INTRODUCTION

When the word pneumonia is used in medical practice, it almost refers to a syndrome caused by an acute or chronic infection involving the pulmonary parenchyma. Most cases are caused by microbial pathogens, usually bacteria or viruses and less often fungi or parasites. Pneumonia may also refer to inflammation involving the pulmonary parenchyma due to non-microbial causes such as chemical pneumonia. Other modifying terms are used as follows: pneumonia may be acute, sub-acute, or chronic, depending on the duration of symptoms; it may be described as bronchopneumonia, consolidated (lobar) pneumonia, interstitial pneumonia, or necrotizing pneumonia based on changes seen on chest radiography; or it may be named after the putative agent, e.g. pneumococcal pneumonia, mycoplasma pneumonia, pneumocystis pneumonia, etc. Pneumonia is also identified by the place of acquisition, e.g. community-acquired pneumonia (CAP), nursing home-acquired pneumonia, or hospital-acquired pneumonia (HAP).(1)

Pneumonia is the most important infectious disease in terms of morbidity and mortality.(2) It is estimated that in the United States of America there are 4 million cases of pneumonia per year (45.000 deaths), and worldwide there are 4400 million cases per year (4 million deaths). In the United States of America, data suggest that between 20 and 30% of all patients with a diagnosis of pneumonia are hospitalized, and that the mortality rate for this subpopulation is about 14%.The rate associated with community acquired pneumonia ranges from less than 5 % in mildly ill outpatients to somewhat greater than 12 % overall in patients who are admitted to a hospital. Mortality is even greater in patients who have severe invasive disease, which is often associated with bacteremia, and in elderly nursing home patients.(3) Mortality from pneumonia can exceed 40 % in patients who require management in intensive care unit (ICU).(4)

Classification of pneumonia

No categorization of pneumonia is entirely satisfactory (Table 1), but for descriptive purposes. The classification should be both anatomical (the terms used communicate the extent and distribution of the process in the lung or lungs) and causal (the responsible microorganism is named). When, as often the case, the infective organism is not known, it is useful to consider whether the pneumonia is CAP or HAP. It is useful to consider whether the pneumonia may have resulted from overt pharyngeal aspiration and whether it is occurring in immunocompetent or immunosuppressed patients.(1)

Table (1): Classification of pneumonia (1)

Morbid anatomist's classification
➢ Lobar Pneumonia. ➢ Segmental Pneumonia. ➢ Sub segmental Pneumonia. ➢ Bronchopneumonia.
Microbiologist's classification
➢ Bacterial Pneumonia. ➢ Non bacterial Pneumonia.
Empiricist's classification
➢ Community acquired Pneumonia. ➢ Hospital acquired Pneumonia. ➢ Aspiration Pneumonia.

The anatomical terms used indicate whether the pneumonia involves one or more entire lobes or whether the process in confined to a segment or segments. Such anatomical descriptions are in life entirely dependent upon the chest radiographic appearance, which show the extent of pneumonia more accurately than can be done by clinical examination. Bronchopneumonia was regarded as a complication of bronchitis in which the patchy inflammatory process was confined to that territory of small or terminal bronchi and the lung lobules subtended by them, hence the alternative term Lobular pneumonia. Lobar pneumonia, on the other hand, frequently occurred denovo in a previously healthy lung and was characterized by an inflammatory outpouring or exudation of fluid extending throughout most of a lobe or lobes.[(1)]

It is common place for the term lobar pneumonia to be used when there is clinical and radiological evidence of confluent consolidation occupying the greater part of one or more lobes of one or both lung. The term segmental pneumonia is used when such consolidation is not extensive enough to occupy most of a lobe but corresponds more closely to the anatomy of a bronchopulmonary segment, in one or more lobes. Where the area of radiographic shadowing is even more confined, then subsegmental pneumonia is an appropriate descriptive term, although this still implies a confluent and localized process where subsegmental shadowing is patchy and poorly localized being scattered throughout part or the whole of one or both lungs, the term bronchopneumonia remains entirely acceptable. Bronchopneumonia therefore tends to be multifactorial and pathologist commonly finds it to be bilateral and often basal. [(5)]

Epidemiology:

Community-acquired pneumonia (CAP) is defined as an acute infection of the pulmonary parenchyma in a patient who has acquired the infection in the community, as distinguished from hospital-acquired (nosocomial) pneumonia. The overall rate of community-acquired pneumonia (CAP) in adults is approximately 5.16 to 6.11 cases per 1000 persons per year; the rate of CAP increases with increasing age. There is seasonal variation, with more cases occurring during the winter months. The rates of pneumonia are higher for men than for women and for black persons compared with Caucasians. The etiology of CAP varies by geographic region; however, Streptococcus pneumoniae is the most common cause of pneumonia worldwide.[6]

In 2005, pneumonia and influenza combined was the eighth most common cause of death in the United States and the seventh most common cause of death in Canada [7, 8]. There were over 60,000 deaths due to pneumonia in the United States. Mortality is highest for CAP patients who require hospitalization, with a 30-day mortality rate of up to 23 percent in such patients. All-cause mortality in patients with CAP is as high as 28 percent within one year. Given the aging population in North America, it is expected that the burden of CAP will increase. [7]

Pathogenesis:

The lungs are constantly exposed to particulate material and microbes that are present in the upper airways and, by microaspiration, enter the lower respiratory tract. Nevertheless, the lower airways usually remain sterile because of the pulmonary defense mechanisms. These host defenses can be categorized as innate (nonspecific) or acquired (specific). The development of community-acquired pneumonia (CAP) indicates either a defect in host defenses, exposure to a particularly virulent microorganism, or an overwhelming inoculum. [8, 9]

Although microaspiration is the most common mechanism through which pathogens reach the lung, haematogenous spread from a distant infected site, direct spread from a contiguous focus, and macroaspiration are other mechanisms. [10, 11]

Virulence factors:

Some microorganisms have developed specific mechanisms to overcome pulmonary host defenses and establish infection [10]. Examples include:

- Chlamydophila pneumoniae produces a ciliostatic factor.
- Mycoplasma pneumoniae can shear off cilia.
- Influenza virus markedly reduces tracheal mucus velocity within hours of onset of infection and for up to 12 weeks post infection.
- Streptococcus pneumoniae and Neisseria meningitidis produce proteases that can split secretory IgA. In addition, the pneumococcus produces other virulence factors, including: the capsule that inhibits phagocytosis, pneumolysin, a thiol-activated cytolysin that interacts with cholesterol in host cell membranes, neuraminidase, and hyaluronidase.
- Mycobacterium spp, Nocardia spp, and Legionella spp are resistant to the microbicidal activity of phagocytes.

Predisposing host conditions:

In addition to microbial virulence factors, diseases and conditions in the host may lead to impairment of pulmonary defense and increased risk of CAP. These conditions include [12]:

- Alterations in the level of consciousness, which predispose to both macroaspiration of stomach contents (due to stroke, seizures, drug intoxication, anaesthesia, and alcohol abuse) and to microaspiration of upper airway secretions during sleep.
- Smoking tobacco.
- Alcohol consumption.
- Hypoxemia.
- Acidosis.
- Toxic inhalations.
- Pulmonary oedema.
- Uremia.
- Malnutrition.
- Administration of immunosuppressive agents (solid organ or stem cell transplant recipients, or patients receiving chemotherapy).
- Mechanical obstruction of a bronchus.
- Being elderly; there is a marked increase in the rate of pneumonia in persons ≥65 years of age.
- Cystic fibrosis.
- Bronchiectasis.
- Chronic obstructive pulmonary disease (COPD).
- Previous episode of pneumonia or chronic bronchitis.
- Immotile cilia syndrome.
- Kartagener's syndrome (ciliary dysfunction, situs inversus, sinusitis, bronchiectasis).
- Young's syndrome (azoospermia, sinusitis, pneumonia).
- Dysphagia due to esophageal lesions and motility problems.
- HIV infection (especially for pneumococcal pneumonia), viral respiratory tract infection, especially influenza; influenza can cause viral pneumonia and predispose patients to bacterial pneumonia.
- Lung cancer.
- Bronchial obstruction due to stenosis, tumour, or foreign body.

Drugs:

Several studies have suggested an increased incidence of nosocomial pneumonia when the gastric pH is increased by the use of H2 blockers, proton pump inhibitors (PPIs), or antacids. Several studies have also shown an increased risk of CAP among patients taking gastric acid-suppressive therapy, including PPIs and H2 blockers [13-15]. However, one large case-control study found an increased risk of CAP only among patients who started a PPI within the previous 30 days and particularly in those who initiated therapy within the previous 48 hours. The significance of this finding is uncertain since maximum acid-blocking effect takes at least one week to develop. [16]

In a cohort study, not only CAP, but also several other conditions that are unlikely to be caused by PPI use (chest pain, osteoarthritis, urinary tract infection), were more likely to occur in patients receiving a PPI, suggesting that confounding could be causing the observed associations.[17]

Several studies have shown an association between use of antipsychotic drugs and CAP, although the mechanism remains unclear. In one case-control study, use of antipsychotic drugs was associated with an almost 60 percent increase in the risk of pneumonia among elderly persons requiring hospitalization [18]. In another case-control study, current use of atypical (odds ratio [OR] 2.61, 95% CI 1.48-4.61) or typical (OR 1.76, 95% CI 1.22-2.53) antipsychotic use was associated with a dose-dependent increased risk for CAP compared with past use. Atypical antipsychotic use was also associated with an increase in the risk of fatal CAP (OR 5.97, 95% CI 1.49-23.98).[19]

In a case-control study that evaluated inhaled drugs as possible risk factors for CAP, patients with COPD who were receiving inhaled glucocorticoids were at increased risk for CAP (OR 3.26, 95% CI 1.07-9.98), and patients with asthma who were receiving inhaled anticholinergic agents (ipratropium bromide) were at increased risk for CAP (OR 8.80, 95% CI 1.02-75.7). It was not possible to determine definitively whether these associations were due to the inhaled drugs or to the severity of the underlying pulmonary disease. Inhaled glucocorticoids did not increase the risk for CAP among patients with chronic bronchitis or asthma. [20]

Microbiology:

There are more than 100 microbes (bacteria, viruses, fungi, and parasites) that can cause community-acquired pneumonia (CAP). Most cases of pneumonia are caused by four or five microorganisms, but the distribution of pathogens varies with the clinical setting. [21]

Streptococcus pneumoniae is the most frequently isolated pathogen. [21-27] Other common causes include respiratory viruses, Mycoplasma pneumoniae, and Legionella spp. Chlamydophila pneumoniae is often ranked as the fourth or fifth most common cause of pneumonia, but there is considerable controversy over where it fits as a cause of pneumonia given the lack of reliable diagnostic tests. The "atypical" pathogens (M. pneumoniae, Legionella spp, C. pneumoniae, Chlamydophila psittaci) are not often identified in clinical practice, because there are no specific, rapid, or standardized tests for their detection with the exception of Legionella pneumophila.[22, 23]

Influenza remains the predominant viral cause of CAP in adults. Other viral pathogens include respiratory syncytial virus (RSV), parainfluenza viruses, adenovirus, and, less commonly, human metapneumovirus (HMPV), varicella, and severe acute respiratory syndrome (SARS). [25]

Staphylococcus aureus, Enterobacteriaceae, and Pseudomonas aeruginosa are pathogens in a selected group of patients (post-influenza, prior antimicrobial treatment, or pulmonary comorbidities). In another specific group, patients admitted to the ICU with severe CAP, the predominant pathogens are S. pneumoniae, enteric gram-negative bacilli, S. aureus, respiratory viruses, Legionella spp, and Haemophilus influenza. [28]

Definitions:

Bacteria are the most common cause of CAP and have traditionally been divided into two groups, "typical" and "atypical" agents:

- "Typical" organisms include S. pneumoniae, H. influenzae, S. aureus, Group A streptococci, Moraxella catarrhalis, anaerobes, and aerobic gram-negative bacteria.
- "Atypical pneumonia" refers to pneumonia caused by Legionella spp, M. pneumoniae, Chlamydophila (formerly Chlamydia) pneumoniae, and C. psittaci; although imprecise, we use this term because of its acceptance amongst clinicians.[24]

Microbiologic diagnosis:

A microbiologic diagnosis was confirmed in 42 to 67 percent of cases of CAP in studies that used specialized tests to detect various pathogens [21, 22, 26], but in a lower percentage of cases in studies that did not used specialized tests. As an example, in a study of inpatients with CAP that used only routine cultures and urinary antigen testing for L. pneumophila, a pathogen was identified in 24 percent of patients[24]. In another study of inpatients with CAP that used only blood and/or respiratory cultures, an etiology was found in 17 percent of patients [29]. In clinical practice, an etiologic agent is identified even less frequently. In a review of 17,435 cases of CAP in the Medicare database for United States emergency departments, an etiologic diagnosis was reported in only 7.6 percent of cases [30]. It is important to note that studies that included serologic testing may have overestimated the incidence of CAP caused by specific pathogens, such as M. pneumoniae and C. pneumoni, since positive serologic results may represent recent infection rather than active infection. [21, 26]

When considering the etiology of CAP it is useful to categorize patients into those who can be treated on an ambulatory basis, those who require hospitalization, and those who require admission to an intensive care unit. The rank order of the most common causes of pneumonia varies according to the severity of illness, as illustrated in the following studies:

- In a prospective study of 507 patients treated in an ambulatory setting in Canada, the most commonly identified microorganisms were M. pneumoniae (17 percent), C. pneumoniae (14 percent), S. pneumoniae (6 percent), and H. influenzae (5 percent)[27]. Despite considerable effort, an etiologic diagnosis could not be determined in 52 percent of cases.
- In a prospective study from Spain that included 2521 ward patients with CAP, the most commonly identified organisms were S. pneumoniae (18 percent), respiratory viruses (5 percent), L. pneumophila (4 percent), and H. influenzae (2 percent)[26]. An etiology could not be determined in 59 percent of cases.
- In the same study from Spain, among 488 patients admitted to the intensive care unit, the most commonly identified organisms were S. pneumoniae (23 percent), L. pneumophila (4 percent), Pseudomonas aeruginosa (3 percent), C. pneumoniae (2 percent), and H. influenzae (2 percent). No pathogen was identified in 47 percent of patients.[24]

Epidemiologic clues:

The presenting clinical manifestations cannot reliably differentiate between different etiologies, but there are a few epidemiologic and/or clinical clues that can be helpful and must be taken into account when considering the etiology of CAP [(29)]:

- Know the local epidemiology and the patient's travel history (endemic fungi, such as Histoplasma, Blastomyces).
- Elicit history of specific exposures (Histoplasma spp and bat or bird droppings, C. psittaci and birds).
- Be aware of national and international outbreaks (influenza or SARS).
- Methicillin-resistant S. aureus (MRSA) is an increasingly recognized cause of severe, occasionally necrotizing CAP.
- MRSA and multidrug-resistant gram-negative bacilli, such as P. aeruginosa and extended-spectrum beta-lactamase producing gram-negative bacilli, should be considered in patients presenting with pneumonia who have been hospitalized for at least 48 hours within the preceding 90 days, reside in a long-term care facility, receive hemodialysis chronically, or are critically ill[(31)]. Patients who have any of these historical features (recent hospitalization, long-term care facility residence, or hemodialysis) are classified as having healthcare-associated pneumonia rather than CAP.[(29, 31)]

Bacteria:

Bacteria are the most common cause of CAP. The true incidence of these infections is uncertain because of the difficulty in distinguishing colonizing organisms from pathogens.[(26, 27)]

S. pneumoniae:

S. pneumoniae is the most common cause of CAP. Many studies have isolated the organism in only 5 to 18 percent of cases. However, the rate of isolation increases when more invasive methods are used for obtaining specimens, such as transtracheal aspiration, which eliminates contaminating oropharyngeal flora. It is currently believed that many culture-negative cases are caused by pneumococcus.[(26)]

H. influenza:

H. influenzae is an important cause of pneumonia in elderly adults and in patients with underlying pulmonary disease, such as cystic fibrosis and COPD. The clinical features are indistinguishable from CAP caused by other organisms.[(27)]

M. pneumoniae:

M. pneumoniae is one of the most common causes of atypical pneumonia in series from the United States and other parts of the world, accounting for up to 15 percent of cases of pneumonia treated in an ambulatory setting.[(27)] M. pneumoniae is transmitted from person-to-person by infected respiratory droplets during close contact. Infection rates are highest in school-aged children, military recruits, and college students. Substantial rates of macrolide resistance have been observed in certain regions, such as Asia.[(32)]

C. pneumoniae:

The incidence of C. pneumoniae in adults with CAP has varied in different studies from 0 to 20 percent [21, 23, 26], although the validity of these data is in question due to problems with diagnostic testing.[33] One problem is the use of a serologic test in many studies, which lacks both sensitivity and specificity for C. pneumoniae. In addition, positive serologic results may represent either current or past infection.[34]

Transmission of the organism is thought to be person-to-person and has been implicated in outbreaks of pneumonia in residents of long-term care facilities and military recruits. Unlike other respiratory infections, which have peak rates in the winter months, C. pneumoniae infection does not vary significantly by season. Pneumonia and bronchitis are the most common respiratory infections associated with C. pneumoniae.[35, 36]

Legionella:

Legionella accounts for 2 to 9 percent of cases of CAP. Legionella can occur as a sporadic infection or cause outbreaks. Travel-associated legionellosis is becoming more common. In most instances Legionella is transmitted to humans by inhalation of aerosols containing the bacteria. Outbreaks have been associated with exposure to a variety of aerosol-producing devices, including showers, a grocery store mist machine, cooling towers, whirlpool spas, and decorative fountains.[37]

Gram-negative bacilli:

Gram-negative bacilli, especially Klebsiella pneumoniae, Escherichia coli, Enterobacter spp, Serratia spp, Proteus spp, Pseudomonas aeruginosa, and Acinetobacter spp are uncommon causes of CAP except in patients with severe pneumonia requiring admission to an intensive care unit where, as a group, they are among the most commonly isolated organisms after S. pneumoniae.[38, 39]

- Klebsiella pneumoniae: K. pneumoniae is responsible for approximately 6 percent of cases of CAP in Asia, but is less common in other regions. K. pneumoniae must be considered as a cause of severe CAP in patients who have significant underlying disease, such as COPD, diabetes, and alcohol abuse. In a study of 112 immunocompetent patients with severe CAP, multivariate analysis found K. pneumoniae was an independent risk factor for mortality[39]
- Pseudomonas aeruginosa: Risk factors for community-acquired P. aeruginosa pneumonia include bronchiectasis (due to cystic fibrosis) and the use of repeated antibiotic courses or prolonged glucocorticoids in patients with other structural lung abnormalities, such as COPD and pulmonary fibrosis[28, 39]. Immunocompromise (neutropenia, HIV infection, solid organ or hematopoietic stem cell transplantation) and previous hospitalization are other risk factors for Pseudomonas pneumonia.
- Acinetobacter spp: Acinetobacter spp are well-recognized as pathogens causing nosocomial pneumonia. In addition, Acinetobacter baumannii is emerging as a cause of severe CAP with high mortality. Multidrug resistance is an increasing problem with Acinetobacter infection.[40]
- Moraxella catarrhalis: Moraxella is a gram-negative diplococcus that can cause lower respiratory tract infections in adults with COPD and in immunocompromised persons. In a review of 58 patients with M. catarrhalis bacteremia, 70 percent had predisposing factors, such as neutropenia, malignancy, or COPD, either alone or in

combination. Many patients with this infection are malnourished. Not infrequently, it is a copathogen.[40, 41]

S. aureus:

S. aureus pneumonia that is community-acquired is usually seen in elderly adults and in younger patients who are recovering from influenza (postinfluenza pneumonia). However, the pneumococcus remains the most frequent pathogen in this setting. [42, 43]

During the 2003 to 2004 influenza season, 17 cases of S. aureus CAP were reported to the United States Centers for Disease Control and Prevention (CDC) from nine states; 15 cases were CA-MRSA. [43] All isolates had community-associated genetic characteristics; 12 of 13 available S. aureus isolates had the Panton-Valentine leukocidin gene. Influenza virus infection was also documented in 12 (71 percent) of cases. All patients were hospitalized and death occurred in five (29 percent); four of the deaths were in patients with MRSA infection. Another outbreak of 10 cases of severe CA-MRSA pneumonia occurred in association with influenza during the 2006 to 2007 influenza season.[44, 45]

In a study of 627 patients who presented to emergency departments in 12 cities in the United States between the winter of 2006 and the spring of 2007 and who were hospitalized with CAP, S. aureus was cultured from the blood and/or respiratory tract in 24 patients (4 percent); of these S. aureus infections, 9 (2 percent) were caused by methicillin-susceptible S. aureus and 14 (2.4 percent) were caused by methicillin-resistant S. aureus (MRSA). Isolation of MRSA (as compared with any other or no pathogen) was associated with a patient history of MRSA; nursing home admission in the previous year; close contact with someone with a skin infection during the previous month; multiple infiltrates or cavities on chest radiograph; and comatose state, intubation, receipt of pressor agents, or death in the emergency department.[29]

Community-associated methicillin-resistant S. aureus (CA-MRSA) is often associated with severe necrotizing pneumonia.[42, 46-50] The tendency to necrotizing pneumonia may be mediated by Panton-Valentine leukocidin (PVL), which is typically present in CA-MRSA strains. This was illustrated in a study that compared the clinical features of 16 patients with PVL-positive S. aureus pneumonia to 36 cases of PVL-negative S. aureus pneumonia.[47] Hemoptysis was significantly associated with pneumonia in patients with PVL-positive strains compared with those with PVL-negative strains (38 versus 3 percent).[50-52]

The role of PVL was more directly demonstrated in a mouse model of acute pneumonia that included PVL-negative and PVL-positive CA-MRSA strains, as well as purified PVL; PVL alone was sufficient to cause necrotizing pneumonia.[53] PVL induced global changes in the transcriptional levels of genes encoding multiple staphylococcal proteins, including the lung inflammatory factor staphylococcal protein A. However, subsequent reports have disproven the role of PVL as a virulence factor in MRSA pulmonary infections.[54-58]

Group A streptococcus:

Group A streptococcus (GAS, S. pyogenes) can cause a fulminant pneumonia with early empyema formation even in young, immunocompetent hosts. In a prospective surveillance study for invasive GAS infection, pneumonia accounted for 11 percent of cases with a mortality rate of 38 percent compared with 26 percent for necrotizing fasciitis and 12 percent for the entire cohort of invasive disease.(59-61)

Anaerobes:

Anaerobic organisms may be the cause of aspiration pneumonia and lung abscess. However, their role in CAP is not clear since detection in routine sputum cultures is not possible. Some studies using transtracheal and bronchoscopic aspirates with quantitative cultures suggest that anaerobes may account for 20 to 30 percent of pneumonias.(62)

M. tuberculosis:

M. tuberculosis is an important cause of CAP in developing countries and in some regions of the United States. Missed diagnosis is common as illustrated in report from Baltimore in which 16 of 33 patients (48 percent) with culture-confirmed pulmonary TB were initially treated for presumed CAP.(63, 64)

Viruses:

The frequency of specific viral pathogens varies with the diagnostic study used for detection.(65) The use of the polymerase chain reaction (PCR) has increased the diagnostic yield compared with conventional tests, such as viral culture and antigen detection assays.(66, 67) As an example, in a randomized controlled trial that included 107 inpatients with CAP, real-time PCR increased the diagnostic yield compared to conventional diagnostic procedures (43 compared to 21 percent) with 26 viral etiologies identified by PCR compared to only 16 by conventional methods. In other studies that used PCR with or without other methods, viruses were detected in approximately one-third of cases of CAP in adult.(67, 68) Since respiratory virus can be present in the upper airways without causing illness, studies using multiplex PCR may overestimate the frequency of viruses as a cause of CAP. Using PCR, nasopharyngeal swabs are positive for respiratory tract viruses in 20 to 30 percent of healthy adults.(69)

Influenza remains the predominant viral cause of CAP in adults; other common viral pathogens include RSV, parainfluenza viruses, and adenovirus.(67) Other viruses that have been detected in patients with CAP include rhinoviruses, coronaviruses, and HMPV. However, in a study that used multiplex PCR, in 30 of 32 patients in whom rhinovirus or a coronavirus was implicated, another organism was also identified.(70) The most likely reason for this is that rhinovirus and coronavirus were not causing the pneumonia, but impairing upper airway defenses so that pathogens can establish themselves in the lower respiratory tract.(70, 71)

Diagnosis:

The approach to the patient with community-acquired pneumonia (CAP) begins with the clinical evaluation followed by chest radiograph with or without microbiologic testing. A systematic review highlighted the lack of sensitivity of the clinical criteria for an accurate diagnosis of CAP; even a combination of symptoms (cough) and signs (fever, tachycardia, and crackles) did not have a sensitivity above 50 percent when using chest x-ray as the standard. [(72)]

Common clinical features of CAP include cough, fever, pleuritic chest pain, dyspnea and sputum production. Mucopurulent sputum production is most frequently found in association with bacterial pneumonia, while scant or watery sputum production is more suggestive of an atypical pathogen. Although there are classic descriptions of certain types of sputum production and particular pathogens (eg, pneumococcal pneumonia and rust-colored sputum), these clinical descriptions do not help in clinical decision-making regarding treatment because they are rarely seen. Other common features are gastrointestinal symptoms (nausea, vomiting, diarrhea), and mental status changes. Chest pain occurs in 30 percent of cases, chills in 40 to 50 percent, and rigors in 15 percent. Because of the rapid onset of symptoms, most individuals seek medical care within the first few days. [(73)]

Clinical Prediction Rules For Sepsis:

Since 1987, at least 16 studies have been conducted to identify independent predictors of adverse medical outcomes for the purpose of objectively assessing the severity of illness for patients presenting with CAP. Each of these prediction rules for prognosis should satisfy rigorous quality standards for validity before widespread application to clinical decision making. The quality of these prediction rules for application in emergency department and ambulatory care settings will be reviewed using the evaluation standard described below. [(74)]

CURB-65 score:

The CURB-65 score is based upon five easily measurable factors from which its name is derived [(75)]:

- **C** onfusion (based upon a specific mental test or new disorientation to person, place, or time)
- **U** rea (blood urea nitrogen in the United States) >7 mmol/L (20 mg/dL)
- **R** espiratory rate ≥30 breaths/minute
- **B** lood pressure [BP] (systolic <90 mmHg or diastolic ≤60 mmHg)
- Age ≥ **65** years

The British Thoracic Society found a 21-fold increase in mortality in patients who had two or more of the following findings:

- Blood urea nitrogen greater than 20 mg/dL (7 mmol/L)
- Diastolic blood pressure less than 60 mmHg
- Respiratory rate above 30 per minute

The predictive value of these findings was validated in 245 patients hospitalized for CAP in the United States, 20 of whom (8.2 percent) died. The presence of all three variables predicted a nine-fold greater risk for death with 70 percent sensitivity and 84 percent specificity. These three findings plus confusion (based upon a specific mental test or new disorientation to person, place, or time) and age greater than 65 years constitute the five factors at presentation that make up the CURB-65 score, which is a prediction rule for prognosis used to determine whether a patient should be admitted to the hospital. [76]

The authors of the original CURB-65 report suggested that patients with a CURB-65 score of 0 to 1, who comprised 45 percent of the original cohort and 61 percent of the later cohort, were at low risk and could probably be treated as outpatients, those with a score of 2 should be admitted to the hospital, and those with a score of 3 or more should be assessed for care in the intensive care unit (ICU), particularly if the score was 4 or 5. [77, 78]

Among the 718 patients (mean age 64) in the derivation cohort of CURB-65, 30-day mortality was 0.7, 2.1, 9.2, 14.5, and 40 percent for 0, 1, 2, 3, or 4 factors; only a small number of patients had five factors. Similar findings were noted in the separate validation cohort. When the two cohorts were combined, the mortality rate was 0.6 percent with 0 factors (1 of 173 patients) and 1.7 percent with one factor (4 of 241 patients). The authors suggested that patients with a CURB-65 score of 0 to 1 could probably be treated as outpatients, those with a score of 2 should be admitted to the hospital, and those with a score of 3 or more should be assessed for ICU care, particularly if the score was 4 or 5. [79-81]

The Role of Biomarkers:

At present, CAP is difficult to diagnose with high sensitivity and specificity. The variable manifestations of the condition and the clinical and biochemical similarities to other, noninfective, systemic inflammatory state present multiple challenges to optimal patient management. A biomarker is defined as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention.[82]

C-Reactive Protein

C-reactive protein (CRP) and procalcitonin (PCT) are probably the two most widely used clinical tests to diagnose and manage patients with sepsis, with the exception of lactate. Elevations of both CRP and PCT were added to the updated definition of sepsis in 2003. CRP was first described in 1930, when Tillet and Francis reported that serum from individuals acutely ill with lobar pneumonia was able to precipitate a substance derived from the C polysaccharide of Streptococcus pneumoniae, which they called fraction C.[82] Importantly, they noted that when serum was taken from patients when they were acutely ill there was a strong precipitation reaction but the strength of the reaction decreased as the patients recovered. This observation suggested that this reaction could be used as a marker of disease. The investigators also reported that this precipitation reaction was not specific to pneumococcal infection but was also present in patients with bacterial endocarditis and acute rheumatic fever.[83]

It was later determined that the reactive substance being precipitated by fraction C was a protein.[84] and because this substance was present in many different infections, it could not be derived from the bacteria per se, but from the host as a result of pathologic changes induced by or associated with acute infection.[85] CRP is synthesized predominantly in hepatocytes but also in alveolar macrophages in response to a variety of cytokines, particularly IL-6.[86] CRP plays a role in immune modulation, with both pro- and anti-inflammatory effects. It has been shown to modulate the complement cascade and regulate bacterial opsonization and phagocytosis in the face of host infection.[87, 88]

The plasma half-life of CRP is about 19 hours. In healthy young adults, the normal plasma concentration of CRP is about 8 mg/L.[89, 90] During infection or acute inflammation, these values can increase by some 10,000-fold.[91] The plasma clearance of CRP is similar in healthy individuals and in those with disease, and the synthesis rate is the only significant determinant of its plasma level, making measurement of CRP levels a useful objective index of the acute phase response although its kinetics may not be as favorable as those of PCT.[92-94]

Elevations in CRP have been demonstrated in a variety of noninfectious states, including in postsurgical and postmyocardial infarction settings and in rheumatologic disease. Similarly CRP is used in gastroenterology, with high levels present in patients with acute relapses of Crohn disease. Increased serum CRP concentrations are also considered a severity marker in pancreatitis.[95, 96]

Numerous studies have demonstrated CRP levels to be elevated in sepsis,[97-101] but the data supporting its use as a diagnostic biomarker are less convincing.[102-104] The marker performs better than standard clinical parameters, such as white blood cell count and temperature, in predicting infection.[97, 105, 106] Alone and combined with five variables in a clinical prediction score, CRP had reasonable diagnostic accuracy.[105] It has been suggested that CRP may be used to follow response to antibiotic therapy, but CRP performs poorly in discriminating septic from nonseptic shock and is less accurate than PCT in differentiating SIRS (systemic inflammatory response) from sepsis.[104] Designating an appropriate cut-off (eg, > 50 mg/mL) may help to identify infection as the cause of inflammation and improve CRP sensitivity.[100]

Just as CRP's use as a diagnostic tool in sepsis has been challenged, so has its role as a prognostic measure. Numerous studies have shown CRP to be poorly predictive of outcome in sepsis.[94, 102, 107, 108] It is unclear whether significant increases in CRP occur with worsening sepsis severity. Because of the mixed results in published studies, although serial CRP monitoring may have some value in predicting infection and response to antibiotics in the ICU, its role as a singular diagnostic and prognostic biomarker in sepsis remains limited. [108]

Procalcitonin

PCT is a propeptide of calcitonin that is expressed as part of the host's inflammatory response to a variety of insults.[109, 110] Although calcitonin is a neurohormone classically produced in the thyroid and involved in calcium homeostasis, PCT is one of several calcitonin precursors involved in the immune response, acting as a so-called "hormokine" in a variety of inflammatory states. [111] PCT levels start to increase upon an infectious stimulus somewhat slowly after 2 hours and peak at 24 hours, provided no second infectious hit occurs. This response is considerably faster than that of CRP, whose levels increase slowly and only peak at 48 hours.[112] In the normal physiological condition, PCT is not released into the bloodstream and its concentration in the blood remains low (below 0.05 ng/mL); however, in severe infectious conditions, the concentration of PCT in the blood can rise above 100 ng/mL.[113]

Table 2 summarizes the findings of studies that assessed the potential of PCT in several clinical settings, such as presence and severity of a systemic inflammatory response caused by infection, differential diagnosis between infectious and noninfectious causes, and the effectiveness of measures of source control.[112]

Table (2): Potential benefits of the measurement of PCT levels.[112]

Aim of the Study	Findings
PCT levels in patients with sepsis, severe sepsis, and septic shock	PCT is significantly elevated in patients with sepsis, severe sepsis, and septic shock. Especially high concentrations were found in patients with severe stages of the disease (severe sepsis, septic shock).[101, 114-119]
PCT in severe bacterial infection	PCT levels were significantly higher in patients with severe bacterial infection[101, 114, 118, 120-125] than in those with viral and fungal infections.
PCT as a marker for effectiveness of source control and prognosis	PCT levels decline by successful measures of source control, and sustained elevated PCT levels are associated with poor prognosis. This finding was demonstrated in adult and pediatric patients with sepsis, and CAP.[111, 114, 123, 126-129]
Usefulness of PCT for antibiotic stewardship	PCT-guided antibiotic therapy may result in a 20%–70% decrease in antibiotic exposure without a negative effect on patient outcome.[130-133]

CAP, community-acquired pneumonia.

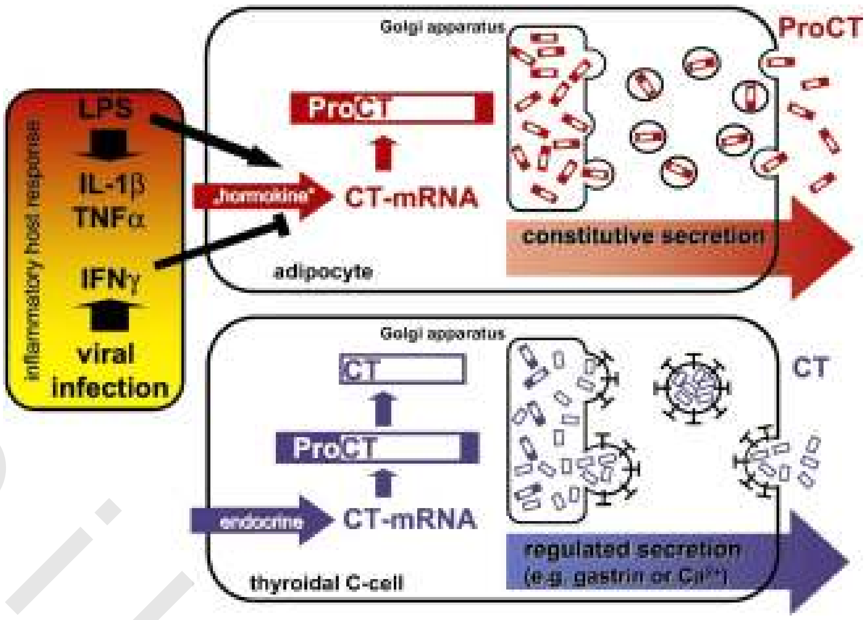

Figure (1): **Procalcitonin (ProCT) as a "hormokine".[134]** Calcitonin 1 (CALC 1) expression is restricted to neuroendocrine cells, specifically C cells of the thyroid, in the normal state. In sepsis, constitutive synthesis and release occurs in response to the host inflammatory response. (Reprinted from Ventetuolo CE, Levy MM. Biomarkers: diagnosis and risk assessment in sepsis. Clin Chest Med 2008;29(4):591-603, with permission from Elsevier.)

As shown in table 2, a growing body of literature suggests that PCT is a specific marker for severe bacterial infection[101, 114, 118, 120-125] and, in clinical context, may distinguish patients who have sepsis from patients who have SIRS. It has been shown to be superior to IL-6 and CRP in diagnosis.[114]

PCT concentrations have been correlated to sepsis-related organ failure scores[93] and may be useful in risk assessment. Higher absolute concentrations[114] and, perhaps more important clinically, persistent elevations in PCT after ICU admission have been associated with poor outcomes, distinguishing survivors from nonsurvivors.[102, 108, 129, 135] In a large, diverse cohort of critically ill patients followed serially with PCT, white blood cell counts, and CRP levels, only maximum PCT level and a day-to-day increase in PCT (≥ 1.0 ng/mL) were associated with septic episodes and independently correlated with mortality. Based on the results of several encouraging studies,[114, 118] the US Food and Drug Administration (FDA) has approved the use of PCT "in conjunction with other laboratory findings and clinical assessments to aid in the risk assessment of critically ill patients on their first day of ICU admission for progression to severe sepsis and septic shock.[107]

PCT-based treatment strategies have been used successfully in the management of lower respiratory tract infections. [113] a single-center randomized control trial in patients with severe sepsis or septic shock examined a PCT-based protocol to limit antibiotic therapy in response to baseline and serially decreasing PCT levels. The intervention group had significant reductions in antibiotic use and shorter ICU lengths of stay without increased mortality or rates of recurrent infection. It is important to realize that this study excluded patients who were immunosuppressed or had infections that warranted prolonged treatment (eg, endocarditis), which highlights the importance of using biomarkers to enhance - not replace - clinical judgment. (114)

PCT and CAP severity:

Some investigators reported that PCT levels correlate with severity of illness and prognosis in CAP (115,116). In a study involving 185 patients (144 inpatients and 44 outpatients) who had PCT levels measured within 24 h after the diagnosis of CAP, higher levels correlated with CURB-65 risk classes 3, 4, 5 than for risk classes 0, 1 and 2, also for the development of complications (PCT levels were higher for those with empyema, those receiving mechanical ventilation, and those with septic shock), and mortality (116). Interestingly, PCT levels were higher for patients with a low mortality risk (CURB-65 risk class 0, 1, 2) and CAP with a bacterial etiology than for those with a low mortality risk and no bacterial infection. This may mean that low PCT levels in outpatients could indicate that it is safe to withhold antibiotic therapy. This study accounted for confounding conditions by calculating CURB-65 for all patients. Serial measurements of PCT are reported to define prognosis for patients with severe CAP. In one study involving 110 patients who had only 1 measurement taken within 48 h after ICU admission, levels of PCT were higher in those with positive bacteriological results than in those who had negative results and were higher in those with complications (septic shock and organ dysfunction) or who died than in those without complications who survived (117).

Bolstered by these findings, the same investigative group collected serial PCT levels in 100 ICU patients with CAP on days 1 and 3 (116). Not only did nonsurvivors have significantly higher PCT levels on day 1 than did survivors, but, with serial measurement, survivors had a decrease in PCT levels by day 3, whereas nonsurvivors had an increase. Numerous clinical parameters were also measured, as well as serial levels of CRP, but, in the multivariate prediction of mortality, the relevant factors were need for mechanical ventilation , multilobar infiltrates, increasing PCT levels, and worsening of a multiorgan failure score. In addition, a low PCT level at day 3 was associated with a low mortality rate. Serial measurements of CRP did not have any predictive value in this study. (117)

From the available data, PCT seems to be the most promising biomarker for defining the need for antibiotic treatment among patients with radiographic evidence of CAP. PCT level is more valuable than other markers, such as CRP level. The basis for this value is the ability of PCT measurement to differentiate bacterial CAP (and probably CAP caused by atypical pathogens) from viral pneumonia. In addition, high PCT levels may identify patients with a worse prognosis and a greater severity of illness, as reflected by the CURB-65 score. Thus, if outcomes in a trial of treatment for CAP are examined to see the differences between 2 drugs, inclusion of only patients with high PCT levels should enrich the study population with patients with bacterial infection who could benefit from antimicrobial therapy and thus increase the validity of the measured end points. In addition, serial measurements of PCT have prognostic value and might serve as a surrogate marker for rate of clinical response to therapy. For all trials, it appears desirable to exclude patients with radiographic evidence of CAP who have a low PCT level (cut off level, 0.1 or 0.25mg/L), unless there are clinical signs of severe illness. Patients with low PCT levels are unlikely to benefit from antibiotic therapy, compared with no therapy.(99,100)

MANAGEMENT:

A major goal of therapy is eradication of the infecting organism, with resultant resolution of clinical disease. As such, antimicrobials are a mainstay of treatment. Appropriate drug selection is dependent on the causative pathogen and its antibiotic susceptibility. Acute pneumonia may be caused by a wide variety of pathogens. However, until more accurate and rapid diagnostic methods are available, the initial treatment for most patients will remain empirical. Recommendations for therapy apply to most cases; however, physicians should consider specific risk factors for each patient. A syndromic approach to therapy (under the assumption that an etiology correlates with the presenting clinical manifestations) is not specific enough to reliably predict the etiology of CAP. [(135)]

The majority of antibiotics released in the past several decades have an FDA indication for CAP, making the choice of antibiotics potentially overwhelming. Selection of antimicrobial regimens for empirical therapy is based on prediction of the most likely pathogen(s) and knowledge of local susceptibility patterns. Recommendations are generally for a class of antibiotics rather than a specific drug, unless outcome data clearly favour one drug. Because overall efficacy remains good for many classes of agents, the more potent drugs are given preference because of their benefit in decreasing the risk of selection for antibiotic resistance. Other factors for consideration of specific antimicrobials include pharmacokinetics/pharmacodynamics, compliance, safety, and cost, likely pathogens in CAP. Although CAP may be caused by a myriad of pathogens, a limited number of agents are responsible for most cases.[(136)]

Recommended empirical antibiotics for community acquired pneumonia:[(137-146)]

Outpatient treatment:

1. Previously healthy and no use of antimicrobials within the previous 3 months

- A macrolide (strong recommendation; level I evidence)
- Doxycyline (weak recommendation; level III evidence)

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 (in which case an alternative from a different class should be selected).

- A respiratory fluoroquinolone (moxifloxacin, gemifloxacin, or levofloxacin [750 mg]) (strong recommendation; level I evidence).
- A beta-lactam plus a macrolide (strong recommendation; level I evidence).

Inpatients, non-ICU treatment:

- A respiratory fluoroquinolone (strong recommendation; level I evidence)
- A beta-lactam plusa macrolide (strong recommendation; level I evidence)

Inpatients, ICU treatment:

- A beta-lactam (cefotaxime, ceftriaxone, or ampicillin-sulbactam) plus either azithromycin (level II evidence)or a respiratory fluoroquinolone (level I evidence). (for penicillin-allergic patients, a respiratory fluoroquinolone and aztreonam are recommended)

Special concerns:

If Pseudomonas is a consideration, an antipneumococcal, antipseudomonal beta-lactam (piperacillin-tazobactam, cefepime, imipenem, or meropenem) plus either ciprofloxacin or levofloxacin (750 mg).

or

The above beta-lactam plus an aminoglycoside and azithromycin.

or

The above beta-lactam plus an aminoglycoside and an antipneumococcal fluoroquinolone (for penicillin-allergic patients, substitute aztreonam for above b-lactam) (moderate recommendation; level III evidence)

If community-acquired methicillin-resistant Staphylococcus aureus (CA-MRSA) is a consideration, add vancomycin or linezolid (moderate recommendation; level III evidence)

Time to first antibiotic dose for CAP has recently received significant attention from a quality-of-care perspective. This emphasis is based on 2 retrospective studies of Medicare beneficiaries that demonstrated statistically significantly lower mortality among patients who received early antibiotic therapy. The initial study suggested a breakpoint of 8 h, whereas the subsequent analysis found that 4 h was associated with lower mortality. Studies that document the time to first antibiotic dose do not consistently demonstrate this difference, although none had as large a patient population. Most importantly, prospective trials of care by protocol have not demonstrated a survival benefit to increasing the percentage of patients with CAP who receive antibiotics within the first 4–8 h. [147, 148]