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# **Pneumonia: A Challenging Health Concern with the Climate Change**

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## **Abstract**

Pneumonia is still a global health concern with high mortality rate, mainly among children under 5 years and adults over 65 years. In addition to pathogen virulence, immunoevasion capacity, and drug resistance ability, risk factors for the patient include aging, comorbidities, malnutrition, and all causes affecting the immune system. The extent to which environmental disorders affect the respiratory health is established for chronic diseases such as asthma, COPD, and cardiovascular diseases, but less is known about the underlying mechanisms of their impact on infectious diseases of the respiratory system. This chapter aims to recall the epidemiology, diagnosis, and treatment of pneumonia, with a focus on the impact of climate change and related risk factors on acute low tract respiratory infections.

**Keywords:** pneumonia, risk factors, climate change

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## **1. Introduction**

Pneumonia is a challenging health concern worldwide and more acutely in developing world, where healthcare facilities are less available. It is a leading cause of mortality due to infectious agents. Insufficient or inappropriate treatment contributes to the emergence of pathogen resistance to antibiotic or increased mortality. A recent report from UNICEF shows 1.4 million deaths per year among children attributable to pneumonia and diarrhea [1]. Both killers remain major contributors to child mortality worldwide, and could be fueled by climate change and related environmental deleterious effects. Pneumonia, a common lower respiratory infection accounted for 2.7 million deaths worldwide [2]; being the leading cause in children under 5 years, adults over 65 years, and immunocompromised subjects [3].

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According to the setting of occurrence, pneumonia is characterized as community acquired (CAP) or nosocomial, the latter occurring in the hospital after at least 48 h of admission or in a patient who has been hospitalized within the last 3–6 months and received antimicrobial treatment. Hospital-acquired pneumonia (HAP) includes really hospital acquired, ventilator-acquired pneumonia (VAP), and healthcare-associated pneumonia (HCAP) with extension to disease affecting patients in nursing homes and in dialysis services [4].

CAP represents a disease contracted out of the hospital, in the community. Clinical features allow the categorization in classic pneumonia due to bacteria such as *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, *Staphylococcus aureus*, and viruses such as respiratory syncytial virus (29%) and influenza virus (17%); most prevalent in children and influenza virus most common in adults [4]. Atypical pneumonia results from the infection with intracellular bacteria such as Chlamydia and Mycoplasma. Nosocomial pneumonia may affect ventilated patients or not and the former group is identified as ventilator-associated pneumonia (VAMP) with a greater risk of multidrug resistance and subsequent poor prognosis. Pneumonia in the immunosuppressed host is a severe form of the disease, which may affect individual whatever the setting, with a poorer prognosis due to the underlying immune status.

Many traditional risk factors have been previously identified including extreme age (children under 60 months and adults aged  $\geq 65$  years), poverty, and comorbidities. Malnutrition, low birth weight, nonexclusive breast-feeding, lack of measles vaccination, outdoor and indoor air pollution and crowding, mother's education, parental smoking, vitamin A and/or zinc deficiencies are thought to influence children susceptibility to infections in developing countries. Possible additional risk factors thought to increase the susceptibility to respiratory infections and allergic diseases include climate change with the potential of affecting dispersion, timing, and quality of aeroallergens and the lifecycle of some vectors of diseases, high altitude, humidity, and concomitant diseases [5, 6].

This chapter aims to recall the epidemiology, diagnosis, and treatment of pneumonia, with a focus on the impact of climate change and related risk factors on acute low tract respiratory infection (ALTRI).

## 2. Climate change and respiratory health

The extent to which outdoor and indoor environments affect the respiratory health is established for chronic diseases such as asthma, COPD, and cardiovascular diseases, but less is known about the underlying mechanisms of their impact on infectious diseases of the respiratory system. Climate change is claimed to be a great global health concern. The impact of industrialization and anarchic urbanization in developing countries contributes to high production of greenhouse gases, carbon dioxide ( $\text{CO}_2$ ), methane ( $\text{CH}_4$ ), etc., which affect the earth temperature. The monthly average temperature is increasing leading to many weather-related events such as heat waves, humidity, precipitations, floods, storms, dry conditions, and wildfires, which affect differently the environment and human health between temperate and

tropical regions [7, 8]. The increased morbidity and mortality due to ALRTI in children and adults over 65 years are linked to many risk factors, the additional effect of weather change could be powered by the inadaptability of the metabolism of these vulnerable populations to heat stress and temperature variations; emphasizing the need for further research addressing health effects of climate variations. Strategies addressing climate change are getting more and more relevant to give strong support to clean environment. There is a need to better understand the underlying mechanisms of the human, animal, or plant reactions to the changing weather to develop appropriate policies with a real impact on the susceptibility of humans to deleterious effects of the phenomenon. New technologies are underdeveloped to address the physiological responses of human and animal to the environmental-induced stress and survival, relaying on DNA/RNA sequencing as reported by Biggar et al. [9]. Stress biology research will allow implementation of targeted responses to the health effects of climate change. Direct or indirect health effects act through warming temperatures with increase in atmospheric ozone, nitrogen oxide, particulate matter (PM), sulfur dioxide, and ultraviolet (UV) radiation, resulting in many conditions such as: exacerbations of chronic respiratory diseases (asthma, COPD) and respiratory infections, as well as nonrespiratory diseases including heat stress, water-borne diseases, transmittable diseases (malaria), and malnutrition.

Heat waves, floods, wildfires may influence the incidence of respiratory infection through the shift in the epidemiology of climate sensitive pathogens. The threat on global health are highlighted by many previous studies such as one report from Australia about an increased incidence in childhood pneumonia associated with sharp temperature drops from 1 day to the next [10], or the outbreak of Hantavirus, which occurred in Panama in 2000, linked to the increase in rodent population attributed to a substantial increase in rainfall [11]. A report from Japan about aspergillosis among survivors of tsunami in 2011 is one more illustration of the link between climate change and respiratory health [12].

Respiratory infection results from inhaled aerosols or hematogenous spread of pathogens. Pathogen-related compounds (virulence, concentration, survival) or host related (immunity, comorbidities, aging) play a key role in the incidence and severity of the illness. Climate alterations could impact the disease by affecting the vectors or the host immunity [13]. The seasonality of respiratory infections has been demonstrated for influenza and streptococcal pneumonia during winter months in temperate climate [14, 15]. The later study reported a 2% incidence of CAP for all overnight hospital admissions, with a significantly higher rate during winter and spring, mainly in December and January [15].

Possible explanations of the seasonality seem to be the closer contact as a result of indoor crowding, lower humidity, induced variations in the human immune responses, indoor air pollution, low exposition to sunlight and ultraviolet (UV) radiation, keeping in mind the bactericidal effect of the latter [16]. In tropical regions, climate change also affects the pattern and seasonability of infections. Temperature, moisture and dehydration, and UV light greatly influence the pathogen cycle and survival in the environment and act on the transmission of air-borne aerosols. Dry air and wind-driven atmospheric pollutants could act on mucociliary escalator of the respiratory mucosa, impairing its defense mechanisms [17], and there is evidence from animal and human

studies for the induced weaknesses of the immune system during winter [18]. Immune system is also under influence of adrenocortical hormones known to be more expressed during winter season than summer, and increased secretion of steroids is associated with immunodeficiency [19]. The rainy period is more prone to water-borne diseases such as cholera following floods and storms. The changing pattern in vector and pathogen infectivity, the low exposure to sunlight during rainy seasons, people spending more time indoor in crowded environment, with subsequent seasonal variations in vitamin D levels could explain the seasonability of infectious diseases. The deficiency in vitamin D linked to the reduced exposure of skin surface to sunlight has harmful effect on human immunity [20, 21] and could increase the vulnerability to infections, mainly in people at extreme ages.

Previous studies have emphasized the harmful role of ambient air pollution and particulate matter and the heat effect of high temperature on daily mortality [22, 23]. Climate change stands as a new health challenge for the increasing morbidity due to respiratory and cardiovascular diseases worldwide. These changes affect physical and biological systems through environmental conditions including air and water pollution, water heating, increasing the risk of transmission of water-borne pathogens. The impact of air pollution on chronic respiratory diseases such as asthma and COPD is well established. The extent to which weather patterns could influence respiratory infections is still debatable. Heat, air pollution, change in quantity and quality of aeroallergens, and shift in infectious diseases linked to changing ecology of the pathogens have been previously reported as strong risk factors affecting respiratory health. Direct health effects of climate changes include heat-related illness, exacerbations of chronic cardiorespiratory diseases such as COPD and asthma due to the changing pattern of environmental exposure [24]. Previous epidemiological studies suggest the seasonal variability of respiratory infections, but the pathobiology of this link is far from being clearly assessed. Cold and dry conditions in temperate regions power the transmission of influenza and respiratory syncytial viruses, while the wet conditions of the tropics seem to reduce the aerosol transmission of the influenza virus [25]. Studies addressing the link between climate change and pneumonia still need to be conducted worldwide, mainly in poor resource countries and also in the most affected by lack of hygiene and unpreparedness. Lower respiratory tract infections seem to be more frequent during winter in temperate areas and during rainy season in tropical regions [25, 26]. Studies in Hong Kong [27] and China [28], respectively support the impact of the changing weather pattern on the magnitude of respiratory infection and the seeking of emergency healthcare. The pattern of seasonality on viral respiratory infections has clearly been reported in temperate countries, but data from tropical regions are sparse [29]. The vulnerability of children under the tropics could be emphasized by poverty-related conditions such as malnutrition and helminth infections as well as poor access to healthcare facilities. Chronic helminth infections stimulate the T-cells to produce more Th2 type cytokines (IL-3, IL-5, IL-13) than Th-1 profile (IL-2, IFN-gamma). This imbalance could be a possible explanation for the increased susceptibility to bacterial infections in affected individuals. Lozano et al. have illustrated the negative role of air and water pollution linked to storms and floods affecting agricultural products. These authors reported an increase in pneumonia deaths in children under 5 years due to malnutrition [30]. Malnutrition predisposes to immunosuppression through lack of many elements or oligo-elements such as zinc and copper, involved in the functionality of many components of the immune system.



Biggar et al. have illustrated the relevance of studying stress biology to characterize human responses to environmental challenges [9]; the way we will act to reduce greenhouse gas emissions will really benefit to global health.

How the climate change could impact on the transmission and outcome of infectious diseases needs to be elucidated for appropriate preparedness of the healthy systems around the world. Health effects of air pollution are of concern; atmospheric pollutants in gaseous (mainly carbon dioxide, methane, nitrous oxide) or particulate forms may affect respiratory system according to their physical properties (solubility), their concentration, and the rate and depth of the ventilation of the subject. Use of biomass fuel for cooking in many developing countries increases the risk of exposure to outdoor or indoor pollution. Biologic agents such as fungi in indoor air could trigger the respiratory system through direct toxicity, infection, or induced immune hyperresponsiveness. Smith et al. have described the risk for pneumococcal infection in children living in a low air exchange rate environment in developing countries [31]. There is a body of evidence for the association between the increasing global mean temperature and increasing global mortality [32]. The heat-related risk of mortality for respiratory diseases needs to be addressed for relevant environmental measures focusing on the one health concept. Evidence of associations between outdoor heat and respiratory hospitalizations has been reported in previous studies in developed countries, but data are lacking on the harmful effects of climate change on health in developing regions, where global warming and progressive population aging are expected with the improved accessibility to ARVs and anti-tuberculosis treatments resulting in the reduction of the mortality linked to both killers. The role of sociodemographic components and low education as well as poor accessibility to healthcare in general are strong modifiers of treatment outcomes suggesting the relevance of their regular assessment as risk factors of respiratory illnesses. Along with the changing warming climate, the role of air pollution, evidenced in respiratory exacerbations of chronic diseases such as asthma, COPD, and cardiovascular diseases, following the inhalation of ozone, SO<sub>2</sub>, CO<sub>2</sub>, CH<sub>4</sub>, and particulate matters (PM<sub>10</sub>) (from increased forest fires, wild urbanization, desertification) with aerodynamic diameters <10 µm is reported in many studies [32, 33]. Greenhouse gas emissions generated by human activity are pointed as the main provider of the changing Earth's climate through thermal stress, extreme weather events, and changing pattern of infectious diseases, suggesting the urgent need to develop strategies addressing human, animals, and plants health as a whole (one health concept). The climate change is expected to affect mainly vector-borne and water-borne infectious diseases, with a potential of increasing the range in case of nonadopting early preventive and warning measures [34]. Indirect effects of increased warming include shifts in vector-borne illness, increase in allergen concentration, loss of biodiversity, degradation of ecosystem, desertification, all with a negative impact on human health. Among realistic measures to reduce climate change-related respiratory morbidity, green structures development has been considered. Whittford et al. [35] and Burgess et al. [36] have reported the environmental benefits of green spaces on the stabilization of ecological system and the reduction of the risk of respiratory mortality. These authors showed that largest patch percentage of green structures reduces the mortality of pneumonia and lower respiratory diseases through the reduction of primary and secondary air pollutants; while their fragmentation has deleterious effect by increasing the temperature

and the air pollutants. Green spaces are shown to block secondary air pollutants (ozone and PM 2.5). Rationale management of green structures needs to be encouraged in the urbanization policies among other preventive measures to improve respiratory health [37–39].

### 3. Community-acquired pneumonia (CAP): epidemiology, clinical feature, and treatment

#### 3.1. CAP: epidemiology

Community-acquired pneumonia (CAP) is still the leading cause of death attributable to infectious diseases, and epidemiological data show that its attributable mortality rate remains static or is rising, while declining for cardiovascular diseases and many cancers in developed countries [40]. Mortality in European adults varies from country to country and based on the age, it ranges from 4.5 to 5 per 100,000 in Turkey and Georgia to 30 to 35 per 100,000 in Portugal and UK [41]. Near a half of under-five deaths worldwide are due to preventable diseases including pneumonia, diarrhea, and malaria with 2.2 million deaths in children under 5 years in 2012, in Nigeria, Democratic Republic of Congo, India, Pakistan, and China [42]. The overall prevalence of CAP in Africa is unknown, due to the lack of standardized protocols and reporting. A study in Uganda reported *Klebsiella pneumoniae* as the prevalent pathogen in neonates and *S. pneumoniae* was the most common etiological agent in those aged between 3 months and 5 years [43–45].

Outcome of pneumonia is still a health concern, mainly in developing countries, despite the development of new antibacterial agents. This phenomenon relies on the emerging antibiotic resistance of the pathogen on one hand and on host-related factors (impaired immunity, poor hygiene, age, malnutrition, comorbidities) on the other. Innovative approaches through better understanding of pathophysiology of the disease and environmental changes, early diagnosis techniques, multidisciplinary approach, and host-driven measures (behavior, accessibility to health facilities) need to be developed to improve the control of respiratory mortality.

Community-acquired pneumonias is the leading cause of death due to the infectious disease in both developed and developing world [22]. Developing countries are also the most affected due to many additional conditions such as poverty, low economic access to healthcare, lack of appropriate tools for early diagnosis, many socio-cultural barriers, and the unpreparedness against environmental changes. A study from Tanzania has identified the negative role of difficult diagnoses and comorbidities in the prognosis of CAP [46]. Children under 5 years and elderly are the most vulnerable population, and 30-day mortality has not been improved since the 1950s, despite the availability of new antibiotics [47]. CAP occurs in almost 1–10 per 1000 of the adult population each year and more commonly in extreme ages. According to the WHO European region report in 2010, lower respiratory tract infections ranked fifth in the global burden disease study [30]. The same report identified infectious diseases, childhood illnesses, and maternal causes of death as accounting for 70% of the burden of diseases in sub-Saharan Africa, while representing <20% in all other countries. Even reduced compared to two decades ago, the

rate of mortality caused by diarrheal and low tract infection diseases remains high and the major cause of early deaths in the country. The big five, COPD, asthma, low respiratory tract infections, TB, and lung cancer are among the most common causes of severe illness death worldwide.

The lack of standardized protocols and regular statistic reports does not allow the assessment of accurate incidence rate of CAP across the sub-Saharan region. In Europe, this incidence rate in adults is between 1.07 and 1.2 per 1000 person year and 1.54 and 1.7 per 1000 population according to a report by Torres et al. [48]. Older age and underlying comorbidities including COPD, cardiovascular and liver diseases, diabetes, cancers as well as all causes of immunosuppression (steroids treatment, malnutrition, HIV-AIDS) affect the prognosis of the disease and this is highlighted by the CURB 65 criteria in use for assessing the severity of CAP. There is a regular increase in the incidence of CAP worldwide, may be associated to demographic changes, increasingly aging population, growing poverty, low accessibility to healthcare facilities, precarity and war displacements, smoking and alcohol consumption. It is more and more clear that air pollution and climate change play important roles in the rising morbidity and mortality related to respiratory diseases. The heat stress linked to the warming of the climate induces environmental changes allowing the emergence of new pathogens worldwide. The real involvement of these ecological modifications needs to be addressed.

### 3.2. Pathophysiology

Pneumonia could result from infectious pathogens including bacteria, viruses, fungi, and parasites, or from noninfectious agents, of physical or chemical nature (aspiration pneumonia, gas inhalation). The main route for bacterial contamination is bronchogenic dissemination following microaspiration of pharyngeal secretions. Hematogenous spread follows bloodstream invasion by pathogens; and infection could also spread from contiguous tissues. In the alveolar space, host local defenses through humoral or cellular-mediated immune responses or mechanical processes (mucociliary escalator, cough reflex) when overwhelmed, allow the infection onset. The inflammation in the lung structures results in the release of mediators and accumulation of an exudate impairing the local immune system. The thickening of the alveolocapillary membrane alters the gas diffusion, inducing hypoxemia. The mismatch in the ventilation-perfusion ratio due to the reduced minute-ventilation increases the hypoxemia. Pneumococcal carriage in the posterior nasopharynx is a prerequisite for the development of pneumonia due to *S. pneumoniae*. Human to human transmission occurs through inhaled aerosols or close contact. The virulence of the pathogen is carried by factors allowing adhesion to the respiratory epithelium and released virulence factors such as pneumolysin and neuraminidase, which can damage the lung structures. The concentration of the pathogens is also a requirement for the onset of disease. Host immunity through humoral- and cell-mediated immunity is the main way of defense. Airway epithelium secretes also lactoferrin with the potential of deprecating the pathogen from iron, and then impairing the growth of the bacteria. Lysozyme and human defensins are along with cathelicidin-related antimicrobial peptides LL-37, also involved in the lysis of bacteria [49]. The classic evolution of acute pulmonary inflammatory response will turn in red hepatization, gray hepatization, and resolution. Main causes of CAP are *S. pneumoniae*, *M. pneumoniae*, *H. influenzae*, *C. pneumoniae*, *Legionella* sp., or respiratory virus with influenza A and B, respiratory



syncytial (RSV), rhinovirus, and parainfluenza as the most encountered. Fungal infection mainly affects immunocompromised patients and parasitic infections are mainly endemic [50]. Clinical syndrome of condensation and radiological alveolar syndrome occur in few days. Pathogens implicated in nosocomial infection include a larger panel with methicillin-resistant staphylococcus aureus (MRSA), Enterobacteriaceae, and different types with a potential of resistance and difficult to treat infections.

### 3.3. Diagnosis of CAP

Patient with CAP mainly complaints of cough, fever, shivers, pleuritic chest pain of abrupt onset. Dyspnea may occur when the involved pulmonary sector is large. Sputum production is not rare, of purulent aspect or blood stained. Physical examination may reveal a condensation syndrome with focal crackles. It is of great importance to consider also extrathoracic signs (mouth, nose, ear).

History should be extended to demographic and behavioral considerations (age, gender, style and site of living) and comorbidities. CRB65, which is a clinical score for assessment of CAP is recommended in many guidelines. It includes data about confusion, respiratory rate, blood pressure, and age  $\geq 65$  years. A CRB65n score of 0 seems a patient at low risk of death and not normally requiring hospitalization.

Additional investigations are required to guide the diagnosis setting, such as inflammatory markers (leukocytosis and differential counts, ESR, CRP) and etiological identification of pathogens through conventional microbiological analyses of samples (sputum, nasotracheal aspirates, bronchoalveolar lavage), the latter could be positive in only 15% of cases. The quality of the specimen to be examined by gram stain is a prerequisite, and the sputum should contain more than 10–25 polymorphonuclear cells by microscopic screening to be suitable. Culture-based techniques are widely used for the diagnosis of pneumonia. That is the case of blood, sputum cultures, or endotracheal aspirates, which can allow pathogen identification and antibiotic sensitivity tests. Urinary antigen tests are helpful for *S. pneumoniae* and *L. pneumophila*. Molecular diagnosis tools are currently more and more used for diagnosis of infectious diseases. CRP, an acute-phase protein during acute inflammation has not proven to be accurate in differential diagnosis between bacterial or viral infections; it is nevertheless an indicator of response to the treatment. Other biomarkers are being developed, such as procalcitonin, a pro-hormone elevated in response to bacterial infections. Studies using this biomarker have not provided sufficient probes for large clinical use [51]. Otherwise, both biomarkers are useful in the assessment of response to treatment and suitability of the antibiotic prescribed.

Serological tests find applicability in the diagnosis of pneumonia due to atypical pathogens such as Chlamydia, Mycoplasma, and viral infections, not easy to identify by current culture-based techniques.

Molecular techniques are now developed ensuring an early diagnosis and sensitivity tests for resistance to treatment. Dried blood spots have been used for bacterial identification and have proven to be a useful and easily accessible tool for molecular diagnosis in poor resources countries [46]. Urinary antigen tests are available for *S. pneumoniae* and *L. pneumophila*.

Bronchoscopic aspirations are more relevant than sputum samples culture to minimize the likelihood of commensal flora.

Chest radiograph demonstrating a peripheral airspace consolidation pattern is relevant in the diagnosis of pneumonia. Lung shadowing of lobar pattern associated to air bronchogram is common, while centrilobular and peribronchiolar opacity are defining the bronchopneumonia pattern. The lower lobes are most commonly affected. Recent literature illustrates the relevance of lung ultrasound in the diagnosis of CAP. A multicenter study in 14 European centers has shown a sensitivity of 93.4% and a specificity of 97.7% in the confirmation of the diagnosis [52].

The differential diagnosis should consider all illness expressed with dyspnea such as pulmonary embolism, COPD exacerbations, bronchiectasis, exacerbation of fibrosis, or with cough and associated fever such as acute bronchitis.

### **3.4. Complications of CAP and prevention**

CAP mortality remains high despite the development of new antibiotics and new tools for early-onset diagnosis. Main complications are sepsis and respiratory failure, but about 50% of CAP mortality in the first month is due to comorbidities [53]. Respiratory infections through hypoxemia and oxidative stress are a potential determinant of cardiovascular adverse events. The underlying atherosclerosis as shown by the increased rate of inflammatory biomarkers (fibrinogen, CRP, cytokines) in infectious status may impact on prothrombotic vascular conditions and subsequent cardiovascular ischemic diseases [54, 55]. The prognosis of acute myocardial infarction, cardiac arrhythmias, and heart failure is often worsened by respiratory infections according to few previous studies [55–57].

CAP is not simply a local but systemic inflammatory response as expressed by the measurable increase in serum biomarkers such as IL-6, IL-8, and TNF-alpha. To improve patients' outcomes, preventive measures are strongly recommended such as smoking cessation interventions and accurate screening of comorbidities. About a half of CAP mortality within the first month is due to the comorbidities such as cardiovascular complications, cancer, chronic lower respiratory diseases renal failure, and infections, mainly involving the elderly [58, 59]. Cardiovascular mortality contributes for almost 30% of deaths after CAP; that is the case of myocardial infarction in a multicenter study by Lichtman et al. reporting a 7.2% of CAP in patients admitted to the hospital with an acute myocardial infarction [60]. Cardiac arrhythmias are also observed sometimes induced by the use of macrolides alone or in combination therapy [61]. Respiratory infections were more frequent (19 vs. 6%) in a comparison study of stroke patients and control [62], suggesting the comorbidity of this condition.

Empyema is a harmful complication of pneumonia occurring mostly in more vulnerable subjects (comorbidities, immune disorders).

Preventive measures through behavioral changes such as smoking cessation and vaccination in vulnerable populations such as drepanocytosis patients, COPD, renal insufficiency patients with influenza, and pneumococcal vaccines need to be largely implemented to reduce the mortality rate.

### 3.5. Treatment of CAP

Severity assessment is a prerequisite to an accurate decision for the place of care (ICU or not). Empirical antibiotic therapy is widely used in the treatment of CAP and should include pneumococcal coverage. The promptitude of the treatment (less than 8 h from diagnosis) has been shown to improve mortality rate. Few recommendations by the American Thoracic Society (ATS) emphasize the relevance of some conditions such as the severity of the pneumonia, the previous health status of the patient, the comorbidities, and a previous use of antibiotic therapy less than 3 months. The combination therapy or the monotherapy is regularly questioned, but evidence shows the superiority of the combination therapy in severe patients [57, 63, 64]. The use of pneumonia severity index and CURB 65 will help to improve the outcomes of CAP, by a relevant orientation of the patients. In ambulatory patients with mild to moderate disease, monotherapy, and mainly by oral route is a common practice. The empirical choice is the class of  $\beta$ -lactamases (amoxicillin) or macrolides in case of allergy to the former. Fluoroquinolones in monotherapy, even recommended in some developed countries such as the North America should be discouraged in the settings where TB is a great concern, because of the influence of these drugs on the delay of TB diagnosis and the lack of alternative diagnosis tools for smear-negative tuberculosis. Macrolides and doxycycline are suitable when mycoplasma or chlamydia are the suspected etiologic agents. A previous history of antibiotic therapy in the latter 3 months guides the choice for a not yet used antibiotic by the patient. This is to minimize the emergence of resistance to antibiotics. In hospitalized patients, a part from taking care of the comorbidities, monotherapy using amoxicillin-clavulanic acid may be a choice according to the severity of the illness; combination therapy of the latter with advanced macrolides (clarithromycin, azithromycin) is often recommended. In case of a risk of aspiration pneumonia (Dementia, Alzheimer, Diphtheria), the clindamycin should be added. Patients admitted in ICU need combination therapy as first choice and G3-cephalosporins; or carbapenems are regularly prescribed. The emergence of resistance is nevertheless a threat in these critically ill subjects. Adjunctive therapies in hospitalized patients include oxygen supplience if necessary, low doses corticosteroids in suspected adrenal insufficiency following the bacteremia phase may be added to improve outcomes. Nonsevere CAP could be treated ambulatory with a 7-day monotherapy with oral antibiotics. The use of pneumonia severity index and CURB 65 or serum biomarkers may improve the prognosis of the illness. Among the biomarkers, the procalcitonin has been assessed in the decision of initiation or discontinuation of antibiotic therapy in adults. The discontinuation may be applied if the PCT level after 3 days is lower than 0.25 ng/mL or as decreased by more than 80–90% relative to the initial value [65].

## 4. Conclusion

Pneumonia remains a global threat despite the development of newer antibiotics. Early diagnosis tools need to be widely available, including easily accessible molecular analyzes. The empirical antibiotic treatment should relay on site of care, severity index of the disease, comorbidities, cost effectiveness, but also on identifications of new risk factors challenging the outcomes of patients such as climate changes.

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