

# Chapter 3

## Issues in Community-Acquired Pneumonia



### 3.1 Introduction

Community-acquired pneumonia [CAP] is a common infectious disease encountered in all communities of the world, most frequently affecting the very young and the elderly. It is associated with significant mortality and morbidity in severe cases and pneumonia is the third most frequent cause of death worldwide [1]. However, statistics on the global or regional incidence and economic burden of CAP is lacking. It has been estimated that 4–6 million cases of CAP occur each year in the USA and approximately 20–25% require hospitalization [2, 3]. In the USA, CAP in all ages account for about 10 million physician visits annually and 600,000–1.1 million hospitalization each year with an estimated cost of over \$17 billion annually [4, 5]. In Holland, it has been estimated that the incidence of CAP average 295 per 100,000 population per year and cost \$711 [European Union] million over 4 years, total population of 16–17 million [6]. However, this analysis only included direct costs from hospitalization and not indirect economic burden from loss of employment. Limited data is available for the incidence and economic burden of CAP in the working-age population [age 18–64 years]. In a study from the USA, the overall incidence rate of CAP in this low-risk group was 10.6 per 1000 person years and 19.5% required hospitalization [7]. The average annual incremental cost ranged from \$39,889 to \$113,837 for inpatient management of patients with CAP and from \$4170 to \$31,524 for outpatient management.

### 3.2 Airway Defenses and Pathogenesis

The nasopharynx and the normal respiratory tract provide a complex series of mechanisms to protect the lower respiratory tract from noxious agents and microbial pathogens. Initially this includes the aerodynamic barriers of the nasopharynx,

cough reflex, and mucociliary clearance of foreign material and invaders of the tracheobronchial tree. Local production of immunoglobulins [IgA, IgG, and IgE] in the mucosa of the respiratory tract provides another layer of protection against invading microbes. The relative proportion of IgA and IgG in the respiratory tract changes with the location, greater ratio of IgA to IgG in the nasal mucosa, trachea and bronchial tree and reversed ratio in the alveoli with greater proportion of IgG [8]. IgA may be more important in protecting against viral infections, as it can neutralize several respiratory viruses such as rhinovirus, influenza, and respiratory syncytial virus [8]. But it may be involved in the mechanisms of preferential bacterial adherence. Whereas, most individuals with IgA deficiency do not have increased respiratory infections, those with IgG or certain IgG subclass deficiency have recurrent respiratory infections [8].

IgG limits the invasion of microorganisms in the epithelium by opsonization and complement fixation and the concentration can increase a hundred-fold in the respiratory tract in the presence of infection and increased vascular permeability. Protection of the respiratory tract from microbial invaders is a complex process that involves many immune cells: dendritic cells, B and T-lymphocytes, neutrophils and macrophages and their secretory products [immunoglobulins, cytokines, opsonins, enzymes, and oxygen metabolites]; and nonimmune opsonins such as surfactant, fibronectin fragments, and possibly C-reactive protein [8]. Recent studies indicate that progranulin, an autocrine growth factor expressed in a variety of tissues and cell types, plays a protective role in lung immunity during bacterial pneumonia [9]. Elevated progranulin levels were observed in clinical and experimental bacterial pneumonia and it mediated host defense in both Gram-positive and Gram-negative bacterial pneumonia.

The healthy mucosa is colonized by a complex milieu of microorganisms, not exclusively aerobic and anaerobic bacteria, that probably plays an important protective role against invading pathogens. These normal microbes prevent the establishment of invading pathogenic microbes in the respiratory epithelium, the first step to induce infection. In the past decade, there has been marked interest and research on the role of the normal microbiome of the respiratory tract in health and disease. This has been facilitated by modern sophisticated, molecular, multiomics techniques. Recent studies of the human microbiome, including the respiratory tract, have demonstrated that the resident microflora is much more abundant and diverse than previously realized; including many species of nonculturable bacteria, viruses [virome], fungi, and protozoa. Present data indicate that the microbiome of the gut and the lungs are linked, by immune cells and mediators, and maybe important and associated with the pathogenesis of respiratory diseases [10–12]. The bronchial tract harbors a complex and dynamic microbial milieu of about 500 species, which overlaps with the oral microbiome [10]. The lung is also colonized by airway microbiota that resembles the microbiome of the mouth but not the nostrils at a lower density. Studies [10–12] have linked dysbiosis of the respiratory microbiome with asthma and chronic lung diseases such as cystic fibrosis, bronchiectasis, and chronic obstructive pulmonary disease [COPD]. However, there is no data as yet on association with acute pneumonia.

It is generally believed, that CAP occurs from aspiration of pathogenic microbes colonizing the nasopharynx in situations where there is defect of the normal airway defenses. Inciting factors that may play a role in the development of pneumonia include preceding viral upper respiratory tract infections [seen in nearly 50% of bacterial CAP]. These minor infections can result in defect in mucociliary function and clearance of aspirated bacteria and allow adherence of pathogens to the mucosa. It is quite possible that upper respiratory virus infections can result in dysbiosis of the commensal respiratory microbiome. Cigarette smoking can have a similar effect on airway defense and has been associated with dysbiosis of the resident microbiota.

### 3.3 Microbial Etiology of Community-Acquired Pneumonia

Although numerous microorganisms can cause lung involvement or pneumonia [estimated about 100], only several have been associated with CAP in children or adults. In clinical practice the identification of etiologic microbes in CAP is usually achieved in <30% of cases. Sputum cultures are often nonspecific and difficult to interpret because of contamination of oral-pharyngeal commensals, and blood cultures are positive in only 5–14% of adults and even less in children with bacterial pneumonia [13]. Urinary antigen detection of *Streptococcus pneumoniae* may improve the sensitivity compared to culture [70–80% sensitive], but can be false positive from colonization in children [14]. In recent years studies have applied molecular assays for viruses and bacteria for microbial diagnosis. Results have indicated that the etiology of CAP may vary with age.

In children <5 years of age CAP is most commonly due to viruses [mainly respiratory syncytial virus or RSV], especially in the absence of lobar consolidation and effusion [15]; but even with extensive testing a pathogen cannot be identified in 14–23% of children with CAP [16, 17]. In a recent study of 70 children <5 years of age hospitalized for CAP without an identifiable etiology and 90 asymptomatic controls, metagenomics [next-generation sequencing] and pan-viral PCR were able to identify a putative pathogen in 34% of unidentifiable cases from nasopharyngeal and oropharyngeal swabs [18]. Putative viral pathogens included human parainfluenza virus 4, human bocavirus, Coxsackieviruses, and rhinovirus A and C. Human bocavirus was the most commonly detected virus [19%]. It is plausible that these viruses were causing upper respiratory tract disease that resulted in CAP from bacterial pathogens. Although cultures and PCR for bacterial pathogens were obtained, endobronchial secretions were not routinely obtained. In a meta-analysis of detection of viruses by PCR in childhood CAP, the pooled incidence was 57.4% with mixed infection in 29.3% [19]. Rhinovirus, RSV, and bocavirus were the three most common viruses in childhood CAP. Respiratory viruses were detected in 76.1% of patients aged ≤1 year, 63.1% of patients 2–5 years, and 27.9% of children aged ≥6 years [19]. It was estimated that more than half the viral infections were probably concurrent with bacterial infections. The etiology inference of identifying viruses in the upper respiratory tract in children with CAP is still unclear. Although higher viral loads can

be found in children with pneumonia compared to controls with some viruses, the utility to diagnose viral pneumonia with quantitative PCR was equivocal [20].

It is still the opinion of experts that most CAP in children with radiographic alveolar infiltrate is due to bacteria, predominantly *S. pneumoniae*. Previous studies have reported an association of upper airway density of *S. pneumoniae* and pneumococcal pneumonia, and nasopharyngeal bacterial load with this pathogen is significantly higher in viral infection compared with no viral infection [21]. In a case-control study from seven developing countries, colonization density of *S. pneumoniae* in the upper airway was compared in children [ $<5$  years of age] with proven pneumococcal pneumonia and controls [22]. Pneumococcal colonization density  $>6.9 \log_{10}$  copies/mL was strongly associated with confirmed pneumococcal pneumonia, with a sensitivity of 64% and specificity of 92% but not sufficiently accurate for clinical diagnosis. The same group of investigators also assessed the colonization density in the upper respiratory tract and confirmed pneumonia with *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and *Pneumocystis jirovecii*. There was an association of colonization density [ $5.9 \log_{10}$  copies/mL] and *H. influenzae* confirmed pneumonia, with a sensitivity of 86% and specificity of 77%, but not with the other respiratory pathogens [23].

In adults, the microbial diagnosis of CAP with conventional microbiology, urine antigen detection and commercial PCR for viruses in two prospective studies in the USA have had low yield [24, 25]. Each study failed to identify a respiratory pathogen in about 55–62% of cases, pneumococci was found in  $<10\%$  of cases, respiratory viruses in 20–27%, and atypical organisms in about 5% of cases in one study [25]. A prospective study of 505 hospitalized patients with CAP in the Netherlands, using similar investigative techniques but added real-time PCR for “atypical organisms” [*Mycoplasma pneumoniae*, *Legionella pneumophila*, *Coxiella burnetii*, and *Chlamydophila* sp.], identified *S. pneumoniae* in 25%, *C. burnetii* in 6%, *H. influenzae* in 5%, and atypical bacteria including *Legionella* in 9% [26]. Some European studies have used advanced microbiological techniques with identification of pneumococcus in 30–64% of cases and identification of a pathogen in 63% of cases [27, 28]. In Norway, bacterial etiology was found in 47% and viruses in 34%, including viral–bacterial coinfections [28]. A prospective study from China, beside viral culture and nucleic acid amplification assessed paired sera for antibody response, and viral etiology was established in 34.9% of CAP [29]. In a review and meta-analysis of the incidence of viral infections in adult CAP, incidence ranged from 8.6 to 56.2%; lower tract samples were associated with higher viral yield and the three main viruses were influenza virus, rhinovirus, and coronavirus [30]. In a similar review by other investigators, the pooled proportion of patients with viral infection was similar, 24.5%, but in studies that obtained lower respiratory samples the proportion increased to 44.2% [31].

More recently in Britain, 325 adult patients with confirmed pneumonia admitted to two tertiary-care hospitals had cultures and comprehensive molecular testing [multiplex real-time PCR for 26 respiratory viruses and bacteria] from sputum [96%] and endotracheal aspirate [4% or 13 cases] [32]. An etiology agent was identified in 87% with molecular testing compared to 39% with culture-based methods.

Bacterial pathogen was detected by PCR in 78% and culture in 32% but most patients [85%] received antibiotics before admission. Viruses were present in 30% of cases but 82% were co-detected with bacterial pathogens. It was surprising that *H. influenzae* was the most common bacteria in 40.2%, followed by pneumococcus in 35.6%, *M. catarrhalis* in 13.6%, *S. aureus* in 10.2%, *Klebsiella pneumoniae* in 4%, and atypical organisms in <5% [32]. It is questionable that mere detection of a pathogen is sufficient to attribute causality, unless there is evidence of acute immune response, as most specimens were sputa and not aseptically collected endotracheal secretions. The high incidence of *H. influenzae* could represent oropharyngeal colonization with non-typeable strains, high prevalence of COPD [about 40%] and high proportion of older patients above 65 years of age [56.3%]. The low prevalence of atypical organisms [mycoplasma and *Chlamydia pneumoniae*] is not surprising as the patients had severe pneumonia requiring hospitalization. It is likely that mild-moderate CAP receiving ambulatory treatment would have a higher proportion of the atypical bacteria. A similar but smaller study in Japan used conventional methods and real-time PCR for diagnosis of CAP [ $n = 92$ ] from sputa and nasopharyngeal swabs; molecular methods detected a causative organism in 72% versus 57% with conventional methods [33]. *S. pneumoniae* was most frequently identified, followed by *H. influenzae* and *M. pneumoniae* [5%].

Pneumococcus is the most important bacterial cause of CAP, responsible for most CAP mortality in severe cases, but rates of detection have varied from 8 to 48%. Rapid diagnosis of pneumococcal etiology could lead to initiating treatment with a narrow-spectrum antibiotic such as penicillin, which would be cost saving, with decreased risk of superinfection with *Clostridium difficile* and lower rate of predisposing to multiresistant bacteria. Sputum Gram stain at presentation is an inexpensive, rapid, easy to perform test that is underused in clinical settings to assist in the diagnosis and treatment of CAP. In a prospective study of 670 patients with pneumonia [328 CAP], the utility of sputum Gram stain was assessed from 478 good quality samples [34]. The sensitivity and specificity of Gram stain were 62.5% and 91.5% for *S. pneumoniae*, 60.9% and 95.1% for *H. influenzae*, 68.2% and 96.1% for *M. catarrhalis*, 39.5% and 98.2% for *K. pneumoniae*, and 9.1% and 100% for *S. aureus*. Unfortunately about 30% of patients with pneumonia had no or poor quality sputum, which limits the overall diagnostic value. Hence, this simple test should be routinely used in the diagnosis of CAP whenever purulent sputum is available. Detection of pneumococcus C-polysaccharide in urine by immune chromatography is increasingly being used for evaluation of patients with CAP. In a large observational, multicenter, prospective study of 3874 patients admitted to hospital for CAP, pneumococcal infection was diagnosed in 21%, with 71% of the cases diagnosed exclusively by urinary antigen test [35]. The sensitivity and specificity were 60% and 99.7%, respectively. A combination of different methods, however, appears to be more sensitive. Using quantitative [q] PCR on blood samples, multiplex immunoassay for urine antigen and multiplex immunoassay for serologic antibody responses against 14 serotypes were able to detect pneumococcus in 47% of cases and 56% more patients than conventional methods [36]. The qPCR of blood samples, however, was not more sensitive than blood culture.

### 3.3.1 *Comments on Microbial Etiology*

How can we interpret these studies utilizing comprehensive molecular methods for etiology diagnosis of CAP? Finding viruses or pathogenic bacteria from nasopharyngeal and sputum specimens may not prove of causality in pneumonia, as they clearly can just be causing upper tract infection or colonization without producing lower respiratory disease. However, the absence of any specific pathogens from these assays can effectively exclude them as etiology agents, since nearly all CAP is a result of aspiration of upper airway microbes. A combination of tests such as sputum Gram stain and culture, blood culture, urinary antigen and antibody response to the microbe[s] may be the most specific and reliable methods of determining causality, but are not highly sensitive nor provide rapid results to affect management. Future research should focus on rapid, readily available, and inexpensive tests for etiologic diagnosis of CAP that could be used in emergency departments. Such methods may use immunoassays that could detect various bacterial pathogens or antigens semiquantitatively from sputum, blood, and urine in the form of a dipstick, similar to that of a urinalysis test.

## 3.4 **Diagnosis of CAP**

In most cases of CAP, the diagnosis should be straightforward, but since the advent of chest radiograph there has been no significant advance in diagnostic methods. Typical mild cases of CAP with clinical symptoms of recent cough, fever, and the presence of chest crackles may be treated empirically without a chest X-ray or blood tests. However, normal chest examination can be present in about 50% of CAP. Chest radiograph is the standard investigation to confirm pneumonia in suspected cases and should be done in moderate–severe CAP even in the presence of typical chest findings, to define the extent of lung[s] involvement, assess for presence of parapneumonic effusion or possible empyema, and the presence of pulmonary cavitation or abscess. The presence of necrotizing pneumonia restricts the etiologic diagnosis to a few bacteria and usually requires a longer duration of therapy.

Diagnosis of CAP can be difficult in some more complicated cases, often severe cases with multi-organ failure or dysfunction requiring intensive care. In these situations, the difficulty lies in the interpretation of the chest X-ray. Problems arise from differentiating pneumonia from pulmonary edema, hemorrhage, atelectasis, and acute respiratory distress syndrome [ARDS]. Computerized tomography [CT] scan may or may not be able to differentiate these conditions. Bedside ultrasonography has been used for diagnosing pneumonia but is less reliable than radiography, with sensitivity ranging from 57% to 100% and specificity of 54% to 99% [37]. Ultrasound is more useful for defining the presence and severity of associated pleural effusion. Investigators have also assessed the value of molecular biomarkers in severely ill patients to differentiate CAP from noninfectious cause of lung infiltrates. In a study



of 234 patients admitted to the intensive care unit [ICU] with suspected CAP genome-wide transcription profiling of blood leucocytes was investigated. Expression of proinflammatory and anti-inflammatory pathways was similar between patients with and without CAP, and blood concentrations of biomarkers such as procalcitonin, interleukin [IL]-6, and interleukin IL-8 were not discriminatory [38]. Further analysis revealed that the ratio of two genes, FAIM3 and PLAC8, was best for distinguishing CAP from no-CAP. The FAIM3:PLAC8 ratio provided a positive predictive value of 83.1% and negative predictive value of 81.3%. However, the clinical utility for management in seriously ill patients is questionable and further studies are needed.

### 3.5 Markers of Prognosis of CAP

The risk of CAP and invasive pneumococcal infection in adults increases with older age, number of comorbidities, cigarette smoking, and the combination of the above [39]. Proton pump inhibitors [PPI], a commonly prescribed medication, in this high-risk population also may add to the risk of CAP. A systematic review of 26 studies with 226,769 cases of CAP reported a 1.5-fold increased risk of CAP, with the highest risk in the first 30 days after initiating a PPI [40].

CAP is the most common infectious disease leading to hospitalization in the ICU and the leading cause of mortality in patients with infection [41]. Severe sepsis may be present in about one-third of patients presenting with CAP at a hospital. Predictors of severe sepsis and assessment for these factors are important on arrival in the emergency department [ED], to facilitate rapid treatment and close monitoring to avoid high fatality. In a prospective multicenter cohort study of 4070 hospitalized CAP patients, 37.6% presented with severe sepsis [42]. Severe sepsis with CAP was independently associated with age >65 years, alcohol abuse [odds ratio [OR], 1.31], COPD [OR, 1.75], kidney disease [OR, 1.57], *S. pneumoniae* [OR, 1.59], mixed microbial etiology [OR, 1.65], and bacteremia [OR, 1.37]; whereas prior antibiotic treatment was protective [42].

Other comorbid conditions such as cardiovascular disease may not predispose to severe sepsis but may result in higher mortality and morbidity. Previous studies indicate that CAP is associated with increased cardiovascular complications. In a multicenter prospective cohort of 1182 patients hospitalized for CAP, 32.2% experienced cardiovascular complications, including heart failure [23.8%], atrial fibrillation [9.2%], myocardial infarction [8%], ischemic stroke [0.9%], and deep vein thrombosis [0.1%] [43]. The 30 day mortality was significantly higher in patients who developed cardiovascular complications compared to those who did not [17.7% versus 4.55%,  $p < 0.001$ ]. Studies have also reported increased mortality in patients with vitamin D deficiency [44] and extreme thinness [body mass index <16/kg/m<sup>2</sup>] on developing CAP [45].

Various scoring systems and biomarkers have been developed to identify severe CAP, assess prognosis for mortality risk and to assist physicians in making decisions

**Table 3.1** CURB-65 score

	Factors assessed	Total score (1 per factor)	Mortality risk (%)
1.	Confusion [mental test or disorientation]	0	0.7
2.	Urea [BUN >7 mmol/L or 20 mg/dL]	1	2.1
3.	Respiratory rate $\geq 30$ /min	2	9.2
4.	Blood pressure [systolic <90 or diastolic $\leq 60$ ]	3	14.5
5.	Age $\geq 65$ years	4	40

*BUN* blood urea nitrogen

Disposition of patient based on total score: 0–1 treat as outpatient; admit to hospital for 2 and above

on hospital and ICU admission. These scoring systems were designed for the use in non-immunosuppressed patients. The most commonly used scoring system is the CURB-65 score, which is based on five easily measurable factors [see Table 3.1]. The presence of each factor was given a score of 1 to a maximum of 5. In the initial study of 718 patients in the derivation cohort and a separate validation cohort, the 30 day mortality was 0.6–0.7%, 1.7–2.1%, 9.2%, 14.5%, and 40% for 0, 1, 2, 3, or 4 factors [46]. Based on these data, it was suggested that that CAP patients with a score of 0–1 could be treated as outpatients, those with a score of 2 should be admitted to hospital, and those with a score of 3 or more should be assessed for ICU care. However, another large study of 3181 patients with CAP reported a mortality of 3.0% with a CURB-65 score of 1 [47]; which suggests even 1 score should be an indication for hospital admission. But a healthy 65-year-old person without other factors or significant comorbid illness could be treated with outpatient antibiotic. In a more recent study, however, CURB-65 had very good accuracy for predicting the 30-day mortality among 7952 patients with CAP discharged from the ER [48]. Among all ER encounters the CURB-65 threshold of >1 was 92.8% sensitive and 38.0% specific for predicting mortality, with a 99.9% negative predictive value.

A simplified version without blood test to measure blood urea nitrogen [BUN], designated CRB-65, can be used in the doctor's office to assess severity of CAP. If 1 or more score is present then the patient is referred to the hospital for admission. The CRB-65 score has not been extensively evaluated but was found to have good predictive value in 670 patients with CAP [49].

The Pneumonia Severity Index [PSI] assessment is based on the presence of 20 variables and is divided into five strata of increased risk for short-term mortality at presentation [50]. Low-risk patients with cumulative mortality of <1% falls in the class I-III, whereas patients in class IV and V have higher mortality risk of 9% to 30%. Although several large studies have validated its predictive utility, it is more complex to calculate, less user friendly than CURB-65, and the predictive performance is similar in prospective comparison [47]. Hence, CURB-65 is more commonly used by ED physicians to assess CAP severity. The British Thoracic Society and the National Institute for Health and Care Excellence [NICE] guidelines recommend CURB-65 and CRB-65 for severity assessment in CAP [51, 52].



For patients hospitalized for CAP risk prediction can be used to assess the need for ICU care, mechanical ventilation, and mortality. Monitoring the C-reactive protein [CRP] during hospitalization may be useful in predicting response and the risk of death. In a retrospective multicenter study of 814 patients with CAP admitted to three Dutch hospitals, the highest mortality risk was seen in patients who failed to demonstrate a decline in their CRP by 50% after 3 days of treatment, irrespective of the actual value and initial CURB-65 score [53]. This study should be validated by a larger prospective study.

Three scoring systems have been developed to identify severe CAP in hospital and the need for ICU management. These include the severe community-acquired pneumonia score [SCAP], SMART-COP, and the Infectious Diseases Society of America/American Thoracic Society [IDSA/ATS] severity criteria [see Table 3.2]. All three systems utilize a combination of clinical criteria [shock, altered mental state, and respiratory failure], routine blood tests, and arterial blood gas results. A SCAP score of  $\geq 10$  [at least one major and two minor criteria] was superior to CURB-65 in predicting progression to more severe pneumonia [54]. Further validation study showed that the SCAP score was just as accurate as other prediction scoring systems for predicting ICU admission, progression to severe sepsis, treatment failure and need for mechanical ventilation [55]. The SMART-COP scoring system was assessed in a prospective study of 882 episodes of CAP requiring hospitalization, with more than 75% of patients over 50 years old [56]. Each factor led to accrual of one point, except low systolic blood pressure, poor oxygenation, and low arterial pH, each subscribed two points. SMART-COP score of  $\geq 3$  points identified 92% of patients who received intensive respiratory or vasopressor support [56]. The predictability of SMART-COP was less accurate in younger adults <50 years of age, as it failed to identify the need for these critical measures in 15% of patients in this age group [57]. The IDSA/ATS severity system is based on two major criteria and nine minor criteria [58]. Any one of the major criteria, septic shock requiring vasopressors and requirement for mechanical ventilation, are universally accepted and are self-evident. Three or more of the minor criteria indicate need for ICU management. A validation study of 1062 patients with CAP, not meeting the major criteria, found the minor criteria were equivalent to the SMART-COP scoring system for predicting need for mechanical ventilation, vasopressor support, and ICU care [59]. Recently, other investigators have modified the IDSA/ATS minor criteria by excluding four infrequent variables [leucopenia, hypothermia, hypotension, and thrombocytopenia] but adding age  $\geq 65$  years [60]. The modified version best-predicted mortality, but it is unclear whether it is as useful for predicting need for ICU care and vasopressor/ventilation support.

Various blood biomarkers have been studied as prognostic predictors in CAP and these include procalcitonin [PCT], CRP, proadrenomedullin [pro-ADM], presepsin [sCD14-ST], copeptin, and cortisol. The PCT was the most extensively studied in a total of 21 studies with 6007 pneumonia patients. Although elevated PCT level was a risk factor for death in CAP, particularly patients with a low CURB-65 score, the commonly used cutoff, 0.5 ng/mL, had low sensitivity in identifying patients at risk of dying [61]. In a systematic review and meta-analysis of the prediction value of

**Table 3.2** IDSA/ATS guidelines for ICU management

Major criteria [any one]
Septic shock requiring vasopressor support
Respiratory failure needing mechanical ventilation
Minor criteria [ $\geq 3$ ]
1. Altered mental status
2. Hypotension requiring fluid support
3. Temperature $< 36^\circ\text{C}$ [ $96.8^\circ\text{F}$ ]
4. $\text{PaO}_2/\text{FiO}_2$ ratio $\leq 250$
5. Blood urea nitrogen $\geq 20$ mg/dL or 7 mmol/L
6. Leucocyte count $< 4000$ cells/ $\mu\text{L}$
7. Platelet count $< 100,000/\text{mL}$
8. Multilobar infiltrates

$\text{PaO}_2$  arterial oxygen concentration,  $\text{FiO}_2$  fraction of inspired oxygen or percentage by decimal fraction

With nasal cannula or simple face mask each liter/min of oxygen provides 4%/L for the first 3 L and only 3%/L thereafter to their  $\text{FiO}_2$ . Example: nasal cannula with 4 L/min oxygen flow provides an  $\text{FiO}_2$  of  $21\% + [3 \times 4\%] + [1 \times 3\%] = 36\%$ —expressed as 0.36 for calculation

various biomarkers in 10,319 CAP patients, they demonstrated moderate–good accuracy to predict mortality but had no clear advantages over CAP-specific scores [62].

### 3.5.1 Comments on Prediction Scores

CURB-65 should be the standard prediction score applied to patients seen in hospital ED with CAP, the main contentious issue is whether or not patients with a score of 1 should be admitted or treated as outpatients. It may be reasonable to admit patients with one factor, other than age 65 years alone. Using age alone for admission has no supporting evidence for almost every medical illness. However, patients 65 years or older with significant comorbid illness, such as underlying cardiovascular disease, should be admitted and monitored. Once patients are admitted to hospital the IDSA/ATS guidelines maybe the most appropriate to use on deciding on further care in the ICU, although SCAP and SMART-COP scores are suitable as well.

## 3.6 Treatment of CAP

Empiric treatment of CAP is designed to treat common bacterial respiratory pathogens [*S. pneumoniae*, *H. Influenzae*] and atypical bacteria [*M. pneumoniae*, *C. pneumoniae*], but recent etiology studies suggest that a large proportion of CAP is due to

viruses alone in both children and adults. Hence, an accurate test available in any hospital that could differentiate viral from bacterial infection would be cost saving and decrease overuse of antibiotics. Serum PCT levels has been studied for this purpose. PCT concentration, cutoff value 0.10 ng/mL, has been used in 453 patients to differentiate acute heart failure from pneumonia in the ED [62]. The median PCT level was significantly higher in patients with pneumonia than in those without [0.38 ng/mL versus 0.06 ng/mL]. Among patients with >75% clinical likelihood of heart failure, PCT value of 0.10 ng/mL had a sensitivity for identifying pneumonia of 95% and a negative predictive value [NPV] of 99%; but for patients with low likelihood of heart failure, the PCT cutoff value had 85% specificity and 95% NPV [63]. In a large prospective multicenter study of 1735 adult patients with CAP, the accuracy of PCT concentration to discriminate between bacterial and viral pathogens was estimated [64]. Pathogens were identified in only 37%, including 10% with typical bacteria, 4% with atypical bacteria, and 24% with viruses only. The median PCT concentration was lower with viral pathogen [0.09 ng/mL], than atypical bacteria [0.2 ng/mL] and typical bacteria [2.5 ng/mL]. A PCT value of 0.1 ng/mL resulted in 80.9% sensitivity and 51.6% specificity for any bacterial pathogen. No PCT threshold discriminated viral from bacterial etiology with a very high sensitivity and specificity [64].

A contentious issue in the empiric management of CAP is the routine coverage for atypical bacteria with a macrolide, as *M. pneumoniae* and *C. pneumoniae* infection are usually associated with self-limited course and recovery. Whereas, North American guidelines for outpatient treatment of CAP list a macrolide as first choice [65] European guidelines do not [52] and consider macrolides as second choice for penicillin-allergic patients. Moreover, coverage for atypical bacteria routinely in the management of CAP has not been proven to be beneficial. In a systematic review of 28 trials and with 5939 randomized patients, no advantage was found for regimens covering atypical bacteria in the major outcomes tested—mortality and clinical efficacy [66]. Macrolide as a sole therapy for CAP maybe inadequate to cover pneumococcus, as the prevalence of macrolide resistance has been increasing and is currently up to 35%, although the clinical significance is uncertain [67].

For patients with moderate–severe CAP being hospitalized, North American and European guidelines [51, 52, 65] recommend initiating broad-spectrum therapy of a  $\beta$ -lactam agent [often ceftriaxone] and a macrolide or a respiratory quinolone alone. The macrolides have immunomodulatory effects and anti-inflammatory properties that may improve outcome even for pneumococcal infection. Even in Gram-negative sepsis and ventilator-associated pneumonia, clarithromycin has been reported to restore the immunoparalysis and improve outcome [68]. A recent systematic review of antibiotic therapy for hospitalized adults with CAP has been published [69]. Several key aspects of antibiotic therapy can be summarized: (1) eight observational studies showed that antibiotic initiation within 4–8 h of hospital arrival was associated with decreased mortality; (2) stepping down from intravenous to oral therapy once patients are stable shortens hospital stay without affecting outcome; (3) choice of empiric antibiotics on outcome was mixed and inconclusive. Six of eight low-quality observational studies [with up to 24,780 patients] found that the combina-

tion of  $\beta$ -lactam and macrolide was associated with reduced short-term mortality over  $\beta$ -lactam monotherapy. The three largest studies were all retrospective in design. Three observational, mainly retrospective, studies found reduced mortality with quinolone monotherapy compared to  $\beta$ -lactam monotherapy [69].

However, in prospective randomized, trials the results have not confirmed superiority of combination with a macrolide nor quinolone over  $\beta$ -lactam monotherapy. In the first trial in Switzerland, 580 adults with moderate–severe CAP admitted to six acute care hospitals were randomized to  $\beta$ -lactam monotherapy or a macrolide combination [70]. The mortality, ICU admission, length of stay, and recurrence of pneumonia within 3 months were not different between the treatments. In the second prospective multicenter Dutch trial, 2283 patients with CAP admitted to non-ICU wards were allotted to one of three treatments by a cluster-randomized, crossover design with strategies rotated in 4-months period [71]. Monotherapy with a  $\beta$ -lactam was non-inferior to strategies with  $\beta$ -lactam macrolide combination or quinolone monotherapy for 3 months mortality, length of stay, or any complications. Quinolones when used can be given orally from the onset if the patients can take oral medications, since they are fully bioavailable. IDSA guidelines had recommended initial intravenous therapy for severe pneumonia, but well-conducted observational study confirms that intravenous route is not necessary for severe CAP [72].

The duration of treatment for CAP is not well established. IDSA/ATS guidelines recommend at least 5 days treatment in patients who are stable and have been afebrile  $\geq 48$  h [65]; the British guidelines advice 7 days for mild–moderate and 7–10 days for moderate–severe CAP [51]; and the NICE guidelines recommend 5 days for mild and 7–10 days for moderate–severe CAP [52]. In a recent multicenter randomized trial from four teaching hospitals in Spain, the duration of antibiotic treatment was studied in 312 hospitalized patients with CAP [73]. After 5 days of treatment, the intervention group stopped antibiotics if they were afebrile for 48 h and had no more than one CAP-associated sign of instability, and the duration of antibiotics in the control group was determined by physicians. There was no significant difference in the outcome between the two groups. Thus, the IDSA/ATS guideline is safe to implement in hospitalized patients with CAP.

### 3.6.1 Comments on Treatment of CAP

Current data indicates that amoxicillin for outpatient treatment of mild–moderate CAP for 5 days is the preferred therapy. Macrolide monotherapy should be avoided due to high and rising resistance of *S. pneumoniae*. Furthermore, moderate macrolide resistance in *M. pneumoniae* has now been reported with analysis for resistant mutation genes [74]. Amoxicillin/clavulanic acid maybe preferable to cover  $\beta$ -lactamase strains of *H. influenzae* and *M. catarrhalis* in the elderly and subjects with COPD or chronic bronchitis. Patients admitted to hospital for moderate–severe CAP, not requiring ICU care, can be treated with a  $\beta$ -lactam monotherapy [commonly ceftriaxone] but amoxicillin/clavulanic acid can be used or respiratory quinolone orally.

Whenever pneumococcus is shown to be the etiologic agent, penicillin should be used as there is no evidence that the outcome is adversely affected for penicillin non-susceptible [relative resistance] strains in CAP even with bacteremia.

In patients with severe CAP requiring ICU care, a  $\beta$ -lactam [ceftriaxone] with a macrolide or a quinolone alone is suitable. In this setting, the macrolide is used for *L. pneumophila* infection until this organism can be excluded.

### 3.7 Adjunctive Therapy for Severe CAP

Severe CAP has a high mortality [about 38%] despite adequate antibiotic therapy, thus adjunctive therapy has been studied and used empirically to try and improve the outcome. Combination with a macrolide for macrolide-resistant bacteria is a form of adjunctive therapy. Comparative studies on the inflammatory response of patients with severe and non-severe CAP can be useful to guide adjunctive therapy. In one such study, the severe CAP group showed higher plasma levels of pro- and anti-inflammatory cytokines but in contrast, lower sputum concentration of proinflammatory cytokines [75]. Moreover, neutrophils from severe CAP patients showed reduced respiratory burst activity compared to the non-severe group. These results indicate that patients with severe CAP fail to mount a robust local inflammatory response but instead produce a heightened systemic inflammatory response [75].

It has been suggested that statins, primarily indicated for dyslipidemia and cardiovascular disease, have modulation effects on the cytokine cascade and could be useful in severe CAP. In a previous review of the immunomodulatory effects of statins in CAP, 17 experimental and 17 clinical studies were identified [76]. Statins attenuated pulmonary inflammation by reducing cytokine release and expression, modulating neutrophil function, and by protecting against disruption of lung integrity. Observational studies suggested a decrease in mortality due to CAP in current statin users but randomized studies are lacking [76]. A randomized, double-blind, placebo-controlled trial of simvastatin for CAP was initiated in Spain but was terminated after enrolling 34 patients because of slow enrolment [77]. However, after 48 h of statin, there was no difference in concentrations of cytokines compared to patients on placebo. Thus, the benefit of statins in CAP remains unknown.

Corticosteroids [steroids] have been studied for its anti-inflammatory effect in severe CAP in an attempt to reduce mortality, ARDS and need for mechanical ventilation and ICU care with inconclusive results. Although steroids have been shown to improve outcome and decrease risk of respiratory failure in pneumocystis pneumonia, it failed to improve outcome in a major, definitive randomized controlled trial in patients with all cause sepsis [78]. In a previous review of this topic in 2014, it was concluded that steroids should not be used in CAP because of insufficient evidence of the beneficial effect and potential harm [79]. Since then, two other randomized, placebo-controlled trials of adjunct steroids in CAP have been reported. The first study from Spain randomized 120 patients to intravenous methylprednisolone or placebo for 5 days. There was less early treatment failure [composite end

points defined by the study] in the steroid treated group but no difference in mortality [80]. The second study from Switzerland randomized 785 patients to either prednisone 50 mg daily or placebo for 7 days. Prednisone shortened the time to clinical stability by about 1.5 days without an increase in complications but did not improve mortality [81]. In the past 2–3 years four systematic reviews and meta-analyses of the value of steroids in CAP have been published. In the first report, ten randomized controlled trials [RCT] with 1780 cases of hospitalized CAP were reviewed. Mortality was decreased in the severe-case subgroup and patients requiring ICU care. Length of ICU decreased by 1.3 days and length of hospital stay by 1 day [82]. In the second review in 2015, 12 trials were included with 1974 patients and concluded that steroids may reduce mortality by 3%, need for mechanical ventilation by 5%, and hospital stay by 1 day [83]. The third report only included 8 RCTs enrolling 528 more severe CAP patients. Results from this meta-analysis showed steroids significantly reduced mortality [ $p = 0.003$ ], risk of ARDS [ $p = 0.02$ ], need for mechanical ventilation [ $p = 0.026$ ], and length of hospital stay decreased by 4.7 days [ $p = 0.006$ ] [84]. In the final review, nine RCTs [1667 patients] and six cohort studies [4095 patients] were included in the analysis. Steroids treatment was associated with reduced ARDS and reduced length of ICU stay but no effect on mortality [85]. None of the four studies found significant adverse events with steroids except for hyperglycemia.

### ***3.7.1 Comments on Adjunctive Therapy for CAP***

In moderate–severe CAP adjunctive macrolide is not beneficial. Further randomized studies are still needed for the more severe cases at risk for ICU management. Steroids may be beneficial to reduce mortality, ARDS and mechanical ventilation for the severe CAP but the results are not conclusive. Thus, it would be premature to use steroids routinely in severe CAP, pending larger RCT in this subgroup of patients admitted to hospital. In the most recent review and meta-analysis of steroids in hospitalized patients with CAP, with analysis of 1506 cases from six trials, steroids reduced time to clinical stability and length of hospital stay by 1 day but did not reduce mortality and increased risk of hyperglycemia and CAP-related rehospitalization [86]. The state of the art is reminiscent of the data of steroids in sepsis/septic shock, when steroids appeared to be effective in reducing mortality based on small RCTs but was proven ineffective in larger, definitive trials. At least three large trials registered on ClinicalTrials.gov are expected to enroll a total of 2300 patients and are scheduled for completion by October 2018 will provide more definitive data on the use of steroids in CAP. Future trials should investigate the effect of adding non-steroidal anti-inflammatory agents [NSAIDs] for the treatment of CAP. In a recent open randomized trial from Hong Kong, patients hospitalized with severe influenza A [H3N2] with pulmonary infiltrates had significantly lower 30-day mortality and shorter hospital stay after treatment with naproxen–clarithromycin [2 days] + oseltamivir than oseltamivir, both groups received beta-lactam antibiotics [87].



### 3.8 Prevention of CAP

In the past 20–30 years, marked reductions in the total burden and mortality of pneumonia in children <5 years of age have occurred worldwide. This has been attributed to a number of factors, improved healthcare and social-economic conditions in low earning countries, and major contribution due to increased vaccination against measles, pertussis, *S. pneumoniae* and *H. influenzae* type b with conjugate vaccines. However, similar reduction in CAP has not been realized in adults. Smoking cessation may reduce the risk of CAP in chronic smokers but permanent cessation is difficult to achieve. The World Health Organization estimates that >1 billion of the world's population smoke and smoking is a strong risk factor for invasive pneumococcal disease and bacterial pneumonia [88].

In most temperate countries peak incidence of CAP occurs in the winter during the peak influenza season. Thus universal yearly influenza vaccination may decrease the incidence of CAP in children and adults for influenza and bacterial pneumonia. Previous studies have shown that influenza vaccination is effective in preventing hospitalization for acute respiratory illness associated with confirmed influenza. Estimates ranged from 53% to 67% among children, 54% to 71% among all adults, and 42% to 61% for adults 65 years or older [89–92]. However, most of these studies did not specifically assess the effect of influenza vaccination on the prevalence of CAP. In a prospective observational multicenter study of hospitalization for CAP over 2.5 years in four US sites, 2767 patients were hospitalized for CAP. Among children and adults, only those with confirmed influenza-associated pneumonia had lower odds of having received influenza vaccine [93]. Indicating that influenza vaccination reduces CAP from influenza complication, including secondary bacterial pneumonia.

The introduction of the 7-valent and subsequent 13-valent *S.pneumoniae* conjugate vaccine [PCV13] in children in resource-rich countries has resulted in the decline of pneumococcal pneumonia in children and adults as well, through herd protection [94]. The 23-valent pneumococcal polysaccharide vaccine [PPV23] has been available for >30 years and is recommended in many countries for high-risk patients, but its efficacy in preventing CAP is debatable. Three recent reviews and meta-analysis of the benefit of PPV23 in preventing pneumococcal CAP in adults have been published with inconsistent conclusions. One review found no proof that PPV23 can prevent pneumococcal CAP in the elderly population [95]. Another study reviewed seven randomized trials involving 156,010 subjects and concluded that the PPV23 vaccine provided weak protection against all cause pneumonia [96]. The third review, however, reported that PPV23 vaccine effectiveness in preventing invasive pneumococcal disease was 50% for cohort studies and 54% for case-control studies [97]. But lower for prevention of CAP, 4% reduction in trials, 7% for case-control studies and 17% effectiveness for cohort studies. However, the conjugate vaccine appears to be more effective in adults. In a large placebo-RCT involving 84,496 adults 65 years of age and older, the Community-Acquired Pneumonia immunization Trial in Adults [CAPiTA], the PCV13 vaccine was assessed [98]. The vaccine efficacy in preventing

vaccine-type pneumococcal CAP was 45.6% and 75% in preventing invasive pneumococcal disease, but not effective in preventing CAP from any cause.

### ***3.8.1 Comments on Prevention of CAP***

More effective treatment is clearly needed for smoking cessation worldwide to prevent lung cancer, cardiovascular disease, COPD and many associated cancers and illnesses, including possible CAP. Although universal annual influenza vaccination is now recommended for children and adults, the rate of vaccination in all countries has been low [ $<20\text{--}30\%$  of the population]. Improved and more effective, long lasting influenza vaccines [given by nasal or oral route] are needed to facilitate greater compliance and herd immunity. In the meantime, physicians should encourage annual influenza vaccines for all. PCV13 should be offered to all elderly and high-risk adults for CAP. Pending the development and marketing of a 23-valent conjugate pneumococcal vaccine, it is reasonable to administer the PPV23 as well several months later.

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