Pneumonia

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Abstract

Pneumonia is a very frequent problem for old frail patients due to diffusion, mortality, and other negative outcomes. The most complex aspects consist of the formulation of a diagnosis and the choice of an adequate treatment. In this context, optimal management requires the correct definition of the category and the most probable etiology involved in choosing the empiric treatment. Following this, it is crucial to conduct accurate examinations and, whenever feasible, switch to targeted treatments, ensuring timely adoption of oral administration.

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Introduction

Before the COVID-19 pandemic, pneumonia was already the most common cause of mortality since the beginning of the 21st century (2009 H1N1 influenza virus). Actually, it is the third cause of mortality in the world, and 30-day mortality in patients hospitalized due to pneumonia is around 23%.[1]

Among patients over 65 years, the European annual incidence of community-acquired pneumonia (CAP) is estimated at 14 cases per 1000 people. In long-term care facilities, the problem becomes even more serious: incidence is 365 cases per 1000 patients ≥75 years and pneumonia is the main cause of hospitalization (21.6% of cases).[2]

The most complex managing aspects are the formulation of diagnosis and the choice of treatment. To define empiric and targeted treatment, a correct knowledge of local epidemiology and clinical settings (objective examination and investigations) is needed.

Epidemiology

The first classification of pneumonia may be performed according to the setting in which the infection occurs and the associated risk factors. It may include healthcare-acquired pneumonia (HCAP), which encompasses pneumonia acquired in hospitals, dialysis units, residential aged facilities, and ventilator-associated pneumonia (VAP). However, HCAP has been omitted from American guidelines due to a lack of evidence regarding microbiological differences between CAP and HCAP. CAP is acquired outside of healthcare settings, occurring in patients who have not been hospitalized in the last month or had significant contact with healthcare facilities.

Hospital-acquired pneumonia (HAP) develops 48 hours or more after hospital admission and it is not incubating at the time of admission.

VAP is a subtype of HAP, occurring 48-72 hours or more after endotracheal intubation and mechanical ventilation; it is linked to the use of ventilators, which can introduce or promote the growth of pathogens in the lower respiratory tract.

Each category has different risk factors: lifestyle factors (smoking, poor hygiene, alcohol consumption) increase the risk of CAP, while malnutrition, burns, and post-surgery period are more often connected with HAP. Older patients and the presence of comorbidities are more often connected with HAP and CAP while, finally,

dysphagia and bed laying are obviously connected with aspiration pneumonia. Each pneumonia class is also connected with different mortality risks and multidrug-resistant organism (MDRO) incidence (increasing from CAP to HAP). Antibiotic-resistant pathogens, such as *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and methicillin-resistant *Staphylococcus aureus* (MRSA), are virtually absent in CAP but are more commonly associated with HAP and VAP. In VAP, *Acinetobacter baumannii* is also frequently identified.[3]

For what concerns CAP management, *S. pneumoniae* is responsible for 90% of the cases, while MRSA is only responsible for 3% of the cases.[4] Therefore, drugs such as linezolid must be used empirically only if MRSA risk factor is considered (previous MRSA colonization, recurrent skin infections, and severe pneumonia disease). In this situation, the performance of molecular research of MRSA by a nasal swab can be important to confirm MRSA presence and support the use of targeted antibiotics.[5] Empirical therapy should not be considered for other bacteria due to their rare prevalence. Extended-spectrum β-lactamase positive *Enterobacteriaceae* are 0.3-0.5% of cases; among the possible etiologies, although less frequent, *Legionella* deserves special mention. This agent is important, as it is responsible for cases of pneumonia with very high mortality and, if suspected, it is easily detectable by searching for antigens in urine. *P. aeruginosa* is responsible for 3-5% of cases. In addition, there is a strong recommendation to obtain influenza virus testing during periods of community spread.[6] Finally, aspiration pneumonia contributes to 5-15% of CAP, especially in more frail comorbid patients. This subcategory of pneumonia can be considered as a *continuum* between CAP and HAP.[7] It is commonly caused by bacteria from the oropharyngeal flora or gastric contents that are aspirated into the lower respiratory tract. The most frequently involved pathogens are anaerobic bacteria (*Bacteroides* spp., *Fusobacterium* spp., *Peptostreptococcus* spp.) and aerobic bacteria (*S. pneumoniae, S. aureus*, including MRSA, *K. pneumoniae*, and *Escherichia coli*).

In HCAP, *S. aureus* is responsible for nearly 50% of all cases and *S. pneumoniae* for one-third.

Table 1 details the main etiologies of pneumonia.

Clinical presentation and baseline tests

Clinical symptoms of pneumonia in older patients are frequently aspecific. Fever is often absent, whereas the most common symptoms can be confusion, inappetence, urinary incontinence, and exacerbation of chronic diseases, especially in the frailest long-term care residents. A frequent onset symptom is respiratory failure in need of oxygen or non-invasive ventilation (NIV). Moreover, concerning the discrimination between viral and bacterial pneumonia, symptoms have been demonstrated not to be useful.[8]

Regarding laboratory tests, leukocyte count, unlike in younger patients, can be normal or reduced, and in this situation, the prognosis is worse, as in the presence of hypoalbuminemia. Inflammation indices [C-reactive protein and procalcitonin (PCT)] are not equally predictive. Blood gas analysis may be useful for the evaluation of respiratory failure and the need for oxygen or NIV.

Microbiological diagnosis must be strongly pursued only when results can modify the treatment and prevent antimicrobial failure (*i.e.*, as in the case of severe disease or very frail patient). Recommended tests are monocultures, urinary antigens, and molecular research for bacteria and viruses.[5] The utility of radiological examination is commonly known; moreover, lung ultrasound has shown a greater discriminative capacity for bacterial infection compared to radiography.[8]

Treatment

The choice of the best possible treatment must be evidence-based (driven by scientific evidence, clinical experience, and situation-focused) and in agreement with antimicrobial stewardship (AMS) strategies. Four aspects must be considered: i) the patient (kind/severity of the infection and frailty); ii) the bacteria (sensitivity pattern and risk of relapse or resistance); iii) the drug characteristics (penetration, side effects, mono/in combination; route of administration and posology); iv) the society (ward colonization pressure/risk of communitarian resistance).

Patient factors

A thorough assessment of the patient is paramount. This includes evaluating the type and severity of pneumonia, underlying comorbidities (*e.g.*, diabetes, chronic obstructive pulmonary disease, heart disease), and overall frailty. Tools such as the CURB-65 score assist in determining disease severity and guiding treatment decisions. For instance, a higher CURB-65 score may indicate the need for hospitalization and intravenous antibiotics, whereas a lower score might suggest that outpatient management with oral antibiotics is appropriate. Age, immune status, and the presence of chronic diseases also influence the choice of antimicrobial therapy.[9] In older patients with CAP, frailty assessed at admission by the Multidimensional Prognostic Index (MPI) significantly predicted 1-month mortality, with an accuracy improved by the combination with PCT levels.[10]

Microbial considerations

Identifying the causative pathogen is crucial for targeted therapy. Empirical treatment often covers common pathogens according to the kind of pneumonia (as previously defined). Local antibiograms provide data on pathogen prevalence and resistance patterns, guiding initial antibiotic selection. For example, in areas with high rates of macrolide-resistant *S. pneumoniae*, alternative agents may be preferred.[11] Once culture and sensitivity results are available, de-escalation to the narrowest effective antibiotic is recommended to reduce the risk of resistance development.

Table 1. Etiologies of pneumonia classes.

Pneumonia classes	Etiologies
Community-acquired pneumonia	*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, *Moraxella catarrhalis*, *Legionella* spp.
Healthcare-acquired pneumonia	MRSA, *Pseudomonas aeruginosa*, *Enterobacteriaceae*, anaerobic bacteria, *Acinetobacter* spp., *Legionella* spp.
Hospital-acquired pneumonia	*Pseudomonas aeruginosa*, ESBL-producing *Enterobacteriaceae*, *Klebsiella pneumoniae*, *Acinetobacter* spp., KPC-producing, MRSA

MRSA, methicillin-resistant *Staphylococcus aureus*; ESBL, extended-spectrum beta-lactamases; KPC, *Klebsiella pneumoniae* carbapenemase.

Table 2. Antimicrobial empiric treatments according to pneumonia classes.

Pneumonia class	Empiric treatment
CAP	- amino benzylpenicillin ± macrolides (only in the absence of sepsis) - quinolones (associated with a higher risk of *Clostridium difficile* colitis, delirium, and seizures in epilepsy) - cephalosporins ± macrolides
HAP/HCAP	- β-lactam β-lactamase inhibitor, cefepime or quinolones (if not severe cases - carbapenems and linezolid or glycopeptide (if severe cases)
Aspiration pneumonia	- ceftriaxone + metronidazole - β-lactam β-lactamase inhibitor

CAP, community-acquired pneumonia; HAP, hospital-acquired pneumonia; HCAP, healthcare-acquired pneumonia.

Pharmacological properties

The pharmacokinetics and pharmacodynamics of antibiotics are critical considerations. Factors such as tissue penetration, half-life, potential side effects, and the convenience of dosing regimens influence the choice of agent. For instance, fluoroquinolones offer excellent lung tissue penetration and convenient once-daily dosing but are associated with specific adverse effects and increasing resistance rates. β-lactams, while effective, may require more frequent dosing and have varying spectrums of activity. The route of administration (oral *vs*. intravenous) is determined by the severity of the illness and the patient's ability to tolerate oral medications.[12]

Societal impact

AMS programs aim to optimize antibiotic use to combat resistance. Strategies include selecting appropriate empiric therapy based on local resistance patterns, reassessing therapy once pathogen identification and susceptibilities are known, and limiting the duration of antibiotic courses to the minimum effective period.[13] Shorter courses of therapy have been shown to be as effective as traditional longer courses in certain cases of CAP, reducing the risk of adverse events and resistance development. Additionally, monitoring and minimizing the use of broad-spectrum antibiotics help preserve their efficacy and reduce the colonization pressure of resistant organisms in healthcare settings. Empiric therapy should cover likely pathogens but avoid unnecessary broad-spectrum antibiotics to reduce resistance development. Two focal points may be favored in the logic of AMS: i) de-escalation – once microbiological results are available, transition to the narrowest effective agent should be supported); ii) shorter courses – evidence shows that 5-7 days of therapy are sufficient for most CAP cases, reducing adverse events and resistance risk for HAP and VAP cases.[14,15]

Moreover, recent multi-society guidelines moderately recommended the use of specific risk factors (eventually computed into clinical scores) based on local epidemiology and previous colonization to guide drug-resistant pathogens and empirical antibiotic prescription in severe CAP.[16] Several studies have identified reproducible risk factors for drug resistance that can be classified into four categories: i) pathogen acquisition related to healthcare exposure; ii) colonization persistence (immunosuppression, chronic lung disease, history of colonization or infection with drug-resistant pathogens); iii) antibiotic-mediated selective pressure promoting resistance; iv) factors altering host physiology (cognitive/neurological impairment, gastric acid suppression, *etc*.).[17]

Several published drug-related problem risk prediction methods were identified and showed high sensitivity and low specificity, potentially leading to overtreatment. However, their high negative predictive values (often >90%) support their use in guiding broad-spectrum regimens while sparing low-risk patients.[18]

The choice of types of antibiotics, duration, and route of administration are the basis for a successful AMS, whose implementation is the key to limiting therapeutic failures, avoidable adverse reactions, and selection of antimicrobial resistance. Basic empiric drugs are considered in Table 2.

Treatment must be re-evaluated after 72 hours to reduce, if possible, the broad-spectrum antibiotics and to switch as soon as possible to oral regimens. In the case of MDRO isolation, consolidated and new antibiotics must be equally evaluated.

Corticosteroids, oxygen, and non-invasive ventilation

Besides the demonstrated risk of hyperglycemia, the use of corticosteroids must be considered, as they reduce the early clinical failure in severe and not-severe pneumonia, and mortality in severe ones.[19] Recent studies have shown how hydrocortisone use among patients with severe CAP treated in intensive care unit is associated with a lower risk of death by day 28.[20]

Oxygen supplementation may be considered in the case of partial respiratory failure. As for the use of NIV in patients with CAP, it appears controversial since this is associated with high rates of treatment failure, compared with other causes of severe acute respiratory failure. A better response is generally observed in those patients with previous cardiac or respiratory disease.[21]

Conclusions

Pneumonia is a frequent cause of hospitalization and a widespread cause of morbidity and mortality among older patients. Both community-dwelling and long-term care residents may be affected by pneumonia and different etiologies should be considered according to peculiar risk factors. Treatment should be as tailored as possible, whereas empiric therapy needs to be switched to targeted therapy timely.

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