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Recent Advances in the Management of RSV Bronchiolitis: A Comparative and Integrative Study of Traditional Chinese and Western Medical Approaches

Wenting Xue[1], Guocheng Zhang[2,*]

[1]Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
[2]Children's Hospital of the Second Affiliated Hospital of Shaanxi University of Chinese Medicine, Xianyang 712046, Shaanxi, China
Correspondence Author

Abstract: ***To summarize the research on the treatment of RSV bronchiolitis with Traditional Chinese Medicine (TCM) and Western medicine over the past decade, providing a reference for its clinical management. Single herbs and compound prescriptions of Traditional Chinese Medicine have demonstrated good therapeutic effects on bronchiolitis caused by Respiratory Syncytial Virus (RSV).***

Keywords: Respiratory syncytial virus, Bronchiolitis**.**

1. Introduction

Bronchiolitis is primarily caused by infection with the Respiratory Syncytial Virus (RSV) and commonly affects infants and young children under the age of two. It is a leading cause of hospitalization for infants under 12 months of age. Currently, supportive care is recommended for the management of bronchiolitis. Clinical studies have shown that Traditional Chinese Medicine (TCM) has a good therapeutic effect on bronchiolitis. This review summarizes the clinical research progress on the treatment of pediatric bronchiolitis with TCM.

1.1 Understanding Respiratory Syncytial Virus (RSV)

Respiratory Syncytial Virus (RSV), was first discovered in 1945 in nasal lavage samples from a group of chimpanzees suspected of respiratory viral infection. Upon entering the body, the virus initially resides in the airway epithelial cells, causing local damage. It then spreads to the small alveolar cells, exacerbating inflammation in the bronchi and lungs. During this process, inflammatory cells produce mucus and some sloughed necrotic cells within the airway lumen, forming mucus plugs. This thickens the tracheal wall, worsens airway obstruction, and secondarily impairs the body's immune defense capabilities, thereby intensifying inflammation.

Currently, RSV is known to belong to the Paramyxoviridae family, genus Pneumovirus [1]. Because maternal antibodies cannot completely block the occurrence of viral infection, infants can develop the disease shortly after birth [2-3]. In developing countries, over 300 million children under the age of two are affected annually [4]. Compared to adults, this disease is more common in infants and young children with narrower tracheal walls, leading to gas retention in the lungs and atelectasis. This further exacerbates respiratory distress, wheezing, and the critical condition of cerebral hypoxia. Given the complex and variable pathological mechanisms of RSV-induced pathogenesis, and due to the unclear host-virus specific and pathogenic relationships [5], research and treatment methods for RSV-induced respiratory infections are still considered targets for breakthroughs.

1.2 Understanding Bronchiolitis in Respiratory Syncytial Virus (RSV)

Bronchiolitis is a common lower respiratory tract infectious disease in infants and young children. The primary pathogen for this disease is viral, with Respiratory Syncytial Virus (RSV) infection being the most frequent [6]. Bronchiolitis is most commonly seen in infants and young children under two years of age, with the majority of cases occurring within the first six months of life. Due to the difficulty in clinically identifying pure bronchiolitis that does not involve the alveoli and alveolar septa, it is also referred to as "wheezing pneumonia" in China. Its main manifestations are symptoms of lower airway obstruction, characterized by expiratory dyspnea and prolonged expiratory phase with wheezing. In severe cases, pallor, restlessness, and perioral and perioral cyanosis may be observed. Physical examination may reveal nasal flaring and the use of accessory muscles (subcostal, intercostal, and suprasternal retractions), increased heart rate, and pulmonary findings primarily consisting of expiratory wheezing. Fine to medium crackles may also be heard, and percussion may reveal a hyperresonant sound. Episodes of severe dyspnea (wheezing attacks) occur during the course of the illness. The peak of the disease occurs 48-72 hours after the onset of dyspnea, with the illness generally lasting about 1-2 weeks.

1.3 Overview of Modern Medical Treatment for RSV Bronchiolitis

Supportive care is currently the most effective treatment modality for RSV viral bronchiolitis [7]. Patients admitted to the hospital are primarily managed with supportive care, followed by the selection of supplemental oxygen and mechanical ventilation based on the severity of respiratory distress. Other supportive treatments include oxygen therapy,

fluid management, and maintaining airway patency [8-9]. Modern medicine has limited specific drugs for treating RSV bronchiolitis [10]. Ribavirin, first developed in 1972, can inhibit the replication of a few types of viral RNA and DNA [11]. It is used in the treatment of Hepatitis C Virus (HCV) and is currently the only approved drug for treating Respiratory Syncytial Virus [12]. Although Ribavirin has some antiviral effects and can reduce mortality, it also carries potential risks of sequelae and side effects [13]. Palivizumab is a humanized monoclonal antibody derived from mouse protein clones that targets the RSV F protein. This drug prevents the virus from spreading to the lower respiratory tract by blocking the Respiratory Syncytial Virus fusion protein [14-15]. It is currently the only officially approved drug for preventing RSV infection.

Motavizumab is a second and third-generation anti-RSV drug that underwent trials following Palivizumab [16]. The most recent in vitro Phase III clinical trial results confirmed its efficacy to be no less than that of Palivizumab. However, due to hypersensitivity reactions such as urticaria in some patients after use, it has not yet been approved for market [17]. The aforementioned anti-RSV drugs are strictly controlled and limited in clinical use due to their high production costs, expensive prices, and unclear side effects.

1.4 Current Status of RSV Vaccine Development

Developing safe and effective vaccines against RSV remains a formidable challenge [18], with novel RSV vaccines currently still in preclinical and clinical development stages. The development of RSV vaccines has been marked by numerous failures, and new vaccine development projects are met with both attention and challenges due to high costs and high failure rates. With national development progress and significantly shortened social distancing measures, viral transmission has become more rapid and its impact more widespread. To effectively prevent the spread of viral diseases, effective and correct control measures and guidance are necessary. The World Health Organization (WHO) regards this as a critical and urgent global challenge and a high priority concerning the health of people in all nations.

2. Exploration of Traditional Chinese Medicine in Modern Viral Bronchiolitis

2.1 Overview of Traditional Chinese Medicine's Perspective on RSV Bronchiolitis

RSV bronchiolitis is a term within clinical medicine and does not have a direct equivalent in Traditional Chinese Medicine nomenclature. Its initial clinical symptoms may include cough, nasal congestion, and sometimes high fever. In modern pediatric TCM, it is often encompassed by the term "Pneumonia and Wheezing Cough". TCM treatment emphasizes a holistic, person-centered approach, starting from the principle of Yin-Yang balance. During the course of illness, it aims to protect the body from external pathogenic interference and damage, while simultaneously regulating the body's own resistance to disease for recovery.

TCM's holistic philosophy is rich and profound. In recent years, numerous scientific studies have indicated that various single Chinese herbs and compound prescriptions possess the ability to directly inhibit the total viral load in respiratory diseases.

2.2 Literature Review on Pneumonia and Wheezing Cough in Traditional Chinese Medicine

By tracing ancient literature based on the clinical manifestations of Pneumonia and Wheezing Cough throughout its course, the earliest recorded mention in Traditional Chinese Medicine is found in the Huangdi Neijing Suwen, "Discussion on Vacuity and Reality": "Infants suffering from wind-heat, with wheezing and elevated shoulders" This description aligns with symptoms of infants exhibiting wheezing and elevated shoulders, and a forceful pulse, similar to those of Pneumonia and Wheezing Cough, following an exogenous wind-heat attack [19-20]. Prior to the Tang and Song dynasties, it was mostly described as "wheezing and panting" or "lung distention" In the Yuan Dynasty, Zhu Danxi's Yuan Ke Quan Shu states: "Infantile lung distention and wheezing, with qi stagnation in the chest and diaphragm, rapid breathing in the flanks, sunken chest like a pit, distended nostrils, and restless coughing. . . this is spleen wind". In the Qing Dynasty, Wu Qian's Yi Zong Jin Jian states: "Sudden wheezing, also known as spleen wind, with a high and distended chest, flanks forming pits, fluttering nostrils, restless spirit, and severe coughing; the 'Five Tigers Powder' is most effective".

2.3 Overview of Etiology and Pathogenesis of Pneumonia and Wheezing Cough in Traditional Chinese Medicine

As a common ailment of the respiratory system in children, Pneumonia and Wheezing Cough has been observed and summarized by pediatric physicians over generations, leading to the theoretical viewpoints that children are prone to developing the condition and that it can progress rapidly. Due to their delicate organs, insufficient vital qi, and immature yin and yang, children possess a fragile constitution and weaker physiological functions. Furthermore, children cannot regulate their body temperature or control their diet and intake of food. If their care is not properly managed, they are more susceptible to invasion by exogenous pathogens and damage from internal injuries related to diet.

TCM posits that the contagious nature and onset of viral diseases are primarily caused by external pathogenic toxins [21]. In most cases, the etiology is attributed to the invasion of external pathogens or the transformation of other diseases. The internal causes are attributed to the immature physical constitution and qi of children, their delicate organs, and their weak defense against external pathogens. When external pathogens invade the respiratory system, they typically enter the body through the mouth, nose, or skin, disturbing the lung and its protective qi, leading to the obstruction of lung qi and the generation of heat. This heat then burns body fluids, refines them into phlegm, and obstructs the airways, causing discomfort. Depending on the child's age, constitution, and the initial invasion of wind-cold or wind-heat, the severity and depth of the illness can vary significantly. In terms of pathological mechanisms, TCM's holistic view emphasizes the close relationship between the five zang organs and six fu organs. If the spleen loses its function of transportation and

transformation, dampness congeals into phlegm, which accumulates in the lungs, affecting the lung's function of dispersing and descending, thus leading to cough and excessive phlegm. The heart and lungs are both located in the upper jiao. If lung qi remains obstructed for an extended period, and pathogenic toxins are rampant, blood circulation may be impaired, preventing the nourishment of the heart. This can lead to the heart losing its nourishment or even a transformation into heart yang deficiency. The liver governs dispersion and ensures the smooth flow of qi throughout the body, and it controls the sinews and fascia. When pathogenic heat is rampant and invades the jueyin channel, it can cause critical symptoms such as limb convulsions, trismus, and neck rigidity, indicative of extreme heat generating wind. The kidney governs the reception of qi and governs the lungs' inhalation of clear qi, preventing shallow breathing. If there is congenital kidney qi deficiency compounded by external invasion, it can easily lead to symptoms such as difficulty breathing and exacerbation of dyspnea upon exertion [22-23]. In summary, although the primary location of this disease is the lung, it is characterized by rapid progression of the illness and a tendency to involve other organs, triggering aggravation of the condition or the development of acute critical transformations. Clinical differentiation can categorize common patterns such as "External Wind Invading the Lungs" and "Phlegm-Heat Obstructing the Lungs," as well as critical patterns like "Pathogenic Evil Sinking into Jueyin" and "Heart Yang Deficiency," requiring vigilance for severe illness [24].

2.4 Overview of Treatment for Pneumonia and Wheezing Cough in Traditional Chinese Medicine

Pneumonia and Wheezing Cough is characterized by typical symptoms such as fever, cough, phlegm accumulation, rapid breathing, and nasal flaring. In severe cases, symptoms like blocked nasal discharge and tears, pale or cyanotic complexion may be observed. Neonates with the condition may not exhibit these typical symptoms, commonly presenting with poor feeding, lethargy, and frothy saliva [25]. The younger the child, the more prominent the symptoms, the higher the incidence, and the more severe the condition [26]. The pattern of Phlegm-Heat Obstructing the Lungs is the most prevalent and severe type in the classification of viral bronchiolitis, holding significant research value for the TCM diagnostic analysis of this disease [27].

In TCM treatment of Pneumonia and Wheezing Cough, considering the mutual influence and transformation between pathological products such as phlegm-heat and blood stasis with the five zang and six fu organs, different patterns can be broadly categorized into methods such as: expelling lung pathogens and calming asthma, invigorating blood and resolving stasis, and tonifying the righteous qi while expelling pathogens. During the recovery phase, tonification primarily focuses on benefiting qi and nourishing yin, aiming to strengthen the lungs and consolidate the exterior, and fortify the spleen and benefit qi. Nourishing yin follows the principles of clearing and nourishing lung yin, and moistening and nourishing stomach yin. These methods can be used individually or in combination.

Clinical medication must consider the pathological characteristics of children, such as their delicate organs and clear spiritual functions. Treatment requires prompt responses and adaptability, establishing corresponding therapeutic plans for effective treatment.

2.5 Current Status of Modern Traditional Chinese Medicine in the Treatment of RSV Bronchiolitis

2.5.1 Single Herbs and Their Components

Scutellaria baicalensis is a commonly used traditional Chinese medicine for respiratory infectious diseases, possessing actions of clearing excess heat, resolving damp-heat, and stopping bleeding. The Bencao Zheng (Compendium of Materia Medica) records its ability to "clear heat from the upper jiao, resolve phlegm and facilitate qi, calm asthma and cough, stop bleeding, reduce recurring fever, [treat] wind-heat, damp-heat, headache, resolve plague, clear the throat, and treat lung atrophy and lung abscess..." [28]. Studies have confirmed through in vivo and in vitro experiments that baicalin, a component of Scutellaria baicalensis, exhibits significant anti-RSV activity. It can inhibit RSV-induced inflammation in mouse lung tissue, improve pathological damage in lung tissue, and reduce viral titers. Furthermore, it can directly inhibit RSV adhesion to host cells and intracellular viral replication, thereby reducing plaque formation in vitro [28].

Lophatherum gracile (Dan Zhu Ye) is an important medicinal plant with actions of clearing heat, relieving vexation, and promoting diuresis. It has been traditionally used to treat coughs associated with lung heat. In vivo studies have shown that ethanol extracts of Lophatherum gracile can reduce viral load in lung tissue and improve lung tissue pathological damage. The increase in the CD4+/CD8+ ratio mediates anti-viral mechanisms of T cells, and the reduction in IL-1β, TNF-α, and IFN-γ protein levels may be part of its underlying mechanisms [29].

Coptis chinensis (Huang Lian), a key herb for clearing damp-heat from the middle jiao, possesses actions of clearing heat and drying dampness, purging fire, and detoxifying. The Bencao Qiuzhen (Authentic Records of Materia Medica) records its ability to "greatly purge excess heat from the heart fire". In vivo experiments demonstrated that prophylactic gavage with Coptis chinensis aqueous extract could significantly ameliorate RSV-induced lung tissue damage and reduce the transcription level of the viral G protein. Concurrently, the Coptis chinensis aqueous extract could significantly reduce RSV-induced cell death and viral replication within cells, an effect potentially mediated by the induction of Type I interferon-related signaling pathways [30].

In addition to heat-clearing Chinese herbs, other herbs with different therapeutic functions also exhibit anti-RSV activity. Cinnamomum cassia (Rou Gui), despite its pungent, sweet, and hot nature, has an aqueous extract that can also reduce RSV-induced plaque formation. In the early stages of RSV infection, it can inhibit viral adhesion and invasion. It can also inhibit the expression of viral F protein by forming syncytia. The anti-RSV effect of its active component, cinnamaldehyde, may be achieved by regulating pro-apoptotic factor Caspase-9

and anti-apoptotic protein p-AKT [31].

2.5.2 Traditional Chinese Medicine (TCM) Formulas

TCM formulas represent the distinctive characteristic and advantage of TCM in disease treatment. They allow for timely adjustments in medication and syndrome differentiation based on the severity, urgency, location, and nature of the disease, thereby achieving individualized treatment. The TCM formulas employed in basic research for RSV prevention and treatment primarily possess the efficacy of clearing heat and detoxifying, opening the lungs, and resolving phlegm. Dingchuan Tang, originating from the She Sheng Zhong Miao Fang (A Collection of Miraculous Formulas for Health Preservation), has actions of clearing heat, resolving phlegm, and descending lung qi. Research has confirmed that Dingchuan Tang can reduce viral load in the lung tissue of RSV-infected rats and exert a favorable regulatory effect on immunosuppressive cells in peripheral blood [32]. Yinqiao San, from the Wen Bing Tiao Bian (A Systematic Treatise on Warm Diseases), is a representative formula for exterior-releasing with acrid-cool herbs, and its individual components all exhibit good anti-RSV activity [33]. The Jin Xin Oral Liquid and Qing Fei Oral Liquid, formulated by Professor WANG Shou-chuan, are primarily composed of herbs such as Ephedra (Ma Huang), Gypsum (Shi Gao), Apricot Kernel (Xing Ren), Mulberry Bark (Sang Bai Pi), Hogfennel Root (Qian Hu), and Chinese Wormseed (Ting Li Zi). These formulas possess the functions of clearing heat, detoxifying, descending lung qi, resolving phlegm, and relieving cough. A series of studies have confirmed that both formulas can directly act on RSV and improve RSV-induced lung tissue damage [34].

From the aforementioned clinical and basic research on TCM in the prevention and treatment of RSV, it is evident that most anti-RSV TCM herbs or formulas are dominated by heat-clearing herbs or utilize them as the principal ingredient. We must clearly recognize the complexity of TCM and its formula components, as well as the multiple pathways through which active ingredients exert anti-RSV effects. Current research is limited to unclear active components and focuses on a few cytokines and signaling pathways, neglecting the holistic nature and the concept of syndrome differentiation and treatment inherent in TCM. Undeniably, technological limitations of the era have made research on TCM and its formulas arduous. However, the efficacy of TCM and its formulas is the prerequisite, research into the material basis of their effects is crucial, and the elucidation of specific mechanisms of action is an effective driver for TCM to uphold its integrity, innovate, and gain global recognition. We must firmly believe that with the advancement of science and technology, research on anti-RSV TCM will continually achieve breakthroughs, and TCM will make greater contributions to humanity's fight against viral diseases and the safeguarding of human health.

3. Conclusion

The diagnosis and treatment of bronchiolitis caused by Respiratory Syncytial Virus (RSV) using Traditional Chinese Medicine (TCM) are based on the principles of "syndrome differentiation and treatment" and "addressing both the root cause and the symptoms." TCM interventions can effectively alleviate core symptoms such as cough, wheezing, and rattling in the throat in affected children, reduce airway inflammatory responses, shorten the course of illness, and decrease the recurrence rate. Compared to purely symptomatic Western medical treatment, TCM intervention can reduce the dosage and frequency of antibiotic and bronchodilator use, thereby lowering the risk of adverse reactions. Concurrently, it addresses the regulation of the child's visceral functions, improves the weakened pulmonary and splenic constitution, and embodies the unique advantage of "treating the disease by addressing its root cause." This provides diversified strategies for clinical prevention and control.

4. Prospects and Limitations

In the clinical application of Traditional Chinese Medicine (TCM) for the diagnosis and treatment of RSV bronchiolitis, there is a need to optimize dosage forms and administration methods. For young children, oral TCM dosage forms are often decoctions, which present challenges such as bitter taste and difficulty in administration. Future research and clinical applications of TCM for RSV bronchiolitis can be advanced in multiple aspects, achieving a combination of inheritance and innovation. Considering the physiological characteristics of young children, new TCM dosage forms with improved palatability, precise dosing, and convenient administration, such as granules, oral liquids, and atomized preparations, should be developed. Furthermore, standardizing the operational procedures and dosage standards for external therapies, and developing portable and easy-to-use external application devices, will enhance clinical compliance.

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