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Community-Acquired Pneumonia in Adults: What's New Focusing on Epidemiology, Microorganisms and Diagnosis?

INVITED REVIEW

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ABSTRACT

Community-acquired pneumonia (CAP) is one of the most common causes of hospital admissions and death worldwide. The incidence and mortality of CAP are associated with the presence of comorbidities and increasing age. Streptococcus pneumoniae is the most frequent causative microorganism of CAP, although in many patients with CAP, the causative microorganism remains unknown. Currently, antimicrobial resistance is increasing, so the accurate diagnosis and determination of the causative microorganism are even more important. This is a key point in reducing both morbidity and mortality from CAP, and appropriate antimicrobial stewardship is now a global priority. This review summarizes on the epidemiology, microbiological etiology, and diagnosis of CAP in adults.

Keywords: Community-acquired pneumonia, comorbidity, *streptococcus pneumoniae*, epidemiology, microbiological diagnosis, immunological biomarkers

INTRODUCTION

General worsening of health is related to an aging population worldwide. The high proportion of elderly individuals (>65 years) suffering from one or several comorbidities and an increase in the ineffectiveness of the immune system are responsible for the rise of infectious diseases in the elderly and are associated with a higher risk of mortality (1). Pneumonia is an inflammatory disease of the lung due to infectious microorganisms in the lower respiratory tract. It is a serious and progressive infection that affects between 5 and 11 people per 1000 of the adult population each year (2). Community-acquired pneumonia (CAP) is considered to be the most infectious cause of sepsis globally (1). Approximately 50% of the intensive care unit (ICU) admissions due to CAP are associated with septic shock (3).

Community-acquired pneumonia can be caused by many microorganisms including fungi, viruses, and bacteria; thus, it is essential to determine the pathogenic microorganism that causes the infection to provide an adequate clinical diagnosis (4). The most common pathogen causing CAP is *Streptococcus pneumoniae*, but nearly 50% of patients with CAP still have unidentified organisms (5). The objective of this review was to describe the epidemiology, microbiological etiology, and diagnosis of CAP worldwide.

A bibliographic search was performed through ISI Web of Knowledge and PubMed (reports from 2004 onwards) using a comprehensive search strategy. We searched terms relating to community-acquired pneumonia AND microorganisms AND diagnosis. All search results were limited to human adults. Exclusion criteria included patients aged <18 years; those with cystic fibrosis and neutropenia; those in a nursing home; or transplant recipient. The search lasted approximately 3 weeks from July 1, 2018 until July 19, 2018. The English language was used for the bibliographic search. A total of 36 studies were considered for this review.

CAP Epidemiology

Community-acquired pneumonia is the main cause of infectious disease-related mortality worldwide and is responsible for approximately 1 million hospital admissions with a great impact on health care resources. Its incidence and mortality are related to the increase in age and the presence of comorbidities (4). Given that the population is aging, it is expected that CAP will continue increasing as an outstanding public health problem (6).

Community-acquired pneumonia epidemiology can show differences according to geographical areas, health care setting, and study population. According to a report by the National Center for Health Statistics in 2014, both influenza and pneumonia were the eighth cause of mortality in the USA. In addition, in the USA in 2013, CAP incidence reported in adults >65 years ranged from 63 cases to 164.3 cases per 10,000 in adults >80 years (7).

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For the same period in 2013, CAP incidence ranged from 76 to 140 cases per 10,000 adults in patients >65 years in Europe (1). In Turkey, lower respiratory tract infections (including pneumonia) rank fifth among the main causes of death (8). Few studies on CAP epidemiology in Turkey have been found. The study by Koulenti et al. (9) conducted in nine European countries, including Turkey, deals with nosocomial pneumonia, which is out of the scope of this review.

In developed countries, older age is the main risk factor for CAP. In a population-based surveillance study by Jain et al. (7) performed in five hospitals in Chicago and Nashville, USA from January 2010 through June 2012, it was found that the incidence of hospitalized CAP increases with older age. They reported an overall annual incidence of pneumonia of 24.8 cases per 10,000 adults. By age groups, those adults between 65 and 79 years showed a rate of 63.0 cases per 10,000 adults, whereas the group with ≥80 years showed the highest rate, with 164.3 cases per 10,000 adults. In the study by Torres et al. (10) performed in Europe, excluding Turkey, the overall incidence rate for CAP was 68-7000 per 100,000.

In developing countries, few data can be found about population-level pneumonia incidence. Using hospital data, pneumonia is one of the most frequent causes of hospitalization in adults. In developed countries, the main burden of hospitalized patients with CAP is in older patients with comorbidity, whereas in many developing countries, the main burden of hospitalized patients with CAP is among adults in the working age. The World Health Organization reported that the average number of deaths related to CAP was approximately 700,000 deaths per year in developing countries. Moreover, the contracting risk of CAP is strongly linked to the prevalence of the disease in the environment, which is the case of populations with poor access to primary health care services (4).

Risk Factors for CAP

Prompt identification of patients at risk for severe CAP is important to pneumonia prevention and management. The etiology has been related to age and variations in less representative pathogens. The patient's age and comorbidities play an important role in determining the risk and disease severity of pneumonia. Therefore, patients with other diseases, such as diabetes, cancer, chronic heart failure, chronic obstructive pulmonary disease (COPD), Alzheimer, coronary artery disease, cystic fibrosis, renal insufficiency/dialysis, diabetes mellitus (DM), malignancy, chronic neurological disease, or chronic liver disease, have a higher incidence of pneumonia. In addition to comorbidities, toxic habits, such as smoking or alcoholism, have been also reported as risk factors for CAP. In the elderly (≥60 years), the risk increases in the presence of asthma, alcoholism, or immunosuppression (11). Other important factors are male sex and the development of acute respiratory failure (ARF), severe sepsis, and bacteremia (3).

With regard to mortality, the study conducted between 2011 and 2013 by Tokgoz Akyil et al. (12) examined the reasons and factors that underlie the patients' lower survival. According to their study, the risk factors that must be considered include advanced age, male sex, black race, pneumonia associated with medical care, and chronic comorbid diseases. In general, 82% of patients were diagnosed with at least one of the following diseases: asthma, COPD, coronary heart disease, chronic kidney disease, congestive heart failure, malignancy, and DM, among others. During follow-up, it was observed that malignancy, COPD, cardiovascular diseases, and neurodegenerative disorders increased mortality (Table 1).

Causative Microorganisms

Knowledge of the most common causes of CAP is important to initial empirical antibiotic prescription. *S. pneumoniae* caused >90% of cases of pneumonia in adults globally (13). On the other hand, atypical pneumonia is due to fastidious organisms, such as *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Coxiella burnetii*, *Chlamydophila pneumoniae*, and *Chlamydia psittaci* (14), representing up to 22% of all cases. In immunocompromised patients with CAP, Enterobacteriaceae spp., *Pseudomonas aeruginosa*, methicillin-resistant *Staphylococcus aureus*, and extended-spectrum beta-lactamase positive are more frequent (15). The study by Gunduz et al. (16) conducted in Turkey between 2009 and 2013 observed that the causative bacteria isolated most frequently in patients with CAP are *S. pneumoniae*, *P. aeruginosa*, *Escherichia coli*, *Haemophilus influenzae*, *S. aureus*, *Klebsiella pneumoniae*, *Streptococcus* spp. and *Moraxella catarrhalis*. Another study (17) conducted between 2002 and 2009 highlighted that 0.5% to 10% of cases of CAP are attributed to *Legionella*, being the most common specie *L. pneumophila*.

A more useful approach in clinical practice is to classify organisms and episodes based on the degree of severity. Scores, such as CURB-65 (Confusion, Urea nitrogen, Respiratory rate, Blood pressure) or CAP-PIRO (predisposition, insult, response, and organ dysfunction of community-acquired pneumonia), help to stratify severity, being ARF and shock the most important cause of ICU admission (3, 18, 19).

As mentioned above, *S. pneumoniae* is the main bacterial agent that causes CAP. This is consistent with studies conducted in the last 10 years in Europe, Asia, and the USA, showing that the most common bacteria worldwide are *S. pneumoniae*, *P. aeruginosa*, *S. aureus*, and *H. influenzae* (20-25, Table 1).

Diagnosis

Pneumonia is the main cause of sepsis. As a consequence, personalized medicine is an important approach in current management strategies. A detailed review on biomarkers and molecular diagnostic tests is not included in the purposes of this review. We refer the interested reader to the recent ESCMID position paper *Towards a personalized medicine approach in sepsis* (26).

Clinical

An important part of the diagnosis of CAP is a thorough evaluation of the patient's condition. Before making a diagnosis, the patient's history must be acquired, and physical examination and microbiological tests, such as Gram stain and blood cultures, must be performed. It is very important to follow the proposed guidelines of the national and international clinical practice guidelines for the correct microbiological diagnosis of pneumonia (11). According to these guidelines for severe CAP, it is recommended to perform blood cultures, culture and sputum staining, and urinary antigen test for *Legionella* and *Pneumococcus*. For example, sputum culture and urinary antigen test for *L. pneumophila* and *S. pneumoniae* are used for outpatients with failure of antibiotic therapy;

Table 1. Risk factors and prevalence of microorganisms for patients diagnosed with CAP

Citation	Country	Study period	Age ([mean±SD])	Number of patients (Incidence of CAP)	Inclusion criteria	Risk factors	Prevalence of microorganisms (%) **
Jain et al. 2015 (7)	USA (Chicago, Nashville)	2010-2012	57 (46-71)*	n=2488 (93.25%)	Evidence of acute infection, acute respiratory illness and pneumonia as assessed by means of chest radiography.	CLD, CHD, DM, immunosuppression	S. pneumoniae (8%) S. aureus (5%) Enterobacteriaceae (3%)
Erdem et al. 2014 (20)	Southeast Europe, Turkey, and Iran	June - July 2012	56.5±19.5	n=305 (22.62%)	All patients admitted to ICU with infection.	COPD, DM, CVD, burn, hematological malignancy, acute renal failure, solid organ tumor, CRF, peptic ulcer, chronic liver disease, bronchiectasis, asplenia, immunosuppression	Enteric Gram-negatives (28.8%) Acinetobacter spp. (21.9%) P. aeruginosa (13.5%) S. aureus (8%)
Ieven et al. 2018 (24)	Europe (Belgium, UK, Spain, Poland, Italy, Slovakia, Germany, France, Sweeden, Netherlands)	2007-2010	49.8±16.8	n=3.104 (4.54%)	>18 years, with acute cough, or any clinical presentation.	Risk factors not reported	H. influenzae (14.2 %) S. pneumoniae (9.2%) C. pneumoniae (5%)
Turktan et al. 2017 (32)	Turkey	2010 - 2015	45.92±20.16	n=37 (49%)	Adult refugee admitted in ICU with CAP.	COPD, DM, trauma history, CeVD, CAD, CHF, CRF, hematologic malignancy	M. tuberculosis (33.3%) E. coli (16.6%) S. aureus (16.6%) H. influenzae (16.6%)
Gündüz et al. 2016 (21)	Turkey	2009 - 2013	64.9±16.6	n=785 (73.63%)	Nonimmuncompromised > 18 years with radiographic infiltrate and two clinical symptoms.	COPD, cerebrovascular accident, CRF, immunosuppression	S. pneumoniae (3.8%) P. aeruginosa (2.1%) S. aureus (1.6%)
Serin et al., 2014 (25)	Turkey	February - December 2010	57.4±18.9	n=55 (90.91%)	>18 years, respiratory sample with leukocytes > 25 and squamous epithelial cells < 10 per low-power field with acute lower respiratory tract infection.	CeVD, COPD Malignancy, Bronchiectasis, DM, CHF, CRF, Liver disease	H. influenzae (22%) S. pneumoniae (20%)
Menendez et al. 2016 (22)	Spain	2005-2007	74.6±7.5	n=4070 (11.30%)	All individuals who were 65 years or older.	DM, CLD, Heart disease, CRF, Neurological disorder, COPD, Neoplasia	S. pneumoniae (27.2%) S.aureus (1.3%) L. pneumophila (2.8%) P. aeruginosa (1.3%) H. influenzae (1.3%)
Gattarello et al. 2015 (23)	Spain	2000-2002 2008-2014	63.0 (47.5-75)* 62.0 (53-72)*	n=529 (13.61%) n=616 (11.68%)	All patients admitted to ICU with CAP.	COPD, DM, immunosuppression, IMV, ICU, mortality, smoker, alcohol, spread, overweight, AKI, cardiomyopathy, cerebral vascular disease, shock, bacteremia, malignancy, rapid radiographic	S. aureus (22.1%) L. pneumophila (20.7%) H. influenzae (20.7%)

*Median of age and interquartil range; ** Prevalence of the most frequent microorganisms detected. No pathogens detected in all patients
AKI: acute kidney injury; CAD: coronary artery disease; CeVD: cerebrovascular disease; CHD: chronic heart disease; CHF: congestive heart failure; CLD: chronic lung disease; COPD: chronic obstructive pulmonary disease; CRF: chronic renal failure; CVD: cardiovascular disease; DM: diabetes mellitus

Table 2. Future research priority recommendations

Future Research Priority / Recommendations
The main challenges for the future seem to be:
- Obtaining a balance between conventional diagnostic techniques such as sputum, blood culture and antigen detection; and new diagnostic techniques, such as molecular techniques or the use of biomarkers.
- Identifying an etiological agent in half of the cases that are now undiagnosed.
- Further investigating the role of immunological biomarkers such as procalcitonin.
All these factors should be considered as a guide for the management of community-acquired pneumonia.

sputum and blood culture are used for hospitalized patients with positive urinary antigen test for *Pneumococcus* and cavitary infiltrates; sputum, blood culture, and urinary antigen test for *L. pneumophila* and *S. pneumoniae*; tracheal aspirate or bronchoalveolar lavage culture and viral studies also need to be performed and are used for severe CAP admitted to the ICU; urinary antigen test for *Legionella* serogroup 1; and influenza test during influenza season is used for epidemiological factor or specific risk factors suggesting pathogen. The low performance, the long period of response, and the previous antibiotic exposure are the main problems of these diagnostic methods (27).

Conventional Microbiological Diagnosis

Microbiological techniques allow the identification and characterization of the etiological agent of CAP. However, owing to the low sensitivity of microbiological studies, the difficulty in obtaining an adequate sample, and the low cost-benefit ratio, it is not recommended to perform routine microbiological tests (11). For this, the following techniques are available:

1. Blood and pleural cultures: Blood cultures are still the reference technique used for the microbiological diagnosis of infections that occur in the bloodstream. Nevertheless, these methods have limitations, such as false-negatives and long time to positivity. On the one hand, it has some inconveninents, such as the possible presence of non-culturable pathogens and the low number of microorganisms (11). On the other hand, blood cultures are relatively cheap, widely available/accepted technologies, and facilitate the evaluation of the antimicrobial susceptibility of the pathogen (26).

2. Thoracocentesis: It is an invasive technique that is based on surgical puncture to evacuate the pleural fluid from the chest wall for cytochemical study and bacteriological examination. Pleural or molecular technical samples are recommended for the detection of pneumococcal antigen (28).

3. Sputum stain and culture: It is important to perform sputum sample collection before starting antimicrobial therapy. Sputum cannot be processed for the cultivation of anaerobes because it is contaminated when passing through the oral cavity; therefore, it is recommended that the sample be collected and transported to increase the diagnostic accuracy. A good quality sample is considered when the sputum sample contains <10 epithelial cells and >25 lymphocyte cells (28). When a pathogen is isolated from sputum culture, a presumptive diagnosis is considered (29).

4. Antigen detection: It is usually performed in hospitalized patients. Bacterial pneumococcal and *Legionella* serogroup 1 can be detected. The use of previous antibiotics does not affect the detection of antigens. The detection of *Pneumococcus* has sensitivity between 50% and 80% with a specificity from 70% to 90%. The most common serogroup detected is *Legionella* serogroup 1, with sensitivity between 70% and 90% and a specificity of 99% (30).

Immunological Biomarkers

Biomarkers are used to rapidly diagnose disease and to reduce the lenght of antibiotic administration. Therefore, biomarkers can help with the correct choice of antibiotics and aid measure the treatment response (31). In view of the complexity of pneumonia response, it is unlikely that a single ideal biomarker will ever be found. A combination of several biomarkers may be more effective, but this requires further evaluation (26). The role of some interleukins (IL-6, IL-8, and IL-10), C-reactive protein, lipopolysaccharide-binding protein, soluble triggering receptor expressed on myeloid cells, and soluble prolinase-type plasminogen activator receptor has been evaluated in recent studies. Not one of the biomarkers mentioned is specific enough to be used alone. Today, one of the most studied biomarkers is procalcitonin (PCT). PCT is a calcitonin propeptide that is released in response to existing endotoxins in the walls of bacterial cells, cytokines, and chemokines. It is a biomarker that is usually used to determine the dose and duration of treatment with antibiotics for patients with sepsis (32). The arrays of biomarkers available have improved both diagnosis and prognosis and aid a personalized approach for pneumonia treatment (26).

Molecular Diagnosis

Molecular techniques are faster and precise for the detection of respiratory pathogens (33). In addition, they provide information on susceptibility to antibiotics and help control the response to therapy, among others. Currently, the polymerase chain reaction (PCR) technique is widely used for the identification of pathogen from positive blood cultures (sensitivity and specificity >90%). Matrix-assisted laser desorption/ionization mass spectrometry is another technique used to evaluate antimicrobial susceptibility and detect beta-lactam resistance, which can be used in positive blood cultures (34). However, a novel technique is using the Accelerate Pheno system (Accelerate Diagnostics, USA), which identifies microorganisms by fluorescent in situ hybridization and evaluates phenotypic antimicrobial susceptibility testing in positive blood cultures (35). On the one hand, the new techniques allow detecting resistance to antimicrobials, but they are not able to quantify the degree of antibiotic susceptibility. A recent study (36) found that in a sample of the lower respiratory tract, molecular techniques detected pathogens in 87% of cases with pneumonia, and culture-based techniques detected pathogens in 39% of cases. The most frequently detected pathogens were *H. influenzae* and *S. pneumoniae*. That is, molecular techniques improve the detection of pathogens in CAP, even in cases in which patients have been previously treated with antibiotics.

The best strategy for the correct identification of pathogens is through the direct detection of DNA from the blood, but it may be

false-positive results due to bacterial DNA contamination, presence of PCR inhibitors, reagents, and detection of circulating microbial DNA. Another problem with molecular techniques is that they usually provide little information about susceptibility to antimicrobials, especially Gram-negative bacteria (34). In conclusion, these techniques can be very useful for the diagnosis of pneumonia, but they should be complemented with conventional microbiological diagnosis.

CONCLUSION

In this review, CAP has been emphasized as the most frequent cause of morbidity and mortality worldwide. The main trends in the determination of the etiological agents in pneumonia include the continuous identification of *S. pneumoniae* as the most frequent bacterial pathogen, especially in patients with risk factors or comorbidities; a higher frequency of *Pneumococcus* in Europe; detection of other important pathogens, such as *P. aeruginosa*, *H. influenzae* in greater proportion, and atypical pathogens, such as *Mycoplasma* and *Legionella*; and, perhaps most importantly, the impossibility of establishing an etiological diagnosis in >50% of the patients. Therefore, it is important to combine the microbiological and molecular techniques, together with the immunological biomarkers, to help identify the etiology of CAP in patients and to provide guidance on the most appropriate treatment. Table 2 shows the main research priorities.

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