

Pathophysiology of Community Acquired Pneumonia



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Introduction

Constant exposure to contaminated air and frequent aspiration of nasopharyngeal flora make lung parenchyma susceptible to virulent micro-organisms. Most microorganisms reach lower respiratory tract as inhaled and contaminated micro droplets. Complex interactions between virulence and quantum of aspirated or inhaled microorganisms, that arrive at lower respiratory tract, integrity of defence barriers and host immunity status, decide occurrence of pneumonia.^{1,2}

Particles with diameter more than 100 µm precipitate easily and are not inhaled. Particles larger than 10 µm get trapped in nasal secretions. Most particles increase in size due to humidification in trachea and are trapped in major bronchi.³ Particles with diameter less than 5 µm reach the alveoli. Such particles can transport a bacterial inoculum of upto 100 microorganisms depending on bacterial size. Although diameter of most bacteria is 1 µm or more, Mycoplasma, Chlamydomphila, and Coxiella are 5 to 100 times smaller.

Most Community Acquired Pneumonia (CAP) are bacterial in origin and often follow brief viral upper respiratory tract infection. In upright position lower lobes are best ventilated therefore deposition of inhaled micro organisms is higher in these lobes. Inhalation pneumonia is most often due to microorganisms (a) that can remain suspended in air so as to be transported far away, (b) survive long enough while in transit, (c) have a size less than 5 µm (d) carry a high inoculum, and (e) evade local host defence mechanisms. Infection by intracellular bacteria such as Mycoplasma pneumoniae, Chlamydomphila and Coxiella burnetii occurs through contaminated aerosol inhalation route. CAP due to Streptococcus pneumoniae, Haemophilus and gram-negative bacilli occurs through micro aspiration. Some of the important pathophysiologic modes of spread of micro organisms are summarized in Table 1.

Respiratory Defence Mechanisms

A series of immune and non immune respiratory defence mechanisms, working effectively at different levels, keep normal Lung a bacteria free zone.^{1,2}

Table 1 : Pathophysiological modes of spread

Mechanism	Examples
Aerosols Inhalation	Mycoplasma pneumoniae, Chlamydomphila psittaci, Chlamydomphila pneumoniae, Legionella pneumophila
Oropharyngeal secretions	Streptococcus pneumoniae,
Aspiration	Haemophilus influenzae, anaerobes, gram-negative bacilli
Haematogenous spread	Staphylococcus aureus
Reactivation of latent microorganisms	Mycobacterium tuberculosis, Pneumocystis jiroveci

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Some of these important respiratory tract defence mechanisms are summarized in Table 2.

Failure of these defences mechanisms and presence of certain predisposing factors render the person susceptible to infection causing CAP. Some of these conditions are described in brief as under:

- 1. Alteration of normal oropharyngeal flora.** Presence of local immunoglobulins, specially immunoglobulin A, complement, and normal flora also prevents colonization of the oropharynx by virulent micro organisms.⁴ Diabetes, malnutrition, alcoholism and other chronic systemic disorders reduce levels of salivary fibronectin and increase colonization by gram-negative bacilli.⁵ Antibiotics associated suppression of normal oral flora also facilitate colonization by resistant gram-negative bacilli.
- 2. Depressed Cough and glottis reflexes.** This may allow gastric content aspiration specially in old age, in patients with COPD, thoracoabdominal surgery or neuromuscular disease
- 3. Altered consciousness.** Healthy adults have 10 to 100 million bacteria per milliliter of oropharyngeal secretions and upto 50% of healthy adults aspirate small volumes of pharyngeal secretions during deep sleep.⁶ Oropharyngeal contents may be aspirated more often in situations like coma, seizures, cerebrovascular accidents, alcoholism and CNS depressant drugs overdose.
- 4. Impaired mucociliary apparatus mechanism.** Effective mucociliary clearance is dependent on effective ciliary motion and on physical properties of mucus. Submucosal glands and surface epithelial goblet cells produce airway surface fluid. This fluid consists of an upper layer of gel like mucin and a lower non gel liquid. The cilia beat in this special medium and propel the gel towards mouth. Protection offered by the mucus covered ciliated epithelium from larynx to the terminal bronchioles is impaired in many situations like chronic cigarette smoking, viral respiratory infections, exposure to hot/cold air or other harmful gases,

Table 2 : Respiratory tract defence mechanisms

Location	Defence Mechanism
Nasopharynx	Nasal hairs and turbinates Mucocilliary apparatus IgA secretion
Trachea / bronchi	Cough, epiglottic reflex Mucocilliary apparatus Immunoglobulin secretion (IgG, IgM, IgA)
Terminal airways / alveoli	Alveolar macrophages Pulmonary lymphatics Alveolar lining fluid (surfactant, complement, Ig, fibronectin), Cytokines (interleukin-1, tumor necrosis factor) Polymorphonuclear leukocytes Cell mediated immunity

Table 3 : Community acquired pneumonia syndromes

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- A. **Community Acquired Pneumonia (Typical)**
Streptococcus pneumoniae
Haemophilus influenzae
Streptococcus aureus
Moraxella catarrhalis
Klebsiella pneumoniae
Legionella pneumophila
- B. **Community Acquired Pneumonia (Atypical)**
- Mycoplasma pneumoniae*
 - Chlamydia pneumoniae*
 - Chlamydia psittaci*
 - Chlamydia trachomatis*
 - Coxiella burnetii*
 - Respiratory syncytial virus
 - Influenza A and B virus
 - Adenovirus
 - Parainfluenza virus
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immotile cilia syndrome, endobronchial obstruction and old age. These situations thus favour passage of microorganisms into lung parenchyma.

5. **Alveolar macrophage dysfunction.** Monocytes, after transmigration, rapidly differentiate into 'inflammatory' macrophages to supplement the activities and functions of the 'resident macrophages'. In addition to other serum constituents 1-25-Dihydroxyvitamin D₃ and Interleukin-10 are particularly capable of inducing this response.^{7,8} Alveolar macrophages are highly effective phagocytic cells capable of scavenging a wide spectrum of particulate material. Most micro organisms are rapidly broken down within the lysosomal system of alveolar macrophages. Substances incapable of such dissolution are just isolated within secondary lysosomes and reside there for remaining life-span of the macrophage. Other important microbicidal mechanisms of macrophages include Toll Like Receptor proteins, generation of reactive oxygen species and formation of nitric oxide. Chronic cigarette smoking, chronic anaemia, prolonged starvation, hypoxaemia and respiratory viral infections are known to cause alveolar macrophage impairment and assist in occurrence of pneumonia.
6. **Immune dysfunction.** Immune response is the major mode of defence against infection by pathogenic microorganisms, including those that come through, and dwell in, the respiratory tract. These immune responses depend on the specific recognition of antigens by T and B lymphocytes. Such responses are also regulated and supplemented by nonspecific inflammatory cells of the immune system, such as pulmonary dendritic cells, macrophages, neutrophils, eosinophils, and mast cells. Disorder of granulocytes, lymphocytes, congenital / acquired immunodeficiencies and immunosuppressive therapy predispose to pneumonia.

Classification of Pneumonia

Based on the anatomical part of the lung parenchyma involved, traditionally, pneumonia are classified into following three types:

Lobar pneumonia: Occurs due to acute bacterial infection of part of a lobe or complete lobe. Whole lobe is often affected as the inflammation spreads through the pores of Khon and Lambert

Table 4 : Aetiological classification of pneumonia

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- A. **Bacterial Pneumonia**
 Lobar pneumonia
 Bronchopneumonia
- B. **Viral and Mycoplasma Pneumonia**
- C. **Other Pneumonia**
 Pneumocystis pneumonia
 Legionella pneumonia
 Aspiration pneumonia
 Hypostatic pneumonia
 Lipid pneumonia
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channels. Commonly *Streptococcus pneumoniae*, *Staphylococcus aureus*, β Haemolytic streptococci and less commonly *Haemophilus influenzae*, *Klebsiella pneumoniae* are responsible for lobar pneumonia.

Bronchopneumonia: Acute bacterial infection of the terminal bronchioles characterized by purulent exudates which extends into surrounding alveoli through endobronchial route resulting into patchy consolidation. It is usually seen in extremes of age and in association with chronic debilitating conditions. Commonly Streptococci, *Staphylococcus aureus*, β Haemolytic streptococci, *Haemophilus influenzae*, *Klebsiella pneumoniae* and *Pseudomonas* are responsible for Bronchopneumonia.

Interstitial pneumonia: Patchy inflammatory changes, caused by Viral or mycoplasma infection, mostly confined to the interstitial tissue of the lung without alveolar exudates. It is characterised by alveolar septal oedema and mononuclear infiltrates. Commonly *Mycoplasma pneumoniae*, Respiratory syncytial virus, Influenza virus, adenoviruses, cytomegaloviruses and uncommonly Chlamydia and Coxiella are responsible for Interstitial pneumonia.

Clinically it is prudent to classify pneumonia according to setting in which it occurs because it helps the treating physician to give empirical antimicrobial therapy. Accordingly pneumonia may be classified as CAP (Typical and Atypical CAP), Nosocomial pneumonia, Aspiration pneumonia, Pneumonia in immune-compromised host and Necrotizing pneumonia.

Originally, classification of pneumonia into "atypical" and "typical" forms arose from the observation that clinical features and natural history of some patients with pneumonia was different compared with "typical" presentation of patients with pneumococcal infection.^{9,10} "Atypical" pneumonia syndrome was initially attributed to *M. pneumoniae*.¹⁰ Later other bacterial and viral agents were identified that could produce a subacute illness indistinguishable from that caused by *M. pneumoniae*.^{11,12} Although the terms "Typical and Atypical pneumonia" are not an accurate description of the clinical features of CAP now, the use of the term "atypical" has been retained in this article to refer to the specific pathogens listed in Table 3.

With advances in understanding of aetiopathogenesis and investigating tools, current practice is to follow aetiological classification of pneumonia as given in Table 4.

Pathologic Stages of Pneumococcal Lobar Pneumonia

In the pre antibiotic era *S pneumoniae* causing lobar pneumonia was traditionally seen to evolve through four sequential but distinct following stages:

- a. **Stage of congestion:** This stage represents early acute

inflammatory response. Affected lobe becomes red and heavy due to vascular congestion. Copious proteinaceous fluid, abundant neutrophils and many bacteria can be seen in the alveoli. This stage lasts for 1 to 2 days.

- b. **Stage of red hepatisation:** Affected lobe becomes red, firm and acquires liver like consistency. Proteinaceous fluid transforms into fibrin strands with marked cellular exudates of neutrophils. Extravasation of red cells which give red colour to consolidated lung. This stage lasts for 2 to 4 days.
- c. **Stage of gray hepatisation:** Affected lobe becomes dry, firm and gray due to lysed red cells. Neutrophilic cellular exudates decreases due to breakdown of inflammatory cells and macrophages are now seen. Micro organism load also reduces. This stage lasts for 4 to 7 days.
- d. **Stage of resolution:** Due to enzymatic action, fibrinous matter is liquefied and the lung aeration is re-establish gradually. Macrophages are the major cells in the alveoli. There is progressive reduction of fluid and cellular exudates from the alveoli by way of expectoration and lymphatic drainage leading to normal lung parenchyma in over 3 weeks.

Conclusions

Complex interactions between virulence and quantum of aspirated or inhaled microorganisms that arrive at lower respiratory tract, integrity of defence barriers and host immunity status, decide occurrence of pneumonia. Depressed cough reflex, altered consciousness, impaired mucociliary escalator system and immune suppression are important predisposing factors. Most Community Acquired Pneumonia are bacterial in origin and often follow brief viral upper respiratory tract infection. Infection by intracellular bacteria such as *Mycoplasma pneumoniae*, *Chlamydia* and *Coxiella burnetii* occurs through contaminated aerosol inhalation route, whereas CAP due to *Streptococcus pneumoniae*, *Haemophilus influenzae* and other gram-negative bacilli is due to micro aspiration. Typical CAP,

in pre antibiotic era, evolved through four sequential stages of Consolidation, Red hepatisation, Gray hepatisation and Resolution in over 03 weeks. Early antibiotic use has abrogated this duration to just few days.

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