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A comprehensive review study on pneumococcal pneumonia and its association with global mortality and morbidity

Abstract

There are lots of microorganisms which can cause a several types of pneumonia. Pneumococcus pneumoniae is the most common bacterial cause of community acquired pneumonia in all ages; hence it is also called CAP. Pneumonia is an infection of the alveoli which lead to impairment in gas exchange. CAP is a worldwide serious health problem with high morbidity and mortality in all age groups. There are a lot of predisposing factors that is leading to the pneumococcal pneumonia which can affect several people such as aging adult or people how have certain chronic condition. The severity of symptoms of pneumococcal pneumonia is determined mainly by the immune system status of the patient. Pneumococci begin its infection by colonizing nasopharyngeal area, with the help of many proteins and enzymes. To cause pneumonia, pneumococci need to escape from defenses in the mucus. Extremes of ages are one of the main predisposing factors" either very young or very old "Any immunodeficiency may increase the chance of getting pneumonia, by allowing pneumococci to enter or by the improper response from the immune system. The treatment of Pneumococcal pneumonia can be difficult for health providers, because of the similarities between bacterial and viral pneumonia in the clinical symptoms .Pneumococcal conjugate vaccine is one of the main vaccines against Pneumococcal pneumonia which provide a high advantage for the community, like providing herd immunity. It's also well tolerated in adults and young infants. The management of the pneumococcal pneumonia is step by step, so when the diagnosis is established the next step is to decide whether the patient has a need of outpatient care, hospitalization, or admission to the ICU.

Keywords: pneumococcal pneumonia, community acquired pneumonia(CAP), lung disease

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Introduction

2,500 years ago, stated by Hippocrates [460BC–370BC][1] "When pneumonia is at its height, the case is beyond remedy if he is not purged." In Pre-antibiotic era "Pneumonia has become captain of the men of death." Stated by Dr. William Osler, the founder of modern medicine In 1928: The Greatest Discovery in the Medical Field took place by the discovery of penicillin by Alexander Fleming and the subsequent widespread use of antibiotics, penicillin revolutionized the treatment of patients with pneumococcal pneumonia, which previously had been limited to watchful waiting. Today availability of vaccination reduced the frequency of pneumonia. Many diagnostic methods and procedures are used. Despite all the advances, pneumonia remains a huge issue. Even after the introduction of fist-generation antibiotics, the mortality rate for pneumonia has not changed noticeably in the last 50 years.[1]

Morphology of *Streptococcus pneumoniae* (pneumococcus)

Gram-positive, arrowhead (lancet) shaped cells arranged in pairs and short chains. Some pneumococci are encapsulated with complex polysaccharides. Encapsulated organisms are pathogenic, while pneumococci without capsular polysaccharides are not pathogenic.[2] Pneumococcus may cause different diseases at different places, including ear infections and meningitis (Figure 1).[2]

Figure 1

Definition

Definition of pneumococcal pneumonia

A type of pneumonia that is specifically caused by the bacterium *Streptococcus pneumoniae*. Pneumonia is usually caused by infection with bacteria and less commonly viruses and fungi.[3] *Streptococcus pneumoniae* is the most common bacterial cause of community acquired pneumonia in all ages; hence it is also called pneumococcus.[4] *Streptococcus pneumoniae* reside in the pharynx (throat) of most healthy people, who do not have pneumonia. Infection regularly begins in the upper respiratory tract and then travels down into the lungs of susceptible individuals who have lowered defenses.[3]

Definition of pneumonia

In simple terms

Infection of the lung. It may affect one or both lungs.

In medical terms

Pneumonia is an infection of the functional space of the lung, otherwise known as the alveoli. The presence, growth and multiplication of foreign pathogens triggers an immune response causing accumulation of white blood cells, proteins and fluids in the alveoli which lead to impairment in gas exchange.[5]

Epidemiology

5% to 50% of the whole humankind carry *Streptococcus pneumoniae* in the nasopharynx as part of the normal flora. A person is usually infected by his own microorganism. However, it might occur after direct contact with respiratory secretions or airborne droplets from carriers. *Streptococcus pneumoniae* does not last long out of its natural habitat. There are several factors that predispose patients to pneumococcal pneumonia.[5]

Epidemiology of community acquired pneumonia (CAP)

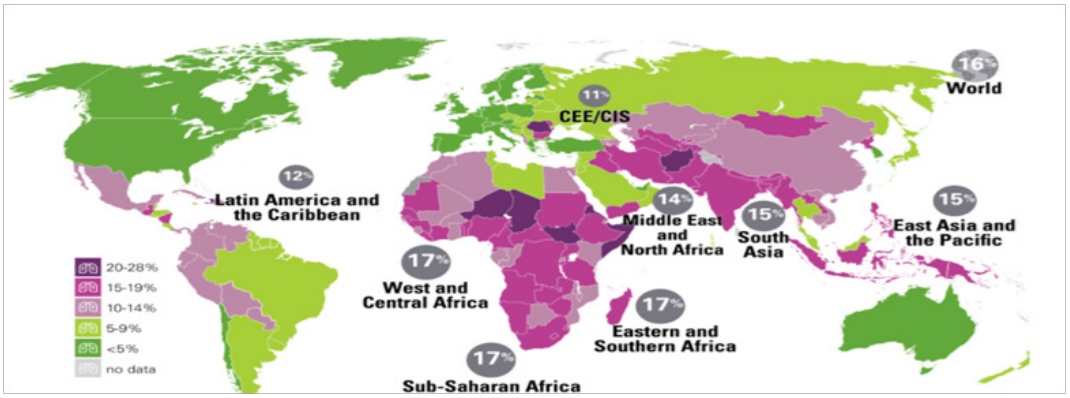
CAP is a worldwide serious health problem with high morbidity and mortality in all age groups.[6] Before the 1930s in pre- antibiotic era, pneumonia was the third leading cause of death in the United States of America.[1] Today, pneumonia remains a leading cause of death. In the U.S. in 2010, pneumonia and influenza deaths and were the ninth leading cause of death.[6] The decline in *Streptococcus pneumoniae* as a cause of community acquired pneumonia in the U.S. is due to several factors, including pneumococcal vaccines in adults, pneumococcal conjugate vaccines in children.[7] Pneumococcal Pneumonia accounts for 40,000 deaths annually in the U.S. (Table 1).[8]

Incidence of community acquired pneumonia

The incidence of CAP increases with age (14/1000 in adults aged ≥65 years), and it appears to be higher in men than in women. Also, it kills too many children.[5] Pneumonia crowned itself as the leading infectious cause of death among children under five, killing 2,500 children a day.[9] According to WHO, 1 out of 6 (16%) childhood deaths were due to pneumonia in 2015 (Figure 2) (Figure 3).[10]

Table 1 Annual child deaths from pneumonia decreased by 47 per cent from 2000 to 2015

	Deaths of children under age 5 in millions 2000	Percentage decline	Deaths of children under age 5 in millions 2015
Pneumonia	1.7	47%	0.9
Diarrhea	1.2	57%	0.5
Malaria	0.7	58%	0.3
Sepsis	0.5	25%	0.4
Pertussis, tetanus, meningitis	0.5	59%	0.2
Measles	0.5	85%	0.1
AIDS	0.2	61%	0.1



Source: WHO and Maternal and Child Epidemiology Estimation Group (MCEE) provisional estimates 2015

Figure 2 Percentage of deaths among children under age 5 attributable to pneumonia, 2015.

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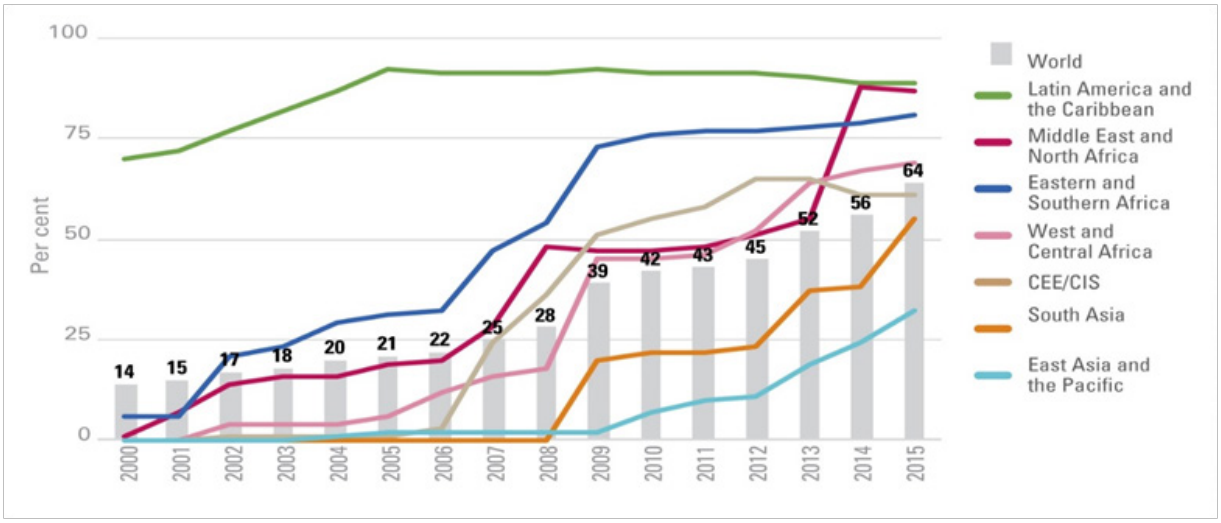

Source: WHO an UNICEF estimates of national routine immunization coverage, 2015 revision (completed July 2016)

Figure 3 Some regions have made great progress in giving key pneumonia-related vaccines to children.

Causes of pneumococcal pneumonia

There are a lot of microorganism which can cause a several types of pneumonia. The most common cause of the pneumonia is viral or bacterial cause which we take by inhaling the air or from the environment that surround us. The immunity in our body is protecting us against the microbes but if there is any defect in our immunity this microbe will penetrate the body.[11] The most common cause of bacterial pneumonia is *Streptococcus pneumoniae*. There are other types of bacteria that also can cause pneumococcal pneumonia. Such as, *Hemophilus influenzae*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Moraxella catarrhalis*. Also, *Mycoplasma pneumonia* can be a causing agent for pneumonia.[12] The distinctive feature of the *Mycoplasma pneumonia* is that produce a mild symptom compared to the other types of bacterial pneumonia. The risk of the infection is varied with age but it's greatest at the extreme of ages. Also, in the individuals who have medical comorbidity. The usual site of the *Streptococcus pneumoniae* is in the nasopharynx which will colonize it. And from the nasopharynx, pneumococci will spread directly to the lower respiratory tract by the airway which will lead to pneumonia. The *Streptococcus pneumoniae* also can cause a medical morbidity. The bacteria also can penetrate the epithelial cells which will lead to local infection.[13] There are some types of the viruses that can cause pneumonia such as the viruses that cause colds or flu. The viral infection is the most common cause of the pneumonia in children who are younger than 5 years. The most cases of the viral pneumonia have a mild symptom but, in some cases, it can be serious.[13]

Risk factors of pneumococcal pneumonia

Pneumonia can affect any one, but some people have a greater chance of developing such condition. There are a lot of predisposing factors that is leading to the pneumococcal pneumonia which can affect several people such as aging adults. These people are at risk because of the deficiency in the immunity. Also, there are other risk factors which are related to certain chronic illnesses such as heart disease, asthma, diabetes, or chronic obstructive pulmonary disease (COPD). There are other conditions that weaken the immune system such as AIDS or cancer. It's obvious that P. pneumonia occurs in the respiratory system. So, recent respiratory conditions, such as flu, can increase the risk in these people. There are other general predisposing factors such as cigarette smoking or drinking alcohol. They also can lead to this condition.[12]

Sign and symptoms of pneumococcal pneumonia

The first and the most important factor when we think about signs and symptoms is the immune system status of the patient.[12] The classical symptoms of a patient with pneumococcal pneumonia is cough, chills, high fever and usually chest pain that make the respiratory movement difficult and the patient will feel breathless.[14,15] Moreover, tachypnea and systemic toxicity follow the initial symptom onset.[15] Most patient with pneumonia have a cough but the features of the cough help us to differentiate between types of pneumonia. In-patients with pneumococcal pneumonia the cough associated with sputum characteristically rust-colored.[12] All these symptoms usually appeared with young patients. On the other hand, as the person gets older, he is more likely to develop pneumococcal pneumonia. Also, he often exhibits fewer symptoms compared to young people.[16]

Pathophysiology of pneumococcal pneumonia

Colonization

Pneumococci take a place in the nasopharynx epithelium when they enter to by nasal cavity. They protect themselves from mucus by negatively charged capsule. Many proteins influence nasopharyngeal colonization, such as: CbpA, CbpG, CbpD, and LPxTG proteins. Moreover, there are some enzymes that affect colonization by cleaving glycoconjugates. For example: NanA, BgaA, SrtH.[17]

Invasion strategy

By inhalation, many microorganisms go from upper respiratory tract to the lower respiratory tract. As bacteria go in. In the beginning of pneumonia, they need to escape from defenses in mucus. After that, entering the alveoli. Neuraminidase "NanA" cleaves mucin,

also uncovers glycoconjugates, such as N-acetylgalactosamine, on host cells that give sites for bacterial attachment. In this case, after attachment and replication of a lot of bacteria to the alveolar epithelium, the initial response of damaged host leads to manifestation of lobar pneumonia. Bacteria also release a pore-forming toxin pneumolysin, and hydrogen peroxide in abundant amounts which disrupt the alveolar epithelium and edema fluid, then accumulates in its space.[17,18]

Immune system

When alveolar epithelium is damaged, the inflammatory process takes its place and a lot of inflammatory mediators enter from the capillaries into the alveoli. White blood cells will migrate to alveoli to attack the foreign body. This process will produce many gaps in the walls of both capillaries and alveoli. As a result of that, fluid will also go inside and maybe some of the red blood cells with other inflammatory mediators. However, bacteria are still growing and changing. So, more fluid and other cells will accumulate. By the time, the wall of alveoli begins to be thick and hard for oxygen to be exchanged with blood cells. Diffusion appears to be hard, and because oxygen diffuse passively, the person will have a difficulty in breathing. Infected alveoli will not allow gas exchange, and it will be a dead space. Finally, the rate of gas exchange will decrease, Oxygen amount will be reduced in blood "hypoxia" and carbon-dioxide will be increased.

Predisposing factors

Predisposing factors of pneumonia can include age. Very young or very old people, who have chronic obstructive pulmonary disease "COPD" or chronic bronchitis. Another predisposing factor is immunodeficiency. Immunocompromised people are more likely to get it. Also, congestive heart failure, diabetes mellitus and cystic fibrosis. Moreover, alcoholics, injection drug users, and people with seizure disorder.[18]

Prevention of pneumococcal pneumonia

The treatment of Pneumococcal pneumonia can be difficult for health providers, because of the similarities between bacterial and viral pneumonia in the clinical symptoms. Although blood culture, chest x-ray, and other tests are effective to diagnose pneumonia, but it is limited by cost. Therefore, the prevention will save a lot of money and effort. In addition to the reduction of the use of anti-biotics that can create resistant strains of bacteria. Fortunately, the prevention of S. pneumonia is low-tech, cost effective and it can prevent the disease before it occurs:

Adequate nutrition helps the Immune system functioning well to protect children from S. pneumonia and other diseases, underweight children are 4 times more likely to die from pneumonia.[19] Exclusive breastfeeding during the first six months is the key component for the infant adequate nutrition. Infants who are not breastfed are twice more likely to die from pneumonia before 18 months age than those who are breastfed.[19] Pneumococcal conjugate vaccines are effective and a well-tolerated option to prevent S. pneumonia diseases among children as well as adults.

Pneumococcal vaccines

When the pneumococcal bacteria are exposed to the immune system, the immune system does not recognize the threat immediately. The delay in response gives the bacteria a chance to cause life-threatening disease, especially in the elderly and young children.[20] If a person is exposed to the same strain of S. pneumonia, the immune system will respond immediately. When a person is vaccinated against S. pneumonia, they are injected with parts of killed bacteria (antigen) to make immune memory of the bacteria so the immune system responses immediately when it's exposed to the bacteria later. There are over 90 serotypes of pneumococcus, many of them do not cause severe diseases. Almost 88% of global diseases is caused by only 23 of the 90 serotypes. Almost 11 serotypes are accounted for more than 80% of diseases in children under age of five.[20]

Types of pneumococcus vaccines

23-valent pneumococcal polysaccharide vaccine (PPV23)

The pneumovax (brand name) is a vaccine used for adults over 65 and immunocompromised children over 2 years old. It contains capsular antigens from the 23 of the most commonly encountered serotypes. But it's not effective for children under 2 years old since they have naïve immune system and they are unable to recognize the polysaccharide in the PPV23 vaccine.[3]

Pneumococcal conjugate vaccine (PCV13 and PCV10)

The 10-valent conjugate vaccine (PCV10) targets 10 different serotypes (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F). While the 13-valent conjugate vaccine (PCV13) targets 13 serotypes. (the PCV10 serotypes +3, 6A, 19A). Both (PCV10 and PCV13) are used with infants and children from 6 weeks – 5 years old, in addition the fact that PCV13 can be also used with adults over 50 years old. The PCV vaccine contains polysaccharides conjugated (attached) to a protein that is more easily recognized by the naïve immune system in young children. These vaccines produce a stronger immune response than polysaccharides vaccines. However, the current (PCV) vaccines don't cover as many serotypes as the (PPV) vaccines.[20] PCV vaccines have many advantages. It is safe and effective (proven in millions of children), well tolerated with HIV positive people, can be administered with other vaccines, well tolerated in adults and young infants and provides herd immunity.[12]

Management of pneumococcal pneumonia

When the diagnosis of CAP is established, the next step is to decide whether the patient has a need of outpatient care, hospitalization, or admission to the ICU.

Management in out patients

Previously healthy patients with low risk of drug-resistant pneumococci should be treated with a macrolide (azithromycin) or doxycycline. However, owing to increased rates of resistance, care must be used with the use of macrolides, which are not always appropriate.[21] Patients with a high risk of drug-resistant pneumococci should be treated with a fluoroquinolone (e.g., moxifloxacin), or a beta-lactam (high-dose amoxicillin or amoxicillin/clavulanic acid is preferred; alternatives include: ceftriaxone, plus a macrolide.[21] Outpatients should be advised not to smoke, to rest and to drink more than a liter of fluid daily.

Patients with comorbidities, those on immunosuppressant drugs, those who have received antimicrobials within the previous 3 months and those with other risk factors for drug-resistant Pneumococcal infection should be treated with a respiratory fluoroquinolone, or a beta-lactam plus a macrolide.[22]

Management in patients

Temperature, respiratory rate, pulse, blood pressure, mental status, oxygen saturation and inspired oxygen concentration should be monitored and reported, initially at least twice a day and more frequently in patients with severe pneumonia and in those requiring regular oxygen therapy. C-reactive protein (CRP) levels are a sensitive marker of progress in pneumonia and should be measured regularly.[23]

If patients in ICU

1st line: fluoroquinolone or combination therapy:

Treatment with a beta-lactam (preferred agents are cefotaxime, ceftriaxone, and ampicillin) plus a macrolide is recommended.

Adjunct: vancomycin or linezolid:

For hospitalized patients where community-acquired MRSA infection is suspected or confirmed, vancomycin or linezolid should be added to the empiric regimen.[21]

Supportive care:

Hospitalized patients should obtain an appropriate oxygen therapy with monitoring of oxygen saturation and inspired oxygen concentration, with the aim of maintaining SaO_2 above 92%.

If patients not in ICU

1st line: combination therapy:

In patients with risk factors for *Pseudomonas* infection, an anti-pneumococcal, antipseudomonal beta-lactam (e.g., piperacillin/tazobactam, cefepime, meropenem) should be given plus either ciprofloxacin or levofloxacin. Alternatively, the beta-lactam can be given with an aminoglycoside plus azithromycin or an anti-pneumococcal fluoroquinolone. Risk factors for *Pseudomonas* infection include recent hospitalization, residence in a nursing home, recent antibiotic use, and advanced chronic respiratory disease, including COPD and bronchiectasis. A history of *Pseudomonas* infection should also be considered.[21]

Adjunct: vancomycin or linezolid.

Supportive care.

Complications of pneumococcal pneumonia

Pneumococcal pneumonia has a various local and systemic complications. One potential complication is Bacteremia, which is the invasion of the causative agent into the blood stream. It's quite rare among patients suffering from pneumococcal pneumonia (9-18 patients per 100,000 adults). The rate is noticeably higher among pregnant women, homeless people and patients in the prison (114 for pregnant women, 267 for homeless people and 52 prisoners per 100,000 adults).[8] Patients with multi-lobar involvement have more tendency to develop Bacteremia.[24] Septic shock can follow in severe cases of pneumococcal pneumonia, which could be fatal without immediate intervention.[25]

Another common complication is the pleural effusions. They are usually sterile parapneumonic effusions. Empyema or Pyothorax, which is the presence of pus in the pleural cavity, could be a complication of pneumococcal pneumonia. Early signs of empyema are ongoing fever and continuously elevated inflammatory markers despite the appropriate antibacterial therapy. About 5-12% of the cases are complicated by empyema.[12,24] Pneumococcal infections rarely cause necrotizing pneumonia or lung abscess (localized suppurative necrosis in the lung parenchyma). Lung necrosis has been reported to be in 6.6% of the overall cases.[26,27] Some complications might occur as a result of the anti-biotic therapy. An example of such complications is the antibiotics-associated Clostridium Difficile colitis. The antibiotics use might disrupt the bowl's normal flora and cause such condition.[25]

Prognosis of pneumococcal pneumonia

The fate of a pneumococcal pneumonia infection is usually determined by three main factors. These factors are: the age of the patient, the general state of health for the patient and the setting where the treatment is held. In general, the mortality rate is less than 1% in outpatients. However, it increases to 10-15% among hospitalized patients and in ICU admission requiring patients it reaches 20-50%. Readmission of the patients suffering from pneumococcal pneumonia infection ranges from 7-12%. Exacerbation of comorbidities is responsible for readmission to the hospital.[28]

Summary and conclusion

While pneumonia is not a new disease, it was the discovery of antibiotics that made it possible to treat patients with such cases. The causative agents for pneumonia may be bacterial, viral or fungal; with the bacterial streptococcus pneumonia being the main responsible genus. The likelihood of a patient to develop pneumonia depends on several factors- such as the extremes of age, immunodeficiencies, chronic illnesses and other debilitating conditions. It may be acquired from the community, the hospital or due to immunosuppression. With the introduction of vaccines, there has been a decline in the disease's incidence. Both inpatient and outpatient modes of management are used to treat the patients; these modalities consider the patient's condition and the cause of the infection. Management covers both pharmacological therapies and supportive care. Even with today's medical advancements, pneumonia remains a disease that has not yet been eradicated. While preventive measures have reduced the overall number of people affected, it still is a leading cause of death. Therefore, it is important for medical students to be taught how to recognize it, identify its causes and manage the patients accordingly.[29–32]

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None.

Conflicts of interest

The authors declare no conflicts of interest.

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