Advances in severe community-acquired pneumonia

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Introduction

Community-acquired pneumonia (CAP) is a common respiratory disease and is considered to be the leading cause of mortality among various infectious diseases.[1,2] A large population-based study showed that among hospitalized patients diagnosed with pneumonia, 21% of them required the intensive care unit (ICU) admission, 6% required invasive mechanical ventilation, and 2% died.[3] Although therapeutic strategies have been significantly improved over recent years, the morbidity and mortality of CAP, especially severe CAP (SCAP), remain high. Mortality of SCAP has been reported to range from 17% to 49% by different multi-center cohort studies.[4] The Infectious Diseases Society of America (IDSA), American Thoracic Society (ATS) and the Infectious Disease Assembly, Chinese Thoracic Society, have published consensus guidelines for CAP (IDSA/ATS 2007, CTS 2016), which clearly defined SCAP criteria.[5] According to IDSA/ATS SCAP criteria, patients with SCAP requiring ICU admission should have at least one major criteria (invasive mechanical ventilation or septic shock with the need for vasopressors) or at least three minor criteria (respiratory rate ≥30 breaths/min, oxygenation index (PaO2/FiO2) ratio ≤250, multi-lobe infiltrates, hypothermia (core temperature <36°C), leukopenia (white blood cell count <4000 cells/mm^3), thrombocytopenia (platelet count <100,000 cells/mm^3), hypotension requiring aggressive fluid resuscitation, confusion/disorientation, and uremia (blood urea nitrogen (BUN) ≥20 mg/dL).[5]

To date, confusion, uremia, respiratory rate, low blood pressure, age 65 years or greater (CURB-65) and pneumonia severity index (PSI), the two primary clinical assessment tools utilized, have been widely used to evaluate the mortality risk of CAP patients in clinical practice.[6,7] Several risk factors associated with high mortality in SCAP have been identified, including antimicrobial resistance, increased age, septic shock, and acute respiratory failure.[8] It is thus greatly beneficial to distinguish high-risk patients with SCAP and formulate personalized treatment strategies. Optimal ICU management and rational application of antibiotics were reported to be two key factors determining outcomes of patients with SCAP.[1] Recently, several advances in SCAP have been made and here we summarized the updated knowledge of diagnostic and therapeutic strategies for SCAP.

Microbiologic Diagnostics are Needed for Antibiotic Selection

Streptococcus pneumoniae is the most common pathogen among patients with CAP. Moreover, the most frequently isolated pathogen in SCAP requiring ICU admission was *S. pneumoniae*, followed by *Haemophilus influenzae (H. influenza)*, *Staphylococcus aureus* (*S. aureus*), and *Legionella spp*.[9,10] In recent years, as the number of patients with influenza in winter has increased, viruses have become a common pathogen among patients with SCAP in the ICU.[11] The most frequent respiratory virus identified is influenza virus A, followed by human rhinovirus, human respiratory syncytial virus and influenza B virus.[12] Adenovirus is another viral etiology associated with high mortality in patients with SCAP. Furthermore, gram-negative bacilli are responsible for a small percentage of CAP cases but can cause severe illness. Indeed, microbiologic diagnosis remains difficult and nearly half of patients with SCAP are treated without having identified any causative pathogens. Different geographical areas and populations often affect the etiology of SCAP. Thus, it is necessary to analyze different samples (blood, sputum, bronchoalveolar lavage fluid, and tissue biopsy) and use a variety of methods (special staining, pathogen culture, multiplex polymerase chain reaction, and next-generation sequencing) to improve the detection rate of pathogenic microorganisms. Infection undiagnosed by conventional methods and severe infection are two major indications for performing molecular diagnostic assays. Microbiologic diagnostics effectively suggest appropriate antibiotic therapy.

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Antibiotic Selection

Early adequate antibiotic treatment has been considered to be associated with better outcomes of patients with SCAP.[13] Empiric antibiotic administration is crucial for such patients early in the course of the condition. At present, it is recommended to start treatment with a beta-lactam (such as amoxicillin-clavulanate, ampicillin-sulbactam, or third generation cephalosporins) plus a macrolide (such as azithromycin or clarithromycin).[14] Findings of meta-analyses revealed that macrolide combination therapy contributed to better outcomes of patients with SCAP as compared with monotherapy.[15] In patients with more than two relevant risk factors, anti-microbials against *Pseudomonas aeruginosa*, *Enterobacterium*, and *Methicillin-resistant S. aureus* (MRSA) should be considered in empiric therapy regimens. In addition, pharmacokinetic/pharmacodynamic (PK/PD) analysis is required to optimize anti-microbial dosing regimens.[16] If necessary, concentration monitoring of antibiotics should be applied for patients with SCAP.

Corticosteroids in Treatment of SCAP

To date, the application of corticosteroids in SCAP treatment has remained controversial. Excessive inflammatory cascade activity has been considered an important pathophysiological response in the setting of SCAP. Corticosteroids, possessing strong anti-inflammatory effects, significantly reduce cytokine expression in such patients.[17] Several recent studies showed that corticosteroid combination therapy reduced mortality, decreased the risk of acute respiratory distress syndrome (ARDS), lengths of hospital and ICU stays, as well as the time to clinical stability in patients with SCAP.[4,18,19] It is likely that low-dose steroid (eg, methylprednisolone) administration can improve patient with SCAP outcomes, especially in individuals with strong inflammatory responses or septic shock. However, some studies reported that corticosteroid combination therapy had no effect on mortality and patients might suffer severe side effects as a result of treatment.[17] Corticosteroid treatment is not recommended for viral patients with SCAP. A meta-analyses further revealed that corticosteroid combination therapy was associated with increased mortality in influenzal patients with CAP.[12,20]

Bacteriophage Therapy

Bacteriophages are viral entities that can infect and lyse bacteria. With an increase in the emergence of drug-resistant bacteria, bacteriophage therapy is emerging as an alternative anti-bacterial approach to control bacterial infection in cases of antibiotic treatment failure.[21] Pre-clinical animal studies have demonstrated that bacteriophage therapy markedly alleviates infections caused by multi-drug-resistant bacteria.[22] Furthermore, several clinical trials also have reported that bacteriophage therapy possesses good prospects in the treatment of patients with SCAP and does not confer any serious adverse effects.[23] Bacteriophages target bacterial pathogens with high specificity and leave the host microbiota unaffected.[24] However, it is necessary to use a cocktail of bacteriophages against a battery of common pathogens for an individual case to improve the therapeutic effect in future clinical practice.

Non-antibiotic Treatment Strategy

Recently, several non-antibiotic therapies have been explored as adjuvant treatments for SCAP, including neutralizing antibody against bacterial toxins, immunoglobulins, thymosin, granulocyte macrophage colony-stimulating factor (GM-CSF), low molecular weight/normal heparin, mesenchymal stem cells (MSCs) and growth factors. François *et al*[25] first showed that adjunctive treatment with *S. aureus* alpha toxin-neutralizing mAb (AR-301) had several clinical benefits for ICU patients with severe pneumonia caused by *S. aureus*. Thymosin-a1 is also a promising beneficial immunomodulatory drug. Wu *et al*[26] conducted multi-center randomized controlled trials and found that adjuvant therapy with thymosin-a1 improved clinical outcomes in patients with severe sepsis. GM-CSF is a cytokine secreted by leukocytes to increase granulocyte and monocyte production. Meisel *et al*[27] showed that GM-CSF could reverse monocyte deactivation and reduce the time required for mechanical ventilation and hospital/ICU stay. MSCs therapy has been reported to be a promising treatment strategy for patients with SCAP. Animal studies have reported immunomodulatory and anti-inflammatory effects exerted by MSCs in the setting of pneumonia caused by different pathogens.[28]

A Global View of Infection, Immunity, and Inflammation

Inflammation and immune responses play an important role in infectious diseases. It is crucial to detect immune and inflammatory dysfunction in patients with CAP while paying attention to features specific to various pathogens. Immune suppression promotes the spread of infection, while excessive inflammation leads to functional damage of different organs and induces hypoxemia.[29] A balanced of pathophysiological response is thus crucial for increasing the likelihood of a positive outcome in patients with SCAP.

Mechanical Ventilation

Lung-protective ventilation with low tidal volumes and driving pressures for ARDS is also suitable for patients with SCAP. Furthermore, non-invasive ventilation (NIV) and continuous positive airways pressure, as well as high flow nasal cannular oxygen inhalation, are utilized to treat respiratory failure in the setting of CAP in many ICUs. Several benefits of NIV in the management of patients with respiratory failure due to CAP were reported in recent studies,[14] as were of nasal high flow oxygen administration.

Due to its high mortality and complications, diagnosis and treatment of SCAP remains a major challenge for clinicians. Definitive diagnosis, rational therapeutic strategies, and protection of organ function are the three fundamental elements of appropriate SCAP patient management. Moreover, these three elements form the core of personalized diagnosis and treatment of patients

with SCAP. As recognition of SCAP has increased, novel diagnostic methods and precision medicine in pneumonia are bound to decrease mortality of patients suffering this condition.

Conflicts of interest

None.

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