Updates on community acquired pneumonia management in the ICU

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ABSTRACT

While the world is grappling with the consequences of a global pandemic related to SARS-CoV-2 causing severe pneumonia, available evidence points to bacterial infection with *Streptococcus pneumoniae* as the most common cause of severe community acquired pneumonia (SCAP). Rapid diagnostics and molecular testing have improved the identification of co-existent pathogens. However, mortality in patients admitted to ICU remains staggeringly high.

The American Thoracic Society and Infectious Diseases Society of America have updated CAP guidelines to help streamline disease management. The common theme is use of timely, appropriate and adequate antibiotic coverage to decrease mortality and avoid drug resistance. Novel antibiotics have been studied for CAP and extend the choice of therapy, particularly for those who are intolerant of, or not responding to standard treatment, including those who harbor drug resistant pathogens. In this review, we focus on the risk factors, microbiology, site of care decisions and treatment of patients with SCAP.

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1. Introduction

Mortality related to severe community acquired pneumonia (SCAP) is still a major concern, especially in the aged, despite advances in rapid diagnostic tests, newer treatment options and vaccine strategies. Pneumonia related mortality in those admitted to ICU is approximately 30% (Fine et al., 1996; Metersky, Waterer, Nsa, and Bratzler, 2012; Walden

Abbreviations: ATS/IDSA, American Thoracic Society/Infectious Disease Society of America; CRP, C-reactive protein; IRVS, Intensive respiratory or vasopressor support; MV, Mechanical ventilation; PCT, Procalcitonin; SCAP, Severe Community Acquired Pneumonia.

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et al., 2014). Although this has generally been described for bacterial pneumonia, recent experience from the pandemic with novel coronavirus (COVID-19) has shown mortality to be 35–50% in patients, who require invasive mechanical ventilation (Richardson et al., 2020). *Streptococcus pneumoniae* continues to be the most common bacterial pathogen responsible of CAP, regardless of patient age and comorbidities (Said et al., 2013). Health care associated pneumonia is no longer recognized as a distinct entity, but as a form of CAP, and there is increasing evidence of Gram-negative pathogens as etiologic agents of CAP (Prina et al., 2015). Recently coined "PES" pathogens (*Pseudomonas aeruginosa*, E*nterobacteriaceae* that are extended-spectrum β-lactamase-positive, and methicillin-resistant *Staphylococcus aureus*) account for up to 6% of hospitalized CAP (Prina et al., 2015). Use of polymerase chain reaction (PCR) tests have led to an increased detection of respiratory viruses in patients admitted with CAP (Jain et al., 2015), and our recent experience

Table 1
Risk factors for severe community acquired pneumonia.

Patient related factors	Pathogen specific	Severity of illness	Process related
Age >65 years	Drug resistant *S. pneumoniae*	Leukopenia/Leukocytosis	Inadequate antibiotics
Co-morbid conditions	*P. aeruginosa*	Platelet count $\leq 10^5/mm^3$ or $\geq 4 \times 10^5/mm^3$	Delay in ICU care
Lack of fever	*Enterobacteriaceae* extended-spectrum β-lactamase positive	PaCO2 <35 mm Hg or >45 mm Hg	Delay with mechanical ventilation
RR > 30/min	Methicillin-resistant *Staphylococcus aureus*	Multi-lobar pneumonia	
Genetic predisposition		Bacteremia	
		Shock	
		Elevated BUN $\geq$ 19.6 mg/dl	
		pH < 7.35	
		Hypoalbuminemia	

with SARS- CoV-2, has further emphasized the importance and high frequency of viral pneumonia.

The American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) recently updated the 2007 CAP management guidelines to streamline diagnostic testing and antibiotic usage (Metlay et al., 2019). The National Institute for Health and Care Excellence (NICE) also published updated guidelines on diagnosis and management of adult CAP patients in 2019 ("Pneumonia in adults: diagnosis and management,"). Although, there is no concrete definition for SCAP, those who are admitted to the ICU because they require mechanical ventilation (MV) or intensive respiratory or vasopressor support (IRVS), and those who have hypotension that is unresponsive to fluids, are considered to have SCAP. Outside of those definitions there is still debate on how best to identify severely ill CAP patients(Torres et al., 2019). Since, delay in ICU care and use of inappropriate antibiotics are associated with worse outcomes in SCAP patients, the site of care decision, and identification of high-risk patients is paramount. Recommended antibiotics in treatment of SCAP remain either a combination of β-lactam plus macrolide or β-lactam plus fluoroquinolone; however, the emergence of PES pathogens requires more closer considerations on the appropriate choice of antibiotics (Postma et al., 2015). In this review, we focus on the current literature and controversies regarding risk factors, microbiology, site of care decisions and treatment of patients with SCAP.

1.1. Risk factors for mortality

The disease burden related to hospitalized CAP is substantial with 102,821 annual deaths in the United States alone, corresponding to a mortality during hospitalization of 7% (J. A. Ramirez et al., 2017). Hayes and colleagues in a recent study showed that the average annual age-adjusted pneumonia associated hospitalization rate was 464.8 per 100,000; however, there was a significant decrease in pneumonia related hospitalizations from 2001–14, despite a significant increase in sepsis or respiratory failure (Hayes et al., 2018).

Risk factors of mortality related with severe CAP include advanced age (>65 years), co-morbid conditions, lack of fever on admission, respiratory rate greater than 30 breaths/min, diastolic or systolic hypotension, elevated blood urea nitrogen (BUN >19.6 mg/dL), pH of less than 7.35, profound leukopenia or leukocytosis, bacteremia, inadequate antibiotic therapy, need for MV and hypoalbuminemia (Mandell et al., 2007; Metersky, Waterer, et al., 2012). In a prospective study including 3700 SCAP patients comparing those who needed MV vs. not, MV was the most predominant driver for mortality (adjusted odds ratio = 3·54, 95% CI: 1·45-8·37, p = 0·006)(Ferrer et al., 2018).Other studies have shown a higher mortality corresponding to severity of illness on admission, lower hematocrit, thrombocytopenia(platelet count $\leq 10^5/mm^3$) or thrombocytosis(platelet count $\geq 4 \times 10^5/mm^3$), hypocapnia (PaCO2 <35 mm Hg) or hypercapnia (PaCO2 > 45 mm Hg), presence of multi-lobar infiltrates on chest imaging and an elevated red cell distribution width, alone or in combination with elevated BUN $\geq$ 30 gm/

dl (Braun, Kheir, Mashiach, Naffaa, and Azzam, 2014; Garau et al., 2008; Laserna et al., 2012; J. H. Lee et al., 2013; Prina et al., 2013; Walden et al., 2014). Waterer et.al. studied avoidable factors contributing to CAP specific short-term mortality from a large prospective study including 832 patients, and found only 2 patients, who died had an identifiable lapse in quality of in-patient pneumonia care with delayed administration of antibiotics in presence of shock or antibiotic therapy not consistent with the IDSA/ATS 2007 CAP guidelines(Waterer et al., 2018). Thus, SCAP mortality is closely associated with older age, presence of comorbidities and severity of disease on admission (Ito et al., 2017) (Table 1).

Another factor that may influence outcomes in patients with SCAP is related delay in receiving appropriate treatment or admission to the ICU (Restrepo, Mortensen, Rello, Brody, and Anzueto, 2010). Most studies use an average of 6 hours as a cutoff for receiving appropriate antibiotics after being evaluated in the emergency department (Mandell et al., 2007; Metersky et al., 2006; Ruiz et al., 1999; Torres et al., 1991; Waterer, Kessler, and Wunderink, 2006). In a study including 453 CAP patients, investigators noted a significant difference in 28-day mortality (11.7% vs. 23.4%) for those who were directly admitted to the ICU from the emergency room with an obvious need for ICU care, compared to those without obvious need for ICU care who had delayed admission (Renaud et al., 2009). Hraiech et.al. noted a mortality advantage with CAP patients, who required mechanical ventilation within 72 hours of the onset of CAP compared to those who required mechanical ventilation 4 or more days after the onset of CAP (28% vs. 51%, p = 0.03) (Hraiech et al., 2013). Hence, any delay in recognizing severe illness, identification of those at risk for mechanical ventilation or need for ICU level of care with an accompanying late delivery of appropriate therapy may adversely impact patient outcomes in severe CAP.

1.2. Determination of site of care

Identification of severe pneumonia early in the course seems favorable, but is fraught with complexity. Several investigators have proposed severity scoring systems to predict the risk of death but none has consistently shown improvement in mortality after implementation in clinical practice (Torres et al., 2019). The most widely used prognostic scoring systems are the Pneumonia Severity Index (PSI), the CURB-65 score, ATS/IDSA criteria for severe CAP, SMART-COP, CAP-PIRO and CURXO-80 (Table 2) (Charles et al., 2008; Espana et al., 2006; Mandell et al., 2007). While both PSI and CURB-65 are good in predicting mortality with CAP patients, there is a poor correlation between mortality risk and the need for ICU admission(Torres et al., 2019). For example, young and previously healthy individuals may have a severe pneumonia, yet a low predicted mortality, but could still benefit from intensive respiratory and vasopressor support in an ICU. (See Table 3.)

The SMART–COP scoring system estimates the need for ICU care by predicting the need for intensive respiratory and vasopressor support (IRVS)(Charles et al., 2008). It assigns points to 8 clinical features associated with the need for IRVS: systolic blood pressure < 90 mm Hg,

Table 2

Severity assessment scores in severe community acquired pneumonia. ATS/IDSA-2007 score is shown in Figure-1. SaO2: Oxygen saturation, PaO2: Partial pressure of oxygen

A-DROP	SMARTCOP	REA-ICU	SCAP SCORE	CAP-PIRO
One point for each of the following variables - Age: Male ≥70 years or female ≥75 years - BUN ≥21 mg/dl - SpO2 ≤90% or PaO2 ≤ 60 mm Hg - Confusion - Systolic BP ≤90 mmHg	Points are assigned to the variables as follows - Low systolic BP <90 mmHg (1 point) - Multi-lobar chest radiography involvement (1 point) - Low albumin level <3.5 g/dl (1 point) - High RR ≥ 25/min in ≤ 50 yrs and ≥ 30/min > 50 years(1 point) - Tachycardia > 125/min (1 point) - Confusion (1 point) - Poor oxygenation SaO2 <93% in ≤50 yrs and ≤90% in > 50 yrs(2 points) - Low arterial pH < 7.35 (2 points)	Points are assigned to the variables as follows - Male gender (1 point) - Comorbid conditions ≥1 (1 point) - RR ≥30/min (1 point) - WBC count <3000 or ≥20,000 /ml (1 point) - HR ≥125/min (1 point) - Age <80 (1 point) - Multi-lobar infiltrates or pleural effusion (2 points) - SpO2 <90% of PaO2 <60 mm Hg (2 points) - Arterial pH <7.35 (2 points) - BUN ≥11mmol/L (2 points) - Sodium <130 mEq/L (3 points)	Major Criteria - pH < 7.30 (13 points) - systolic pressure < 90 mm Hg (11 points) Minor Criteria - RR > 30 /min (9 points) - BUN > 30 mg/dl (5 points) - Altered mental status (5 points) - PaO2/FiO2 <250 (6 points) - Age ≥80 years (5 points) - Multi-lobar or bilateral infiltrates on chest X-ray (5 points)	One point assigned to each of the following variables obtained within 24 hours of ICU admission: - Comorbidities (chronic obstructive pulmonary disease, immunocompromise) - Age >70 years - Bacteremia - Multi-lobar opacities in chest radiograph - Shock - Severe hypoxemia - Acute renal failure - Acute respiratory distress syndrome
Cumulative score 0: Manage at home Cumulative score 1,2: Manage at home or hospital 3: Manage at hospital 4,5: Manage in ICU	Presence of more than 3 points identified 92% of patients who received intensive respiratory care or vasopressor support	Risk Classes based on cumulative scores Score ≤3: Risk class 1 Score 4-6: Risk class 2 Score 7-8: Risk class 3 Score ≥9: Risk class 4 REA-ICU class predicts ICU admission as well as mortality	Severe Community Acquired Pneumonia if Cumulative score of 10 OR At least 1 major criterion OR At least 2 minor criteria	Patients stratified in four levels of risk based on cumulative score - Low, 0–2 points - Mild, 3 points - High, 4 points - Very high, 5–8 points

Table 3

Newer antibiotics in treatment for Community Acquired pneumonia. DRSP: Drug resistant Streptococcus pneumoniae, MRSA: Methicillin resistant Staph aureus, VRE: vancomycin-resistant Enterococcus (VRE)

Drug Name	Class	Activity	Dose in IV
Ceftaroline	5th generation Cephalosporin	Gram-positive including resistant pneumococcus and MRSA and Gram-negatives	600 mg every 12h
Cectobiprole	5th generation Cephalosporin	Extended spectrum activity against Gram- positive, MSSA, Methicillin resistant coagulase negative Staph, DRSP, and Gram-negatives including *Pseudomonas* and *Enterobacteriacae*. No activity against MRSA.	500 mg every 8h
Solithromycin	4th generation macrolide	*S. pneumoniae, H.influenzae*, atypical pathogens and macrolide resistant organisms	400 mg every 24h
Nemonaxacin	Non-fluorinated quinolone	MRSA, DRSP and ertapenem-non-susceptible Enterobacteriaceae	750 mg every 24h
Delafloxacin	Novel fluoroquinolone	Gram-positives including drug resistant S. pneumoniae (penicillin-, macrolide-, multiple-drug resistant), fastidious Gram-negative pathogens including Haemophilus species (β-lactamase producing, macrolide-non-susceptible) and *S. aureus* (MRSA, fluoroquinolone-non-susceptible MSSA)	300 mg every 12h
Omadacycline	Aminomethycycline	*H. influenzae, M. catarrhalis*, Legionella, Chlamydia, Mycoplasma, MRSA, DRSP, *Streptococcus pyogenes, Streptococcus agalactiae* and VRE. Not effective against Proteus, Providencia, Pseudomonas, and Morganella.	100 mg every 12 hours for two doses, then 100 mg every 24 hours
Lefamulin	Semi-synthetic Pleuromutilin	Gram-positive pathogens including DRSP and MRSA, fastidious Gram-negative pathogens and atypical pathogens including *M. pneumoniae* (including macrolide-resistant strains), *C. pneumoniae*, and *L. pneumophila*.	150 mg every 12h

multilobar infiltrates on chest x-ray, albumin < 3.5 g/dL, respiratory rate elevation (>25/min for those ≤ age 50, and > 30/min for those > age 50), tachycardia (> 125/min), confusion, low oxygen (PaO2 < 70 mm Hg or saturation ≤ 93% if ≤ age 50 and PaO2 < 60 mm Hg or saturation ≤90% if > age 50), and arterial pH < 7.35. The abnormalities in systolic blood pressure, oxygenation and arterial pH each received 2 points, while the 5 other criteria received 1 point each. Using a cut off of at least 3 points, SMART COP has a sensitivity of 92.3% and the specificity 62.3% of predicting the need for IRVS.

The 2007 IDSA/ATS guidelines for CAP recommend ICU care be considered if the patient had one of two major criteria (need for mechanical ventilation or septic shock with the need for vasopressors), or 3 of 9 minor criteria (Mandell et al., 2007). The minor criteria include: respiratory rate ≥ 30 breaths/min, PaO2/FiO2 ratio ≤ 250, multilobar infiltrates, confusion/disorientation, uremia (BUN level >20 mg/dL), leukopenia (WBC count <4000 cells/mm3), thrombocytopenia (platelet count <100,000 cells/mm3), hypothermia (core temperature <36 degrees C), and hypotension requiring aggressive fluid resuscitation.

Salih and associates simplified the ATS/IDSA criteria by excluding variables that occurred in <5% of cases -leukopenia, thrombocytopenia and hypothermia, and noted similar predictive value for mortality and intensive care admission as compared to the original ATS/IDSA criteria (Salih, Schembri, and Chalmers, 2014). In a study involving 6,874 patients with 6.4% mortality, Ranzani and associates showed that the Sepsis -3 tool, quick Sequential (Sepsis-related) Organ Failure Assessment -qSOFA can help identify patients at risk of death, but disease-specific scoring systems still outperformed its ability for mortality discrimination(Ranzani et al., 2017). Zhang and colleagues studied 742 CAP patients admitted from the ER and found similar predictive capacity between qSOFA, SOFA and CURB-65 scores for ICU-admission, with AUC of 0.712, 0.744 and 0.705 respectively(Zhang, Liu, Liu, Ma, and Zeng, 2020). The 2007 ATS/IDSA criteria remain the most useful tool to determine ICU level of care and are straightforward for direct admission to ICU for those who require IRVS. Whereas, for those, who do not satisfy criteria for IRVS the latest guidelines recommend using the 2007 ATS/IDSA minor criteria plus clinical judgement.

Since the therapeutic benefit is most certain if patients at risk of severe disease can be discriminated early on and transferred to appropriate setting, phenotyping using biomarkers seems compelling in SCAP. Serum levels of C-reactive protein and procalcitonin (PCT) are the most studied. In patients with SCAP, measurement of initial and serial levels of PCT can help to define those with a poor prognosis (Masia et al., 2005). Kruger et al reported non-survivors had significantly higher median PCT levels on admission than survivors (0.88 vs. 0.13 ng/mL; p= 0.0001)(Kruger et al., 2008). Ramirez found no patient with ≥ 3 ATS minor severity criteria and PCT levels below the cutoff (0.35 ng/mL) needed ICU admission compared with 14 (23%) with levels above the cutoff (p=.032)(P. Ramirez et al., 2011). In a meta-analysis of seven studies, a PCT-based regimen in patients with severe sepsis or septic shock, the 28-day mortality was not different between the PCT-based regimen and standard treatment groups with the exception of shorter duration of antimicrobial therapy in the PCT arm(Prkno, Wacker, Brunkhorst, and Schlattmann, 2013). PCT or other biomarkers are not specific for pneumonia itself, and its overall use for disease severity is best achieved when used in combination with disease specific scoring system and clinical judgement.

2. Microbiology

S. pneumoniae remains the most common bacterial pathogen responsible of SCAP, regardless of age and comorbidities(Mandell et al., 2007). Although antibiotic-resistant variants of *S. pneumoniae*, have become increasingly common, the ICU mortality related with pneumococcal pneumonia has decreased over the last decade (Gattarello et al., 2014). In a study from Spain of SCAP patients spanning 3 time periods from 1999 - 2013, *S. pneumoniae* was the most common pathogen isolated with an overall incidence of 41.7% and over 80% of all causes of bacteremia (Valles et al., 2016). Other pathogens implicated with severe CAP include viruses (e.g., influenza, avian-origin influenza A - H7N9, novel H1N1, H3N2 influenza, respiratory syncytial virus, coronavirus illness of severe acute respiratory syndrome [SARS], Middle East respiratory syndrome coronavirus (MERS-CoV), atypical bacteria including *L. pneumophila*, *M. pneumoniae*, *M. tuberculosis*, and *H. influenzae*. *S. aureus* (including methicillin-resistant forms, or MRSA), enteric gram-negatives and, rarely, anaerobes may also be involved with severe disease based on risk factors.

Recent studies using PCR techniques have shown an increasing frequency of a viral etiology in ICU patients with CAP, but often in combination with a bacterial pathogen(Choi et al., 2012; de Roux et al., 2004; Wiemken et al., 2013). There is a high incidence of post Influenza bacterial pneumonia with significant mortality up to 10% with both seasonal and pandemic influenza(Metersky, Waterer, et al., 2012).In the multicenter EPIC study including 482 SCAP patients, the most common identified pathogens were due to a viral etiology (22%), followed by

bacterial infection alone in 19% and 4% with mixed infection, but many had no identified pathogen. In those with SCAP, the viral pathogens were: rhinovirus (8%), influenza (6%), metapneumovirus, RSV, parainfluenza, coronavirus and adenovirus(Jain et al., 2015). Influenza can lead to a primary viral pneumonia or to secondary bacterial infection with pneumococcus, *S. aureus*, or *H. influenzae*. Pandemics have become a global concern with multiple outbreaks, mostly with Influenza A (H1N1) in 2009, novel avian-origin influenza A (H7N9) in 2013 and in both instances bacterial coinfections, mostly with *S. pneumoniae* were common (Li et al., 2014; MacIntyre et al., 2018; Muscedere et al., 2013). Most recently, a novel coronavirus disease that originated in Wuhan, China in 2019 (COVID-19) developed into a worldwide pandemic with high fatality rates overwhelming healthcare systems in many countries (Wu and McGoogan, 2020).

Enteric gram-negatives (most commonly *P. aeruginosa*) can be found in up to 2% of identified CAP pathogens and are usually seen in patients who have prior structural lung disease, those who are on corticosteroids, those who had prior antibiotic therapy or had septic shock on admission (Falguera et al., 2009). Prina and colleagues report a 6% incidence of PES pathogens (*P. aeruginosa, Enterobacteriaceae* with extended-spectrum β-lactamases, and methicillin-resistant *Staphylococcus aureus*) from a cohort of 1,597 pneumonia patients with an etiological diagnosis (Prina et al., 2015). They noted these patients had advanced age and were admitted with acute kidney injury, and had an increased 30-day mortality risk (adjusted odds ratio = 2.51). Both *S. aureus* and community-acquired strain of methicillin resistant *S. aureus* (CA-MRSA) can cause severe CAP, particularly as a complication of influenza infection (Deresinski, 2005; Mandell et al., 2007; Micek, Dunne, and Kollef, 2005). The Global initiative for methicillin-resistant *Staphylococcus aureus* pneumonia (GLIMP) study reported a prevalence of confirmed MRSA in CAP patients to be up to 3% and MRSA was seen mostly in patients with a history of prior MRSA infection or colonization, recurrent skin infections or in those with severe pneumonia(Aliberti et al., 2016). Immunocompromised patients with CAP are more likely to have *S. pneumoniae, P. aeruginosa*, respiratory syncytial virus, pneumocystis, *Aspergillus fumigatus* and nocardia species compared to immunocompetent patients(Marta Francesca Di Pasquale, 23 August 2018).

Aspiration pneumonia refers to a patient with features of CAP in the setting of oropharyngeal dysphagia or other conditions that promote large volumes of gastric or oropharyngeal contents reaching the lung. The IDSA/ATS 2019 guidelines do not recommend adding antibiotics for anaerobic coverage for suspected aspiration pneumonia in inpatient settings, except when lung abscess or empyema is suspected, as the majority of these pneumonias are caused by Gram negative pathogens (Metlay et al., 2019). However, in the setting of SCAP, antibiotics should be directed towards upper airway colonizers, likely to be present at the time of the event, such as Gram-negative pathogens and *S. Aureus*.

3. Microbial resistance

Due to rampant use of broad-spectrum antibiotics, there is an ever-growing problem with antibiotic resistance. Use of antibiotics such as macrolides, beta-lactams, and quinolones, prior to admission to the ICU is a well-known predisposing factor for subsequent resistance to the same class of antibiotic particularly for Pneumococcus(Clavo-Sanchez et al., 1997; Ho et al., 2001; Ruhe and Hasbun, 2003; Vanderkooi, Low, Green, Powis, and McGeer, 2005). Part of the issue is lack of newer antibiotics to keep up with the emergence of resistance to other classes or earlier generations of antibiotics(Pickens and Wunderink, 2019). Recognizing the importance of curbing antimicrobial resistance, in 2014 White House released a Presidential Executive Order 13676 for Combating Antibiotic-Resistant Bacteria (CARB) (Pickens and Wunderink, 2019).

In a multi-national study, the global prevalence of Drug resistant *S. pneumoniae* (DRSA) CAP was 1.3% with a higher rate in Africa

(Aliberti et al., 2019). Resistance pattern was higher for macrolides (0.6%) followed by penicillin resistance (0.5%). The majority of penicillin resistance is of the "intermediate" type (penicillin minimal inhibitory concentration [MIC] of 0.1 to 1.0 mg/L), but mortality is usually not increased until the penicillin MIC is more than 4 mg/L (Feikin et al., 2000). Thus, it is still uncertain whether penicillin resistance leads to increased mortality(Choi et al., 2012). Levofloxacin resistant pneumococcal pneumonia is seen with recent hospitalization, bronchopulmonary disease, cerebrovascular disease, and prior antibiotic use within 3 months(Seok et al., 2018). Since the CAP guidelines recommend use of combination therapy in SCAP (a beta-lactam with either a macrolide or a quinolone), macrolide–resistance is not an issue, as most patients receive a beta-lactam which is effective against pneumococcus, even if macrolide resistance is present. Recently infections with hypervirulent carbapenem-resistant *K. pneumoniae* are increasingly being detected, but these organisms generally cause sepsis related with blood stream infection or nosocomial pneumonia (C. R. Lee et al., 2017).

Antibiotic stewardship with adherence to clinical pathways is recommended for combating anti-microbial resistance in CAP(Pickens and Wunderink, 2019). These pathways are generally a stepwise, algorithmic approach for antibiotic initiation, de-escalation and duration of therapy. Adherence to CAP guidelines has generally been shown to improve outcomes and reduce pathogen resistance(Asadi et al., 2013).

4. Treatment

Pharmacotherapy in critically ill patients has unique pathobiology with altered pharmacokinetics and pharmacodynamics for most commonly used drugs, including β-lactams. The concentrations of the antibiotics fluctuate in plasma and extracellular fluid especially with acute kidney injury and hyperdynamic circulation, either of which can be seen in septic patients, with an impact on drug efficacy. Timely, accurate and empiric treatment for SCAP is essential to reduce mortality (Kumar et al., 2006; Leroy et al., 1995). The current guidelines recommend the use of dual antibiotics: a β-lactam plus either a macrolide or a respiratory quinolone (levofloxacin or moxifloxacin) for patients with severe pneumonia in the ICU(Fig. 1), with no risks for drug resistant organisms (Metlay et al., 2019). These recommendations are based on the likelihood of covering the common etiologic agents, but there is a lack of randomized controlled trials in patients with SCAP(Torres et al., 2019). In choosing antibiotics for SCAP, one also has to consider the role of emerging pathogens and viruses as etiologic agents for severe pneumonia(Jain et al., 2015). On the other hand, if rapid diagnostic testing shows the presence of a specific pathogen, then therapy should be focused to the identified microbial agent.

Although the guideline provides direction on the best treatment strategies, several important controversies have emerged regarding the optimal course and choices of antibiotics in SCAP treatment. These include: (a) combination therapy vs. monotherapy treatment strategy, (b) optimal treatment with a β-lactam plus macrolide versus β-lactam plus fluoroquinolone, (c) need for additional antibiotics directed towards drug resistant or PES pathogens, (d) need for antibiotics in patients with identified viral pathogen, (e) optimal duration of treatment, (f) addition of corticosteroids.

Earlier evidence showed that combination therapy with a macrolide appeared to have a modest mortality benefit, especially in bacteremic SCAP patients with *S. pneumoniae* probably due to its ability for immunomodulatory effects (Baddour et al., 2004; Lodise, Kwa, Cosler, Gupta, and Smith, 2007; Metersky, Ma, Houck, and Bratzler, 2007; Weiss and Tillotson, 2005). In a study of 865 patients, Adrie and colleagues reported no difference in 60 day mortality between a combination (β-lactam plus macrolide or fluoroquinolone) versus monotherapy (β-lactam alone) in SCAP patients, but there was survival advantage for patients, who had initial adequate antibiotic therapy (Adrie et al., 2013). Rodriguez reported a survival advantage for SCAP patients, who required vasopressors and were on combination therapy with a β-

lactam plus either a macrolide or quinolone compared to the use of monotherapy(Rodriguez et al., 2007). Postma and colleagues in a cluster-randomized, non-ICU, hospitalized CAP patient population, compared β-lactam monotherapy to β-lactam -macrolide and fluoroquinolone monotherapy strategies, and found no statistical difference in 90-day mortality with the addition of a macrolide (Postma et al., 2015). Sligl and associates found in a meta-analysis of severe CAP patients that combination therapy with a macrolide and β-lactam was associated with reduced mortality compared to other regimens (Sligl et al., 2014). In another large systematic review including 137,574 patients, use of a macrolide was associated with reduced mortality (3.7% vs. 6.5%; RR, 0.78) compared with non-macrolide regimens, but the benefits were reduced when the results were restricted to randomized studies(Asadi et al., 2012).Vardakas more recently reported another systematic review including 16,884 patients and found no difference in outcomes between the of a β-lactam plus macrolide versus β-lactam plus fluoroquinolone(Vardakas, Trigkidis, and Falagas, 2017). Leroy and colleagues in a prospective, randomized study of 398 SCAP patients, showed similar clinical efficacy with levofloxacin monotherapy vs. combination therapy with cefotaxime and ofloxacin (79.1% vs. 79.5%, 95% CI, -10.13 - 9.58% after adjustment for disease severity) (Leroy, Saux, Bedos, and Caulin, 2005). However, in that study, combination therapy was better in patients requiring MV and those with septic shock were excluded. Thus, monotherapy is generally avoided in SCAP because effective dosing and safety of any single agent has not been established for ICU admitted CAP patients. Guideline concordant treatment with early initiation of antibiotics has been reliably shown to be effective in reducing CAP mortality(Gattarello et al., 2014).

Early treatment failure in CAP could be due to infection with untreated *Legionella pneumophila*, which might occur in sporadic forms, drug resistant pneumococcus or infection with Gram-negative bacilli. There is an increase in the reported cases of Legionella lately in big cities and in those with diabetes, and those from poor neighborhoods (Farnham, Alleyne, Cimini, and Balter, 2014). Quinolones are preferred over macrolides if Legionella is suspected (Yu et al., 2004). The probability of being infected with drug resistant pathogens or enteric gram-negative organisms is likely related to the presence of cardiopulmonary disease or other risk factors, such as use of corticosteroids or prior history of resistant pathogens. Since the majority of aspiration pneumonia episodes are caused by Gram negative pathogens, the current IDSA/ATS 2019 guidelines do not recommend adding additional anaerobic coverage for suspected aspiration pneumonia (Metlay et al., 2019). If *Pseudomonas aeruginosa* is suspected, treatment can be with a two-drug regimen, using an anti-pseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam) plus ciprofloxacin or levofloxcin. Alternatively, a three-drug regimen can be used, combining an antipseudomonal beta-lactam plus an aminoglycoside plus either an intravenous anti-pneumocccal quinolone (moxifloxacin or levofloxacin) or a macrolide (Mandell et al., 2007). In CA-MRSA, either vancomycin or linezolid is preferred. Some authorities recommend the use of an antibiotic that inhibits toxin production, such as linezolid (used alone) or clindamycin(added to vancomycin) in CA-MRSA, which may be particularly useful for patients with toxin-mediated necrotizing pneumonia (Micek et al., 2005). In a study of 133 patients with Panton-Valentine leucocidin positive *S. aureus*, investigators noted significant survival advantage for patients, who have received treatment with an anti-toxin regimen compared to those without such a regimen (mortality rate of 6.1% vs. 52.3%, p <0.001)(Sicot et al., 2013). The IDSA/ATS 2019 guidelines recommend empiric coverage for Pseudomonas and MRSA based on locally validated epidemiological risk factors for either pathogen to be present(Metlay et al., 2019). However, many institutions do not have information like this, and instead we recommend using some of the traditional risk factors discussed above.

Severe viral CAP, especially with influenza should be treated with anti-viral agents regardless of the duration of illness before diagnosis

SEVERE COMMUNITY ACQUIRED PNEUMONIA

Demographics: Age >65 years, history of cardiopulmonary disease
Prior history of multi-drug resistant pathogens
Vitals on admission: Absence of fever, respiratory rate > 30/min, need for mechanical ventilation and shock state requiring vasopressor support

Labs: Blood urea nitrogen >19.6 mg/dL, pH < 7.35, profound leukopenia or leukocytosis, hypoalbuminemia, lower hematocrit, platelet count ≤ 10^5/mm³ or ≥ 4 × 10^5/mm³), PaCO2 <35 mm Hg or > 45 mm Hg
Culture: Bacteremia
Imaging: Multi-lobar pneumonia

Severity Assessment

ATS/IDSA CRITERIA
Major Criteria
- invasive mechanical ventilation
- hemodynamic compromise needing vasopressor support

Minor criteria
- RR >30 breaths/min
- PaO2/FiO2 ratio <250
- Multi-lobar infiltrates
- Confusion/disorientation
- Uremia (BUN level >20 mg/dL)
- WBC count <4000 cells/mm3
- Platelet count <100,000 cells/mm3
- Hypothermia (core temperature <36 degree Celsius)
- Hypotension requiring aggressive fluid resuscitation

ICU Care
ONE OF MAJOR CRITERIA OR THREE OF THE MINOR CRITERIA

No risk for drug resistant pathogens
- β-lactam plus either a macrolide or a respiratory quinolone (levofloxacin or moxifloxacin)

Risk factors for Pseudomonas
- anti-pseudomonal beta-lactam (cefepime, imipenem, meropenem, piperacillin/tazobactam)
plus, ciprofloxacin or levofloxacin
- three-drug regimen
with anti-pseudomonal beta-lactam
plus, an aminoglycoside
plus, either an intravenous anti-pneumococcal quinolone or a macrolide

Risk factors for CA MRSA
- linezolid or vancomycin + clindamycin

Viral Pneumonia: Anti-viral agents
- **Influenza -** Oseltamivir, Zanamivir, Amantadine
- **COVID-19** – Remdesivir + Dexamethasone

Non-responders evaluate for:
- Drug resistant pathogens
- Complications such as empyema, abscess or endocarditis
- Newer available antibiotics
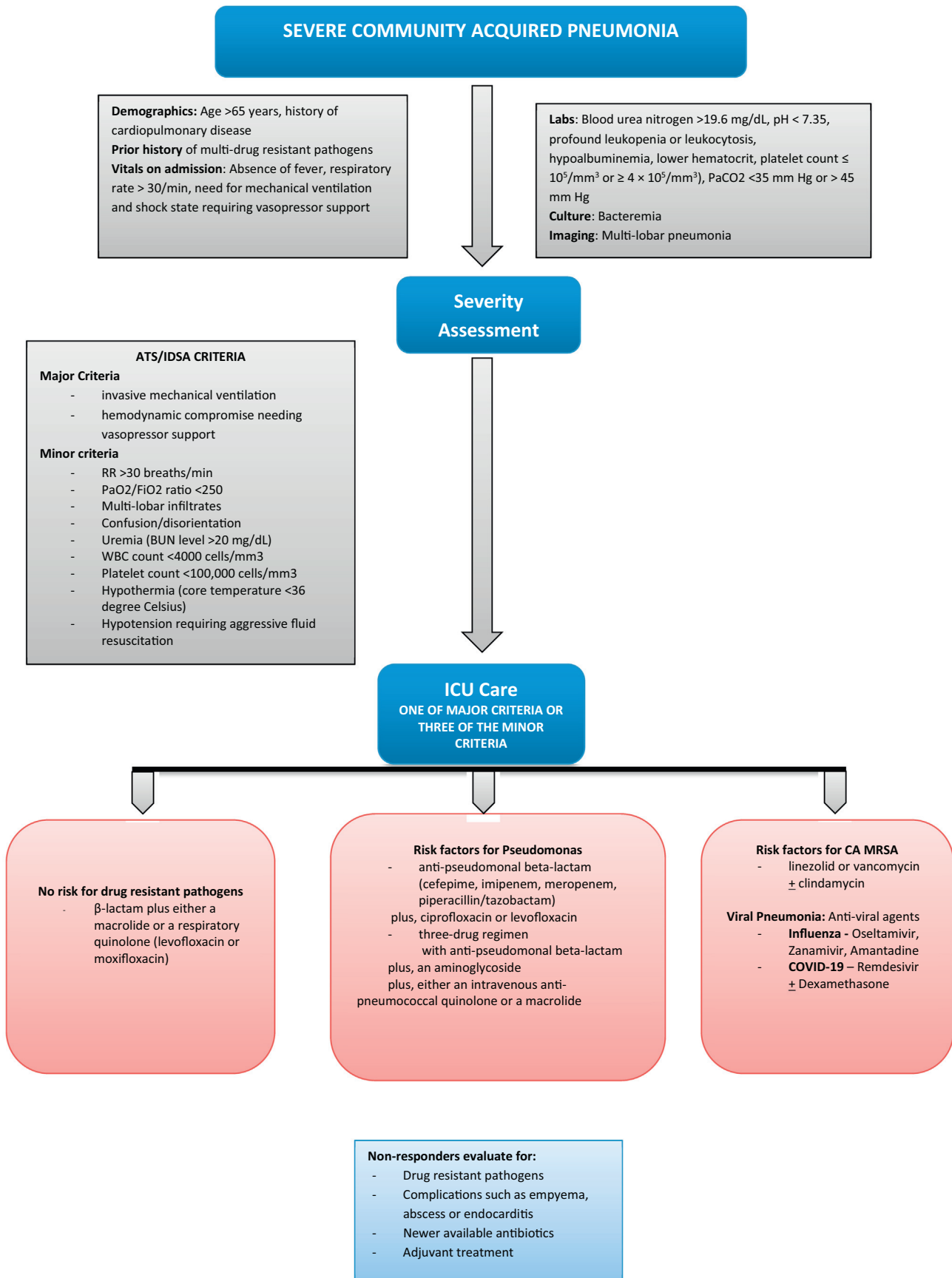- Adjuvant treatment

Fig. 1. Assessment and treatment of patients with severe community acquired pneumonia.

(Metlay et al., 2019). With a high incidence of bacterial pneumonia post viral CAP, antibiotics are recommended in confirmed Influenza with a special focus on *S. aureus, S. pneumoniae, H. influenza* and group A Streptococcus, to account for the possibility of coinfection. The IDSA/ATS 2019 recommend de-escalation of antibiotics in those with no evidence of bacterial superinfection and clinical stability after 48 to 72 hours of initiation of antibiotics(Metlay et al., 2019).

Appropriate duration of treatment in SCAP is not well established, but shorter duration of therapy for 5 to 7 days may be possible even in pneumococcal bacteremia, when patients have adequate clinical response to antibiotics, and no extrapulmonary infection (empyema, meningitis) (J. A. Ramirez and Bordon, 2001). Serial measurements of biomarkers such as PCT can help with antibiotic de-escalation without an increase in either mortality or treatment failure (Muller et al., 2010; Schuetz et al., 2012; Schuetz et al., 2012). In a randomized trial of antibiotic therapy in the ICU, PCT- guidance led to a reduction in duration of therapy compared to standard care in all patients, including those with severe CAP(Bouadma et al., 2010). In a recent meta-analysis of 19 randomized controlled trials of CAP, including 4,861, there were no difference in clinical cure rates between short course treatment defined as ≤6 days versus treatment for ≥7 days irrespective of patient setting or severity of pneumonia(Tansarli and Mylonakis, 2018). In that study, short-course treatment was associated with fewer serious adverse events (RR = 0.73; 95 CI, 0.55–0.97) and potentially lower mortality than long-duration treatment (RR = 0.52; 95% CI, 0.33–0.82). The IDSA/ATS 2019 guideline recommends clinicians to continue antibiotics until the patient achieves stability using a validated measure of clinical stability including normalization of vital sign abnormalities, oxygen saturation, patient's ability to eat and normal mentation and the duration is not less than a total of 5 days(Metlay et al., 2019).

4.1. Newer antibiotics

With growing microbial resistance and continued need for appropriate coverage, several newer antibiotics have been studied in patients with CAP, with an ability to cover both typical, atypical and resistant CAP microbes, including newer generation cephalosporins, such as ceftaroline, ceftobiprole, ceftazidime-avibactam, and ceftolozane-tazobactam; newer macrolides like solithromycin; next generation fluoroquinolones like nemonoxacin zabofloxacin and delafloxacin; tetracyclines like omadacycline, and potent semisynthetic agents such as lefamulin (Table 3) (Amalakuhan, Echevarria, and Restrepo, 2017). However, their usage in SCAP is yet not completely understood, but offers potential antibiotic options that should be reserved for patients with resistant pathogens.

Ceftaroline is a fifth-generation cephalosporin with bactericidal activity against gram positive and negative pathogens, but also against MRSA and particularly against DRSP. In a meta-analysis of three randomized studies including 1916 CAP patients, ceftaroline (600 mg every 12 h) was superior to ceftriaxone (1–2 g every 24 h) for 5–7 days in an intention to treat analysis in patients with severe pneumonia(OR: 1.66; 95% CI 1.34, 2.06)(Taboada et al., 2016). Ceftobiprole is another fifth-generation cephalosporin with extended spectrum activity gram-positive pathogens including MSSA, methicillin-resistant coagulase-negative staphylococci, penicillin and ceftriaxone-resistant *S. pneumoniae* and gram-negative pathogens, such as *P. aeruginosa* and *Enterobacteriaceae*, but limited efficacy against MRSA(Cilloniz, Dominedo, Garcia-Vidal, and Torres, 2019). Nicholson et.al. reported in a randomized study including 706 CAP patients that ceftobiprole (500 mg every 8 h) was not inferior to ceftriaxone as monotherapy (2gm every 24h) or combined with linezolid (600 mg every 12h) in IIT analysis and microbiological cure rates(Nicholson et al., 2012).It is not approved for use in pneumonia in the US. Ceftazidime-avibactam and Ceftolozane-tazobactarm are being tested for nosocomial pneumonia but have excellent activity against *P. aeruginosa*.

Solithromycin is a novel fourth generation macrolide and in two recent double-blind, randomized controlled, non-inferiority trials were comparable oral moxifloxacin in patients with mild to moderate CAP (Port Scores II-IV), buy it is not approved by the FDA (Barrera et al., 2016; File Jr. et al., 2016). Nemonaxacin is a novel non-fluorinated quinolone and in a phase 3 study of CAP patients randomized to nemonoxacin (n = 356) or levofloxacin (n = 171) there was no difference in clinical or microbiological cure rates between the groups at 7–10 days with comparable adverse side effects(Yuan et al., 2019). Delafloxacin is another novel fluoroquinolone and in a phase 3 study in CAP patients, there was a 16-fold greater activity with delafloxacin compared to moxifloxacin for Gram-positive and fastidious Gram-negative pathogens with retained activity against resistant phenotypes found in *S. pneumoniae* (penicillin-, macrolide-, multiple-drug resistant), *Haemophilus* species (β-lactamase producing, macrolide-non-susceptible) and *S. aureus* (MRSA, fluoroquinolone-non-susceptible MSSA)(McCurdy et al., 2019). Omadacycline is a recently approved aminomethycycline and in a recent randomized, double-blind trial, in CAP patients (PORT risk class of II, III, or IV) comparing omadacycline (100 mg intravenously every 12 hours for two doses, then 100 mg intravenously every 24 hours) to moxifloxacin (400 mg intravenously every 24 hours) there was a similar early clinical response with both antibiotics(Stets et al., 2019). Lefamulin is a novel semi-synthetic antibiotic, in the pleuromutilin class, and has also recently been approved for CAP, and in the Phase 3 "LEAP 2", randomized clinical trial comparing early clinical response including CAP patients (PORT risk class of II, III, or IV) 5 days of oral lefamulin was not-inferior to 7-day oral treatment with moxifloxacin(Alexander et al., 2019).

4.2. Anti-inflammatory and immunomodulatory treatment

Lower respiratory tract infections constitute one of the most common causes for septic shock. Although the overall incidence of CAP has come down, mortality related with SCAP and septic shock is still high (Hadfield and Bennett, 2018). The role of corticosteroids in decreasing inflammation in patients with SCAP has been studied extensively with conflicting results. Potentially, corticosteroids reduce overwhelming inflammation by decreasing cytokines and help with inadequate adrenal response in critically ill patients, and may be useful in patients with pneumococcal meningitis (Salluh et al., 2008).

Nie and associates in a meta-analysis involving 1001 patients did not find routine use of corticosteroids in CAP patients to be beneficial in reducing mortality, but in a subgroup analysis in patients with severe CAP, use of corticosteroids was associated with significant reduction in mortality (OR = 0.26, 95% CI: 0.11–0.64) (Nie, Zhang, Cheng, and Xiu, 2012). In another randomized, prospective study administration of intravenous methylprednisolone (bolus of 0.5 mg/kg per 12 hours) in those with severe CAP and an elevated CRP >150 mg/L at admission, led to less treatment failure compared to placebo, without mortality benefit (Torres et al., 2015). Cheng and associates in another meta-analysis involving 4 randomized trials in severe CAP with 264 patients found significant in-hospital mortality benefit in the corticosteroid group compared with conventional therapy (OR = 0.39, 95% CI 0.17–0.90) (Cheng, Pan, Yang, and Gao, 2014). More recently, another meta-analysis of severe CAP, including 8 RCTs with 528 patients found adjunctive corticosteroids use was associated with reduced all-cause mortality, ARDS and need for IMV(Bi et al., 2016). Both the latter two studies should be looked at with caution as there was significant variation within the studies included and overall instability of pooled estimates. Briel and associates pooled data from 1506 individual patients in 6 RCTs and analyzed the benefits of adjunctive corticosteroids using uniform outcome definitions(Briel et al., 2018). In that study, corticosteroids in hospitalized CAP patients was not associated with mortality reduction, but improved time to clinical stability and length of hospital stay by 1 day.

The IDSA/ATS 2019 guideline gives a strong conditional recommendation against routine use of adjunctive steroids in patients treated for CAP(Metlay et al., 2019). However, the data in severe CAP suggest that this group may be different, and recent studies with COVID-19 also suggest a benefit from corticosteroids for those with severe disease requiring either MV or oxygen alone compared to no respiratory support at the time of randomization(Horby et al., 2020). We suggest using adjunctive glucocorticoids in SCAP patients with septic shock refractory to fluid resuscitation and with vasopressor use, especially in those with an elevated CRP >150 mg/L. Treatment can be with methylprednisolone 0.5mg/Kg IV every 12 hours for 5 days and in those who can take oral medication, Prednisone 50 mg daily should be adequate. However, there should be caution in the setting of viral CAP, since meta-analyses in influenza patients, show increased mortality with corticosteroid use(Yang et al., 2015).

Adjunctive immune therapy with different agents has been tried with limited success in SCAP. Welte and colleagues in a phase II, double blind study of 160 SCAP patients, compared the efficacy of novel human polyclonal antibody preparation called Trimodulin, which contains different fractions of Immunoglobulins: IgG-56%, IgM-23% and IgA-21% to placebo in reducing ventilator free days and mortality (Welte et al., 2018). Although the study did not show significant improvement in the primary end points, a subset analyses revealed Trimodulin to have significant mortality reduction in SCAP patients, who had high CRP and low IgM at baseline. Adjuvant granulocyte colony-stimulating factor (G-CSF) to antibiotics in severe CAP did not show benefit in mortality or in the course of illness resolution(Root et al., 2003). Immunomodulatory therapy with mesenchymal stem cells showed potential benefits in animal models of pneumonia and is being studied in early clinical trials as adjunct therapy(Hackstein et al., 2015).

5. Conclusion

Early initiation of appropriate antibiotics is the key element in reduction of adverse outcomes in patients with SCAP. The current ATS/IDSA guidelines reinforce the use of ATS -2007 major and minor criteria for site of care decision and antibiotic decision with SCAP patients. Newer antibiotics choices offer opportunities to treat patients, who do not respond to traditional choices or when infected with drug resistant pathogens, but many of these new agents have not been studied in SCAP. Immunomodulatory and anti-inflammatory therapies have a limited role in treatment except in septic shock. Further improvement in SCAP mortality can be achieved by appropriately phenotyping patients at high risk of death, institutional risk stratification based on local antimicrobial guidelines and resistance patterns, and appropriate antibiotic stewardship with clinical care bundles.

Declaration of Competing Interest

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