

Research Progress of Chinese Medicine in the Treatment of Influenza A in Children

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Abstract: *Influenza A (H1N1) is an acute respiratory infection caused by the influenza virus subtype H1N1. Among the serious complications include severe pneumonia, acute respiratory distress syndrome, fulminant myocarditis and necrotizing encephalitis, the most serious of which may be life-threatening. The main treatment for influenza A in Western medicine is the use of antiviral drugs, but the phenomenon of drug resistance has emerged, and there are certain limitations in clinical application. Vaccine is an effective measure to prevent and control influenza virus, but in the face of mutating influenza virus, the developed vaccine gradually loses its protective effect, and the new vaccine is unable to control the influenza that occurs in the current season in a timely manner. The genetic characteristics of influenza viruses make vaccines lagging behind and easily induce resistance to some antiviral drugs. In addition, the antigenic drift of influenza viruses makes it difficult to develop vaccines and drugs. In recent years, traditional Chinese medicine (TCM) has shown good results in the treatment of influenza A through the four diagnostic methods of diagnosis and treatment, and the exploration of TCM treatment of influenza A has received more and more attention and has become a hot issue in current research. At present, a variety of formulas have been proved to be effective in the treatment of influenza A. The existence of TCM provides more diversified choices for the research and development of new antiviral drugs and the prevention and treatment of influenza pandemic in the future, and provides a new way of thinking and direction for the prevention and treatment of influenza A.*

Keywords: Influenza A, Chinese medicine.

1. Introduction

Influenza A (H1N1) is a respiratory infectious disease caused by the H1N1 subtype of the influenza virus. Children are particularly susceptible to the disease, with those under 2 years old being at a higher risk of complications. Serious complications of influenza A include pneumonia, acute respiratory distress syndrome, myocarditis, and encephalitis. Currently, antiviral drugs like oseltamivir are used for treatment, but there are limitations to their effectiveness. Traditional Chinese medicine (TCM) has shown promise in treating influenza A through various formulas and diagnostic methods. TCM provides alternative options for antiviral drugs and pandemic prevention. A review of current research in TCM for influenza A treatment aims to contribute to the scientific basis for further study and clinical application of TCM treatment. Chinese medicine views influenza A as a type of seasonal influenza and employs different treatments based on symptoms. The pathogenic mechanism of influenza A involves the activation of innate and adaptive immune responses, resulting in cytokine release and potential immunopathological damage. Chinese medicine can regulate the immune response and inhibit viral replication. Formulas like Yin Qiao San and Gui Zhi Ma Huang Tang have shown anti-inflammatory and antiviral effects. In conclusion, Chinese medicine offers potential as an alternative treatment for influenza A.

2. Recognition of Influenza A in Modern Medicine

H1N1 virus belongs to enveloped single-stranded RNA virus. The viral envelope is derived from the bilayer lipid-like membrane of the host cell, which is embedded with three membrane proteins, namely hemagglutinin (HA), neuraminidase (NA) and matrix channel (M2) protein [1]. The

nucleocapsid inside the viral particle is in the form of a helical filament with a diameter of about 10nm and a length between 50and60nm. The nucleocapsid consists of nucleoprotein (NP) and RNA polymerase complex (PB1, PB2 and PA) bound to eight RNA genes of the virus. The virus is sensitive to commonly used disinfectants such as ethanol, povidone-iodine, tincture of iodine, etc. it is sensitive to heat and can be inactivated at 56°C for 30min [2]. After virus infection in humans, it successively produces immunoprotective and immunopathologic responses. Immunoprotective response through the Toll-like receptor-13 followed by the production of NKcell response, interferon α and β , neutralizing antibodies and cytotoxic Tcells, cytotoxic Tcells can inhibit the immunopathological response. The immunopathologic response produces a large number of cytokines, inflammatory mediators, and adhesion molecules, etc. which worsen the condition [3].

Influenza is the most common infectious disease in the world, and after infection, there is a transient immunity to the same type of virus, but there is no cross-immunity between types and subtypes, coupled with the fact that the virus is highly mutable, everyone is infected with influenza virus, and can also be infected with recurrent morbidity. Global influenza pandemics in human history have been caused by influenza A viruses. Influenza A (H1N1) is mainly transmitted through droplets and aerosols via the respiratory tract between people in close contact, but also through direct or indirect contact with mucous membranes in the mouth, nasal cavity, eyes, etc. The virus is spread by contact with respiratory secretions, nasal mucous membranes, and mucous membranes of patients. Contact with respiratory secretions, body fluids, and virus-contaminated objects may also cause infection. Children are the most susceptible group. On the one hand, because children's immune function is still not well developed, humoral immune function at the age of 3 years to reach the level of adults, the body lacks antibodies against influenza A

virus; secondly, because the virus is transmitted by droplets and contact, children are easy to set up, can not avoid contact with the source of infection; thirdly, the virus can be on the surface of the object to survive a certain period of time, the children negligence is easy to contact with the virus, which increases the chance of infection. Its general clinical manifestations are fever, accompanied by chills, chills, headache, muscle, joint pain, extreme fatigue, loss of appetite and other systemic symptoms, often with a sore throat, cough, there may be nasal congestion, runny nose, post-sternal discomfort, flushing, and there may be vomiting, diarrhea and other symptoms.

At present, anti-influenza vaccine and anti-influenza drugs are still the main means of treating influenza. Vaccination is the most important measure to prevent the H1N1 pandemic in children, but the continuous evolution of influenza viruses can easily lead to the ineffectiveness of the influenza vaccine; children are susceptible to influenza viruses, and they have the weakest immune response reduction and protection after vaccination against influenza viruses. Currently available antiviral drugs include (1) neuraminidase inhibitors (NAI), such as oseltamivir, zanamivir, paramivir, and ranitamivir; (2) ion channel M2 blockers, such as amantadine; (3) inhibitors of viral RNA synthesis, such as ribavirin; and (4) polymerase inhibitors, such as farfilavir. Two classes of drugs are currently approved for use in influenza, amantadine and neuraminidase inhibitors [4]. Of these, amantadine is not approved by the Food and Drug Administration (FDA) for use in children. Influenza A H1N1 virus is resistant to amantadine. Oseltamivir is used in children over the age of 1 year and zanamivir is used only in children over the age of 7 years [5]. While anti-influenza drugs have proven to be effective measures against influenza, resistance to commonly used influenza virus inhibitors has been a problem. Currently, influenza virus vaccines, and anti-influenza virus chemicals play an important role in the fight against influenza viruses, but due to the problem that influenza viruses are prone to mutation and drug resistance, these treatments are not yet fully effective in controlling influenza epidemics, and therefore new therapeutic strategies need to be sought.

In conclusion, Western medicine for influenza A treatment is mainly the use of antiviral drugs, such as oseltamivir, paramivir, etc. but there has been the emergence of drug resistance phenomenon, and the clinical application still has certain limitations. In the prevention and control of influenza virus, vaccine is an effective preventive measure. However, in the face of constantly mutating influenza viruses, the developed vaccines gradually lose their protective effect, and the new vaccines are unable to control influenza occurring in the current season in a timely manner. In addition, it has been clinically found that for severely infected patients with influenza virus, the plasma levels of cytokines affect the survival rate of the patients, and the therapeutic effect can be effectively improved if anti-inflammatory combination therapy is used. There is a realistic need and significance for the development of novel drugs with dual antiviral and anti-inflammatory effects.

3. Chinese Medicine's Understanding of Influenza A

Chinese medicine has no name for influenza, but according to its clinical manifestations, it is believed that influenza A should belong to the category of "seasonal influenza", "warm disease", "epidemic", "plague", "fever", and so on. 'fever' and other categories, 'Huangdi Neijing' 'typhoid fever and miscellaneous diseases' and many other Chinese medical texts have a lot of records. The understanding of Chinese medicine on seasonal colds is a process of gradual deepening and continuous improvement. The earliest discussion about it is found in Suwen-Yin and Yang Yingxiang Daxian: "When winter is injured by cold, spring will be warm". "The origin and symptoms of all diseases "also recorded that 'seasonal diseases, spring should be warm and cold, summer should be hot and cold, autumn should be cool and hot, winter should be cold and warm, not its time and its gas, is a year, the disease is not long and few, rate similar, this is the gas of the seasonal line also', pointing out that seasonal diseases have the characteristics of epidemic, and at the same time put forward with the abnormal changes in the climate. It also suggested that it was related to abnormal changes in the climate. Lin Peiqin, a medical doctor in the Qing Dynasty, first proposed the term "seasonal cold" in his book "Classical Evidence and Treatment". In the Ming and Qing dynasties, with the establishment of the warm disease theory, the system summarized the system of Chinese medicine for the identification and treatment of warm-heat and damp-heat type of exogenous fever, and Ye Tianshi in the Qing dynasty pioneered the system of identification of Wei Qi and Ying Blood, and in the "theory of warmth", he said, "In the spring month, when the wind is blowing, the gas has been warmed up." Wu Jutong in the Qing Dynasty wrote "Warm Diseases", created the San Jiao system of diagnosis, which believes that: "wind and warm people, early spring Yang Qi rising, syncopated yin order, wind and warm." From the "Evil enters through the mouth and nose" of the warm disease scholar Wu Yike, to the "Warm evils are received upwards and first offend the lungs" of Ye Tianshi, to the "Evil is received upwards and tends directly to the middle way" of Xue Shengbai, etc. , all of them explicitly proposed that external evils can enter through the mouth and nose directly, and that external evils can enter through the mouth and nose directly. This disease is located in the Lung Wei, and the lungs are the most important part of the lungs.

This disease is located in the lungs and guards, mostly due to the deficiency of positive qi, the low function of guards and guards, the evil of epidemic and poison invades the lungs and guards, the guards and guards are out of harmony, and the lungs are not pronounced and the disease develops. In the early stage of the disease, the main evidence of surface heat, with the changes in the condition of more from the surface into the internal, visceral dysfunction of the gas Ying two burnt, internal closure of the evidence of the external; later the evil retreat is deficient, mainly manifested in the evidence of qi and yin two injuries. Children are mostly categorized into two types of evidence: wind-heat in the lungs and wind-heat and phlegm-heat obstructing the lungs. The main symptoms of influenza are fever, cold, headache, accompanied by general malaise, fatigue, etc. often with cough, phlegm viscous, sputum, thirst and drink, sore throat, red eyes and other symptoms of wind-heat. Diagnosis and treatment mostly adopt the system and treatment of six meridians identification, Wei qi and Ying blood identification, and San Jiao

identification, focusing on supporting the positive and dispelling the evil, and treating the disease in phases and stages. The 2018 version of the influenza diagnosis and treatment program adopts the treatment of pungent and cool relief of the epidermis and clearing away heat and toxins mainly based on the basis of the "Diagnosis and treatment program of Influenza A (H1N1) (the third edition of 2009)" and the "Guidelines for the Diagnosis and Treatment of Influenza (the 2011 edition)" in the context of the actual situation. From the perspective of traditional Chinese medicine, wind, cold and dampness are especially prevalent, and the human body is more susceptible to the invasion of seasonal epidemics and external evils, and the positive qi fights with the evils, resulting in a loss of the lungs to promote and purify the lungs, and the disease and heat are embedded in the lungs. In addition, in spring, when the wind and wood are at their peak, the climate is warm and windy, and Yang Qi rises, making it easy to form wind-heat illnesses. From the characteristics of influenza symptoms and pathogenesis, "heat evidence" is a common symptom element in all stages of influenza A, and is also an important pathogenetic feature. Therefore, Chinese medicine treatment of influenza mostly adopts heat-clearing and detoxifying traditional Chinese medicines, and pays attention to the time, place, and person, and flexibly recognizes the evidence, and adds and subtracts according to the evidence. In general, according to the type and severity of the symptoms, internal and external treatments such as cooling and relieving the epidermis, clearing heat and removing toxins, clearing the qi and cooling the camps, and timely application of qi and yin to support the positive and eliminate the evil spirits, and balance the yin and yang, can be achieved.

4. Analysis of the Pathogenic Mechanism of Influenza A (H1N1) in Chinese and Western Medicines

When the influenza virus infects host cells, during its RNA proliferation and replication, it activates the innate immune response of the host through three pathways: i.e., vitamin Toll-like receptor, retinoic acid-induced gene-1 (RIG-I) protein. During the adaptive immune response phase, the body's role in virus clearance is exerted through the activation and regulation of T-cell subsets and type 2 innate lymphocytes (ILC2) [6]. There are two waves of cytokine release in this process; when respiratory epithelial cells are infected, endothelial cells and alveolar macrophages produce and release the first wave of cytokines; subsequently adaptive immune cells are activated and play an immunoregulatory role, secreting the second wave of cytokines for virus inactivation and clearance [7].

Firstly, Toll-like receptor (TLR) is a very important pattern recognition receptor (PRR) in the human body, and secondly, through the recognition of one or more pathogenic microorganisms, the body system is enabled to function as it should, which is the process of pathogen-associated molecular pattern (PAMP) [8, 9]. Retinoic acid-inducible gene protein I (RIG-I)-like receptors are predominantly distributed in the cytoplasm and tend to be expressed through epithelial cells, dendritic cells, and macrophages. After successful recognition of viral RNA, the RIG-I structural domain binds to adenosine triphosphate and produces other substances through

caspase-recruiting structural domains that bind to mitochondrial antiviral signaling proteins (MAVS), which transmit signals downward, inducing IRFs and NF- κ B to secrete I-type IFNs and pro-inflammatory cytokines such as IL-6, IL-1 β , and TNF- α , respectively, and participate in intrinsic immune response. The cytokines play an antiviral role in the intrinsic immune response [10].

Cytokines are essential for signaling, activation of expression, and viral killing and clearance of various signaling pathways in the immune system. However, excessive cytokine release can trigger severe immunopathologic damage, especially the resulting cytokine release syndrome. Cytokine release syndrome (CRS), which can also be referred to as cytokine storm, is characterized by a variety of clinical manifestations, including elevated levels of circulating cytokines, acute systemic inflammatory response, and secondary multi-organ dysfunction. And severe CRS is often life-threatening [11]. Studies have reported that cytokine storm is the most important and direct cause of lung injury [12], and cytokine production is closely related to the activation of multiple signaling pathways. Among them, NF- κ B is located at the hub of the signaling pathway [13]. It can participate in the initiation and regulation of gene expression of many cytokines and inflammatory mediators. NF- κ B can form a complex circulatory network with the participation of certain cytokines [14,15]. Its signaling pathway plays a key role in the expression of inflammation-associated cytokines. TNF- α acts as an initial driver of the nuclear factor- κ B (NF- κ B) signaling pathway, inducing anti-apoptotic processes and pro-inflammatory factor production and expression through activation of the type I TNF receptor (TNFR1) and intermediate adapters. At the same time, NF- κ B also inversely induces the expression of TNF- α , an important member of the inflammatory cytokine family, which is secreted by activated macrophages, NK cells, and T cells and is involved in the early inflammatory response of the organism. TNF- α also regulates the immune cells, and acts as an endogenous heat source to induce fever and interfere with apoptotic cell death. In addition, TNF- α , as a cytokine produced in the early stages of viral pneumonia, can regulate other pro-inflammatory factors downstream. These cytokines can regulate each other and form a vicious circle, causing a cytokine storm, which in turn exacerbates the patient's condition. IL-6, a common cytokine, is one of the most induced immune markers produced during viral infections [16]. IL-6 is also an important link in the functioning of the body's immune defense mechanism, and its expression and release is a key factor in determining the cytokine network associated with normal immunoregulation and immune imbalance and its release is a key factor in determining the cytokine network associated with normal immune regulation and immune imbalance. As a pleiotropic pro-inflammatory cytokine, it has both pro- and anti-inflammatory functions. In conclusion, the immune response elicited by an influenza virus-infected host is an intricate process that coordinates with each other and plays an important role in protecting the host against influenza virus.

In recent years, more and more scientific studies have focused on the anti-influenza effects of traditional Chinese medicines, and it is believed that Chinese medicines can prevent and control influenza at both the host and pathogen levels: on the

one hand, they can regulate the immune response induced by the host after viral infection, i.e., modulate the host signaling pathway to inhibit the viral proliferation process in host cells; regulate the body's immune activity, and ameliorate the clinical symptoms caused by viral infection; and, on the other hand, they act directly on the virus. On the other hand, it acts directly on the virus itself to inhibit viral replication. Studies have shown that Chinese medicine combinations based on multi-components and multi-targets can not only inhibit viral replication, but also exert comprehensive anti-influenza viral efficacy by improving clinical symptoms and regulating host immunity to control inflammation progression [17].

In the course of development, Chinese medicine has accumulated a wealth of clinical experience and has developed many formulas with excellent efficacy in treating influenza, such as Elevating and Dispersing Powder, Yin Qiao Powder, Jade Screen Wind Powder, Ge Ge Ge Tang, Ma Xing Gan Shi Tang, Gui Zhi Tang, Zhen Zhen Chai Hu Drink, Chai Hu Gui Zhi Tang, Ephedra and Gui Zhi Gao Zhi Tang, Xin Jia Xiang Elsholtzia Drink, and Artemisia Scutellariae Bile Clearing Tang, and so on. A researcher chose one of these formulas for experimentation. Yin Qiao San has the effects of clearing heat and removing toxins and anti-inflammation [18, 19]. Zhang Zhaoyan et al [20] found that Yin Qiao San could reduce the expression of inflammatory factors when inhibiting the proliferation of influenza A virus, attenuate the damage caused by inflammatory response, and inhibit apoptosis of toxic host cells. Gui Zhi Ma Huang Tang has the functions of anti-influenza virus [21], antipyretic and analgesic, anti-inflammatory [22] and asthma. The results found that Yin Qiao San and Gui Zhi Ephedra Soup had a defensive effect on influenza virus infection, could reduce the expression of inflammatory factors in the TLR7/NF-KB pathway, could regulate immune function, could restore the inflammatory response caused by influenza virus, and achieve viral clearance [23]. Xinjia Elsholtzia drink has the pharmacological effects of clearing heat and dampness, antibacterial and anti-inflammatory effects [24]. TianBo Zhang et al. [25] found that lifting and spreading the NA in vitro and in vivo by inhibiting its anti-influenza effect.

Other studies [26, 27] found that baicalein exerted anti-influenza virus effects in vitro and in vivo and attenuated lung injury and lung tissue peroxide levels in infected mice in vivo. Pang P et al [28] found that baicalein controlled influenza A virus infection by down-regulating the RLRs signaling pathway, and it was suggested that influenza A virus infection resulted in low body mass, high viral load, and high RIG-I expression, while baicalin reduced the rate of body mass loss and down-regulated key factors of the RLRs signaling pathway, and also reduced the high expression of inflammatory cytokines in lung tissues, activated a balanced host inflammatory response, and limited the immunopathological damage, which helped to improve the clinical and survival outcomes. CHANG CH et al [29] found that mulberry leaf extract had a good effect on inhibiting IL-6 and TNF- α of adipocyte origin. good effect. LI L et al [30] showed that Honeysuckle and Forsythia are commonly used anti-HIV Chinese medicines, and they each have specific immunomodulatory pathways; Honeysuckle increased the phagocytosis rate of macrophages and the conversion rate of lymphocytes, and Forsythia increased the splenic index in

mice with immunosuppressed status. Huang Zhisheng et al [31] found that both baicalin and forsythine inhibited the expression of influenza A NP and down-regulated the expression of influenza A virus NP in transfected Hela cells, and their combined use showed synergistic effects. Both single herbs or pairs of herbs synergistically acted against influenza A virus to a certain extent.

5. Summary and Prospects

At present, both Chinese and Western medicine have achieved certain results in the treatment of influenza A, with good clinical therapeutic effects. Western medicine mainly adopts antiviral and vaccination treatments, but drug resistance or adverse reactions often occur in children. In contrast, the treatment of influenza A by Chinese medicine focuses on the overall regulation, clearing heat and removing toxins, and has better efficacy and safety. Combining the advantages of Chinese and Western medicine can improve the therapeutic effect and reduce the adverse reactions, which is of positive significance for the treatment of AFL. In future research, it is still necessary to strengthen the clinical research on the combination of Chinese and Western medicines to explore more effective treatment options; in addition, by combining the concept of individualized medical treatment, personalized treatment plans can be formulated according to the characteristics of different patients to improve the pertinence and effect of treatment, and to give full play to the unique advantages of traditional Chinese medicine in the treatment of this disease.

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