HISTORICAL REVIEW

100 years of respiratory medicine: Pneumonia

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Summary
In this review, we aim to lead the readers through the historical highlights of pathophysiological concepts and treatment of pneumonia. Understanding the aetiology, the risk factors and the pathophysiology influenced our management approaches to pneumonia. Pneumonia is still associated with significant morbidity and mortality, presents in a variety of healthcare settings and imposes a considerable cost to healthcare services. Guidelines have been issued by international and national scientific societies in order to spread the scientific knowledge on this important disease and to improve its management.

Introduction
Pneumonia has been recognized as a disease entity since remote times, with definitions of the condition traceable in ancient Greek, Roman, and Arabic writings. Definitive recognition of the etiologic role of microorganisms in pneumonia, and the identification of Streptococcus pneumoniae as the most common causative agent was only achieved roughly 120 years ago. The introduction of antibiotics has obviously modified the impact of the disease on society, but pneumonia is still associated with considerable morbidity and mortality. Over the last decade, important step forwards have been made in improving pneumonia management through the availability of scores for patient admission decisions, timing and choice of empirical antibiotic treatment, and vaccination prevention strategies. The development of international and local guidelines has helped condense the ever-expanding scientific knowledge on pneumonia into statements and recommendations of clinical use for the bedside physician. This is certainly welcome as studies indicate that patient management is amenable to improvement in aspects such as hospitalization of mild pneumonia cases with low mortality risk, lack of association between microbiological investigation and pneumonia severity, inadequate antimicrobial treatment with over-treatment of non-severe cases, and under-treatment of severe cases.1

Epidemiology and clinical presentation
Community-acquired pneumonia (CAP) is a common health problem that may still be life threatening in an age of wide availability of effective antibiotic therapy. The annual incidence rate rises from 6/1000 in the 18–39 age group to 34/1000 in people aged 75 years and over.2 Geographical variations in incidence rates are present, with, for example, lower rates being recorded in Southern Europe compared to Northern countries.3 Hospital admission is deemed...
necessary in 20–40% of cases, with 5–10% of these patients being admitted to an intensive care unit (ICU). Overall mortality from CAP is 5–10%.4

In addition to increasing age, comorbidities have long been recognized as risk factors for CAP.2 Currently identified risk factors for CAP include male sex, chronic obstructive pulmonary disease (COPD), cigarette smoking, heart disease, occupational dust exposure, and single marital status.6

Up until the early 1940s textbooks of medicine recognized that pneumonia could present only as lobar pneumonia or bronchopneumonia, with the small residue dubbed as “unresolved”. Pneumonia has largely changed its character from the old classical lobar pneumonia to “atypical” clinical and radiological descriptions.7 In a case series in the 1950s, Wingfield6 found “atypical” lobar or lobular consolidation in over 50% of patients, with classical lobar pneumonia in less than 10% of cases.

As from the 1980s, the classification of pneumonia based on lists of different pathogens was abandoned in favour of a more practical classification that helps to guide investigation, management and therapy: CAP,9 hospital-acquired (or nosocomial) pneumonia,10 and pneumonia in the immuno-compromised host.11

Common clinical symptoms of CAP include cough, fever, chills, fatigue, dyspnea, rigor, and pleuritic chest pain. Cough may be persistent and dry, or it may produce sputum in no more than 50% of patients. Other presentations may include headache and myalgia. Physical examination may reveal dullness to percussion of the chest, crackles or rales on auscultation, bronchial breath sounds.

Etiology

Most studies investigating the microbiological causes of patients with CAP involved cases admitted to hospital, with only a limited number of studies have investigated etiology of CAP in the community. However, available information regarding mild CAP suggests that overall microbial etiology is not substantially different from that of hospitalized patients, with few important exceptions.12

Analysis of CAP etiologic studies reveals variations in terms of the frequency of individual microorganism, probably related to differences in studied populations (associated with age or other risk factors), geographical area, and the presence of intercurrent epidemics. Results may also be biased by the use/non-use of specific samples and microbiological methods, or primary attention devoted to particular agents (e.g. viruses or intracellular bacteria).

Regardless of the extent of microbiological investigation, diagnostic yield in CAP rarely reaches 60% of cases. Therefore, in all studies, the most frequent category includes cases with no pathogen identified. This finding is probably attributable to multiple factors including presence of organisms undetectable by conventional microbiological methods, ambulatory antibiotic pretreatment, presence of as yet unknown microorganisms, and non-infective diseases that mimic pneumonia. Age ≳ 70 years, and presence of cardiac or renal comorbidity have been identified as factors associated with undetermined etiology.13 Interestingly, the introduction of sensitive new diagnostic techniques does not appear to associate with a meaningful increase in diagnostic yield compared to the etiologic determination rates of 40 years ago.14

Etiology of out-patient pneumonia

It has been estimated that 50–80% of pneumonia cases may be treated outside the hospital and this group therefore constitutes the majority of patients with CAP. The most important pathogens causing pneumonia in this setting are Streptococcus pneumoniae, intracellular bacilli such as Mycoplasma pneumoniae and Chlamydia pneumoniae, followed by Haemophilus influenzae.15–20 Streptococcus pneumoniae is more common among older patients or those with underlying disease whereas M. pneumoniae is more often detected in patients younger than 50 years and without important comorbid conditions.21 Viruses are reported to be involved in 5–20% of cases, either as sole pathogens or as part of a mixed infection. Influenza viruses are the agents most commonly associated with pneumonia.22 Unlike adults, approximately 60% of lower respiratory tract infections may be viral in origin in children. Incidence varies in different age groups, reaching as much as 80% during the first years of life and up to school age, and thereafter decreasing to 40–50%. In many cases viral infections are complicated by superimposed bacterial involvement. Metapneumovirus is a recently described paramyxovirus, which appears to be a potentially important viral respiratory tract pathogen, causing pneumonia in both adults and children.23 M. pneumoniae may present cyclic epidemics every 4–7 years during which a peak incidence of 30% may be reached, with more sporadic cases being registered at other times.24 This agent is also particularly common in younger individuals, and may be among the most common bacteria in adolescent/young adult populations. Staphylococcus aureus, Legionella and gram-negative enteric bacteria are uncommon in disease managed outside the hospital.

Etiology of hospital-treated pneumonia

Between 20% and 50% of patients with pneumonia are hospitalized for treatment.16 Streptococcus pneumoniae is the most commonly identified pathogen in cases of CAP, incidence ranging from 3% to 76%.25–27 Moreover, since even a single dose of antibiotic treatment prior to pneumonia diagnosis may hinder pneumococcal detection, it is felt that this organism is probably the leading cause of pneumonia of unknown etiology.28 Bacteremia may develop in 10–20% of cases, and this pathogen alone accounts for about two thirds of all cases of bacteremic pneumonia cases, with mortality rates approaching 30%,29 and rarely evolving into necrotizing pneumonia.30 H. influenzae and M. pneumoniae are frequently the second most common pathogens, and some but not all studies attribute a greater propensity for the former agent among smokers and COPD patients. C. pneumoniae accounts for 3–20% of CAP cases depending on several factors such as setting of the studied population, age group examined, and diagnostic methods used.31,32 The clinical course may vary from a mild, self-limiting illness to a severe form of pneumonia, particularly in elderly patients, and in patients with coexisting cardiopulmonary diseases. This agent is
present as part of a coinfection involving other bacterial agents in approximately 30% of cases.28

Among the most relevant differences between etiology of community- and hospital-treated pneumonia is the substantially higher incidence of L. pneumophila cases among the latter. The incidence of Legionella infection in different studies ranges from 0.5% to 6% of CAP cases in most hospital-based series.13

Etiology of severe pneumonia
A limited number of episodes of CAP (roughly 2% of all cases) are sufficiently severe to require admission to an ICU. Along with Streptococcus pneumoniae, Legionella spp. are identified consistently as among the most common causative agents of severe CAP, particularly among patients sufficiently severe to require intubation.34–37 Legionella was 1 of 2 major respiratory tract pathogens in patients with CAP who required admission to the ICU, according to 7 of 9 recent reviews.38 In terms of frequency, Streptococcus pneumoniae and L. pneumophila are followed at a distance by Staphylococcus aureus and gram-negative enteric bacteria, particularly Pseudomonas aeruginosa.39 Aspiration pneumonia is a common cause of severe pneumonia, particularly among alcoholics, injections drug abusers, persons with poor dental hygiene and the elderly. Etiology is generally polymicrobial with both Gram-positive and Gram-negative anaerobes playing a leading role in this form of pneumonia.40 Viral infections are uncommon, and are mostly due to influenza virus with bacterial Streptococcus pneumoniae or Staphylococcus aureus superinfection.

Etiology of nursing home-acquired pneumonia
Elderly residents of long-term care facilities have been found to have a particular spectrum of pathogens. In a study of 104 patients age 75 years and older with severe pneumonia, El-Solh found Staphylococcus aureus (29%), enteric gram-negative rods (15%), Streptococcus pneumoniae (9%), and Pseudomonas species (4%) as the most frequent causes of nursing home-acquired pneumonia.37 In another study of 52 long-term care residents aged 70 years and above who failed to respond to first line antibiotics, MRSA (33%), gram-negative enterics (24%), and Pseudomonas species (14%) were the most frequent pathogens isolated by invasive diagnostics (bronchoscopy).41 In the latter study, 72% had at least two comorbidities whereas 23% had three or more.

Mixed infections
Mixed community-acquired lower respiratory tract infections are more common than previously recognized.42,43 In the setting of pneumonia, polymicrobial infections are present at all ages, although there may be important differences. In children mixed viral–bacterial are highly prevalent, with an increase in bacterial-atypical bacterial co-infections after school-age that appears to persist into adult-hood. Elderly patients, on the one hand are at risk for Gram-negative and anaerobic polymicrobial aspiration pneumonia, and on the other are more prone to bacterial superinfections following influenza infection. Presentation characteristics do not help to distinguish between monomicrobial and polymicrobial infections, although the latter tend to be associated with greater underlying diseases and may be linked to a more severe clinical course.

Streptococcus pneumoniae is the leading pathogen in the etiology of CAP. It is important to bear in mind that between 16% and 45% of pneumococcal infections are mixed, generally involving an atypical bacteria or a virus. The potential importance of mixed infections is highlighted by recent retrospective studies showing that combined antimicrobial therapy that includes a macrolide, given empirically, may reduce mortality associated with bacteremic pneumococcal pneumonia.44 Recent treatment recommendations have incorporated the idea that atypical pathogen infection should be considered in all patient groups, sometimes in the form of mixed infection.

The observed rate of mixed viral–bacterial infections in pneumonia may also lead to treatment considerations. In individual patients during influenza epidemics, use of rapid detection techniques such as real-time PCR may allow the use of effective neuraminidase inhibitors such as oseltamivir and zanamivir with 36–48 h of symptom onset, thus reducing the emergence of secondary bacterial complications (including pneumonia) by up to 50%.45 On a larger scale, the known association between influenza and excess mortality for pneumonia underscores the importance of widespread influenza vaccination in eligible patients as this has shown to reduce pneumonia hospitalizations and deaths.46

Diagnostic methods
The traditional microbiological approach to CAP relies on staining or culture of easily obtainable samples such as respiratory secretions, blood or pleural fluid. Up to about 30 years ago, additional culture methods such as mouse intraperitoneal homogenized sputum inoculation were still in use.14 Serological determinations are the basic method to identify atypical bacterial and viral pathogens difficult to grow in culture. The results of applying the above techniques is far from optimal, with etiologic diagnosis being reached in a minority of cases.13 The results of diagnostic procedures such as microbiological cultures or serological tests have delays of days to weeks and are therefore not suitable guides to therapy in an early stage of the disease. Concerns regarding low yield, expenses, and delay in response have raised questions on the cost-effectiveness of systematic use of microbiological testing in patients with pneumonia. Furthermore, studies disagree about the impact of laboratory based microbiological testing on the outcome of CAP.47,48 Introduction of novel techniques such as urinary antigen detection and nucleic acid amplification tests allows rapid identification of a number of causative agents, but further effort is needed to identify rapid (almost instantaneous), easily performed, accurate, cost-effective diagnostic tests.

There is considerable debate as to the extent of microbiological work up that should be undertaken in patients presenting with CAP. Arguments against microbiological studies include the low yield in many reports, and the evidence that, even in patients with severe CAP, outcome is not improved by establishing a specific etiologic diagnosis.49 On the other hand there is a perception that the quality of microbial studies in the context of pulmonary infections has
declined substantially in the current era compared to 3 decades ago, and this poses questions on whether this change is acceptable or reversible.50 There are a number of potential advantages in endeavoring to identify causative agents, for individual patients, society, and in economic terms.51 Nonetheless, performing diagnostic tests should not result in the delay of initiation of appropriate therapy as an increased 30-day CAP mortality was registered when administration of the first dose of antibiotic was delayed more than 8 h from the time of arrival in hospital, and antibiotic treatment prior to 4 h following admission reduces length of hospital stay.52,53

Recent guidelines have provided a series of recommendations that constitute a reasonable framework for microbiological investigations in CAP patients.54–57 All guidelines recognize that the extent of microbiological work up should vary according to the site of management of CAP, with cases managed in the community requiring minimal assessment compared to hospitalized patients, and subjects with severe pneumonia admitted to the ICU deserving maximal efforts to achieve etiological diagnosis. The Infectious Diseases Society of America (IDSA) guidelines54 place a greater emphasis on the identification of the responsible agent to guide antibiotic therapy as compared with other international guidelines.55,56

In general terms, outpatients with CAP should have a chest radiograph (whenever possible), but sputum culture and Gram stain are generally not required outside epidemiological surveys. Sputum examination may be considered in patients who do present purulent sputum, particularly if they do not respond to empirical antibiotic treatment.

All hospitalized patients with CAP should undergo chest radiography, routine blood chemistry and blood counts, and blood gas analysis. All guidelines recommend two sets of blood cultures. Blood cultures have a low sensitivity and a high specificity, and are positive in about 4–18% of untreated CAP patients, most commonly associated with severe illness.58 The yield is generally greater if the blood specimen is collected prior to the patient having received antibiotic treatment.59 Assessment of specific factors associated with greater likelihood of positive blood culture may reduce the overall burden of tests performed with little negative impact on the diagnostic yield.60 Gram stain and culture are advised if the patient is able to expectorate purulent samples and has not received prior antibiotic therapy.61,62 This is particularly true if a drug-resistant pathogen, or an organism not covered by usual empiric antibiotic treatment, is suspected. Although sputum testing cannot be used to focus initial empiric antibiotic treatment, it may be used to redirect treatment once results have been obtained. The pneumococcal urinary antigen assay is considered an acceptable test to augment standard diagnostic methods for Streptococcus pneumoniae detection.63 Similarly, testing for Legionella is considered appropriate in hospitalized patients with enigmatic pneumonia, or unresponsive to β-lactam treatment.64 A very recent study found that addition of rapid urine antigen tests for Streptococcus pneumoniae and L. pneumophila increased the diagnostic yield by 17.8%.65 Thoracentesis should be performed in the presence of significant pleural effusion, with stain, culture, pH, and leukocyte count.66 There is some debate as to how extensively serology should be applied to hospitalized patients. Serologic determinations for C. pneumoniae, M. pneumoniae, and L. pneumophila may be considered in patients unresponsive to β-lactam treatment, during outbreaks, or when there is strong suspicion of an “atypical” pathogen on clinical radiographic, or epidemiological grounds.

In severe CAP cases, subjects requiring admittance to an ICU, or those failing initial empiric antibiotic all the following are recommended: blood culture, respiratory sample Gram stain and culture, thoracentesis. On the basis of local availability pneumococcal and Legionella urinary determinations should be performed together with serological testing for atypical pathogens and viruses. In this setting addition of invasive techniques such as bronchoscopy (protected brush specimen and bronchoalveolar lavage)67,68 or transthoracic needle aspiration,69 depending on local expertise, may be of use.

**Hospital admission**

The decision whether outpatient or inpatient management is needed for a patient with CAP is of primary importance. Hospital admission requirements depend on many possible variables including disease severity, coexisting illness, risk factors, adequate family support/home facilities, and patient compliance to treatment. Recently, two main tools have been put forward to objectively assess pneumonia severity and guide admission decisions.

The pneumonia severity index (PSI) was developed in the United States and validated on over 38,000 patients.70 The system was primarily developed to detect patients with low mortality risk who could be safely treated as outpatients. Patients with CAP are stratified into one of five categories with a score system based on age, presence of coexisting illnesses, and vital signs. Patients in classes I–III present a low mortality risk (<3%), whereas classes IV–V have a high mortality risk (8–30%). These finding have been extrapolated to guide hospital admission decisions, with inpatient treatment suggested for higher mortality PSI classes. Application of this score system has been shown to reduce avoidable hospital admission without increasing mortality.71 A number of limitations have been recognized. Age affects overall score very heavily, potentially underestimating need for hospitalization in younger patients. The score may also overestimate the need for hospitalization and use of expensive resources by a heavy emphasis on age and coexisting illnesses rather than on severity features of pneumonia. A total of 20 variables are involved in generating the score, making the system rather cumbersome and unfit for rapid mnemonic recall at the patient bedside.

The British Thoracic Society guidelines advocate the use of a clinical score that identifies of a limited number of variables (three clinical, one laboratory) recognized as strong adverse prognostic factors for pneumonia. The factors include age over 65, mental confusion, elevated urea nitrogen, and respiratory rate > 30 breaths per minute, condensed in the acronym CURB-65. Patients who do not present any of the factors have been shown to have a mortality risk close to 1%, and may be considered for outpatient management, whereas presence of two or more adverse factors suggest the need for hospital admission.72,73
The CURB-65 scoring system is undoubtedly simpler than the PSI and measures pneumonia disease severity more directly. However, some adjustment must be made for the presence of comorbidities, not directly accounted for by the score. It has been suggested that both systems should be used conjunctly. Either can successfully define low risk patients not requiring hospitalization. In addition to the PSI, vital sign and CURB-65 severity evaluation should be added. When employing the CURB-65, an assessment of comorbid illness and its stability should be added.\(^{74}\)

**Antibiotic treatment**

Recent international guidelines have provided a framework for initial empirical antibiotic selection in patients with CAP.

For outpatients with pneumonia, North American guidelines suggest the use of a macrolide, doxycycline, or a fluoroquinolone agent, as appropriate empiric outpatient treatment for low-risk patients (i.e., otherwise young healthy individuals). Alternatives to these agents in low-risk patients are amoxicillin/clavulante and some second-generation cephalosporins (e.g., cefuroxime, cefpodoxime, or cefprozil).\(^{54,56}\) Recent European guidelines on lower respiratory tract infection suggest tetracycline and amoxicillin are antibiotics of first choice. In case of hypersensitivity a newer macrolide like azithromycin, roxithromycin or clarithromycin is a good alternative in countries with low respiratory tract infection suggest tetracycline and amoxicillin/penicillin or moxifloxacin as alternative monotherapy. In patients with risk factors for fluoroquinolone (levofloxacin, moxifloxacin) as alternative in) plus a macrolide are suggested, with a respiratory combination of an antipseudomonal cephalosporin or acylureido-monothiazine. Generally an association between guidelines from both sides of the Atlantic is more consistent. Generally an association between a beta-lactam (amoxicillin, amoxicillin/clavulanate, non-antipseudomonal II or III generation cephalosporin) plus a macrolide are suggested, with a respiratory fluoroquinolone (levofloxacin, moxifloxacin) as alternative monotherapy. In patients with risk factors for *P. aeruginosa* pneumonia, combination therapy is generally advocated, involving an antipseudomonal cephalosporin or acylureido-penicillin/β-lactamase inhibitor or carbapenem, together with ciprofloxacin.

**Future strategies**

Current treatment of pneumonia is largely based on timely prescription of adequate antibiotic therapy. However, antimicrobial treatments are hampered by the ever-increasing problem of resistant strains, and the prospects for future antibiotics preparations are gradually slimming. Alternative strategies are therefore needed based on a better knowledge of microbial pathogenetic mechanisms and a more complete comprehension of host defense systems.

The complexity of the mechanisms and mediators involved in inflammation and infection is increasingly being unraveled, and the genetic regions controlling these factors have been partly elucidated. Soluble and membrane-based receptors have been identified that are capable of recognizing non-mammalian microbial motifs and mobilizing close to instantaneous inflammatory reactions towards infection. An increasing number of peptides exerting antimicrobial activity are being recognized in airway secretions, associated with chemokines, cytokines, proteinase inhibitors, and surfactant proteins.

Genetic polymorphisms in genes for important inflammatory molecules such as tumor necrosis factor, the interleukin-1 family, interleukin-10, and angiotensin converting enzyme, as well as molecules involved in innate immunity antigen recognition, such as the mannose-binding lectin, CD-14, and Toll-like receptors (TLRs), have been investigated as potential modifiers in the natural history of sepsis and pneumonia.\(^{75}\) Better knowledge of underlying genetic traits may help identify patients at greater risk of severe complications following infection. On the other hand, over-activation of innate immune responses may be associated with excessive inflammation and tissue damage such as may be observed in sepsis.

In the future it may be possible to modulate the innate immune response in order to downplay pathways leading to tissue inflammation while enhancing mechanisms involved in microbial elimination. Antimicrobial peptides (AMPs) present in airway surface fluid are effector molecules of the innate immunity with direct antimicrobial and mediator function. They provide an initial host defense mechanism that protects mucosal and dry epithelial surfaces of all multicellular organisms. Several diseases in humans and laboratory animals are characterized by impairment in the function of an AMP.\(^{76}\) AMPs qualify as prototypes of innovative drugs that might be used as antibiotics, anti-polyasaccharide drugs or modifiers of inflammation. Antibiotics based on these naturally occurring mammalian peptides might elicit fewer allergic reactions compared to conventional antibiotics. Synthetic analogs of AMPs may evolve into novel and independent classes of antibiotics.\(^{77}\)

Recently identified mammalian TLRs are capable of distinguishing pathogen from self-components, triggering cytokine production, and expressing co-stimulatory molecules necessary for lymphocyte activation. Central to the signaling cascade triggered by TLRs is the activation of transcription factors such as nuclear factor κB (NF-κB) and activator protein-1 (AP-1), key regulators of inflammatory and immune responses.\(^{78}\) Given their central role in activating and modulating host responses to infection, and acting as a bridge between innate and adaptive immunity, TLRs are being currently studied as potential therapeutic targets. Soluble forms of TLRs may be made to bind and neutralize natural ligands before they activate potent proinflammatory responses in the host. Alternatively, antibodies or molecules similar to natural ligands could be employed in order to bind with TLR extracellular or intracellular domains, though failing to activate intracellular signaling. This may result in inhibition of pro-inflammatory cascades initiated by TLRs, while retaining TLR-related protective responses.\(^{79}\)

Hepatocyte growth factor (HGF) is a is a heterodimeric protein produced, among others, by lung fibroblasts and macrophages, that promotes proliferation of type II epithelial cells following lung injury, restoring alveolar and bronchial epithelial integrity.\(^{80}\) Recently, HGF levels have been tested in serum and exhaled breath condensate of patients with pneumonia and other non-respiratory conditions.\(^{81}\) During the first days of the infections, pneumonia...
patients had higher HGF serum levels compared to controls, followed by a marked drop at days 4–7 that persisted up to 4–6 weeks. Conversely, exhaled breath HGF levels were also higher than controls during the acute phase, but showed non-drop through all the observation period, suggesting that local production of this factor is active during pneumonia. Future studies will be needed to determine whether local inhalation of HGF may be considered as an adjuvant treatment, particularly in severe or complicated pneumonia cases.

References


