Universe Scientific Publishing

Immunoinflammatory mechanism of severe pneumonia and the application of inflammatory markers in clinical practice

Yanxin Xu, Lixia Qian, Feiyan Wu, Yuanyuan Liu, Shoude Jin*

Department of Respiratory Medicine, The Fourth Affiliated Hospital of Harbin Medical University, Harbin150000, China.

Abstract: Pneumonia is a common disease and one of the leading causes of morbidity and mortality worldwide. [1] Severe pneumonia is a unique clinical disease that is highly life-threatening, characterized by severe sepsis, septic shock, or respiratory failure. Usually, treatment is required in the intensive care unit (ICU). Approximately 10% of community-acquired pneumonia (CAP) patients require hospitalization, with a mortality rate of 21% -47%. Most patients with severe community-acquired pneumonia have complications, including chronic obstructive pulmonary disease, diabetes and coronary heart disease. Streptococcus pneumoniae, Staphylococcus aureus, Mycoplasma pneumoniae, aaLegionella, Klebsiella pneumoniae, Haemophilus influenzae, novel coronavirus, respiratory virus and Pseudomonas aeruginosa are important pathogenic microorganisms for severe CAP. [2] Host autoimmune factors, patient clinical manifestations, and laboratory and imaging examination results at admission can help identify high-risk populations for this disease. Early identification and timely empirical application of antibiotics are particularly important for the prognosis of patients.

Keywords: Severe Pneumonia; Immune Inflammation; Inflammatory Markers

1. Immunoinflammatory mechanisms in severe pneumonia

The strength of the immune function of the lungs determines the severity of the disease following infection with pathogenic bacteria. Innate and adaptive immune responses to lung microorganisms play a crucial role in maintaining a healthy respiratory system and preventing lung disease. Initiation of antimicrobial defenses and mitigation of the risk of lung injury during acute infections, and the shaping of lung immunity by respiratory infections also helps to improve autoimmune function, and a small number of less virulent pathogenic microorganisms can be eliminated by physical defenses in the respiratory tract, such as the ciliary system and alveolar macrophages in the airways. [3]

The role of T cells in the immune system is particularly important, as CD4-positive (CD4+) T cells, also known as helper T cells, aid in the production of antibody responses by B cells and provide feedback to dendritic cells (DCs) through the production of cytokines and co-stimulatory molecules, as well as augmenting and sustaining the responses of CD8-positive (CD8+) T cells, also known as cytotoxic T cells.CD8+ T cells CD8+ T cells contribute to cytokine production and, more importantly, directly kill virus-infected cells. Invariant natural killer T (iNKT) cells and γδ T cells and and the newly discovered innate lymphoid cells (ILCs) also play a key role in the early response to many lung infections. cD4+ T cells and cD8+ T cells can form an immune memory that can benefit the host when it encounters a secondary attack from a related or the same pathogen.[4] CD4+ T cells and CD8+ T cells are also known as cytotoxic T cells, and are also known as cytotoxic T cells. [4] Inadequate T cell responses during persistent infections increase the likelihood that the body will become infected and delay pathogen clearance. In addition to this, insufficient T cell immunity may also increase the likelihood of pathogen transmission through the lungs.

2. Severe pneumonia and immune cells

2.1 Severe pneumonia and macrophages

Alveolar macrophages are key sensors and effectors of the lung's innate immune response to infection,[5] roaming the lumen of the alveolar ducts, are the first line of defense of the respiratory tract, and are also referred to as dust cells because of their ability to clear and digest relatively inert inhaled material. They send warning signals like the body when the lungs are infected and secrete a variety of cytokines and chemokines to regulate pulmonary innate and adaptive immunity. [6,7]

2.2 Severe pneumonia and neutrophils

During lung infections, neutrophils migrate from the pulmonary capillaries into the airspace. It has been suggested that neutrophils are excellent microbial defense cells. After exerting phagocytosis, neutrophils destroy microorganisms with reactive oxygen species (e.g., hypochlorite), antimicrobial proteins (e.g., bactericidal permeability-inducing proteins and lactoferrin), and degradative enzymes (e.g., elastase). [8]

Inadequate numbers of neutrophils (neutropenia) and defective quality (e.g., chronic granulomatousdisease) predispose patients to opportunistic lung infections, as do complement and immunoglobulin deficiencies. Since neutrophils and plasma proteins mediate innate immune function and are necessary to prevent lung infections, acute inflammation can be considered an essential innate immune response in the lung.

2.3 Severe pneumonia and lymphocytes

Lymphocytes not only exert immune effects in the human body, but also participate in immunoregulation, among which T cells play a key role in the immune system and are of interest in lung host defense against bacterial, viral, and fungal pathogens.T-lymphoid progenitor cells can differentiate into CD4+ and CD8+ T cells in the thymus, and then migrate to peripheral immune organs, such as the spleen, and the lymph nodes, to become primitive T cells.When the organism is infected by a When the organism is infected by a pathogen, the cellular antigen receptor (TCR) complex binds to peptide antigens presented to them by antigen-presenting cells (APCs), and T cells can be activated through cell-cell interactions.APCs present antigens through major histocompatibility complexes I or II (MHCI and MHCII), which interact with the two major subpopulations of T cells, the CD8+ and CD4+ T cells, respectively.CD8+ T cells are known as CD4+ and CD4+ T cells, and CD8+ T cells are known as CD8+ T cells. CD8+ T cells are called cytotoxic T lymphocytes (CTL), while CD4+ T cells are referred to as T helper cells (Th). [9,10]

CD4+ T cells are a major T cell subset that play a central role in immune system function when naïve CD4+ T cells differentiate into effector and or memory cells after encountering cognate antigens via antigen-presenting cells (APCs).CD4+ T cells are an important component of the lung host's defense against a variety of pathogens, as can be demonstrated in HIV.CD4+ T cells can be categorized as helper T cells (Th)1 (Th1), Th2, Th9, Th17, Th22 as well as follicular helper T (Tfh) cells and regulatory T cells (Treg). [11,12,13] Th1 cells are characterized by the production of their signature cytokine, interferon gamma (IFN-γ), which is primarily involved in intracellular immune responses to viruses and bacteria. Th2 immune responses are characterized by the production of interleukin-4 (IL-4), which can act as an autocrine factor for Th2 differentiation, and can stimulate activated B cells to promote the differentiation of B cells into plasma cells. Th2 cells are involved in worm-induced immunopathology and are responsible for the initiation and maintenance of allergic diseases. [14,15]

Treg cell production depends on productive antigen presentation by APC in a microenvironment enriched with tumor necrosis factor-β (TGF-β) and interleukin-2 (IL-2). [16] Depending on the type and stage of infection, inhibition of the inflammatory response by Treg cells can be both beneficial and detrimental to host defense. In the lung, these cells play an important role in mediating the response to inhaled antiplays a key role in the tolerance of the original. [17]

3. Severe pneumonia and inflammatory markers

Localized inflammation in pneumonia is caused by pathogen infection and organism reactivity. Entry of infectious agents into the lungs can stimulate alveolar macrophages, produce large amounts of inflammatory factors, mediate the migration of inflammatory cells in the peripheral circulation, and exacerbate the severity of pneumonia. Inflammatory mediators are closely related to lung inflammation, and their roles in disease exacerbation and progression are critical. Interleukin-6 (IL-6) and C-reactive protein (CRP) are widely recognized as typical inflammatory factors, which contribute significantly to the pathogenesis of a variety of inflammatory diseases,[18] and have been associated with the development of pneumonia. [19,20] Recent studies have shown that calcitoninogen is also of value in the diagnosis of severe pneumonia. [21] The combined detection of multiple inflammatory markers shows promising applications.

3.1 Severe pneumonia and C-reactive protein

CRP is considered a valuable marker of inflammation, and CRP has an important role in host defense against pathogen invasion as

well as in the inflammatory response.CRP consists of five identical subunits arranged to form a cyclic pentamer.CRP currently exists in at least two different conformational forms, including the natural pentameric CRP (pCRP) and the modified/monomeric CRP (mCRP). These isoforms bind to different lipid rafts and receptors while exhibiting different functional properties. In the inflammatory microenvironment pCRP dissociates into subunits and the newly formed mCRP may help to localize the inflammatory response. [21] Recent studies have shown that early identification of patients with poor prognosis in moderate to severe pneumonia can be achieved by measurement of CRP sequential ratios. [22]

3.2 Severe pneumonia and interleukin-6

IL-6, an inflammatory interleukin, is produced primarily by T lymphocytes and macrophages in response to pathogens and is critical for the control of many viral infections. Although steady state values of IL-6 contribute to the regression of infections and tissue lesions, its exacerbated production is decisive for cytokine storm. [23] It has been found that in patients with severe neocoronary pneumonia, its levels are negatively correlated with peripheral oxygen saturation (SpO2) and partial pressure of arterial oxygen (PaO2), which are associated with respiratory failure, and that there is a positive correlation between IL-6 and C-reactive protein (CRP.) IL-6 behaves as a predictor of disease progression.

3.3 Severe pneumonia and calcitoninogen

Calcitonin (PCT) is a calcitonin hormone produced by C cells in the thyroid gland. The calcitonin 1 gene (CALC-11) on chromosome 11 controls its production. The product of this gene, precalcitoninogen precursor (prePCT), undergoes proteolytic cleavage to produce PCT, which is further processed into the mature calcitonin molecule.Transcription and translation of the CALC-1 gene is usually restricted to thyroid C cells and, to a lesser extent, to other neuroendocrine cells. Production is activated in all parenchymal tissues under bacterial infection mediated by the cytokines IL-6, TNF-α, and interleukin-1β (IL-β). Other tissues lack the ability to cleave PCT into the mature form of calcitonin, resulting in the accumulation of PCT. [26] In contrast, interferon gamma, which is secreted primarily in response to viral infection, attenuates PCT production. Therefore, plasma PCT concentrations, which are low in healthy individuals and elevated during bacterial, parasitic, or fungal infections and remain at normal levels during viral infections or noninfectious inflammatory responses, have been used as a biomarker to aid in the diagnosis of bacterial infections or sepsis, (as well as to differentiate between bacterial versus viral pneumonia and chronic obstructive pulmonary disease (COPD). Although elevated serum concentrations of PCT are not specific to infection, PCT is still considered one of the best biomarkers for the diagnosis of sepsis. Early diagnosis facilitates timely initiation of therapeutic measures, whereas delays result in severe infection-related morbidity and mortality.

Summary and Outlook

Severe pneumonia is an increasing incidence worldwide in recent years, which starts as a localized infection of the lungs and can easily lead to serious complications such as respiratory failure and circulatory failure if the initial antimicrobial therapy is inappropriate and the infection is not controlled in a timely manner. Early, rapid, and accurate diagnosis is essential for the treatment of severe pneumonia and for improving survival and prognosis. Immunity and inflammation are present throughout the pathogenesis of severe pneumonia, leading to extensive lung damage. The strength of the pulmonary immune response is closely related to the severity of the disease following infection with the pathogenic organisms; an under-response can lead to life-threatening infections, but an over-response can lead to life-threatening inflammatory damage.

References

[1] Lanks CW, Musani AI, Hsia DW (2019) Community-acquired Pneumonia and Hospital-acquired Pneumonia. Med Clin North Am 103: 487-501.

[2] Ewig S, Torres A (1999) Severe community-acquired pneumonia. Clin Chest Med 20: 575-587.

[3] Mizgerd JP (2012) Respiratory infection and the impact of pulmonary immunity on lung health and disease. Am J Respir Crit Care

Med 186: 824-829.

[4] Marshall NB, Swain SL (2011) Cytotoxic CD4+ T cells in antiviral immunity. J Biomed Biotechnol 2011: 954602.

[5] Lumeng CN (2016) Lung Macrophage Diversity and Asthma. Ann Am Thorac Soc 13 Suppl 1: S31-34.

[6] Hussell T, Bell TJ (2014) Alveolar macrophages: plasticity in a tissue-specific context. Nat Rev Immunol 14: 81-93.

[7] Takabayshi K, Corr M, Hayashi T, et al. (2006) Induction of a homeostatic circuit in lung tissue by microbial compounds. Immunity 24: 475-487.

[8] Mizgerd JP (2008) Acute lower respiratory tract infection. N Engl J Med 358: 716-727.

[9] Park BV, Pan F (2015) Metabolic regulation of T cell differentiation and function. Mol Immunol 68: 497-506.

[10] Niedzwiedzka-Rystwej P, Tokarz-Deptula B, Deptula W (2013) [Characteristics of T lymphocyte subpopulations]. Postepy Hig Med Dosw (Online) 67: 371-379.

[11] Zhu J, Paul WE (2008) CD4+ T cells: fates, functions, and faults. Blood 112: 1557-1569.

[12] Zhou L, Chong MM, Littman DR (2009) Plasticity of CD4++ T cell lineage differentiation. Immunity 30: 646-655.

[13] Luckheeram RV, Zhou R, Verma AD, et al. (2012) CD4+(+)T cells: differentiation and functions. Clin Dev Immunol 2012: 925135.

[14] De Carli M, D'Elios MM, Zancuoghi G, et al. (1994) Human Th1 and Th2 cells: functional properties, regulation of development and role in autoimmunity. Autoimmunity 18: 301-308.

[15] Peiris JS, Hui KP, Yen HL (2010) Host response to influenza virus: protection versus immunopathology. Curr Opin Immunol 22: 475-481.

[16] Chang YJ, Kim HY, Albacker LA, et al. (2011) Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. Nat Immunol 12: 631-638.

[17] Bilate AM, Lafaille JJ (2012) Induced CD4++Foxp3+ regulatory T cells in immune tolerance. Annu Rev Immunol 30: 733-758.

[18] Fu B, Zhang P, Zhang J (2023) Diagnosis and Prognosis Evaluation of Severe Pneumonia by Lung Ultrasound Score Combined with Serum Inflammatory Markers. Mediterr J Hematol Infect Dis 15: e2023057.

[19] Wang C, Deng R, Gou L, et al. (2020) Preliminary study to identify severe from moderate cases of COVID-19 using combined hematology parameters. Ann Transl Med 8: 593.

[20] Howie SR, Morris GA, Tokarz R, et al. (2014) Etiology of severe childhood pneumonia in the Gambia, West Africa, determined by conventional and molecular microbiological analyses of lung and pleural aspirate samples. Clin Infect Dis 59: 682-685.

[21] Wu Y, Potempa LA, El Kebir D, et al. (2015) C-reactive protein and inflammation: conformational changes affect function. Biol Chem 396: 1181-1197.

[22] Coelho LM, Salluh JI, Soares M, et al. (2012) Patterns of c-reactive protein RATIO response in severe community-acquired pneumonia: a cohort study. Crit Care 16: R53.

[23] Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, et al. (2019) The Role of Interleukin 6 During Viral Infections. Front Microbiol 10: 1057.