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Pneumonia

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Introduction

Pneumonia is defined as an acute respiratory infection that affects lung parenchyma. Despite the availability of antibiotic therapy and severity of illness assessments, pneumonia continues to be a leading cause of death worldwide. In the elderly population, the impact of pneumonia is greater than in other age groups. The mechanisms that increase the incidence and mortality rates in elderly pneumonia patients are not fully understood. The immunological changes that called immunosenescence are known to be responsible for the increased sensitivity of elderly people to infection diseases.

The world population reached 7.6 billion and the people 60 years and over amounted 13% of the total, 962 million according to data United Nations World Population Prospects (Kaplan et al., 2002). The annual incidence of pneumonia in the elderly is four-times that of the younger population. Older adults have also higher rates of hospitalization and mortality (Chong and Street, 2008). Therefore, a better understanding of the pathophysiology, microbiology, treatment, and prevention of this common affliction is required. For proper diagnosis and treatment advice, pneumonia is classified as community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and ventilator-associated pneumonia (VAP) along with the recent guidelines.

In this section, the most recent data regarding the epidemiology, microbiology, diagnosis, classification, treatment, and prevention strategies are presented.

Physiological Changes Associated With Aging

Effect of Aging on Respiratory System

Several physiologic changes in elderly have been implicated as risk factors for pneumonia. Decreased elastic recoil, decreased compliance of the chest wall, increased air trapping (senile emphysema) and reduced respiratory muscle strength are the basic changes in lung physiology (Tople and Kelsen, 1993).

Despite adequate gas exchange during the entire lifespan, the maximum capacity of the respiratory system shows a progressive decline with aging. These changes cause an increase in functional residual capacity. Elderly patients thus breathe at higher lung volumes with increased workload imposed on respiratory muscles. Calcification of the rib cage leads to stiffening of the chest wall and decreased compliance. As a result of osteoporosis, vertebral fractures result in dorsal kyphosis and negative effect on its force-generating capabilities. Nutritional deficiencies and age-associated sarcopenia decrease the respiratory muscle strength also. Decreased muscle strength has been described also in patients with chronic heart failure, chronic obstructive lung disease (COPD), Parkinson's disease and cerebrovascular disease. These comorbidities are frequently seen in elderly. An additional load on respiratory muscles as are pneumonia may lead to hypoventilation and respiratory failure.

Effect of Aging on Airway Defenses

Although chemotaxis, adherence, and phagocytosis capacities of monocytes, macrophages, and neutrophils are unaffected, declined blocking antibodies, increased self-reactive antibodies and the diminished ability of T cell-mediated immune response has been documented in older patients (Gyetko and Toews, 1993). In these patients, there is a high incidence of silent aspiration. In patients with neurological impairment of the glottic barrier, gastrostomy or nasogastric tubes there is no reduction for the risk of aspiration pneumonia. Colonization of the upper respiratory tract by both gram-negative and gram-positive bacteria is more prevalent. Pharmacological agents like antidepressants, antiparkinsonian medications, diuretics, antihypertensive agents and antihistamines were lead to decreased salivation and oropharyngeal gram-negative bacterial colonization (Clegg et al., 2013; Flaatten et al., 2017). Comorbidity is another important risk factor for this age group. Diabetes, chronic respiratory disorders, chronic kidney disease, chronic heart failure, malignity are all increasing the likelihood of pneumonia (Chong and Street, 2008).

At the present time, the physiological decline in the later life characterized by vulnerability to adverse health outcomes is defined as frailty. Frailty is age-associated and its prevalence rises steadily with older age group (Rockwood et al., 2005). Measurement for frailty should be done in order to improve the management of elderly patients with pneumonia. Along with there is no international standard for its measurement, the Frailty Index proposed by Rockwood et al. is one of the most frequently used. It includes variables such as disability, mobility, self-rated general health, seeing, hearing and chronic diseases (Rockwood et al., 2005).

Elderly patients with mild frailty perform basic activities of daily life, but an acute functional and/or cognitive impairment can develop with pneumonia. Elderly patients with moderate to severe frailty require help or are dependent for daily life activities. They present with severe comorbidity, polypharmacy, dementia, and malnutrition (Jain et al., 2015).

Epidemiology

The incidence of pneumonia varies according to geographical location, healthcare setting, and population. Including pneumonia, lower respiratory tract infections are the fourth most common cause of death all over the world. In a study carried out in the US, the annual incidence of pneumonia was observed as 24.8 cases/10,000 adults, with the highest rates among adults between 65 and 79 years of age; 63.0 cases/10,000 adults and in patients up to 80 years old; 164.3 cases/10000 adults (Konomura et al., 2017). In terms of economic impact, two studies carried out in the Netherlands and Japan, sustained remarkable results. The majority of CAP episodes (64%) occurred among patients 50 years and older and these episodes incurred 76% of the costs. The second study included 29,619 patients with CAP aged 65 years and over and reported median treatment costs of US\$ 346 per outpatient CAP and US\$ 4851 per hospitalized CAP (Klausen et al., 2012; Kothe et al., 2008). Mortality in elderly patients may be 25% higher than in the general population (10%). In this population group, hospitalization rates are five times more likely than other patients' groups also (Chong and Street, 2008).

Because of these negative impacts, several studies have attempted to identify risk factors. A population-based cohort study with 46,237 elderly patients found that immunosuppression, COPD, smoking, congestive heart failure, diabetes, malignancy, and previous hospitalizations for pneumonia are independent risk factors for developing the disease in this age group (Barlow et al., 2007). For mortality risk, available data is useful. Comorbid illness (including cerebrovascular disease, congestive heart failure, and chronic liver disease), higher infection activity index and ineffective therapy were presented along with higher mortality risk in elderly. Other factors linked to increased mortality are accepted as bedridden status, delirium, the absence of fever, tachypnea, C-reactive protein levels greater than 100 mg/L, hypoalbuminemia, acute organ failure, suspicion of aspiration and swallowing disorders (Centers for Disease Control and Prevention (CDC), 2012).

Microbiology

Microbial Etiology of Community-Acquired Pneumonia

Identifying the causative agent can be useful for guiding antimicrobial therapy. Although the microbiological diagnosis is fundamental to ensure appropriate therapy, it is achieved in less than 50% of the cases. In order to avoid the delaying that associated with increased mortality, antimicrobial therapy should be administered empirically. Pathogens associated with community-acquired pneumonia in elderly patients are presented in [Table 1](#).

Table 1 Pathogens associated with community-acquired pneumonia in elderly patients

Gram-positive cocci	Gram-negative bacilli	Atypical pathogens	Viral pathogens	Other
<i>Staphylococcus aureus</i>	<i>Escherichia coli</i>	<i>Mycoplasma Pneumoniae</i>	Influenza (e.g., H1N1 and seasonal flu)	<i>Mycobacterium Tuberculosis</i>
Community-acquired methicillin-resistant <i>Staphylococcus aureus</i>	<i>Haemophilu influenzae</i>	<i>Chlamydomphila pneumoniae</i>	Parainfluenza	Nontuberculous <i>mycobacteria</i>
<i>Streptococcus pneumoniae</i>	<i>Klebsiella</i> species	<i>Legionella</i> species		Anaerobes
Drug-resistant <i>Streptococcus pneumoniae</i> (penicillin and macrolide resistant)	<i>Pseudomonas aeruginosa</i>			Endemic and Opportunistic infections

In this age group, the possibility of obtaining a diagnostic sputum sample has been very low. Causative organisms are only identified in 5%–20% of the cases. Globally *S. pneumoniae* is accepted as being the most common pathogen. Also in elderly, this microorganism remains the single most common organism identified in hospitalized patients. The diagnosis of pneumococcal pneumonia has increased in recent years, due to the introduction of the pneumococcal urine antigen test. But the incidence has probably decreased because of pneumococcal vaccines along with the decreased rate of smoking (Garcia Vidal et al., 2010). The differences in the chemical and antigenic composition of the pneumococcal capsule result in 93 different serotypes. Serotype 3 is the most common serotype associated with adult pneumococcal infection and with septic shock (Cilloniz et al., 2016).

Haemophilus influenzae was also frequently isolated accounting for 5%–14% in elderly. In patients with chronic obstructive lung disease, infection with this organism may be more common. *Moraxella catarrhalis* and *Staphylococcus aureus* (methicillin sensitive) have also been described as pathogens, with frequencies 4% and 7%, respectively (CDC, 2012).

Intracellular pathogens are one of the other frequent microorganisms (Donowitz and Cox, 2007). The incidence is variable depending on the difficulties with microbiological cultures. They grow poorly in standard culture media and performing additional serologic tests on all patients is not common practice.

Legionella pneumophila, *Mycoplasma pneumoniae*, *Chlamydomphila pneumoniae*, *Chlamydomphila psittaci*, and *Coxiella burnetii* are the well-established intracellular pathogens. No clinical features exist that make it possible to distinguish intracellular pathogens from classical ones. But extra-pulmonary manifestations are often associated with intracellular pathogens. Severe pneumonia caused by these pathogens accounts for 1%–7% of the cases. The major problem with these pathogens is that most antibiotics are unable to access intracellular spaces and to reach the optimal therapeutic concentrations is difficult.

In those aged over 65 years, the atypical organisms are less frequently encountered but play a significant role in the clinical spectrum (Macfarlane et al., 1984). *Chlamydomphila pneumoniae* is the most common, with rates of 16%–28%, *Mycoplasma pneumoniae* is less frequently encountered (0%–13%) and *Coxiella burnetii* is a rare causative agent in elderly (CDC, 2012). Although *Legionella pneumophila* is relatively uncommon in the elderly, it should be considered presenting with atypical symptoms for example, headache, altered mental status, gastrointestinal signs or bradycardia (Ruuskanen et al., 2011). It appears to be reasonable to exclude this bacteria with urinary antigen testing in all elderly patients with pneumonia before atypical coverage is discontinued.

Infections with Gram-negative bacteria are often related to comorbid illnesses. Excluding nursing-home residents and hospitalized patients, these infections are infrequent in the elderly. But in severely debilitated or chronically ill elderly patients from the community, especially in those who fail to improve on standard therapy, a high index of suspicion may be warranted for this bacteria (CDC, 2012).

Among other pathogens, respiratory viruses are considered responsible in one-third of the cases. *Influenza viruses (A and B)*, *Respiratory syncytial virus (RSV)*, *parainfluenza viruses 1, 2, 3*, *coronaviruses* and *rhinoviruses*, are the most commonly encountered ones. It is estimated that 100 million cases of viral pneumonia occur annually (Ruuskanen et al., 2011). *Influenza virus (A and B)* is usually self-limiting, but severe complications like pneumonia can occur especially in high-risk patients like elderly with comorbidities along with increased mortality risk. Routine influenza screening appears reasonable in an elderly presenting with pneumonia-like complaints, but the sensitivity of available screening tests is poor and treatment decisions should not be based only the results of rapid flu testing.

Aspiration pneumonia is another common cause of CAP. The most frequent microorganisms are anaerobic bacteria and microaerophilic streptococci from the oral flora. Aspiration pneumonia may be the second most common etiology of CAP in patients 80 years and older (Teramoto et al., 2015).

Approximately 6% of the CAP cases, a Multidrug-Resistant (MDR)-resistant to more than three classes of antibiotics-pathogen is an agent that most frequently being *S. aureus* and *P. aeruginosa*. In a recent European study, MDR pathogens were presented as 3.3% of the 7.6% CAP cases with most commonly presented with methicillin-resistant *S. aureus* (MRSA) (Aliberti et al., 2013). Community-associated methicillin-resistant *S. aureus* (CA-MRSA) raises concern for infection in elderly adults. The production of the toxin Pantone-Valentine Leukocidin (PVL) is the main characteristic of CA-MRSA. This toxin causes leukocyte destruction and tissue necrosis. In elderly, CA-MRSA should be considered in presentation with influenza, such as prodromes, skin lesions, cavity infiltrates, hemoptysis or rapidly progressing pneumonia.

Table 2 The pathogens most commonly identified in patients with hospital-acquired pneumonia

<i>Staphylococcus aureus</i>	30%
<i>Pseudomonas aeruginosa</i>	24%
<i>Klebsiella</i> species	11%
<i>Escherichia</i> species	8%
<i>Acinetobacter</i> species	7%
<i>Enterobacter</i> species	7%
<i>Serratia</i> species	4%
<i>Stenotrophomonas maltophilia</i>	3%
<i>Streptococcus pneumoniae</i>	3%
<i>Haemophilus influenzae</i>	3%

P. aeruginosa is not a frequent pathogen in the CAP but severe CAP requiring intensive care unit (ICU) admission it was the causative agent in 1.8%–8.3% of the cases with the mortality rate of between 50% and 100% (Yoshimoto et al., 2005). Prior antibiotic treatment is the only risk factor associated with CAP caused by MDR *P. aeruginosa*.

Also, *S. pneumoniae* has increased its resistance to several antibiotics (cephalosporins, macrolides, and fluoroquinolones) in the last two decades. Between 20% and 30% of pneumococcus disease cases worldwide have MDR pattern. Nevertheless, the therapeutic failure involving β -lactams has not been reported because of pharmacodynamic properties (Draghi et al., 2006).

Microbial Etiology of Hospital Acquired Pneumonia and Ventilator-Associated Pneumonia

HAP is defined as pneumonia occurring 48 h or more after hospital admission. VAP is defined as pneumonia occurring > 48 h after endotracheal intubation. HAP is the second most frequent nosocomial infection and is considered the main cause of mortality for nosocomial infections. VAP is considered the main nosocomial infection in the ICU.

HAP is divided into two groups according to the time of onset from admission. Early onset is defined when pneumonia development within the first 4 days of hospitalization. This presentation is associated with better clinical prognosis. Late onset is defined when pneumonia occurs after 5 days of hospitalization. The recently published guidelines propose that the presence of risk factors for MDR should take precedence rather than early or late onset pneumonia distinction (Kalil et al., 2016). The top six pathogens causing 80% of the HAP cases are *S. aureus*, *P. aeruginosa*, *Klebsiella* spp., *Escherichia coli*, *Acinetobacter* spp., and *Enterobacter* spp. (Table 2).

Gram-negative bacteria are the major agent with 50%–80% for HAP cases in ICU. The most frequent pathogens include *P. aeruginosa*, *A. baumannii*, *H. influenzae*, and *Enterobacteriaceae* spp. (*K. pneumoniae*, *E. coli*, *Enterobacter* species, *Serratia* species, *Proteus* species, etc.). The mortality increase to 42% with advanced age, increased disease score and inadequate initial antimicrobial treatment. An independent factor for predicting the mortality is the using of vasopressors in the case of VAP where *P. aeruginosa* is isolated (Micek et al., 2015). Gram-positive pathogens account for 20%–30% of HAP cases. The most frequent microorganisms; Methicillin-resistant and methicillin-sensitive *S. aureus*, *S. pneumoniae*, and *Streptococcus* spp.

Pneumonia caused by more than two pathogenic microorganisms is defined as a polymicrobial infection. Approximately 30%–70% of VAP cases are considered to have polymicrobial etiology. Polymicrobial etiology generally did not influence the outcome when empiric antibiotic treatment was appropriate.

MDR pathogens are a major problem for this group of patients. The 2016 Clinical Practice Guidelines summarize the following risk factors for MDR (Weiskopf et al., 2009).

- Risk factors for MDR HAP; Prior intravenous antibiotic treatment within 90 days.
- Risk factors for MDR VAP; Prior intravenous antibiotic treatment within 90 days, septic shock the time of VAP, ARDS preceding VAP, five or more days of hospitalization prior to the occurrence of VAP, acute renal replacement therapy prior to the occurrence of VAP.
- Risk factors for *P. aeruginosa* and MRSA HAP/VAP: Prior intravenous antibiotic treatment within 90 days, need for ventilatory support for septic shock.

Clinical Presentation of Pneumonia

Elderly persons suffer from a variety of comorbidities. Associated factors predisposing patients to develop pneumonia are presented in Table 3. Also, multimorbidity was associated with death, hospitalization or return to the emergency department within 90 days of discharge. In a recent study 80% of the cases presented with at least one comorbidity according to the aging group: 65–74 years old, 77.6%; 75–84 years old, 80.6% and > 85 years old, 80.8%. The most frequent comorbidity was presented as chronic pulmonary disease. Because of immunosenescence in elderly, the risk of misdiagnosis or delayed diagnosis is more frequent.

Table 3 Factors associated with community-acquired pneumonia in elderly

<i>Comorbidities</i>	<i>Other factors</i>
<ul style="list-style-type: none"> ○ Previous pneumonia ○ Chronic obstructive pulmonary disease, ○ Asthma ○ Congestive heart failure ○ Diabetes mellitus ○ Cerebrovascular disease/stroke or dementia ○ Immunosuppression (cancer, HIV infection) ○ Chronic liver disease ○ Chronic kidney disease ○ Aspiration risk factors (seizure disorders, dysphagia/reflux) 	<ul style="list-style-type: none"> ○ Contamination of air conditioning or warm water systems (<i>Legionella pneumophila</i>) ○ Overcrowded institution (mycobacteria) ○ Nonhuman hosts; Cats, goats, birds Rabbits, rodents (<i>Coxiella burnetii</i>, <i>Chlamydomphila psittaci</i>, <i>Francisella tularensis</i>, and <i>Yersinia pestis</i>) ○ Smoking ○ Alcoholism ○ Poor dental hygiene ○ Poor nutritional status ○ Drug use

Specific symptoms of pulmonary infection such as a cough, sputum, fever, chills, and chest pains may not be available. The complaints must be taken care of are altered mental status (i.e., delirium), falls, fatigue, lethargy, delirium, anorexia, tachypnea, tachycardia, and, less commonly, pleuritic pain, cough, and fever (Rockwood et al., 2005). In elderly, pneumonia sometimes presents as an exacerbation or decompensation of previous comorbidities and also 30% of the cases the radiographic findings are inconclusive or difficult to interpret. Many biomarkers of infection such as leukocyte count, C-reactive protein (CRP), procalcitonin have been found to play a role in the early diagnosis, but in elderly with CAP, the reliability on these biomarkers is limited (Liu et al., 2013). All patients should be screened by pulse oximetry, for unsuspected hypoxemia in patients with diagnosed pneumonia or to determine the presence of pneumonia without obvious signs.

Laboratory Diagnosis of Pneumonia

Since the microbiological diagnosis of pneumonia is important for a better clinical outcome, to follow national and international guidelines is recommended. These recommendations regarding samples and diagnostic tests are presented in Table 4. Clinical indications for more extensive diagnostic testing should be decided on a clinical basis (Table 5). Some etiologic diagnoses have important epidemiologic implications and agents that should be reported to public health officials vary according to countries. In general, legionnaires disease, SARS (severe acute respiratory syndrome) psittacosis, avian influenza (H5N1), and possible agents of bioterrorism (plague, tularemia, and anthrax) are accepted as microorganisms to be notified.

Clinical Samples to Be Collected

Community-acquired pneumonia

In low to mild cases of CAP, recommendations for the microbiological diagnostic test is optional. In the case of the severe CAP, to take blood cultures, sputum staining, sputum culture, urinary antigen test for Legionella and Pneumococcus are recommended. The main problems from these methods are the low yield, long turnaround time (48–72 h) and the effects of previous antibiotic use on microbiological results (Chastre and Fagon, 2002).

Table 4 Samples and diagnostic testing in pneumonia

<i>Condition of pneumonia</i>	<i>Respiratory sample</i>	<i>Blood culture</i>	<i>Urinary antigen test for legionella</i>	<i>Comments</i>
Outpatient	Sputum culture			Serology test when pathogens are suspected through epidemiological evidence
Failure of outpatient antibiotic treatment	Sputum culture		x	Serology for intracellular pathogens
CAP cases who do not respond to treatment or suspicion of uncommon pathogens	BAL Mycobacterial a mycological culture Nasopharyngeal swab for respiratory viruses	x		
Hospital acquired pneumonia	x	x	x	Influenza test during influenza season
Ventilator-associated pneumonia	BAL/BAS in intubated patients	x	x	Serology test when pathogens are suspected through epidemiological evidence

Abbreviations: BAL, bronchoalveolar lavage; BAS, bronchoaspirate; ICU, intensive care unit.

Table 5 Clinical indications for more comprehensive diagnostic testing

Indication	Sputum culture	Blood culture	Legionella UAT	Pneumococcal UAT	Other
Intensive care unit admission	x	x	x	x	x ^a
Failure of outpatient antibiotic therapy	x		x	x	
Cavitary infiltrates	x	x			x ^b
Leucopenia		x		x	
Active alcohol abuse	x	x	x	x	
Chronic severe liver disease		x		x	
Obstructive/structural lung disease	x			x	
Asplenia		x		x	
Recent travel			x		x ^c
Pleural effusion	x	x	x	x	x ^d

Abbreviations: UAT, urinary antigen test.

^aEndotracheal aspirate if intubated (possibly with bronchoscopy or nonbronchoscopic bronchoalveolar lavage).

^bFungal and tuberculosis cultures.

^cEpidemiologic conditions and/or risk factors related pathogens.

^dThoracentesis and pleural fluid cultures.

The clinic presentations where microbiological tests should be applied:

- (i) Outpatients with a failure of antibiotic therapy
- (ii) Hospitalized patients with positive urinary antigen test for pneumococcus
- (iii) Severe obstructive lung disease
- (iv) Presence of pleural effusion
- (v) Presence of cavitary infiltrates
- (vi) Active alcoholism
- (vii) Severe CAP admitted to ICU
- (viii) Epidemiological factor or specific risk factors suggesting the pathogen.

Hospital acquired pneumonia

For all cases of HAP, microbiological tests should be performed on respiratory samples. Samples can obtain spontaneous expectoration, sputum induction, nasotracheal suctioning, and endotracheal aspiration in a patient with requires mechanical ventilation. For VAP cases noninvasive sampling with endotracheal aspiration cultures and blood culture is recommended (Kalil et al., 2016).

Diagnostic Tests for Pneumonia

Conventional microbiological diagnosis

Blood and pleural cultures: Before antimicrobial treatment, performing blood culture have a high specificity but a low positivity (less than 20% of the cases). Blood cultures are optional but especially in patients with host defect, for example, asplenia, complement deficiencies, chronic liver disease or leukopenia is indicated along with in patients with HAP, the positivity of blood cultures varies from 8% to 20%. Because the spreading of the infection to the blood occurs in <10% of VAP cases, blood cultures availability is limited. Approximately 40% of CAP cases have a pleural effusion. Patients with pleural effusions 15 cm in height on a lateral upright chest radiograph should undergo thoracentesis because of empyema is considered a risk factor for poor outcome. In pleural fluid samples, pneumococcal antigen or molecular detection are recommended also (Falguera et al., 2002).

Sputum gram stain and culture: Before antimicrobial therapy, sputum sample collection is performed. For diagnostic accuracy, an adequate collection and transport of the sample are recommended. The good quality sample is considered when the sputum sample contains less than 10 epithelial cells and more than 25 lymphocyte cells. The benefits of a sputum Gram stain; it broadens initial empirical therapy for a less common etiologies such as *S. aureus* and gram-negative organisms and it validates the subsequent sputum culture results. For pneumonia caused by *S. pneumoniae*, the sensitivity of the Gram stain is ~80% and for *S. aureus*, it is 78% (Anevlavis et al., 2009). The endotracheal aspirate is the equivalent of sputum in VAP cases. Gram stain and culture of the endotracheal aspirates are recommended for intubated patients. Both samples share the same criteria for quality. In VAP cases, for distinguishing colonization from infection, a threshold $\geq 10^5$ colony forming units/mL is recommended (Cook and Mandell, 2000).

Antigen tests: Legionella serotype 1 and pneumococcus antigens are renally excreted and can be detected. Sensitivity for pneumococcus ranges from 50% to 80% with specificity from 70% to 90%. For pneumococcal pneumonia, disadvantages of this test are costing amount (~\$30 per specimen) and false positive results with children and with chronic respiratory diseases who are colonized with *S. pneumoniae* (Navarro et al., 2004). Along with Legionella serogroup 1, 70%–90% sensitivity and 99% specificity was

reported. The problem is that the recommended empirical antibiotic regimens will cover both of these microorganisms and further researches are necessary to investigate the clinical usefulness of this method.

The rapid antigen detection test for influenza can help for consideration of antiviral therapy. Although test performance varies according to patient age, the test used, sample type and duration of illness, 50%–70% sensitivity and ~100% specificity was observed in adults. The disadvantages include cost (~\$30 per specimen), high rates of false-negative results and false-positive results with adenovirus and not superiority according to physician judgment.

Molecular microbiological diagnosis

In the last 10 years, for microbiological diagnosis of respiratory pathogens, molecular diagnostic tests are investigated. These tests provide identification of specific pathogens and differentiate bacterial and viral infection. Antibiotic susceptibility, response to antibiotic therapy, assessment for prognosis and disease surveillance is evaluated with these techniques. The methods are approved by the Food Drug Administration (FDA) (Gadsby et al., 2016). Approximately 50% of the cases remain without microbiological identification. Conventional methods together with molecular testing will improve the microbiological diagnosis and clinical management of cases with pneumonia.

Radiological Diagnosis of Pneumonia

A chest radiograph is required for the routine evaluation the patients who are likely to have pneumonia. Chest radiographs are sometimes useful for suggesting the etiologic agent, alternative diagnoses and associated conditions. Computerized tomography scans may be more sensitive when findings of radiography are negative or unclear. For patients who are hospitalized for suspected pneumonia but who have negative chest radiographic findings, it is advanced to treat presumptively with antibiotics and repeat the imaging in 24–48 h.

Evaluation of Severity

When managing elderly patients who present with pneumonia, evaluation of severity and site-of-care decisions are critical. In elderly patients with CAP, several mortality predictors have been reported. Chronic comorbidities were the main predictors of mortality and readmission. The prognostic value of glucose levels was investigated and markedly elevated blood glucose levels on admission were associated with increased short-term and long-term mortality. In another study, the neutrophil-to-lymphocyte ratio was evaluated and presented better for prediction 30-day mortality according to the pneumonia severity index (PSI) and CURB-65 (Fine et al., 1997; Lim et al., 2003). When a comparison is made in terms of mortality, between CRP, white blood cell (WBC) count and these indexes, PSI and CURB-65 are observed significantly associated with mortality and ICU admission.

The PSI is based on 20 parameters that are evaluated at the time of clinical presentation as three demographics, five comorbid conditions five physical examination findings, and seven laboratory/imaging variables (Table 6) (Fine et al., 1997). The primary purpose of this score is to distinguish patients that could be safely treated in an outpatient setting versus inpatient observation and treatment. The major limitations of the PSI score are its focusing by age and comorbidity and not consider psychosocial variables, infrequent comorbidities, or patient preferences regarding treatment. The CURB-65 is a less complex scoring system only requires six variables to be evaluated at presentation (Table 7). (Lim et al., 2003). For severity assessment and hospitalization decision, the usefulness of these scores are presented in Table 8. In CURB-65, age is an extremely significant variable. These scores highlight that elderly patients with pneumonia are at risk for higher severe disease and poorer clinical outcome, but the limitations of the CURB-65 score that not contain data such as hypoxemia, electrolyte disturbance or the inability to take oral medications. For prediction ICU admission and the risk of death in patients with severe CAP, several other tools have also been designed. The examples include the PS-CURXO80, SMART-COP, and CAP-PIRO scores. All of these guidelines—except one—include age as one of the variables associated with poor outcomes. PS-CURXO80 uses age above 80 years old as one of the minor criterion for determining the severity of illness. The SMART-COP scoring system evaluates the need for respiratory and vasopressor support. In this score, age is not one of the severity markers but tachypnea and poor oxygenation are used as an adjustment tool. Rello and colleagues developed the CAP-PIRO score. This score evaluates predisposition, infection, response, and organ dysfunction variables (España et al., 2006; Charles et al., 2008; Rello et al., 2009). Detailed information for all of these scores is presented in Table 9.

ICU admission is another important medical decision for these patients. Direct admission to an ICU is required for patients with septic shock requiring vasopressors or with acute respiratory failure requiring intubation and mechanical ventilation. Also, for patients with three of the minor criteria for severe CAP listed in Table 10, direct admission to an ICU or high-level monitoring unit is recommended (Mandell et al., 2007). But it must bear in mind that early recognition of sepsis in elderly compromised patients can be challenging. The classical criteria to define the systemic inflammatory response syndrome can be absent in anergic patients.

In conclusion, in addition to objective criteria such as age, the clinician experience, and clinical judgment is always recommended for proper evaluation. CURB-65 is practical and functional in order to decide when to admit a patient to the hospital and IDSA/ATS guidelines major and minor criteria are proper parameters to admit a patient to the ICU (Mandell et al., 2007).

Table 6 Pneumonia severity index score (PSI)

<i>PSI</i>	<i>Pneumonia score interpretation</i>
1. Three demographics <ul style="list-style-type: none"> • age [1 point per year of age] • female gender [− 10 points] • nursing-home residency [+10 points] 	0–50 points: Class I 0.1% mortality 51–70 points: Class II 0.6% mortality 71–90 points: Class III 0.9% mortality 91–130 points: Class IV 9.3% mortality 131–395 points: Class V 27.0% mortality
2. Five comorbid conditions <ul style="list-style-type: none"> • neoplasia [+30 points] • liver disease [+20points] • congestive heart failure [+10 points] • cerebrovascular disease[+10 points] • renal disease [+10 points] 	
3. Five physical examination findings <ul style="list-style-type: none"> • confusion [+20 points] • tachypnea[+20 points] • hypotension [+20 points] • temperature [+15 points] • tachycardia [+15 points] 	
4. Seven laboratory/imaging variables <ul style="list-style-type: none"> • arterial pH [+30 points] • elevated blood urea [+20 points] • hyponatremia [+20 points] • hyperglycemia[+10 points] • anemia by hematocrit [+10 points] • pleural effusion [+10 points] • poor oxygenation [+10 points] 	

Note: A total of 20 parameters are evaluated and scored at the time of clinical presentation.

Table 7 CURB-65 parameters

- Confusion, altered mental status; 1 point
- Urea nitrogen in serum >19.6 mg/dL; 1 point
- Respiratory rate >30 breaths/min; 1 point
- Blood pressure minus systolic BP <90 mmHg or diastolic BP <60 mmHg; 1 point
- Age of 65 years or older; 1 point

CURB-65: confusion, urea nitrogen, respiratory rate, blood pressure, and age of 65 years or older.
 0–1 points: low risk; 2–5 points: higher risk

Table 8 Evaluation of severity and need for hospitalization in patients with community-acquired pneumonia^a

<i>CURB-65</i>			<i>Pneumonia severity index score</i>		
<i>Risk class</i>	<i>Mortality (%)</i>	<i>Site of care</i>	<i>Risk class</i>	<i>Mortality (%)</i>	<i>Site of care</i>
0	0.7	Outpatient	I	0.1	Outpatient
1	2.1	Outpatient	II	0.6	Outpatient
2	9.2	Inpatient	III	2.8	Outpatient or brief inpatient
3	14.5	Inpatient	IV	8.2	Inpatient
4–5	40–57	Inpatient (possible need of intensive care unit care)	V	29.2	Inpatient

CURB-65: Confusion, urea nitrogen, respiratory rate, blood pressure, and age of 65 years or older.

^aRisk class I: age <50 years, no comorbidities and absence of vital-sign abnormalities.

Therapeutic Strategies to Manage the CAP

Antimicrobials are the mainstay of treatment for elderly patients with CAP. Selection of antimicrobials for empirical therapy is based on the prediction of the most likely pathogen and knowledge of local susceptibility patterns. Unless outcome data clearly do not favor one drug, recommendations generally take place for a class of antibiotics. Overall efficacy remain the major factor for many classes of agents, other factors like pharmacokinetics/pharmacodynamics, compliance, safety, and cost must be into consideration. The most common pathogens of CAP are presented in **Table 11** according to the severity of illness as judged by the site of care.

Table 9 Scores evaluate the severity of illness in patients with severe community-acquired pneumonia and need for intensive unit care

<i>PS CURXO80</i>	<i>IDSA/ATS</i>	<i>SMART-COP</i>	<i>CAP-PIRO</i>
<p>Major criteria</p> <ul style="list-style-type: none"> – pH < 7.30 – Systolic blood pressure < 90 mmHg <p>Minor criteria</p> <ul style="list-style-type: none"> – Confusion or altered mental status – Urea nitrogen > 30 mg/dl – Respiratory rate > 30 breaths/min – X-ray finding: multilobar/bilateral lung infiltrates – Oxygen arterial pressure < 54 mmHg or ratio of arterial oxygen tension to fraction of inspired oxygen < 250 mmHg – Age of 80 years or more 	<p>Major criteria</p> <ul style="list-style-type: none"> – Mechanical ventilation with endotracheal intubation and/or septic shock requiring vasopressors <p>Minor criteria</p> <ul style="list-style-type: none"> – Respiratory rate ≥ 30 breaths/min – PaO₂:FiO₂ ratio ≤ 250 – Bilateral or multilobar infiltrates – New onset confusion/disorientation – Uremia (BUN level > 20 mg/dl) – Leukopenia (WBC count < 4000 cells/mm³) – Thrombocytopenia (platelets < 100,000 cells/mm³) – Hypothermia (core temperature < 36°C) – Hypotension requiring aggressive fluid resuscitation 	<ul style="list-style-type: none"> – Low systolic blood pressure (1 point) – Multilobar chest radiography involvement (1 point) – Low albumin (1 point) – Age-adjusted high respiratory rate (1 point) – Tachycardia (1 point) – Confusion (1 point) – Age-adjusted poor oxygenation (2 points) – pH arterial low (< 7.35) (2 points) 	<p>Predisposition</p> <ul style="list-style-type: none"> – Comorbidities (1 point) <p>Age</p> <ul style="list-style-type: none"> – > 70 years (1 point) <p>Infection</p> <ul style="list-style-type: none"> – Bacteremia (1 point) – Multilobar opacities (1 point) <p>Response</p> <ul style="list-style-type: none"> – Shock (1 point) – Severe hypoxemia (1 point) <p>Organ dysfunction</p> <ul style="list-style-type: none"> – Acute respiratory distress syndrome (1 point) – Acute renal failure (1 point)

ATS, American Thoracic Society; CAP, community-acquired pneumonia; ICU, intensive care unit; IDST, Infectious Diseases Society of America; PIRO, predisposition, infection, response and organ dysfunction score; PS CURXO80, pH, systolic blood pressure, confusion, urea nitrogen, respiratory rate, x-ray finding, oxygen arterial pressure and age of 80 years or more; SMART-COP, systolic blood pressure, multilobar chest radiography, albumin level, respiratory rate, tachycardia, confusion, oxygenation and pH; BUN, blood urea nitrogen; WBC, white blood cell.

Table 10 Criteria for severe community-acquired pneumonia

<p>Major criteria</p> <ul style="list-style-type: none"> • Invasive mechanical ventilation • Septic shock with the need for vasopressors <p>Minor criteria^a</p> <ul style="list-style-type: none"> • Respiratory rate > 30 breaths/min • PaO₂/FiO₂ ratio > 250 • Multilobar infiltrates • Confusion/disorientation • Uremia (BUN level > 20 mg/dL) • Leukopenia^b (WBC count < 4000 cells/mm³) • Thrombocytopenia (platelet count < 100,000 cells/mm³) • Hypothermia (core temperature < 36°C) • Hypotension requiring aggressive fluid resuscitation

Note: BUN, blood urea nitrogen; PaO₂/FiO₂, arterial oxygen pressure/fraction of inspired oxygen; WBC, white blood cell.

^aOther criteria include, hyponatremia, unexplained metabolic acidosis or elevated lactate level, hypoglycemia (in nondiabetic patients), acute alcoholism/alcoholic withdrawal, cirrhosis, and asplenia.

^bAs a result of infection alone.

In terms of analyzing the microbial etiology in elderly, a cohort study with 2149 CAP patients was shown that when patients divided by age, the microbiological diagnosis possibility decreases steadily with age; 65–74 years old, 44%; 75–84 years old, 41%; and 85 years and older, 31% (Cillóniz et al., 2013). In this age group, to consider the substantial risk factors can help for prediction the responsible microorganisms and finally select the proper antimicrobial therapy (Table 12). Current international guidelines for the treatment of CAP do not have specific recommendations for elderly patients. In this guidelines, evaluation, following, and treatment of the patients is taking place into three categories; outpatient treatment, inpatient-non ICU treatment and inpatient ICU treatment (Mandell et al., 2007).

The recommendations for outpatient treatment with the listed clinical risks:

1. Previously healthy and no use of antimicrobials within the previous 3 months
 - A macrolide (azithromycin, clarithromycin, or erythromycin) (strong recommendation)
 - Doxycycline (weak recommendation)
2. Presence of comorbidities such as chronic heart, lung, liver or renal disease; diabetes mellitus; alcoholism; malignancies; asplenia; immunosuppressing conditions or use of immunosuppressing drugs; or use of antimicrobials within the previous 3 months
 - A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation)

Table 11 Most common pathogens of community-acquired pneumonia according to severity of illness (along with not in order of frequency)

Patient type	Pathogen
Outpatient	<i>Streptococcus pneumoniae</i> <i>Mycoplasma pneumoniae</i> <i>Haemophilus influenzae</i> <i>Chlamydia pneumoniae</i> Respiratory viruses ^a
Inpatient (non-ICU)	<i>S. pneumoniae</i> <i>M. pneumoniae</i> <i>C. pneumoniae</i> <i>H. influenzae</i> <i>Legionella</i> species Aspiration Respiratory viruses ^a
Inpatient (ICU)	<i>S. pneumoniae</i> <i>S. aureus</i> <i>Legionella</i> species Gram-negative bacilli <i>H. influenzae</i>

Note: ICU, intensive care unit.

^aInfluenza A and B, parainfluenza, adenovirus, and respiratory syncytial virus.

Table 12 Risk factors for specific microorganisms in community-acquired pneumonia in elderly

Microorganism	Risk factor
<i>Streptococcus pneumoniae</i>	Dementia, seizure disorders, congestive heart failure, cerebrovascular disease, COPD, HIV infection, black race, overcrowded living, and smoking
<i>S. pneumoniae</i> resistant to β -lactam	Use of β -lactam (prior 3–6 months), hospitalization (prior 3 months), COPD aspiration, previous pneumonia in the last year, noninvasive disease, >65 years old attendance in day care
<i>S. pneumoniae</i> resistant to macrolide	Use of macrolide (prior 1–3 months) >65 years old, attendance in daycare centers, recent hospitalization
<i>S. pneumoniae</i> resistant to fluoroquinolones	Prior use of fluoroquinolones COPD nursing home, nosocomial infection, penicillin resistance
<i>Staphylococcus aureus</i> Methicillin-resistant <i>Staphylococcus aureus</i> (MRSA)	Advanced age, underlying lung disease, previous antibiotic use Previous MRSA infection or colonization cerebrovascular disease, diabetes, chronic renal failure, hospitalization for >2 days in the preceding 90 days prior intravenous antibiotic therapy within the last 30 days
Community-acquired Methicillin-resistant <i>Staphylococcus aureus</i> (CA-MRSA)	History of viral upper respiratory infection, smoking, recent hospitalization, chronic pulmonary disease
<i>Haemophilus influenzae</i>	COPD treated with antibiotics or oral steroids within the previous 3 months
<i>Pseudomonas aeruginosa</i> Multidrug-resistant <i>Pseudomonas aeruginosa</i>	Pulmonary comorbidity antibiotic therapy (prior 1 month)

Note: COPD, chronic obstructive pulmonary disease.

A β -lactam plus a macrolide (High-dose amoxicillin [e.g., 1 g three times daily] or amoxicillin-clavulanate [2 g two times daily] is preferred; alternatives include ceftriaxone, cefpodoxime, and cefuroxime [500 mg two times daily]; doxycycline is an alternative to the macrolide) (strong recommendation)

- In regions with a high rate (>25%) of infection with high-level (MIC > 16 mg/mL) macrolide-resistant *S. pneumoniae*, consider the use of alternative agents listed above in (2) for patients without comorbidities (moderate recommendation).

The recommendations for hospital ward treatment with the listed clinical risks:

- A respiratory fluoroquinolone (strong recommendation)
- A β -lactam plus a macrolide (strong recommendation)
Preferred β -lactam agents include cefotaxime, ceftriaxone, and ampicillin;
Ertapenem for selected patients (patients with risks for infection with these pathogens and for patients who have recently received antibiotic therapy) with doxycycline—as an alternative to the macrolide
A respiratory fluoroquinolone should be used for penicillin-allergic patients.

For most hospitals admitted patients, initial treatment should be given intravenously, but some without risk factors for severe pneumonia could receive oral therapy, especially with highly bioavailable agents such as fluoroquinolones. When an intravenous

β -lactam is combined with coverage for atypical pathogens, a macrolide or doxycycline with oral therapy is appropriate for selected patients without severe pneumonia risk factors.

The recommendations for ICU treatment with the listed clinical risks:

Minimal recommended treatment is;

1. A β -lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin or a fluoroquinolone (strong recommendation)

For penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam.

The most common pathogens in the ICU population were (in descending order of frequency) *S. pneumoniae*, *Legionella species*, *H. influenzae*, *Enterobacteriaceae species*, *S. aureus* and *Pseudomonas species*. The recommended standard empirical regimen should routinely cover the three most common pathogens, all of the atypical pathogens, and most of the relevant Enterobacteriaceae species. But for treatment of MRSA or *P. aeruginosa* infection, modification the standard empirical regimen is necessary.

Along with suspicion of these pathogens, modification to the basic empirical treatment is;

1. For Pseudomonas infection, use an antipneumococcal, antipseudomonal β -lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750-mg dose) or the above β -lactam plus an aminoglycoside and azithromycin or the above β -lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone.

For penicillin-allergic patients, substitute aztreonam for the β -lactam.

Structural lung diseases, such as bronchiectasis, or repeated chronic lung disease exacerbations as well as prior antibiotic therapy are other clinical risk factors for infection with Pseudomonas species. Requiring for ICU admission is not routine with these pathogens. In patients with chronic alcoholism other serious gram-negative pathogens, such as *K. pneumoniae* or *Acinetobacter species* are important.

2. For CA-MRSA infection, add vancomycin or linezolid (moderate recommendation).

Clinical risk factors for CAP with *S. aureus* include end-stage renal disease, injection drug abuse, rapid presentation and progression, associated skin lesions, prior influenza, and prior antibiotic therapy. For MSSA empirical combination therapy recommended above is adequate. Actually, vancomycin has never been specifically studied for CAP. Linezolid is detected superior to vancomycin in the retrospective analysis for nosocomial MRSA pneumonia. As newer presently available agents, daptomycin should not be used for CAP, and for tigecycline, there is no available data.

Pathogen-Directed Therapy

1. The etiology of CAP has been identified with reliable microbiological methods, antimicrobial therapy should be oriented at that pathogen (moderate recommendation)

Because of the benefit of combination therapy was also most pronounced in more severely ill patients, after results of cultures, discontinuation of combination therapy is most likely safe in only non-ICU patients (Cillóniz et al., 2013).

2. Early treatment (within 48 h of onset of symptoms) with oseltamivir or zanamivir is recommended for influenza A (strong recommendation).
3. Oseltamivir and zanamivir is not recommended for patients with uncomplicated influenza with symptoms for >48 h, but these drugs may be used to reduce viral shedding in hospitalized patients or for influenza pneumonia (moderate recommendation).
4. Parenteral acyclovir is indicated for varicella zoster or herpes simplex virus pneumonia. No antiviral treatment of proven value is available for other viral types of pneumonia.
5. An increasing greater than 10% is observed for Enterobacteriaceae with ESBL especially in patients with recent hospitalization or elderly. Ertapenem is a good therapeutic option with good sensitivity.

Pandemic Influenza

1. Patients with influenza compatible and with known exposure to poultry in areas with previous H5N1 infection should be tested (moderate recommendation).
2. In patients with suspected H5N1 infection, droplet precautions and routine control measures should be used until the infection is ruled out (moderate recommendation).
3. Patients with suspected H5N1 infection should be treated with oseltamivir and antibacterial agents targeting *S. pneumoniae* and *S. aureus* (moderate recommendation).

Follow Up Advice

1. For patients admitted through the Emergency Department (ED), the first antibiotic dose should be given while still in the ED (moderate recommendation).

Table 13 Clinical stability criteria

-
- Normal mental status^a
 - Ability to maintain oral intake^a
 - Temperature <37.8°C
 - Arterial oxygen saturation >90% or pO₂ >60 mmHg in room air
 - Heart rate <100 beats/min
 - Respiratory rate <24 breaths/min
 - Systolic blood pressure >90 mmHg
-

^aImportant for discharge or oral therapy decision but not necessarily for the decision of nonresponse.

2. Patients should be switched from intravenous to oral therapy when they hemodynamically stable, are able to ingest medications, and have a normally functioning gastrointestinal tract (strong recommendation).
3. Patients should be discharged as soon as they are clinically stable, inpatient observation while receiving oral therapy is not necessary (moderate recommendation).

Patients with higher PSI risk score take longer to reach clinical stability than do patients at lower risk, so elderly patients with multiple comorbidities generally recover more slowly. Appropriate follow-up and rehabilitation planning should be initiated early for these patients. In elderly presented with delirium, its resolution may represent a clinical marker of improvement.

Duration of Antibiotic Therapy

1. Patients with CAP should be treated for a minimum of 5 days, should be afebrile for 48–72 h, and should have not clinical instability sign no more than one before discontinuation of therapy (moderate recommendation) (Waterer et al., 2001; Ramirez et al., 1995).
2. If initial therapy was not active against the identified pathogen or if it was complicated by extrapulmonary infection, a longer duration of therapy may be needed (weak recommendation).
Criteria for clinical stability is presented in Table 13 (Arnold et al., 2009).
3. Most patients with CAP have been treated for 7–10 days or longer, but few well-controlled studies evaluated the optimal duration of therapy. Short-duration may be suboptimal for patients with bacteremic *S. aureus* or *Pseudomonas* infection. The presence of cavities or other signs of tissue necrosis may require prolonged treatment.

Other Important Treatment Considerations

1. Patients with CAP along with persistent septic shock despite adequate fluid resuscitation should be evaluated for therapy with drotrecogin alfa activated within 24 h of admission (weak recommendation)—Advice patients' groups; patients with septic shock, sepsis-induced leukopenia and organ failure criteria.
2. Hypotensive, fluid-resuscitated patients with severe CAP should be screened for adrenal insufficiency (moderate recommendation).
Stress-dose (200–300 mg of hydrocortisone per day or equivalent) steroid treatment improves outcomes of vasopressor-dependent patients with septic shock who have documented inadequate cortisol levels.
3. Patients with hypoxemia or respiratory distress should receive a cautious trial of noninvasive ventilation (NIV) unless they require immediate intubation (moderate recommendation).
4. Low-tidal-volume ventilation (6 cm³/kg of ideal body weight) should be used for patients undergoing ventilation who have diffuse bilateral pneumonia or ARDS (strong recommendation).
5. Other management protocols of severe sepsis and septic shock in patients with CAP do not appear to be different from those patients with other infections.

Advice for Management of Nonresponding Pneumonia

1. 6%–15% of hospitalized patients with CAP do not respond to the initial antibiotic therapy. Mortality among nonresponding patients is increased several-fold according to responding patients. The using a systematic classification for possible causes is recommended (Table 14) (moderate recommendation).
2. Two patterns of undesirable response are seen in hospitalized patients: The first is progressive pneumonia or clinical deterioration, with acute respiratory failure requiring ventilatory support and/or septic shock, within the first 72 h of hospital admission. The second pattern is that of persistent or nonresponding pneumonia.
3. Nonresponding to antibiotics generally result in three patterns of clinical approachment (1) transferring of the patient to a higher level of care (2) further diagnostic testing, and (3) changing the treatment.

Table 14 The treatment respond failure patterns and etiologies

<i>Failure to improve</i>	<i>Deterioration or progression</i>	<i>Exacerbation of comorbid illness</i>	<i>Intercurrent noninfectious disease</i>
<ul style="list-style-type: none"> • Early <ul style="list-style-type: none"> ○ (<72 h of treatment) ○ Normal response • Delayed <ul style="list-style-type: none"> ○ Resistant microorganisms <ul style="list-style-type: none"> ■ Uncovered pathogen ■ Inappropriate by sensitivity ○ Parapneumonic effusion empyema ○ Nosocomial superinfection <ul style="list-style-type: none"> ■ Nosocomial pneumonia ■ Extrapulmonary infection ○ Noninfectious reasons <ul style="list-style-type: none"> ■ Complications of pneumonia misdiagnosis: PE, CHF, vasculitis 	<ul style="list-style-type: none"> • Early <ul style="list-style-type: none"> ○ (<72 h of treatment) ○ Severity of infection at presentation ○ Resistant microorganism <ul style="list-style-type: none"> ■ Uncovered pathogen ■ Inappropriate therapy ○ Metastatic infection <ul style="list-style-type: none"> ■ Empyema/parapneumonic ■ Endocarditis, meningitis ○ Inaccurate diagnosis <ul style="list-style-type: none"> ■ PE, aspiration, ARDS Vasculitis • Delayed <ul style="list-style-type: none"> ○ Nosocomial superinfection ○ Nosocomial pneumonia ○ Extrapulmonary 	Worsening independently from infection	<ul style="list-style-type: none"> • Myocardial infarction • Renal failure • PE, etc.

Note: ARDS, acute respiratory distress syndrome; CHF, congestive heart failure; PE, pulmonary embolus.

Firstly, patients with nonresponding or deterioration are reevaluated for initial microbiological results and further history for risk factors for infection with unusual pathogens. Blood cultures should be repeated. In 44% of the patients with CAP, the etiology determined by bronchoscopy. Rapid urinary antigen test can remain positive for days after initiation of antibiotics and is considered in nonresponding patients an also concomitant or subsequent extrapulmonary infections, such as an intravascular catheter, urinary, abdominal, and skin infections must be kept in mind.

4. Other tests for selected patients with nonresponse: Chest CT, Bronchoscopy with lavage and transbronchial biopsies and thoracentesis.

Current international guidelines for CAP do not provide specific recommendations for elderly patients but convenience to guidelines was associated with shorter time for clinical stability, shorter length of hospital stay, and lower in-hospital mortality (Egger et al., 2016). An international, multicenter observational study for elderly patients is reported that adherence to the 2007 IDSA/ATS guidelines for hospitalized non-ICU elderly patients was cost-effective but was not the most cost-effective strategy in ICU patients (Faverio et al., 2014). In elderly patients, another important issue is age-related changes for antibiotic therapy that modify tolerability, metabolism, excretion of drugs and the risk of drug–drug interactions. In case of QT prolongation or concomitant medication that prolongs QT, using macrolides or fluoroquinolones is not suggested. In elderly, Achilles tendon rupture has been reported with fluoroquinolones. With aminoglycosides, nephro and ototoxicity must be kept in mind and presence and degree of renal and/or hepatic failure is always evaluated when choosing the antibiotic treatment (Faverio et al., 2014).

Another important risk in the elderly is the frequency of aspiration. Risk factors for aspiration pneumonia are age, male gender, neurologic impairment, Parkinson's disease, lung disease, diabetes mellitus, malnutrition, periodontal diseases, poor oral hygiene, vomiting, proven dysphagia, proton pump inhibitor, antipsychotic or sedative drug use. Diagnosing can be challenging, as a diagnostic tool, fiberoptic endoscopic evaluation of swallowing (FEES) can be performed at the bedside. The most common pathogens are oropharyngeal flora including anaerobes, Gram-positive cocci, and Gram-negative bacilli. Antibiotics against indigenous oral flora including anaerobes should be administered and both swallowing rehabilitation and oral healthcare management should be initiated. Percutaneous endoscopic gastrostomy (PEG) is often performed for preventing aspiration, but there is little evidence to indicate that it prevents pneumonia. A head-up position, by ~30 degree and mosapride, a gastroprokinetic agent may be preventing gastroesophageal regurgitation and associated aspiration. Angiotensin-converting enzyme (ACE) inhibitors and cilostazol have been reported effective for prevention of pneumonia, because these medications increase substance P levels in the airways and plasma, improving both swallowing and cough reflexes. For prevention, also anticholinergic agents, tricyclic antidepressants, diuretics, and selective serotonin reuptake inhibitors that which cause dry mouth should be administered cautiously.

In elderly patients with pneumonia, the development of cardiac complications was associated with a 60% increased mortality risk. Even only advanced age is associated with higher risk of long term-mortality. Other causes of death after following an episode were mainly related to comorbidities, malignancy, COPD and vascular diseases. As are cardiovascular and cerebrovascular events, to increase the rehabilitation and nutritional status after a CAP could ameliorate physical dysfunction in elderly.

Therapeutic Strategies to Manage Hospital-Acquired or Ventilator-Associated Pneumonia

1. In these patients, the goal is to choose the target specific antibiotics associated with HAP/VAP as narrowly as possible. Without risk factors for MDR organisms, empiric therapy should include one antibiotic (against *P. aeruginosa*, other gram-negative organisms, and methicillin-sensitive *S. aureus*) Suggested agents include piperacillin-tazobactam, cefepime, levofloxacin, imipenem, or meropenem.
2. In patients with risk factors for MRSA infection, empiric coverage should include vancomycin or linezolid.
3. HAP/VAP treatment should always include antipseudomonal coverage. Dual antipseudomonal agents from different classes are recommended for empiric therapy in patients with a risk factor for MDR gram-negative pathogens. Decisions about dual coverage should be individualized (Mandell et al., 2007).
4. In most patients with HAP/VAP, the recommended duration of antibiotic therapy is 7 days, regardless of the isolated pathogen. There is no difference in regard to mortality, treatment failure, recurrent pneumonia, or duration of mechanical ventilation. A longer duration may be appropriate where the patient may have a delayed clinical response.
5. The guidelines recommend that discontinuation of antibiotics be based on clinical criteria and procalcitonin testing (Schuetz et al., 2012).

Preventive Measures

International guidelines recommend specific measures for preventing pneumonia (Kim et al., 2016).

1. Pneumococcal polysaccharide vaccine is recommended for persons >65 years of age and for those with selected high-risk concurrent diseases (chronic cardiovascular, pulmonary, renal, or liver disease, diabetes mellitus, alcoholism, asplenia, immunocompromising conditions/medications, long-term care facility residents) (strong recommendation).
2. All persons >50 years of age, others at risk for influenza complications; high-risk persons with household contacts and health care workers should receive inactivated influenza vaccine (strong recommendation). Influenza and pneumococcal vaccines can be given at the same time in different arms.
3. Vaccination status should be evaluated at hospital admission for all patients, especially those with medical illnesses (moderate recommendation).
4. Vaccination may be performed either at hospital discharge or during outpatient status (moderate recommendation).
5. Influenza vaccine should be offered to persons at hospital discharge or during outpatient therapy during the fall and winter (strong recommendation).
6. Cases of pneumonia along with public health concern should be reported immediately to the state or local health department (strong recommendation).
7. Respiratory hygiene measures, including hand hygiene and respiratory masks, should be used in outpatient settings and in emergency departments (strong recommendation).

The effectiveness of pneumococcal polysaccharide vaccines for prevention of invasive infections among elderly individuals and younger adults have documented with epidemiologic studies. Currently, two types of vaccine are available: polyvalent pneumococcal polysaccharide vaccine (PPV23)—23 pneumococcal serotypes included—and the pneumococcal conjugate vaccines (PCV13). The only difference of PCV13 is the capsular polysaccharides that conjugated to a carrier protein for enhancement the immunogenicity.

Pneumococcal vaccine naïve >65 years old persons should receive a single dose of PCV13 first, followed by a dose of PPV23 1 year later. Prior vaccination with PPV23 at age >65 years should also receive a dose of PCV13 if they have not yet received one. A dose of PCV13 should be given >1 year after of the most recent PPV23 dose. In patients who need to repeat PPV23, the period between administration of PCV13 and the new dose of PPV23 should be at least 1 and 5 years since the most recent dose of PPV23 (Kim et al., 2016).

For influenza, chemoprophylaxis can be used as an adjunct treatment to vaccination. Oseltamivir and zanamivir are both approved for prophylaxis and may be useful for household exposure to influenza and those who work in institutions with an influenza outbreak (Hayden et al., 2004). As other preventive measures, modifiable risk factors as reducing or cessation of alcohol consumption, smoking cessation, improving oral hygiene, ensuring good nutritional status, avoiding contact with lower respiratory infections were accepted.

Learning Points

CAP is the fifth leading cause of death and the most common cause of death from infectious diseases in people aged 65 years and over. *S. pneumoniae* is still the most common pathogen. Elderly patients have a significant number of risk factors associated with higher risk for MDR pathogens. To establish supportive measures, systematic evaluation of cognitive, nutritional (hydration included) and functional status must be an important part of the clinical examination. Antimicrobial selection for elderly patients with CAP does not differ from that of younger adults. In clinical practice guidelines, early antibiotic administration and strict

adherence to the regimes is recommended. It is not appropriate to restrict intensive care and ventilatory support only on the basis of chronologic age. There is no difference for management the patients with HAP and VAP in this age group. The long-term mortality rate after CAP hospitalization is really high in the elderly population. As prevention, immunization measures must be improved. Vaccination for pneumococcus and influenza and smoking cessation programs may help for decrease the incidence and severity of CAP, especially in this age group.

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