Severe Community-Acquired Pneumonia

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Key Points

- Severe community-acquired pneumonia (SCAP) is a serious form of infection of the lung parenchyma acquired in the community that requires admission to the intensive care unit and has a high risk of mortality.
- Immunocompromised patients and those with medical co-morbidities are more likely to develop SCAP.
- *Streptococcus pneumoniae* remains the most common causative pathogen of SCAP; other common offenders being viruses, *Hemophilus influenzae* and atypical organisms like *Legionella*. Less frequently, gram-negative bacilli and *Staphylococcus aureus* may cause SCAP, particularly in hosts with risk factors for these pathogens.
- Diagnostic evaluation includes a chest radiograph to confirm the diagnosis, and the assessment of the severity of the disease using tools to assess organ dysfunction such as arterial blood gas analysis, renal and liver function tests, blood counts, and coagulation profile.
- Scoring systems such as IDSA/ATS criteria, Pneumonia Severity Index, CURB-65, and SMART-COP may be used to assess the severity, mortality risk, and the requirement of admission to the intensive care unit.
- Blood, respiratory samples (sputum, endotracheal aspirate, or bronchoalveolar lavage) and, if present, pleural fluid must be sent for microbiological analysis as early as possible.
- Empirical antibiotics must be instituted at the earliest after the diagnosis is made. The antibiotic regime must be concordant with local guidelines formulated according to the current scientific evidence, prevalent epidemiology, and local antibiotic susceptibility data.
A combination of a β-lactam antibiotic (such as amoxicillin-clavulanate, ceftriaxone, cefotaxime) and a macrolide (azithromycin or clarithromycin) is the usual choice in most patients, unless they have risk for *Pseudomonas*, *Staphylococcus aureus*, or resistant organisms. Antibiotics must be de-escalated once a pathogen has been identified.

- The total duration of antibiotics in most cases is 5–7 days.
- Supportive treatment including assisted ventilation for respiratory failure and ARDS, vasopressors and inotropes for septic shock, chest drain for empyema, and others are instituted, as required. Glucocorticoids use may benefit certain subsets of SCAP as an adjunctive treatment.
- Newer biomarkers to assess severity and predict outcomes are being studied. Personalized management, using the principles of microbiomics, genomics, transcriptomics, metabolomics, and immunology, is the vision for the future.

### 4.1 Introduction and Definition

Community-acquired pneumonia (CAP) refers to an infection of the lung parenchyma acquired in the community (outside a healthcare setting). CAP forms a part of a larger group of diseases known as lower respiratory tract infections (LRTIs). The term “severe CAP (SCAP)” signifies a more serious form of pneumonia acquired in the community. The consensus guidelines on the diagnosis and management of CAP laid down by the Infectious Diseases Society of America (IDSA) and American Thoracic Society (ATS) have defined SCAP as pneumonia that requires ICU admission (Mandell et al. 2007). In these guidelines, the criteria for admission to the ICU include the requirement of invasive mechanical ventilation or that of vasopressors for septic shock or the presence of at least three markers of organ dysfunction that predict higher mortality (Mandell et al. 2007). In real life, though, the actual reasons for admission to the ICU and the predicted outcomes of CAP may vary across centers depending on the geographical locale, local policies, hospital resources, and prevalent microorganisms. There are various other scores, discussed later in this chapter, which help in categorizing the severity of CAP. However, for the purpose of this chapter, we define SCAP according to the IDSA/ATS criteria, as they are the most widely accepted criteria till date.

### 4.2 Epidemiology

According to the World Health Organization (WHO) estimates 2016, LRTIs accounted for around three million deaths worldwide (World Health Organization 2018). They ranked fourth globally and first among the low-income nations as the leading causes of death. In India, LRTI resulted in 63.1 deaths per 100,000 population and were the fourth biggest killer after ischemic heart disease, chronic obstructive pulmonary disease (COPD), and stroke (World Health Organization 2018). Even these figures may be an underrepresentation since sepsis, the most common cause of which is pneumonia, is coded separately. Similarly, neurological disorders
like parkinsonism and stroke, where the final cause of death is commonly pneumonia, are coded separately (Wunderink and Waterer 2014). In India, as much as 20% of mortality due to infectious diseases has been attributed to LRTI (Gupta et al. 2012). The reported mortality of CAP varies from 3.3% to 11% in studies from India (Gupta et al. 2012). No data on SCAP in adults are available from India. According to one estimate, in 2010, about 3.6 million (3.3–3.9 million) episodes of severe pneumonia and 0.35 million (0.31–0.40 million) all cause pneumonia deaths occurred in children less than 5 years of age (Farooqui et al. 2015).

Community-acquired pneumonia is the third leading cause of hospital admissions (Rider and Frazee 2018). About 20–40% cases of CAP require hospital admission and 5–10% of these need ICU admission (Walden et al. 2014). The 30-day mortality rates and re-admission rates among hospitalized patients with CAP are 10–12% and 18%, respectively (Musher and Thorner 2014). In a large study of patients with SCAP admitted to the ICU across 17 countries of Europe, the 28-day and 6-month mortality were 17% and 27%, respectively (Walden et al. 2014). Despite advances in medicine and technology, the mortality in CAP has not significantly improved over the last 40 years (Rider and Frazee 2018). The data on trends in the mortality due to CAP are conflicting. In an analysis of 800 SCAP patients (requiring ICU admission) enrolled in the CAP Organization International cohort from 2001 through 2013, mortality was found to have increased from 15.7% in the initial years (2001–2004) to 24.3% towards the end (2008–2013) (Cavallazzi et al. 2015). On the contrary, a retrospective single-center cohort study of 458 patients with SCAP concluded that though the incidence of SCAP and its severity increased through the years from 1999 to 2013, the mortality reduced by 18% (Valles et al. 2016). This was attributed to a reduced incidence of bacteremia and increased use of appropriate antibiotics.

4.3 Pathogenesis and Risk Factors

The pathogenesis of CAP involves establishment of an infection of the lung parenchyma by a virulent micro-organism by overwhelming the host defense (Sligl and Marrie 2013). The severity of CAP may depend on certain host- and pathogen-related factors (Table 4.1). Factors such as advanced age, immunocompromised states, malnutrition, and co-morbidities (such as diabetes mellitus, chronic liver, or kidney disease) are well known and easily identifiable factors that increase the risk of severe pneumonia (Falguera et al. 2005). In fact, significant co-morbidities are present in 46–66% of all SCAP patients (Mandell et al. 2007; Torres et al. 2013). Other less obvious factors that may result in SCAP include the load of the infecting micro-organism, the virulence of the pathogen, and subtle (both known and unknown) genetic factors of the host (Sligl and Marrie 2013; Waterer and Rello 2011; Nimmo 2012; Sole-Violan et al. 2011; Rello and Perez 2016).

Recent studies have evaluated the normal lung immune response to infection. Cytokine levels (both pro-inflammatory and anti-inflammatory) in the plasma and the lungs are far higher in SCAP patients and are associated with both ICU admission and mortality (Kellum et al. 2007; Antunes et al. 2002; Martinez et al. 2011; Ramirez et al. 2011). The reasons for this exaggerated response in some individuals
are not well known (Kellum et al. 2007). The administration of the first dose of antibiotics may also cause a massive surge in cytokine levels in some patients. Analysis of transcriptomic data of SCAP patients has led to the detection of defects in host immune response and aberrations in inflammatory milieu such as T-cell exhaustion, endotoxin tolerance, HLA-receptor deactivation, and a metabolic switch to the glycolytic pathway (Hopp et al. 2018). Epigenetic influences like chromatin remodeling have also been detected (Hopp et al. 2018). Apart from this, a variety of largely unknown factors affecting the host response to infection are probably involved in the predisposition to SCAP. These concern metabolomics, microbiomics, genomics, and subtle variations in the immune landscape of the host.

4.4 Etiologic Agent

Even with the availability of an extensive microbiological diagnostic armamentarium, a definite etiological agent is identified in only about 50% cases of SCAP (Mandell et al. 2007; Rider and Frazee 2018). This implies not only the limitations of the existing diagnostic tools but also the lack of awareness on several microorganisms that are responsible for CAP and SCAP. The most common organism implicated in SCAP remains pneumococcus (*Streptococcus pneumoniae*), which is also the commonest organism isolated in any severity of CAP (Prina et al. 2015; Said et al. 2013). The other common organisms causing SCAP include *Hemophilus influenzae*, atypical organisms, viruses, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, other gram-negative bacilli (GNB), and anaerobes (Sligl and Marrie 2013). About 6% of cases are caused by the so-called PES (*Pseudomonas aeruginosa*, extended-spectrum β-lactamase producing *Enterobacteriaceae*, and methicillin resistant *Staphylococcus aureus*) pathogens (Cilloniz et al. 2019).

*S. pneumoniae* is the etiologic agent in about 30% of all cases admitted to the ICU with a known etiology (Walden et al. 2014; Valles et al. 2016). In as many as 40% cases, the isolate may be resistant to penicillin and other antibiotics in vitro studies (Rider and Frazee 2018; Cherazard et al. 2017). Macrolide resistance in pneumococcus has become common with resistance rates ranging from 27% in the USA to as high as 90% in certain parts of Japan (Rider and Frazee 2018). The clinical relevance of the same is uncertain (Mandell et al. 2007; Rider and Frazee 2018).

Infections with atypical organisms such as *Legionella*, *Mycoplasma*, and *Chlamydia* species are also common and often co-exist with simultaneous typical

| Table 4.1 | Risk factors for developing severe community-acquired pneumonia |
|------------|---------------------------------------------------------------|
|            | Delayed diagnosis and absence of antibiotic therapy before hospitalization |
|            | Advanced age |
|            | Co-morbid illness (e.g., chronic respiratory illness like COPD, cardiovascular disease, diabetes mellitus, neurologic illness, renal insufficiency, malignancy) |
|            | Cigarette smoking |
|            | Alcohol abuse |
|            | Increased pathogen load or virulence |
|            | Pharmacological or pathological immunosuppression |
|            | Host genetic polymorphisms affecting the inflammatory and immunological response |
bacterial infection in SCAP. Together, these pathogens may be responsible for 22% of cases of CAP (Prina et al. 2015; Arnold et al. 2007). Hence, it is recommended that the empiric choice of antibiotic therapy for severe CAP should always include antibiotics that are active against atypical organisms (Mandell et al. 2007). Occasionally, tuberculosis may present as SCAP, and may be associated with ARDS (Agarwal et al. 2005; Muthu et al. 2017, 2018a, b). In an endemic region, a high index of suspicion for tuberculosis may thus be kept. Viruses also form a large group among microbes causing SCAP; the commonly implicated ones being influenza, rhinovirus, respiratory syncytial virus, metapneumovirus, and the coronavirus (Musher and Thorner 2014; Klein et al. 2016). The pandemic influenza A H1N1/09 virus caused a major pandemic of viral pneumonia in 2009 and was associated with SCAP in 20% of hospitalized patients (Lum et al. 2009). The virus continues to circulate in several regions of the world causing SCAP. Besides, influenza A H1N1/09 virus, the H5N1 influenza virus, the severe acute respiratory syndrome (SARS) coronavirus, and the Middle East respiratory syndrome (MERS) coronavirus have been implicated to cause SCAP, in the form of outbreaks. In 2019, a novel coronavirus, called the SARS-CoV-2 was reported from China. The virus has caused a pandemic of a severe respiratory illness called the coronavirus disease-19 (COVID-19) in 2020.

*Staphylococcus aureus* can lead to a severe bilateral necrotizing pneumonia, often related to toxin production by the organism (Sligl and Marrie 2013). The organism is more likely to be isolated in elderly patients, in patients with an influenza infection, intravenous drug abusers, in those with underlying cardiopulmonary co-morbidities or end-stage renal disease, and in those living in crowded surroundings or those with frequent or recent contact with healthcare set-up (particularly recent use of antibiotics like fluoroquinolones) (Mandell et al. 2007; Klein et al. 2016; Venezia et al. 2001; Teng et al. 2019). *Staphylococcus aureus* causing SCAP may be drug resistant, and is known as community-acquired methicillin resistant *Staphylococcus aureus* (CA-MRSA). CA-MRSA is distinct from the nosocomial strain of MRSA and is clonal in origin. Although more virulent than hospital-acquired MRSA, CA-MRSA is often sensitive to common non-beta lactam antibiotics (such as clindamycin, trimethoprim-sulfamethoxazole, and tetracycline) (Rubinstein et al. 2008).

Enteric GNB and anaerobes may infrequently be isolated in SCAP. The frequency of gram-negative CAP is difficult to define. In a prospective surveillance study conducted by Asian Network for Surveillance of Resistant Pathogens (ANSORP), 93 of 912 CAP patients (10.1%) had isolation of GNB, with *Klebsiella pneumoniae* being the commonest isolate followed by *Pseudomonas aeruginosa* (Kang et al. 2008). Mortality was higher in the GNB group than non-GNB group. Infection with GNB was more commonly associated with septic shock and was more likely to occur in smokers and those with underlying malignancy or cardiovascular diseases. Patients most likely to have CAP due to GNB are those who have recently been exposed to antibiotics, or were hospitalized, or have multiple medical co-morbidities (including alcoholism) or structural lung diseases.

Around 11% of SCAP patients may have a polymicrobial etiology, especially when they present with ARDS or when they have underlying COPD (Cilloniz et al. 2016a, 2011).
4.5 Diagnostic Evaluation

The evaluation in SCAP is aimed at making a diagnosis of CAP, assessing its severity, identifying complications, deciding the place of care, and identifying the etiologic agent. A focused history and physical examination along with a chest radiograph are usually sufficient to make a diagnosis of CAP. Cough, sputum production, fever, dyspnea, and pleuritic chest pain are the cardinal symptoms of CAP. Patients with SCAP, due to host or pathogen-related factors, have a more profound systemic inflammatory response and are thus more likely to have tachypnea, tachycardia, hypotension, confusion, temperature >40 °C, or hypothermia (Sligl and Marrie 2013). Immunocompromised or elderly individuals may mount an inadequate inflammatory response to CAP and may thus have an atypical presentation (Fernandez-Sabe et al. 2003). In fact, a lack of pleuritic chest pain and an absence of typical symptoms are often associated with poorer prognosis (Musher and Thorner 2014; Fernandez-Sabe et al. 2003; Cilloniz et al. 2016b).

A chest radiograph should be obtained in all suspected cases of SCAP. Illustrative examples of radiographic abnormalities in SCAP are depicted in Fig. 4.1. Consolidation of a part or whole of the lung is the sine qua non of CAP (Fig. 4.1a). Air bronchograms are commonly seen inside the area of consolidation. The consolidation can be localized to a subsegment, segment, or lobe of the lung or can sometimes involve the entire lung. The involvement can also be in the form of more extensive fluffy airspace opacities suggesting bronchopneumonia (Fig. 4.1b) or in the form of interstitial or reticular opacities (Fig. 4.1c). Appearance of specks of airspaces within the area of consolidation indicates the development of necrotizing pneumonia (Fig. 4.1d). Multilobar radiographic abnormalities, bilateral infiltrates, and rapidly progressive radiographic abnormalities during therapy suggest severe pneumonia and are associated with poor prognosis (Marti et al. 2012). The differential diagnoses and mimics of SCAP are described in Table 4.2.

Several of the clinical and radiological features have been incorporated into various scoring systems, along with laboratory data, in diverse combinations to define SCAP. Complications such as sepsis, ARDS, multi-organ dysfunction syndrome (MODS), lung abscess, and parapneumonic effusion/empyema should be identified at the time of diagnosis and during the course of the illness. Computed tomography (CT) of the chest may sometimes be required to confirm pneumonia, characterize the pattern for clues to possible etiology, detect complications like lung abscess and empyema, and exclude alternate possibilities.

4.5.1 Scoring Systems

Various scoring systems can be used to identify SCAP and to decide the need for ICU admission (Marti et al. 2012).

The Pneumonia Severity Index (PSI) was developed by the investigators of the Pneumonia Outcomes Research Team (PORT) study (Fine et al. 1997). The score classifies the patient into one of five classes based on various patient- and
disease-related factors, with each class associated with a different predicted risk for mortality. Points are calculated based on factors such as age, gender, presence of co-morbid medical illness, physical findings, and laboratory and radiographic findings. Patients in classes IV and V have the highest predicted mortality risk of 8.2–9.3% and 27–31%, respectively, and may be considered to signify SCAP. However, PSI has its drawbacks. The score gives disproportionately more weightage to patient-related factors such as age and co-morbidities than to markers specific to the pneumonic illness, per se. Thus, in younger, previously healthy patients, it may underestimate the severity of pneumonia (Niederman et al. 2006). Moreover, pneumonia requiring ICU admission (use of assisted ventilation or vasopressors) does not always translate into higher mortality, and vice versa. Thus, the

Fig. 4.1 Chest radiographs of patients with severe community-acquired pneumonia. (a) Extensive consolidation of left upper and lower lobes. (b) Bilateral fluffy airspace opacities suggesting extensive bilateral bronchopneumonia; (c) Bilateral alveolar and interstitial opacities in a patient with severe community-acquired pneumonia; (d) Extensive consolidation of the right upper lobe with multiple cavitation suggesting necrotizing/cavitary pneumonia.
PSI is an excellent predictor of mortality, but it is an inadequate marker to indicate the severity of pneumonia or decide on ICU admission (Niederman 2009; Valencia et al. 2007). Moreover, it is cumbersome to use in routine practice.

**CURB-65** is an acronym for the clinical features that are used to assess the pneumonia severity and its prognosis. It assigns 1 point, on a 6-point scale (0–5), each to confusion, blood urea >7 mmol/L (42 mg/dL), respiratory rate ≥30 breaths/min, blood pressure <90 mmHg systolic or ≤60 mmHg diastolic, and age ≥65 years. Mortality increases with increasing score and is >20% with a score of 3 or more. Outpatient treatment is recommended when the score is 0 or 1, in-hospital treatment or hospital-supervised outpatient treatment for a score of 2, and in-hospital treatment is recommended for a score of 3 or more. ICU admission should be considered if the score is 4 or 5. The CURB-65 appears to be more discriminatory compared with the PSI on deciding the place of care and is easier to use. On the contrary, the mortality risk may be underestimated in older patients with co-morbidities, who may decompensate significantly even with mild pneumonia (Niederman 2007).

A simplified **CRB-65** has also been described, which can be used in the emergency department, since it does not require any laboratory parameter and is almost as effective as CURB-65. Since CRB-65 can underestimate the mortality risk slightly, it is advocated for outpatients only (Bauer et al. 2006; Capelastegui et al. 2006). Overall, both these scores may perform similarly in pneumonia patients with low risk of death, while CURB-65 may perform better in patients with a higher risk of mortality (Niederman 2009).

The **IDSA/ATS definition of SCAP** relies on the presence of any of the major criteria (need for invasive mechanical ventilation or septic shock necessitating vasoressors) or any three of the following minor criteria: (1) respiratory rate ≥30 breaths/
min; (2) ratio of partial pressure arterial oxygen and fraction of inspired oxygen (PaO2/FiO2 ratio) ≤250; (3) multilobar infiltrates; (4) confusion/disorientation; (5) blood urea nitrogen level ≥20 mg/dL (equivalent to blood urea ≥43 mg/dL); (6) leukopenia (leucocyte count <4000 cells/mm3) resulting from infection; (7) thrombocytopenia (<100,000/mm3); (8) hypothermia (core temperature <36 °C); (9) hypotension requiring aggressive fluid resuscitation (Mandell et al. 2007). Use of non-invasive ventilation can substitute for either of the first two minor criteria. Other criteria that should be considered include acute alcoholism/alcohol withdrawal, cirrhosis, asplenia, hypoglycemia (in nondiabetic patients), unexplained metabolic acidosis or elevated lactate level, and hyponatremia. Several studies have validated the use of these criteria for identifying SCAP (Phua et al. 2009; Liapikou et al. 2009; Chalmers et al. 2011).

Other prognostic scoring systems have also been developed to identify SCAP. Espana et al. have proposed and validated a tool, the CUROX80 for use in the emergency department to predict SCAP or future ICU requirement (Espana et al. 2006). More recent tools have focused on the prediction of the need for intensive respiratory and vasopressor support (IRVS), which is more objective than mere ICU admission, to define SCAP. The SMART-COP score was developed to predict the need for IRVS (Charles et al. 2008). The score uses eight parameters that are associated with the need for IRVS. These include systolic blood pressure <90 mmHg, multilobar infiltrates on a chest radiograph, albumin <3.5 g/dL, respiratory rate elevation (≥25/min for those ≤50 years and ≥30/min for those >50 years of age), heart rate >125/min, new onset confusion, hypoxemia (PaO2 <70 mmHg or SpO2 ≤93% or PaO2/FiO2 <333 for those ≤50 years and PaO2 <60 mmHg or SpO2 ≤90% or PaO2/FiO2 <250 for those >50 years), and arterial pH <7.35. Low blood pressure, hypoxia, and acidosis are given a score of 2, while the other parameters are given a score of 1 each. Using a cutoff of 3 points, the sensitivity and specificity were 92.3% and 62.3%, respectively, for the need for IRVS with a positive and negative predictive value of 22% and 98.6%, respectively. The performance of the score was superior to that of previously established PSI and CURB-65 scores for predicting the requirement for IRVS (Charles et al. 2008).

Currently, we suggest using the IDSA/ATS definition of SCAP till the time, a better definition or criteria are established. In addition to the indices for severity classification of CAP and prediction of mortality, scores such as the Acute Physiology and Chronic Health Evaluation (APACHE) and the Simplified Acute Physiology Score (SAPS) scores may be used to predict mortality in critically ill patients, in general (Knaus et al. 1985; Le Gall et al. 1993).

### 4.5.2 Biomarkers

Biomarkers may be used for different purposes in the context of CAP, including diagnosis, determining severity, risk stratification, initiation and discontinuation of antibiotics, and determining prognosis (Sungurlu and Balk 2018). Important biomarkers that have been tested in pneumonia include leucocyte count, C-reactive protein, procalcitonin, soluble triggering receptor expressed on myeloid cells (sTREM), and pro-adrenomedullin (pro-ADM). Amongst these, procalcitonin is the most
tested. However, serum procalcitonin level does not have sufficient specificity, when used alone, for the diagnostic differentiation from alternate diagnoses (for example, pulmonary edema, pulmonary tuberculosis, cryptogenic organizing pneumonia, viral infection, and others) (Yoon et al. 2018; Huang et al. 2014; Ito et al. 2019; Schuetz et al. 2018, 2017). A meta-analysis showed that the area-under the receiver operator characteristic curve was 0.75 for predicting mortality in patients with CAP, which implies that procalcitonin does not have sufficient discriminatory potential (Viasus et al. 2016). Further, a recent pragmatic, multicentric randomized trial showed that the duration of antibiotics is similar with procalcitonin-directed or a guideline-concordant antibiotic regime (Montassier et al. 2019). Serum lactate level, a marker of sepsis, measured at the time of presentation and its subsequent course may have a prognostic role. It may be measured in SCAP to assess the risk of mortality and as one of several parameters guiding initial resuscitation (Chen and Li 2015).

4.5.3 Identification of the Etiologic Agent

Identification of the pathogen causing SCAP is useful in the choice of the antibiotics being administered, and for gathering epidemiologic data in order to formulate or alter the local antibiotic policy. While a rapid test (such as urinary antigen detection) can direct the choice of the initial antibiotic regimen, tests that give a delayed result, such as microbial cultures are helpful in tailoring the antibiotics started empirically.

The IDSA/ATS guidelines recommend that an effort must be made to isolate pathogens in SCAP (Mandell et al. 2007). Pretreatment blood samples for culture and a sputum sample for Gram stain and culture should be obtained. The yield of blood culture is only 5–14% and is reduced to almost half, if the samples are drawn after antibiotic exposure (Rider and Frazee 2018). It has been estimated that for every case of bacteremic pneumococcal pneumonia, there would be about three cases without bacteremia which would be missed on blood culture (Said et al. 2013). Sputum Gram stain test is a sensitive and highly specific test for the identification of the common etiologic agents of CAP in adults (Del Rio-Pertuz et al. 2019). An endotracheal aspirate sample is obtained in place of sputum, in intubated patients. Endotracheal aspirates and bronchoscopic sampling have a higher yield than sputum (Mandell et al. 2007; Gupta et al. 2012; Musher and Thorner 2014). In case of a pleural effusion, a pleural fluid culture must also be performed.

Urinary antigen tests for Legionella pneumophila and S. pneumoniae should be performed for rapid diagnosis. Serology for other atypical organisms is not routinely indicated (Mandell et al. 2007; Gupta et al. 2012). In the presence of cavitary lesions, testing for Mycobacterium tuberculosis (sputum for acid-fast staining and Xpert MTB/RIF) and fungi (Periodic Acid Schiff and Grocott staining) in respiratory samples is also indicated. In case of an endemic or outbreak setting for influenza, a throat swab should be tested using real-time polymerase chain reaction (RT-PCR) for the influenza virus. In the wake of the COVID-19 pandemic, testing for SARS-CoV-2 using RT-PCR in respiratory samples is indicated in suspected cases, in an epidemiological setting. Other than influenza and SARS-CoV-2, routine testing for other viruses using polymerase chain reaction (PCR) in SCAP is generally not useful, outside the research setting (Mandell et al. 2007; Gupta et al. 2012; Musher and Thorner 2014).
4.6 Treatment

4.6.1 General Management

Patients with CAP are initially screened in emergency departments or outpatient clinics. The severity of pneumonia, risk of mortality, and probability of requirement of IRVS must be assessed using the CAP severity scores detailed above. Some patients may warrant a direct admission to the ICU. Others may initially be shifted to the ward, but may later deteriorate despite therapy and may require shifting to the ICU. Hemodynamic support with intensive monitoring and vasopressors/inotropes should be immediately instituted. Similarly, the patient should be quickly assessed for the need for assisted ventilation (high flow nasal cannula, non-invasive ventilation, or invasive ventilation). ARDS should be managed with lung protective ventilation, neuromuscular blockade and, if required, prone positioning. Appropriate fluid resuscitation must be performed in patients with septic shock along with the rational use of appropriate vasopressors/inotropes, blood components, and glucocorticoids, according to standard guidelines (Rhodes et al. 2017). The timely institution of hemodynamic and respiratory support, and administration of appropriate antibiotics have a significant impact on outcomes in SCAP (Phua et al. 2016).

4.6.2 Antimicrobial Therapy

Antibiotic therapy is the mainstay of treatment of CAP. As the causative pathogen is usually unknown at the time of diagnosis (unless a rapid test is positive), the initial choice of antibiotics is empiric. As the most common cause of SCAP is \textit{S. pneumoniae}, the empiric treatment is directed towards this microbe. However, the initial empiric antibiotic therapy should be different in cases with risk factors or clinico-radiological signs of infections with other organisms such as \textit{S. aureus}, \textit{Pseudomonas}, and other GNB. History, physical examination, and radiological appearance may give clues to the etiological agent. Adherence to antibiotic protocols, based on local microbiologic data and prevalent principles of antibiotic stewardship, results in superior outcomes than individualizing therapy (Martin-Loeches et al. 2010; Sakamoto et al. 2017). Thus, the choice of empiric treatment is guided by the presence or absence of risk factors for unusual or resistant pathogens (Table 4.3 and Algorithm 4.1) (Mandell et al. 2007; Gupta et al. 2012).

No Risk for Unusual or Resistant Pathogens  Combination therapy with a broad spectrum β-lactam antibiotic (such as amoxicillin-clavulanate, ceftriaxone, cefotaxime) and a macrolide (azithromycin or clarithromycin) is recommended according to standard guidelines (Mandell et al. 2007; Lim et al. 2009). This combination covers the most likely organisms including \textit{S. pneumoniae} and atypical pathogens like \textit{Legionella} and \textit{Mycoplasma}. This combination therapy has been found superior to β-lactam monotherapy, in both pneumococcal and non-pneumococcal SCAP (Baddour et al. 2004; Sligl et al. 2014; Gattarello et al. 2015). Although the IDSA/
ATS guidelines recommend that a respiratory fluoroquinolone (levofloxacin or moxifloxacin) may be used instead of a macrolide, fluoroquinolone use is not recommended in regions endemic for tuberculosis (Mandell et al. 2007; Gupta et al. 2012). Moreover, observational studies have suggested that regimens containing macrolides may have superior outcomes compared to fluoroquinolones, possibly due to their immunomodulatory properties (Martin-Löeches et al. 2010; Metersky et al. 2007; Restrepo et al. 2009; Lee et al. 2017). Initiation with parenteral treatment is recommended for SCAP (Lim et al. 2009).

If there are risk factors for or suspicion of unusual pathogens, the empiric antimicrobial therapy should be modified accordingly:

**Table 4.3 Risk factors for unusual pathogens and drug resistance**

| Organism | Risk factors |
|----------|--------------|
| Drug-resistant pneumococcus | Elderly<br>b-lactam or macrolide therapy within 3 months<br>Immunosuppression<br>Alcoholism<br>Day-care centers<br>Medical co-morbidities |
| Gram-negative bacilli | Recent hospitalization/antibiotics<br>Cardiopulmonary co-morbidities<br>Smoking/alcoholism<br>Underlying malignancy |
| Community-acquired methicillin resistant *Staphylococcus aureus* | Elderly<br>End-stage renal disease/renal replacement therapy<br>Prior MRSA infection/colonization<br>Recent hospitalization/antibiotics (particularly fluoroquinolones)<br>Contact sports<br>Men who have sex with men<br>Medical co-morbidities |
| *Pseudomonas spp* | Chronic obstructive pulmonary disease<br>Structural lung disease like bronchiectasis<br>Immunosuppression/recent steroid exposure<br>Recent antibiotics/recent hospitalization |

ATS guidelines recommend that a respiratory fluoroquinolone (levofloxacin or moxifloxacin) may be used instead of a macrolide, fluoroquinolone use is not recommended in regions endemic for tuberculosis (Mandell et al. 2007; Gupta et al. 2012). Moreover, observational studies have suggested that regimens containing macrolides may have superior outcomes compared to fluoroquinolones, possibly due to their immunomodulatory properties (Martin-Löeches et al. 2010; Metersky et al. 2007; Restrepo et al. 2009; Lee et al. 2017). Initiation with parenteral treatment is recommended for SCAP (Lim et al. 2009).

Risk Factors for *Pseudomonas aeruginosa* and Other GNB A prior infection/colonization with *Pseudomonas*, prior tracheostomy, structural lung diseases (like bronchiectasis and severe COPD), and immunosuppression (including repeated or chronic glucocorticoid use) have been implicated as risk factors for infection with *Pseudomonas aeruginosa* (Mandell et al. 2007; Cilloniz et al. 2019, 2016b; Restrepo et al. 2018; Sibila et al. 2015). Exposure to antibiotics in the recent past additionally predicts infection with drug-resistant *P. aeruginosa* (Cilloniz et al. 2016b). If risk factors for *Pseudomonas* CAP are present, an anti-pseudomonal b-lactam antibiotic (piperacillin-tazobactam, cefoperazone, cefoperazone-sulbactam, ceftazidime, cefepime, or a carbapenem) must be considered for the initial treatment in combina-

tation with either a fluoroquinolone or macrolide (for atypical organisms) (Mandell et al. 2007; Gupta et al. 2012; Rider and Frazee 2018). As risk factors for *Pseudomonas* and other GNB overlap, the same antibiotics should be utilized, if such risk factors are present or GNB is detected on gram staining, until the culture results confirm non-pseudomonal GNB. This strategy has been shown to reduce the risk of inappropriate empiric therapy (Mandell et al. 2007). If a non-pseudomonal GNB is confirmed, treatment can be tailored according to the sensitivity profile. Most such pathogens can be treated with a cephalosporin like cefuroxime, cefotaxime or ceftriaxone, β-Lactam/β-lactamase inhibitor, fluoroquinolone, or carbapenem (Lim et al. 2009).

**Risk Factors for *Staphylococcus aureus*** If there is a strong clinical suspicion of *Staphylococcus aureus* infection in SCAP, due to the presence of risk factors (Table 4.3), or if there is cavitary pneumonia or empyema, addition of vancomycin or teicoplanin must be considered until the results of culture are available (Rubinstein et al. 2008). Linezolid can also be used, but in countries with high burden of tuberculosis including India, empiric use of linezolid is discouraged (Gupta et al. 2012). Once the organism has been isolated and if found methicillin-sensitive (MSSA), the antibiotic should be changed to cloxacillin, oxacillin, or nafcillin (Rubinstein et al. 2008).

**Suspicion of Influenza or COVID-19** During a pandemic/epidemic of influenza or the influenza season, a high index of suspicion should be kept for influenza pneumonia, especially in the presence of nasal discharge, sore throat with diffuse ground glass opacification, or infiltrates on chest radiograph. It may or may not be associated with a secondary bacterial infection. Antiviral therapy with oseltamivir or zanamivir is warranted, preferably within 24 h, along with antibacterial therapy as per the local guidelines (Fiore et al. 2011). Since 2019, coronavirus disease caused by SARS-CoV-2 has also become an important diagnostic consideration in SCAP.

**Other Factors Affecting the Choice of Antibiotics** The empiric regimen will also be guided by the results of sputum or pleural fluid Gram stain report, which can usually be obtained in a few hours, the presence of renal or hepatic dysfunction, recent exposure to antibiotics, and known drug allergies. In case of penicillin allergy, β-lactams (including cephalosporins) should be avoided and aztreonam can be used.

**Timing of Initiation of Antibiotics** It is recommended that antibiotics should be initiated as early as the diagnosis of SCAP is made, preferably within 4 h, and ideally within 1 h (Mandell et al. 2007; Gupta et al. 2012; Rider and Frazee 2018). Time to first antibiotic dose may affect the outcome in SCAP, especially if the patient has sepsis or septic shock (Daniel et al. 2016; Houck et al. 2004; Lee et al. 2016).

**Route and Doses** Initiation with parenteral route is recommended for SCAP due to variable absorption via the oral route (Lim et al. 2009). Maximal doses should be used to ensure attainment of drug levels above the minimum inhibitory concentra-
tion (MIC). Pharmacokinetic and pharmacodynamic aspects must also be taken into consideration. β-lactams should ideally be given as extended infusions, whereas azithromycin, aminoglycosides, and fluoroquinolones must be used as once daily bolus dosing (Table 4.4).

**Change of Antibiotics After Results of Cultures**  The combined yield of cultures of blood and respiratory samples cultures in CAP is universally low and only about a quarter to one-third CAP patients can be microbiologically defined in the therapeutic time-frame (Lim et al. 2009). It has also been observed that results of blood culture prompt a change in antibiotic prescription in a very small number of cases (Afshar et al. 2009; Campbell et al. 2003; Kennedy et al. 2005). Empirical antibiotic approach and pathogen-directed antibiotic approach have been shown to have similar efficacy. However, the latter approach has lesser adverse effects and may theoretically reduce the emergence of drug-resistant microorganisms (van der Eerden et al. 2005). It is thus recommended that if the culture results identify a definite pathogen, antimicrobial therapy must be narrowed to a pathogen-directed specific therapy (Lim et al. 2009).

The choice of therapy should be based on results of in vitro susceptibility or local antibiotic policies based on sensitivity patterns. For example, amoxicillin,
clarithromycin, cefuroxime, ceftriaxone, or cefotaxime may be chosen if *S. pneumoniae* is isolated. Similarly, fluoroquinolones or macrolides are appropriate choices for *Legionella* species (Lim et al. 2009). If CA-MRSA is identified, clindamycin, trimethoprim/sulfamethoxazole, rifampicin, vancomycin, or linezolid may be chosen based on sensitivity pattern and inducible resistance (in case of clindamycin) (Lim et al. 2009; Liapikou et al. 2014). It must be re-iterated here that 11% cases of CAP will have mixed infections (Cilloniz et al. 2016a, 2011). However, the co-pathogens in most such instances would be viruses and hence tailoring of the antibiotic therapy can be safely carried out (Lim et al. 2009).

**Failure of Response to Initial Therapy**  Clinical response to appropriate antimicrobial therapy in terms of improvement in fever, tachycardia, confusion, and hypotension usually occurs within 2–4 days (Halm et al. 1998; Menendez et al. 2004a). However, rate of resolution also depends on age and co-morbid conditions (Low et al. 2005). Failure to achieve adequate response or clinical/radiological worsening after initial therapy may occur in about 15% cases of CAP of which most failures occur in the first 72 h (Menendez et al. 2004b). In SCAP managed in ICU, failure rate may be as high as 40% and is responsible for significant increase in mortality (Sligl and Marrie 2013; Morgan and Glossop 2015). The most common cause of treatment failure is an inadequate host response to infection, rather than inappropriate therapy (Sligl and Marrie 2013). Higher severity score of pneumonia, multilobar infiltrates, cavitation, pleural effusion, leukopenia, and presence of comorbidities are associated with treatment failures (Low et al. 2005; Menendez et al. 2004b; Roson et al. 2004). Among specific etiologic microorganisms, *Legionella pneumophila* and gram-negative pathogens are associated with a higher incidence of treatment failures (Low et al. 2005; Roson et al. 2004). Various factors that must be considered when there is a perceived failure of the initial therapy are mentioned below.

a. **Incorrect diagnosis**—Almost 16% of treatment failures are due to non-infective causes (Menendez et al. 2004b). Inflammatory disorders like vasculitis, organizing pneumonia, eosinophilic pneumonia, and other non-infective interstitial pneumonia may sometimes mimic CAP. Also, heart failure, alveolar hemorrhage and, less commonly, neoplasms can sometimes mimic CAP (Low et al. 2005). In such cases, detailed clinical evaluation, and advanced imaging modalities like computed tomography, when feasible, with or without percutaneous or bronchoscopic sampling may lead to a revision of the diagnosis.

b. **Targeting incorrect pathogen**—Uncommon presentations of tuberculosis, fungal pneumonia, or *Pneumocystis* pneumonia can lead to inappropriate therapy if managed empirically as CAP (Low et al. 2005). Pneumonia due to viral infections like influenza; or, severe acute respiratory syndrome, Middle East Respiratory Syndrome, or COVID-19 all caused by different coronaviruses may lead to progressive pneumonia and treatment failure (Low et al. 2005). Also, secondary nosocomial infection may occasionally lead to late treatment failure (after 72 h) (Genne et al. 2003). Also, in the presence of uncontrolled blood sugar with or without acidosis, neutropenia, or prior use of high-dose systemic glucocorticoids, a possibility of invasive fungal infection such as aspergillosis or mucormycosis should be considered.
c. Drug-resistant pathogens—Drug-resistant organisms account for only about 6% of treatment failures, if guideline-concordant antibiotic policy is used in initial therapy (Menendez et al. 2004b; Genne et al. 2003). It is important, therefore, that antibiotic policy adapted in a particular ICU is guided by the local antibiotic susceptibility data.

d. Patient-related factors—Decompensation of underlying co-morbid illness may lead to both early and late treatment failure (Sligl and Marrie 2013). Also, mechanical factors like an obstructed bronchus due to a mass or sequestration may lead to a poor response to antimicrobial therapy (Low et al. 2005).

e. Complications of SCAP and adverse effects of therapy—These are usually responsible for late failures and include ARDS, undrained empyema, lung abscess, and metastatic pyogenic abscesses (Sligl and Marrie 2013). In an analysis of treatment failures in patients recruited in 16 CAP trials, 30% of perceived treatment failures were because of adverse effects of antibiotics (Genne et al. 2003).

It is recommended that on perceived failure of initial antimicrobial therapy and once non-infective causes of the same are excluded (as elucidated above), microbiological analysis should be reviewed and repeated to rule out unusual organisms and mixed infections (Lim et al. 2009). However, a definite cause of treatment failure is elusive in nearly half of the failures (Menendez et al. 2004b; Genne et al. 2003). In the absence of definite microbiological data to guide therapy, addition of a fluoroquinolone (to β-lactam-macrolide combination) and/or vancomycin, and bronchoscopic sampling may be considered (Lim et al. 2009). Similarly, computed tomography scan of the chest or pleurocentesis may be carried out where indicated (Sligl and Marrie 2013).

Duration of Antibiotics Most patients of SCAP do not require treatment for more than 5–7 days. If azithromycin is used as the macrolide, a 3-day course of 500 mg/day is usually sufficient. If the patient has attained clinical stability and has remained afebrile for 2–3 days, antibiotics can be stopped in 5–7 days (Mandell et al. 2007; Gupta et al. 2012; Tansarli and Mylonakis 2018; Uranga et al. 2016). Procalcitonin levels <0.25 ng/ml or greater than 80% decline from the peak value can also be used to discontinue antibiotic therapy. However, procalcitonin levels should be interpreted together with clinical course, and not in isolation (Schuetz et al. 2018, 2017).

Pathogens such as Pseudomonas and Legionella may require 7–10 days of therapy and often longer, depending on the clinical response. Uncomplicated MRSA CAP may be treated with 7–10 days of antibiotics, but longer treatment may be required when there is bacteremia (2 weeks) or metastatic infections (4–6 weeks) (Mandell et al. 2007; Gupta et al. 2012; Tansarli and Mylonakis 2018; Uranga et al. 2016). Despite achieving clinical stability and a decline in procalcitonin levels, prolonged antibiotic therapy may be required in lung abscess, empyema, or necrotizing pneumonia or if extrapulmonary infections like endocarditis or meningitis are detected (4–6 weeks).
4.6.3 Adjunctive Therapies

Glucocorticoids In the last decade there have been several studies on the use of adjunctive glucocorticoids in SCAP, with the premise that exaggerated inflammation increases the mortality and morbidity in SCAP (Blum et al. 2015; Tagami et al. 2015; Torres et al. 2015). Use of anti-inflammatory glucocorticoids along with appropriate antibiotics may lead to improved outcomes. At present, however, the evidence is conflicting, and the routine use of glucocorticoids cannot be recommended.

A systematic review and meta-analysis involving nine randomized controlled trials and six cohort studies till 2015 concluded that use of glucocorticoids in CAP was safe, reduced the duration of illness, and prevented progression to ARDS (Wan et al. 2016). A Cochrane analysis published subsequently concluded that glucocorticoids have a mortality benefit in SCAP but not in non-severe CAP. The numbers needed to treat (NNT) was 18 patients to prevent one death from SCAP (Stern et al. 2017). More recently, one systematic review and individual patient data meta-analysis found that glucocorticoids reduced time to clinical stability and length of hospitalization without any mortality benefit and at the cost of increased risk of CAP related rehospitalization and hyperglycemia (Briel et al. 2018). In contrast, another recently published meta-analysis focused on glucocorticoids use in SCAP showed mortality benefit and reduced hospital stay with the use of glucocorticoids (Wu et al. 2018).

Overall, it appears that glucocorticoids may have a role in the management of SCAP to hasten recovery, but further studies will be required to identify the characteristics of patients in whom the benefits will outweigh the risks and also to establish the timing, dose, and duration. A large ongoing trial—ESCAPe trial (Extended Steroid in CAP(e); ClinicalTrials.gov NCT01283009) is likely to answer some of these questions.

Other Systemic Adjunctive Therapies Intravenous Immunoglobulin (IVIg) in general and IgM, in particular, have a vital role in host defense mechanisms in SCAP. IVIg preparations, specially, IgM-enriched formulations have been studied for their potential role as an adjunctive therapy in SCAP, with less than promising results (Garnacho-Montero et al. 2018). A recently concluded phase II trial failed to show benefit of IgM-enriched IVIg therapy in mechanically ventilated SCAP patients (Welte et al. 2018). Post-hoc analysis suggested that a few subgroup populations may benefit from such therapy.

Statins may be potential candidates for adjunctive therapy in SCAP due to their anti-inflammatory and antioxidant properties. However, prospective trials have found no role of statins in improving the outcomes in SCAP and cannot be recommended at present (Havers et al. 2016; Viasus et al. 2015).

Chest Physiotherapy There is no role of routine chest physiotherapy in all patients with SCAP. Hospital-based physiotherapy, after achieving clinical stability, may be useful in elderly patients admitted with CAP, who have declining physical function and difficulty in clearing respiratory secretions. It may reduce the re-admission rates and should be encouraged (Sun Jung Kim et al. 2015).
4.6.4 Management of Parapneumonic Effusion

In every case of SCAP, pleurocentesis should be carried out if significant pleural effusion is present on imaging (Skouras et al. 2010). Loculated effusions and presence of enhancing thickened parietal pleura on CT portend a poor prognosis and must be subjected to diagnostic thoracentesis, even if small in size (Colice et al. 2000). If the fluid is frank pus or has positive gram stain or culture, intercostal chest drainage must be done. Other indications for the same are an effusion occupying greater than half of the hemithorax, loculated effusion, effusion with thickened parietal pleura, pleural fluid glucose less than 60 mg/dL, or pH less than 7.2 (Colice et al. 2000). A few patients with loculated effusions may require intrapleural fibrinolytics, thoracoscopic adhesiolysis, or surgical decortication (Ferreiro et al. 2018; Dhooria et al. 2014).

4.6.5 Assessing Response to Treatment

With appropriate treatment, clinical response should be achieved in 2–3 days, especially improvement in fever, hypotension, oxygenation, tachycardia, and tachypnea. Cough and fatigue may take up to 2 weeks to resolve and resolution of radiological infiltrates may lag behind by a month or more. Radiological resolution may be delayed particularly in the elderly, in those with multilobar presentation at presentation and in those with underlying structural lung disease. However, a lack of clinical response by the third day of treatment indicates a possibility of either an inappropriate antibiotic or sometimes an incorrect diagnosis, as discussed earlier (Halm et al. 1998; Menendez et al. 2004a; Bruns et al. 2007; Morley et al. 2017). Routine chest radiograph during the course in hospital is not warranted if the patient is clinically improving (Bruns et al. 2007).

When the patient is hemodynamically stable and has a functional gastro-intestinal tract, switch-over must be made to appropriate oral antibiotics (Gupta et al. 2012; Oosterheert et al. 2006). The choice of oral antibiotic can be deduced directly from the intravenous combination to which the patient has responded, if an effective oral formulation is available (Mandell et al. 2007). In case of intravenous cephalosporins, however, a switch to oral amoxicillin-clavulanate is preferred (Lim et al. 2009). Narrowing to monotherapy can be considered if culture results have not shown polymicrobial infection (Mandell et al. 2007; Lim et al. 2009).

4.6.6 Discharge

Patients can be discharged once they have been switched to oral antibiotics, have attained clinical stability, and have an unequivocally improving clinical course. Follow-up must be done after a week, on an outpatient basis. A chest radiograph must be performed after 2–3 months to look for any underlying lung disease, especially in the elderly and in smokers.
At the time of discharge of patients with SCAP, the status of pneumococcal and influenza vaccination must be enquired, and those not immunized must be advised to do so, as per the local guidelines. Smoking cessation must be re-iterated at this point and optimization of other medical illnesses must be ensured with advice on regular medical follow-up for each of those illnesses. Even after discharge, the mortality of SCAP patients remains higher than controls at the end of 1 year and 2 years, even when they have no co-morbidities. Cardiovascular risk may remain high even up to 5–10 years and therefore appropriate therapy must be resorted to reduce the risk, like institution of antiplatelet or statin therapy, when eligible (Rider and Frazee 2018).

4.6.7 Prevention of SCAP

**Pneumococcal Vaccination**  There are two kinds of pneumococcal vaccines currently available: 23-valent pneumococcal polysaccharide vaccine (PPV23) and 13-valent pneumococcal conjugate vaccine PCV13 (van Werkhoven and Huijts 2018). PPV23 has been shown to prevent invasive pneumococcal disease in all age groups except those less than 2 years of age but its efficacy to prevent pneumonia has not been conclusively established in elderly patients and those with chronic co-morbid condition (van Werkhoven and Huijts 2018). On the other hand, PCV13 has demonstrated efficacy to prevent vaccine-type invasive disease as well as pneumonia in immunocompetent elderly patients.

**Influenza Vaccination**  Influenza vaccines are available as trivalent/quadrivalent inactivated, quadrivalent live-attenuated, and quadrivalent recombinant vaccines (Grohskopf et al. 2018). Efficiency of influenza vaccines to prevent pneumonia or hospitalization has varied from 25% to 53% in various meta-analyses (Heo et al. 2018). The vaccine preparations are updated annually based on the prevalent strains (Grohskopf et al. 2018). Currently, in India, annual vaccination with influenza vaccine is recommended for all individuals with co-morbid conditions, immunocompromised patients (only inactivated vaccine), pregnant women, and health care workers. Vaccination is desirable for elderly individuals (≥65 years) and children between ages of 6 months and 8 years (Ministry of Health and Family Welfare Directorate General of Health Services (National Centre for Disease Control) 2018).

4.7 Future Directions

**Biomarkers**  Presepsin is the soluble fragment of CD14 (monocyte lipopolysaccharide receptor). Levels of presepsin correlate with increased bacterial phagocytosis and correlate with development of sepsis and shock (Klouche et al. 2016). Fatty acid binding proteins (FABP) have been found to help in predicting the severity, risk stratification, and assessment of the response to treatment effectively, when
measured in serum or urine (Chen and Li 2014; Tsao et al. 2016). Adrenomedullin (ADM) and its product mid-regional-pro ADM have been studied as markers of severity of CAP and its outcome with some promising results (Leoni and Rello 2017; Elke et al. 2018; Pereira et al. 2006). Expression of monocyte human leukocyte antigen-DR (mHLA-DR) on monocyte membranes, 24 h after admission in SCAP patients, is lower in individuals who are not likely to survive by day 28 (Zhuang et al. 2015). These novel biomarkers probably indicate the virulence of the pathogen, but more importantly, they signify the dysregulated immune response of the host and other unknown host characteristics that are associated with the development of severe pneumonia (Leoni and Rello 2017).

Detection of Pathogens Conventional culture and serological methods have a high turnaround time and lack sensitivity and specificity, thus leading to dependence on appropriate empiric treatment. A large number of SCAP are due to viruses as expounded earlier, implying that a lot of unnecessary antibiotic use is in practice. Novel molecular techniques like multiplex real-time PCR can reduce the turnaround time and improve the detection accuracy in identifying the causative pathogens in SCAP (Gelfer et al. 2015). Also, there is a difference in the genetic expression of host in non-infective inflammation, bacterial infection, and viral infection. An understanding and detection of the same may avoid the overuse of antibiotics (Sweeney et al. 2016).

Personalized Treatment Apart from the virulence of pathogens and immunity of the host, there are probably several other factors that predict progression to dysregulated immunity, development of SCAP, and poor response to treatment. These might include the inherent metabolic processes of the host and the way they get affected during an infection. Metabolomics is an emerging branch that deals with these aspects. Using liquid chromatography tandem mass spectrometry, a host of metabolites, particularly lipid metabolites, have been identified that may serve as biomarkers of SCAP and may predict development of sepsis and poor outcome (Neugebauer et al. 2016; To et al. 2016). Similarly, sick-euthyroid syndrome characterized by low levels of free triiodothyronine (FT3) with low to normal levels of other thyroid hormones has been associated with poor outcomes in CAP suggesting a possible mal-adaptive response (Liu et al. 2016). Genetic factors also probably have a role and individual genetic polymorphisms may dictate not only susceptibility to severe infection but also response to treatment. In a recent genome-wide association studies in patients admitted to ICU with pneumonia and sepsis, several single nucleotide polymorphisms were identified on FER gene on chromosome 5, that were strongly associated with clinical outcomes (Rautanen et al. 2015). Defects in transcriptional signatures pertaining to immunological and inflammatory response have been studied in the blood transcriptome of SCAP patients (Hopp et al. 2018). Besides, the intrinsic pulmonary flora of the host, as judged by microbiota profiles of sputum/other respiratory samples, may predict the severity of CAP, length of stay, and outcome (Pettigrew et al. 2016). Developments are underway in the fields of vaccination, immunomodulation, use of monoclonal antibodies against pathogens and their
toxins, and use of nanotechnology for intensifying the attack on pathogens (Rello and Perez 2016). Hence, metabolomics, genomics, microbiomics, transcriptomics, and immunology are the way forward in our understanding of SCAP. They may lead to the development of valuable biomarkers and targeted treatment strategies paving way for personalized management in SCAP.

Algorithm 4.1 Approach to Management of SCAP

- Assess the need for assisted ventilation or oxygen support
- Assess the need for vasopressor and inotropic support
- Hemodynamic monitoring
- Blood sample for culture before the first dose of antibiotic
- Sputum/endotracheal aspirate or bronchoalveolar lavage Gram stain culture

No risk factors for Pseudomonas

- Amoxicillin-clavulanate, Ceftriaxone, or Cefotaxime
  AND
- Azithromycin or Clarithromycin

Risk factors for Pseudomonas

- Piperacillin-tazobactam, Cefoperazone, Cefoperazone-sulbactam, Ceftazidime, or Cefepime, Carbapenems
  AND
- Fluoroquinolone or Aminoglycoside + Macrolide

Add Vancomycin or Teicoplanin or Linezolid if Staphylococcus aureus infection suspected

Clinical improvement in 2-3 days

- Culture positive
  - De-escalate to monotherapy and stop antibiotics in 5 to 7 days
- Culture negative
  - Stop antibiotics in 5-7 days

No clinical improvement in 2-3 days

- Culture positive
  - Change antibiotics as per culture report
  - Look for empyema, lung abscess, metastatic abscesses
- Culture negative
  - Look for non-infective pneumonia mimics like ARDS, heart failure, diffuse alveolar hemorrhage

**De-escalate to monotherapy and stop antibiotics in 5 to 7 days**
**Stop antibiotics in 5-7 days**
**Change antibiotics as per culture report**
**Look for empyema, lung abscess, metastatic abscesses**
**Look for non-infective pneumonia mimics like ARDS, heart failure, diffuse alveolar hemorrhage**
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