first 72 h after diagnosis of community-acquired pneumonia that can reduce adverse outcomes and complications, including cardiovascular events?
7. Can new pathways be identified in the microbiome and our knowledge of host–pathogen interaction be improved to identify new management strategies and treatment targets in patients with community-acquired pneumonia?
8. How can new, rapid, cost-effective, sensitive, and specific diagnostic tests effect treatment decisions and improve outcomes in patients with community-acquired pneumonia?

Long-term outcomes

Re-admission rate of patients with community-acquired pneumonia within 30 days ranges from 15% to 20%, with a median all-cause 30-day re-admission rate reported to be 17%.[121,122] The major reasons for re-admission were not only related to community-acquired pneumonia (up to 25% of the cases), but also related to the occurrence of cardiovascular events.[123] Predictors for re-admission, include medical comorbidities, demographics, socio-economic status, previous health-care use, laboratory values, vital signs, medications, and in-hospital evolution of clinical severity.[124] Pneumonia causes long-term mortality, up to 23·4% at 6 months and 30·6% at 12 months.[11] Predictors of long-term mortality include age, comorbidities, frailty, cardiovascular complications, inflammation, and initial insult severity.[125]

Cardiovascular events and cognitive implications

Cardiovascular complications occur in up to 30% of hospitalised patients with community-acquired pneumonia and includes new or worsening heart failure or arrhythmia and myocardial infarctions or strokes, both acute and up to 10 years thereafter.[126] In the case of pneumococcal community-acquired pneumonia, almost 20% of patients had one or more of these cardiac events. Cardiac complications might be due to several scenarios including pre-existing conditions, relative ischaemia, upregulation of the sympathetic system, pneumococcal protein virulence factor, systemic inflammation, and direct pathogen-mediated damage to the cardiovascular system.[127–129] A prospective cohort study showed that one in four hospitalised patients with community-acquired pneumonia had moderate to severe cognitive impairment, which persisted at least 1 year after pneumonia and a third had mild cognitive impairment.[130]

Prevention

Influenza vaccines can significantly decrease the risk of influenza and bacterial pneumonia. The estimated vaccine effectiveness for the prevention of influenza-associated pneumonia ranges from 56·7% to 60·2%.[131,132] The effectiveness of influenza vaccines against hospitalisation related to influenza or pneumonia in individuals aged 60 years or older, living in community or nursing homes, ranged from 25% to 53%.[133–139] However, the effectiveness of influenza vaccines can vary from year to year depending on several factors, including the antigenic matching between circulating influenza strains and vaccine-related antigens.[140]

Lower respiratory tract infections related to *S pneumoniae* can be prevented after the administration of two types of vaccines: unconjugated pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccines (PCV).[141–151] Polysaccharide vaccines produce an independent T-cell response without the activation of memory B cells, whereas conjugated

vaccines elicit a T-cell dependent response through an immunogenic protein with a B-cell memory and long-term immunisation.[142] The potentially long-lasting activity is a strength of conjugated vaccines, although they cover fewer pneumococcal serotypes in comparison to polysaccharide vaccines (appendix p 8). If both vaccines are suggested, the conjugated vaccine should be administered first because of its ability to enhance the immune response to unconjugated vaccines. Vaccine-type bacteraemic and non-bacteraemic community-acquired pneumonia, and invasive pneumococcal disease, were successfully prevented in individuals aged 65 years and older.[143] Pooled PPSV efficacy and effectiveness against pneumococcal pneumonia ranged from 48% to 64%.[144] From 2000 to 2017, invasive pneumococcal disease incidence caused by PCV-7 and PCV-13 types has decreased by 97% in England and by a further 64% after the introduction of the PCV-7 and PCV-13 in Wales.[146] However, the disease events caused by non-PCV-13 serotypes have doubled in both England and Wales.[146] After the implementation and scale up of PCV, the trends for pneumococcal pneumonia have been similar to those of invasive pneumococcal disease for patients aged 15–24 years, with the exception of those estimated in older population groups according to Public Health England.[146] The polysaccharide vaccine is currently recommended in older individuals in whom the risk of infection caused by strains related to PCV-13 is low (ie, countries where childhood PCV-13 immunisation strategy has been widely and successfully implemented).[148,149] Studies have shown mixed results related to vaccine effectiveness of PPSV23 in older people.[144,150,151]

Immunosuppressed patients

The ageing of the global population and increased number of individuals with chronic diseases or undergoing immunosuppressive therapies will lead to a substantial increase of immunocompromised patients, who may be hospitalised because of community-acquired pneumonia. International guidelines on the management of community-acquired pneumonia and hospital-acquired pneumonia have not addressed this important population of immunosuppressed patients.[1,47,48] There is no consensus regarding the definition of immunosuppression in community-acquired pneumonia, nor the initial management of immunocompromised patients with suspected community-acquired pneumonia. A global initiative defined immunocompromised patients with community-acquired pneumonia as patients with at least one of these risk factors: AIDS, aplastic anaemia, asplenia, haematological cancer, chemotherapy during the past 3 months, neutropenia, biological drug use, lung transplantation, chronic steroid use (>10 mg/day of prednisone or ≥3 months before hospital admission), lung cancer with either neutropenia or chemotherapy, and another solid tumour with either neutropenia or chemotherapy.[20] The same study reported that one in five hospitalised patients with community-acquired pneumonia have at least one risk factor for immunosuppression and that chronic steroid use seems to be the most common, followed by haematological malignancies and chemotherapy.[20] The spectrum of potential pathogens causing community-acquired pneumonia might expand according to the type and severity of immunosuppression to include fungal infections, less common viral infections, and even parasitic infections.[20] In 2020, international experts achieved consensus on the initial strategies for immunocompromised patients admitted to hospital with pneumonia, which should be based on a multidisciplinary approach.[152] The task force highlighted the importance of establishing a rapid and accurate causal diagnosis and of de-escalating therapies as soon as the presumptive pathogen is ruled out. A prompt transfer to a tertiary care facility is recommended in case of infections requiring highly specialised management if experienced pulmonary and infectious disease specialists are not already involved in the patient's management. Immunocompromised patients are usually excluded from randomised controlled trials on pneumonia, and strong evidence is urgently needed for this patient population.

In conclusion, community-acquired pneumonia poses a substantial public health burden in terms of mortality, morbidity, cost, and several controversies and uncertainties. Important research questions have been identified for future work (panels 2, 3).

Contributors

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

Declaration of interests

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