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Review Article

Advances in the research on the treatment of community-acquired pneumonia complicated with acute respiratory failure

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Abstract Community-acquired pneumonia (CAP) is a common pulmonary infectious disease. Its potential complication, acute respiratory failure, poses a significant threat to patients' lives, significantly increasing mortality and the consumption of medical resources. For patients with CAP complicated by acute respiratory failure, the selection of appropriate antibiotics and respiratory support therapy can effectively reduce mortality, improve treatment outcomes, and enhance patient prognosis and quality of life. This review will investigate the pathogenesis, antibiotic use, and respiratory support methods of CAP complicated by acute respiratory failure, providing some reference and guidance for the treatment of this disease.

Keywords: Community-acquired pneumonia; Acute respiratory failure; Novel antibiotics; Respiratory support therapy

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Community-acquired pneumonia (CAP) refers to a lung infection that occurs outside of a hospital or within the first 48 hours of hospitalization. It commonly causes fever, cough, sputum production (with or without purulent sputum), chest pain, dyspnea, and hemoptysis. Severe pulmonary infections can lead to acute respiratory failure. Acute respiratory failure (ARF) is characterized by the rapid onset of respiratory failure, resulting in acute impairment of lung ventilation and/or gas exchange. Its main characteristics include hypoxemia ($PaO_2 < 60$ mmHg) and hypercapnia ($PaCO_2 > 50$ mmHg), specifically manifesting as acute dyspnea, insufficient oxygenation, and carbon dioxide retention. In severe cases, it can lead to altered consciousness and multiple organ failure. According to global epidemiological data, CAP is one of the leading causes of hospitalization and death among the elderly and patients with underlying diseases. The annual incidence of CAP is 5 to 11 cases per 1,000 people, of which about 10%-20% require hospitalization, and about 5%-10% of hospitalized patients progress to acute respiratory failure. Among patients with severe pneumonia admitted to the intensive care unit, the incidence of respiratory failure is 30%-50%, and the incidence increases significantly with age [1]. In summary, CAP patients complicated with ARF have a serious deterioration of the disease, increased treatment costs, and prolonged hospitalization, which has a heavy burden on the medical system. Moreover, with the decline in the effectiveness of traditional antibiotics and the increase in bacterial resistance, the treatment difficulty has increased and the mortality rate has risen. For the treatment of CAP complicated by ARF, there is currently a lack of objective and individualized treatment plans for selecting and applying antibiotics and respiratory support therapy, which leads to treatment deviations and even delays in optimal treatment timing. Therefore, the use of appropriate

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antibiotics in combination with respiratory support therapy plays a crucial role and has significant value in the treatment of patients with CAP complicated by ARF. It can effectively control lung tissue inflammation, maximize oxygen exchange, reduce carbon dioxide retention, and minimize patient mortality. The research progress on the treatment of CAP complicated with ARF is summarized as follows.

1 Pathogenesis of Community-Acquired Pneumonia (CAP) Complicated with Acute Respiratory Failure (ARF)

The pathogenesis of community-acquired pneumonia complicated with acute respiratory failure (ARF) is related to the type of pathogen, the body's immune status, and the degree of inflammatory response. Pathogen invasion is the direct cause of pneumonia. Common CAP pathogens include bacteria, viruses, fungi, and atypical pathogens. The pathogenic mechanisms of each type of pathogen differ: bacteria (such as Streptococcus pneumoniae and Staphylococcus aureus) can directly damage alveolar epithelial and capillary endothelial cells, leading to the alveolar cavity being filled with a large number of neutrophils, erythrocytes, fibrin, and other inflammatory exudates, thus hindering gas exchange; viruses (such as influenza virus and SARS-CoV-2) can damage alveolar epithelial and vascular endothelial cells and inhibit the secretion of surfactant, leading to alveolar collapse and atelectasis; while atypical pathogens (such as Mycoplasma, Chlamydia, and Legionella) cause inflammatory damage primarily through toxic effects or immune-mediated damage.

Host factors such as advanced age, weakened immune function, or coexisting chronic underlying diseases (such as chronic obstructive pulmonary disease, heart failure, cor pulmonale, etc.) can weaken cardiopulmonary reserve function and pathogen clearance capacity, which not only increases the risk of pulmonary infection but also makes it easier to progress to severe pneumonia and respiratory failure[2]. In addition, the inflammatory response caused by pneumonia leads to alveolar congestion and exudation, as well as fluid accumulation in the alveoli, resulting in decreased lung compliance, destruction of the alveolar structure, a reduced effective diffusion area, and a ventilation-perfusion mismatch, which seriously affects oxygenation and carbon dioxide excretion [3]. At the same time, activated neutrophils and macrophages release a large number of inflammatory factors (such as TNF-α and IL-6), which increase alveolar-capillary membrane permeability and form pulmonary edema; excessive inflammatory response can also induce acute respiratory distress syndrome (ARDS), further impairing lung oxygenation function [4].

2 Treatment of CAP with ARF

The treatment of CAP with ARF is mainly divided into drug therapy and respiratory support therapy. Drug therapy includes antibiotics, mucolytics, antitussives, etc. to control the cause and inducing factors. Respiratory support therapy encompasses a range of interventions, including traditional oxygen therapy, non-invasive ventilation, high-flow nasal oxygen therapy, and invasive mechanical ventilation, aimed at alleviating symptoms of respiratory failure in patients.

2.1 Drug therapy

For pneumonia patients, antibiotic therapy is the core measure. Clinically, it is emphasized that the first dose of anti-infective drugs should be administered as soon as

possible after a clear diagnosis to control the infection in a timely manner, reduce the risk of complications, and improve the patient's survival rate. Cough and sputum are the most common clinical symptoms of CAP. The use of antitussive drugs should be carefully evaluated, as excessive suppression of the cough reflex may lead to sputum retention, which can aggravate airway obstruction and progression of infection. According to previous guidelines [5], if a patient's cough seriously affects their quality of life or has caused related complications, and after ruling out organic diseases, it is considered an idiopathic cough, central antitussive drugs such as codeine or pentoxyverine may be used as appropriate. However, strong antitussives should be avoided in patients with copious sputum. Instead, patients should be encouraged to cough effectively, and mucolytics such as ambroxol, carbocysteine, and acetylcysteine should be used in combination. These drugs can break down the viscous components in sputum, reduce its viscosity, enhance airway clearance, and thereby promote sputum expectoration, improving respiratory symptoms.

2.1.1 Selection and Application of Antibiotics

The selection of antibiotics for community-acquired pneumonia (CAP) requires careful consideration of factors such as pathogen type, drug characteristics, patient immune status, underlying diseases, and disease severity. Clinically, scoring tools such as CRB-65 and CURB-65 (including indicators such as altered consciousness, blood urea nitrogen > 7 mmol/L, respiratory rate ≥ 30 breaths/min, hypotension, and age ≥ 65 years) and the Pneumonia Severity Index (PSI) are commonly used to stratify patients into low-risk, intermediate-risk, and high-risk groups. This stratification strategy enables the accurate assessment of condition, prediction of mortality risk, and provides a basis for determining the treatment location (outpatient, general ward, or ICU), thereby significantly improving patient prognosis and quality of life [6][7]. According to the 2016 guidelines for pneumonia [8], patients with mild CAP should be given priority for oral antibiotics with high bioavailability, such as penicillins or first-generation cephalosporins (e.g., amoxicillin, cefadroxil). For patients with underlying diseases requiring hospitalization, respiratory quinolones (e.g., levofloxacin) or second- and third-generation cephalosporins (e.g., cefuroxime, cefotaxime) are generally recommended, or β-lactam antibiotics can be used alone. For severe CAP patients without underlying diseases who require ICU admission, penicillins/β-lactamase inhibitors (e.g., amoxicillin-clavulanate), third-generation cephalosporins (e.g., ceftazidime), ertapenem, or a combination of tetracyclines and macrolides, or respiratory quinolones can be used alone. For hospitalized CAP patients aged ≥65 years or with underlying conditions such as chronic respiratory diseases, heart failure, or cerebrovascular diseases, high vigilance should be exercised for infections caused by Enterobacteriaceae, extended-spectrum β-lactamase (ESBL)-producing strains, and quinolone-resistant bacteria. Empirical treatment for this high-risk population is recommended to include combinations of cephalosporins (such as cefoxitin), piperacillin/tazobactam, cefoperazone/sulbactam, or ertapenem, along with broad-spectrum antibiotics. In summary, clinicians should rationally select antibiotics based on comprehensive assessment and severity stratification to effectively control pulmonary infections and improve patient clinical outcomes.

2.1.2 The Potential of Novel Antibiotics

In recent years, with the increasing prevalence of antibiotic

resistance, the efficacy of traditional antibiotics has gradually weakened. The development and application of various novel antibiotics have shown promising clinical prospects, especially in the treatment of pneumonia patients. Lefamulin is a novel semi-synthetic pleuromutilin antibiotic that was approved by the U.S. Food and Drug Administration in 2019[9] for the treatment of community-acquired bacterial pneumonia (CABP) in adults. Lefamulin inhibits protein synthesis by blocking the binding of transfer RNA to bacterial ribosomal peptidyl transferase (PTC), thereby combating a variety of typical and atypical pathogens, including Streptococcus pneumoniae, Haemophilus influenzae, and Mycoplasma. This action reduces the risk of cross-resistance and effectively interferes with the growth and reproduction of bacteria. In terms of safety, Amiel et al. pointed out through clinical trials that the efficacy of lefamulin in the treatment of CABP is comparable to that of some traditional antibiotics, such as moxifloxacin, and the incidence of adverse reactions is similar, usually mild to moderate gastrointestinal discomfort, such as nausea, vomiting and diarrhea[10]. In two important phase III clinical trials (LEAP 1 and LEAP 2), Tang et al. found that the early clinical response rate of lenvastatin reached 89.3%, similar to that of moxifloxacin (90.5%). In subgroup analysis, the early clinical response rate of lenvastatin in early clinical assessment and the clinical response rate in cure test were similar to those of moxifloxacin in different subgroups and all baseline CABP pathogens [11]. Omadacycline is a novel tetracycline antibiotic belonging to the aminomethylcycline class, specifically for the treatment of CABP and skin structure infections. Omadacycline binds to the 30S ribosomal subunit of bacteria, preventing the binding of transfer RNA and thus interfering with peptide chain elongation. This process significantly slows down or even stops bacterial growth and reproduction when antibiotics are applied [12][13]. Compared with traditional tetracycline antibiotics, omadacycline shows higher activity against drug-resistant strains, especially against atypical pathogens such as Mycoplasma pneumoniae and Legionella, where its efficacy is particularly significant [14][15]. Lascufloxacin is a novel fluoroquinolone antibiotic characterized by good lung tissue penetration, high bioavailability, and the ability to maintain prolonged blood concentrations, thereby enabling it to effectively reach the site of infection when treating lung infections and enhancing its antibacterial effect [16]. Studies by Deshpande et al. have demonstrated that lascufloxacin exhibits significant inhibitory effects against various anaerobic bacteria, Gram-positive bacteria, and Gram-negative bacteria, as well as some drug-resistant strains, particularly showing good antibacterial activity against common pathogens such as Streptococcus pneumoniae [17]. In a retrospective clinical study comparing the efficacy of different antibiotics in patients with CAP and lung abscess, the conclusion was that the clinical improvement rate of patients treated with lascufloxacin was as high as 81.5%, of which 85.5% were CAP cases, and patients with lung abscess also showed significant improvement after lascufloxacin treatment [16].

In conclusion, further research and clinical application of novel antibiotics will accelerate improvements in patient prognosis and reduce the treatment failure rate caused by antibiotic resistance. Future research should continue to focus on the efficacy, safety, and application of novel antibiotics in various populations, aiming to provide more effective solutions for the treatment of CAP.

2.2 Respiratory Support Therapy

For patients with CAP complicated by ARF, oxygen should be provided to correct hypoxia while relieving airway obstruction, correcting CO2 retention, and reducing respiratory muscle load. This approach is based on eliminating the cause and risk factors, as well as actively managing potential complications. Arterial blood gas analysis to clarify respiratory function and oxygenation status is beneficial for understanding the degree of ARF. Arterial oxygen saturation (SaO2), oxygenation index (OI), PaO2, and PaCO2 are crucial for evaluating pulmonary exchange function and the severity of acute ventilatory dysfunction. Studies have found that hypoxia (SaO2 < 88%) is one of the risk factors for adverse outcomes in CAP patients. Therefore, clinical practice requires strengthening blood oxygen monitoring for hospitalized CAP patients. When patients develop hypoxemia, oxygen should be administered promptly via a nasal cannula or face mask to achieve an SpO2 of≥ 92%. For patients with hypercapnia, blood oxygen saturation should be controlled at 90%-92%. Administering excessive oxygen therapy blindly should be avoided to prevent worsening of the condition [18].

2.2.1 Conventional Oxygen Therapy

Conventional oxygen therapy (COT) is a basic respiratory support method that primarily uses low-flow oxygen delivery devices (nasal cannulas/Venturi masks) to provide patients with a certain concentration of inhaled oxygen to improve their hypoxic state. It is a commonly used respiratory support therapy. Nasal cannulas are easy to operate and readily accepted by patients with mild respiratory failure, and can partially improve their hypoxic symptoms. However, the output oxygen concentration delivered through a nasal cannula is easily affected by the patient's respiratory rate, respiratory amplitude, and mouth breathing, making it difficult to maintain stability. Prolonged continuous oxygen delivery can also cause dryness, cracking, or even damage to the nasal mucosa, as well as local infection and nasal cannula dislodgement. If the oxygen flow rate is set too high (> 5 L/min), problems such as persistent forehead pain and worsening mucosal damage may occur, making it difficult for patients to tolerate and reducing the effectiveness of the therapy. Venturi masks offer a higher and more stable oxygen delivery rate compared to nasal cannulas and are usually equipped with humidifiers to reduce airway irritation. However, they cannot precisely regulate the output gas flow rate. When administering high-concentration oxygen, they may suppress the respiratory center, potentially worsening carbon dioxide retention in patients at risk (e.g., those with COPD or type II respiratory failure). Face masks themselves create dead space, leading to the buildup of carbon dioxide, which can exacerbate the condition in some cases.

2.2.2 Non-invasive Ventilation

Non-invasive ventilation (NIV) is a technique that utilizes non-invasive interfaces, such as nasal masks or face masks, to deliver mechanical ventilation in respiratory emergencies (e.g., acute respiratory failure, acute respiratory distress syndrome (ARDS), acute exacerbation of chronic obstructive pulmonary disease (AECOPD)). Its two main mechanisms are: ① using PEEP to re-expand collapsed alveoli and correct ventilation-perfusion imbalance to improve oxygenation; ② using PSV or BiPAP mode to provide respiratory support to patients, reduce respiratory muscle burden, relieve respiratory acidosis, and increase minute ventilation. Compared with conventional oxygen therapy, studies have found that NIV can more effectively improve oxygenation, reduce the rate of endotracheal intubation and significantly shorten the

length of hospital stay[19]; and compared with invasive mechanical ventilation, NIV preserves the patient's upper airway defense function and cough and expectoration ability, avoids airway damage, ventilator-associated pneumonia and other intubation-related complications, has a low mortality rate and low medical cost[20]. Although the use of NIV can ensure that patients can at least achieve partial spontaneous breathing, it has its own disadvantages: some patients cannot tolerate NIV, such as claustrophobia, mask discomfort or mask leakage; it will affect patients' eating, speaking and coughing; in addition, long-term use will cause facial pressure skin lesions or even pressure sores; in addition, "human-machine asynchrony" will occur when using NIV, especially when sedation is insufficient and parameter settings are not good, so it is difficult to achieve the expected effect for some elderly and unconscious patients[21].

2.2.3 High-flow nasal cannula oxygen therapy

(HFNC) is a newly emerging and widely used oxygen therapy method in recent years. This oxygen therapy system uses high flow rate, high flow velocity and heating and humidification devices. The high-flow-rate gas, at a temperature of approximately 37°C and 100% relative humidity, can generate a flow rate of up to 80 L/min. Its oxygen concentration can be adjusted in the range of 21% to 100%. The mechanism of action includes the following aspects [22]: First, it generates a constant and precise high flow rate and high flow velocity air-oxygen mixture to flush the anatomical dead space of the nasopharynx, reduce the re-inhalation of exhaled gas, deliver a stable oxygen concentration to the patient, and improve the patient's comfort; Second, it generates a certain positive end-expiratory pressure in the airway by overcoming the exhaled airflow through the self-regulated high flow rate. And can promote alveolar re-expansion and pulmonary water transfer from alveoli to perivascular interstitium, avoid airway collapse, increase the patient's end-expiratory volume, improve respiratory muscle fatigue, and help improve oxygenation; Third, the active warming and humidification effect reduces the bronchoconstriction caused by dry and cold stimulation, reduces airway resistance, reduces the work of breathing, improves the function of mucociliary mucosa, maintains sputum fluidity, promotes sputum dilution and discharge, improves airway patency, and improves the patient's comfort and tolerance. HFNC is mainly used for acute hypoxic respiratory failure, some COPD acute hypercapnia and chronic respiratory failure. Zhang Yan et al. [23] found through a clinical study on HFNC treatment of CAP combined with ARF that, compared with mask oxygenation, HFNC can rapidly improve the symptoms of respiratory failure in patients, has a better prognostic value for improving respiratory function, and improves the clinical efficacy rate. Compared with non-invasive ventilation (NIV), high flow nasal cannula oxygen therapy (HFNC) can effectively reduce sputum viscosity and promote sputum discharge, and has better treatment compliance and clinical compliance for patients with viscous sputum [24]. In recent years, HFNC has gradually replaced NIV treatment in clinical applications; however, it should still be used with caution and closely monitored in real time for patients with severe carbon dioxide retention.

2.2.4 Invasive mechanical ventilation

Invasive mechanical ventilation (IMV) is an important respiratory support method for critically ill patients with pneumonia and acute respiratory failure. It can quickly correct hypoxemia and hypercapnia. If the patient has

impaired consciousness, altered mental status, respiratory failure that has not been corrected by non-invasive ventilation, and the condition continues to deteriorate, invasive mechanical ventilation should be used as early as possible to improve the patient's ventilation and relieve ventilator fatigue, prevent the progression and deterioration of the condition, provide time for basic treatment, and improve the success rate of rescue[25]. Invasive mechanical ventilation requires the insertion of an artificial airway (endotracheal tube or tracheostomy tube) connected to a ventilator to provide mandatory ventilatory support. While a life-saving treatment, it also carries several inherent risks, including ventilator-induced lung injury, ventilator-associated pneumonia (VAP), neurocognitive sequelae associated with prolonged sedation, and prolonged hospital stays. Reducing the duration of mechanical ventilation significantly reduces its side effects and complication rates.

For patients requiring mechanical ventilation, endotracheal intubation is usually the first-line treatment to establish an artificial airway for short-term respiratory support. However, if the patient cannot be successfully weaned off the ventilator within 7 to 10 days, a tracheostomy should be considered for long-term ventilatory support. To avoid complications such as patient-ventilator asynchrony, sedation and analgesia are often intensified clinically. However, these measures suppress the patient's autonomic nervous system function and gastrointestinal motility, increasing the risk of gastric retention, gastroesophageal reflux, and aspiration, which can lead to intestinal dysfunction and VAP. Once VAP occurs, it not only significantly prolongs the mechanical ventilation time and increases the difficulty of weaning, but may also cause complications such as deep vein thrombosis (DVT) and pressure sores due to prolonged bed rest [26], leading to increased hospitalization costs. Therefore, its use should be strictly controlled.

3 Summary

Community-acquired pneumonia complicated by acute respiratory failure is a rapidly progressing, complex, and critical condition, a common cause of death, and significantly impacts patient prognosis. Prompt identification and timely intervention are crucial. A comprehensive treatment approach combining anti-infective therapy and respiratory support is essential. Anti-infective treatment should be based on the pathogen's characteristics, drug resistance, and disease severity, with targeted empirical antibiotics administered as early as possible. Furthermore, research should be conducted on the application prospects and value of novel antibiotics, such as lefamulin, omadacycline, and lascufloxacin, in treating drug-resistant infections and severe cases. In terms of respiratory support, the method should be individualized according to the patient's oxygenation and ventilation dysfunction, and different levels of support should be used sequentially. For patients with mild hypoxemia, traditional oxygen therapy (nasal cannula/Venturi mask) can be the first choice; for patients with moderate hypoxemia and some hypercapnia, high-flow nasal cannula oxygen therapy (HFNC) or non-invasive positive pressure ventilation (NIV) should be the first choice to improve oxygenation and reduce the need for endotracheal intubation; for critically ill patients who fail NIV, have altered consciousness, or have severe hypercapnia, invasive mechanical ventilation (IMV) should be used decisively to maintain vital signs and buy more time for further treatment of the primary disease, but care should be taken to avoid ventilator-related

injury or infection caused by invasive mechanical ventilation.

Conflict of Interest

None.

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None.

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