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• REVIEW •

Current status of severe acute respiratory syndrome in China

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Abstract

Severe acute respiratory syndrome (SARS), also called infectious atypical pneumonia, is an emerging infectious disease caused by a novel variant of coronavirus (SARS-associated coronavirus, SARS-CoV). It is mainly characterized by pulmonary infection with a high infectivity and fatality. SARS is swept across almost all the continents of the globe, and has currently involved 33 countries and regions, including the mainland China, Hong Kong, Taiwan, North America and Europe. On June 30, 2003, an acumulative total reached 8450 cases with 810 deaths. SARS epidemic was very rampant in March, April and May 2003 in the mainland of China and Hong Kong. Chinese scientists and healthcare workers cooperated closely with other scientists from all over the world to fight the disease. On April 16, 2003, World Health Organization (WHO) formally declared that SARS-CoV was an etiological agent of SARS. Currently, there is no specific and effective therapy and prevention method for SARS. The main treatments include corticosteroid therapy, anti-viral agents, anti-infection, mechanical ventilation and isolation. This disease can be prevented and controlled, and it is also curable. Under the endeavor of the Chinese Government, medical staffs and other related professionals, SARS has been under control in China, and Chinese scientists have also made a great contribution to SARS research. Other studies in developing new detection assays and therapies, and discovering new drugs and vaccines are in progress. In this paper, we briefly review the current status of SARS in China.

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INTRODUCTION

On November 16, 2002, the first case of SARS patient was found in Foshan city, Guangdong Province, China[1]. Severe acute respiratory syndrome (SARS) is different from ordinary pneumonias caused by bacteria, other viruses, chlamydia and mycoplasma. The disease starts with an abrupt onset of fever, progresses swiftly, and is subjected to acute respiratory failure. Furthermore, it results in multiple organ dysfunctions with a higher infectivity and fatality. The main clinical manifestations of the patient are high fever, non-productive cough, myalgia and dyspnea. The patient has no response to any antibacterial therapy. At the beginning, the experts in Guangdong Province believed that it might be caused by a novel virus infection, and designated it as "atypical pneumonia" based on its clinical manifestations. On April 8, 2003, the State Council of the People' s Republic of China classified this illness as a legal infectious disease, and named it as infectious atypical pneumonia according to its higher infectivity, quick transmission and high mortality. The same kind of patients was found in Hong Kong and Vietnam at the end of February[2,3]. Dr. Carlo Urbani, an Italian epidemiologist working at the Hanoi Office of the World Health Organization (WHO), first reported to WHO and named this disease as severe acute respiratory syndrome. Later, Dr. Urbani caught the disease himself and died on March 29, 2003. In memory of Dr. Urbani' s great contributions in fighting against this disease, WHO formally designated this disease with unknown causes as SARS on April 16, 2003[4]. Ksiazek and his colleagues proposed that their first isolate be named the Urbani strain of SARS-associated coronavirus (SARS-CoV)[4,5].

On March 12, 2003, WHO issued a global alert of SARS outbreak, and called upon 11 laboratories (including the Institute of Virology, Center of Disease Control and Prevention, China, and Guangdong Center of Disease Control and Prevention, China) in 9 countries to join a collaborative multi-center research project on SARS. Chinese medical and health care workers have been keeping abreast of the advances in SARS research, and have achieved a number of success while fighting against SARS. In this paper, we briefly reviewed the current status of SARS research in China.

EPIDEMIOLOGY

General situation

During the period from November 16, 2002 to April 16, 2003, 13 cities had reports of SARS cases in Guangdong Province, China. Among the 13 reported cases of SARS, 3 were cooks, 3 officers, 2 farmers, 2 retired persons, 2 workers, and 1 businessman. Their age ranged from 18 to 84 years, the majority (77 %) was between 30-50 years. No evidence of mutual transmission was found between the reported cases[6]. The first case of SARS in Guangzhou was found on January 2, 2003. The epidemic broke out and reached the peak early in February, and then the incidence started to decline. As to age distribution of the patients, most patients were between 20-50 years. The patients were present in all the 13 counties and cities, but concentrated in 7-city areas, accounting for 95 % of the total cases, in which 28.7 % of the patients were healthcare workers. Of the 36 deaths, their age ranged from 5 to 89 years, and half of them were older than 60 years. Some of the deaths (38.9 %) were complicated with underlying diseases, including hypertension, diabetes, heart disease, and pulmonary emphysema. There was also a clustering trend: more than 2 patients were found in 42 families, 277 cases of healthcare workers were from 28 hospitals and institutes[7]. The incidence in Beijing had a similar feature to Guangdong (Table 1)[8]. Till June 30, 2003, an acumulative total reached 8 450 cases with 810 deaths. In the mainland of China, there were 5 327 cases

Table 1 History of SARS contact and incubation period in 80 cases

	Male (*n*, %)	Female (*n*, %)	Age (year)	Contact history	Incubation period (d)
Total	28 (35 %)	52 (65 %)	31.6±10.1	72 / 80(90 %)	7.6±4.3
Healthcare worker	13 (24.5 %)	40 (7.5 %)	30.8±8.4	49 / 53(92.5 %)	7.8±4.5
Non-healthcare worker	15 (55.6%)	12(44.4%)	36.4±12.1	23 / 27(85.2 %)	7.7±3.1

of SARS in which 348 patients died, and 1 755 cases with 298 deaths and 681 cases with 84 deaths occurred in Hong Kong and Taiwan, respectively. The national case reports showed that SARS patients were distributed in almost all professions, and healthcare workers with the infection accounted for 20-30 % at the early stage of SARS epidemic. There was no difference between both sexes in the incidence. SARS patients were found in every age group, and predominant in 20-49 years group (about 80 % of cases). The mortality in senile patients was significantly higher than that in young patients[9,10].

A professor from Zhongshan University in Guangzhou suffering from SARS stayed at Jinghua Grand Hotel, and a 28-year-old resident in Hong Kong got infected there, leading to SARS outbreak in the Prince Wales Hospital. However, a study made by Medical College of Zhongshan University indicated that at least 3 sources contributed to the outbreak early in March, that is to say, the source of SARS outbreak in Hong Kong was more than one. The mainland of China reported for the first time that no new case was found on June 2, 2003. No confirmed, suspected cases and deaths occurred for the first time on June 19, 2003 in China. Xiaotangshan Hospital, a speciality SARS hospital in Beijing, was then closed, demonstrating that a decisive victory has been won in fighting against SARS in China.

Infectious source

Currently, the known patient with SARS is the only infectious source. In the primary stage, symptoms are more obvious and it has high infectivity, while in the recovery stage, its infectivity is lost. Not all the cases have the same infectivity. Highly contagious cases are those who deliver a large amount of viruses for a long time, especially with severe cough, or those who undergo an endotracheal intubation with a splashing of droplets. Few cases with very strong infectiousness are called "super-spreader", who usually are the first cases or the first cluster of SARS patients during the outbreak. Usually, the early cases of SARS have a high infectivity and a strong pathogenicity, which would decrease later with progression of the epidemic. It is still unclear that why some individuals exposed to the patient did not contract SARS. Does occult infection of SARS exist? If yes, what role it plays in transmission and what is its epidemiologic significance? All these need to be further studied.

The initial results of epidemiologic surveys showed that the first reported cases or the first cluster of SARS were cook and market purchasers in some cities of Guangdong Province. A certain number of the sporadic cases did not have a contact history of SARS patients, from which we could deduce that there might be some other route of transmission and animal-mediated route of transmission may play a role in pathogenesis. Sources of infection may include some species of animals and the detail is unclear.

From May 23, 2003, scientists in Hong Kong and Shenzhen have collaborated in search for the origins of SARS. On the basis of population epidemic investigations, researchers have been on the track of animals infected with SARS viruses and have targeted at the wild mammal animals in their study. They have confirmed the kinship relations between these animals and human SARS viruses based on an evolutionary analysis of the SARS virus genes of different genera. It seems that they have observed the origin of the human SARS viruses based on these findings. By nearly a month of painstaking efforts, researchers have isolated 3 SARS specimens from 6 Paguma larvata. The fully genetic sequencing of one specimen showed that the SARS viruses in Paguma larvata bore 99 % homology with the SARS viruses in the human body. A further genetic analysis confirmed that SARS viruses in animals were the precursors of the SARS viruses in humans. The testing and analysis of the SARS antibody were performed in 10 people who were engaged in wild animal businesses, among them, 5 people had a positive response, indicating that the SARS viruses in wild animals may infect those who have close contacts with them. These findings have provided important evidences for further investigation of the origins of SARS viruses in humans, and their associated chains, and will lay a foundation for the future development of SARS vaccines and treatment serum. Currently, there is no strong evidence that demonstrates SARS is transmitted through animals or insects.

Route of transmission

Airborne droplets from the patient are the main route of transmission. It is not clear whether there are other transmission routes, personal touch by hands, playthings contaminated by the secretions from the patient' s respiratory tract. Close contact refers to the direct touch of the patient' s secretions and body fluid during treatment and nursing of the patients. The transmission scope is closely correlated with the environment of the ward, course of treatment, patient' s condition, time of exposure and personal protection of healthcare workers and visitors. Improper protection increases the risk of infection. Rubbing nose and eyes with the contaminated hands may also be a route of the transmission. Sexual transmission of SARS has not been confirmed, but close contact during sexual intercourse may increase the chance to get infected.

Lin *et al*[11] from the Institute of Preventive Medicine, University of Taiwan, also believed that only when respiratory symptoms appeared did the patient have infectivity. As for the route of transmission they have made the following two conclusions. The first is that the special shell antigen of SARS-CoV might come from chromosome 6q in human tissues (MCH/HLA). Once the virus enters human body, the invader is wrapped by the special tissue antigens in some individual hosts, so that the virus loses its capacity to infect other persons. Clinically, this strong tissue antigen might relate to severe leukopenia or lymphopenia in SARS patients. Once the disease progresses to respiratory distress, the lungs would try to dissolve the mucus produced by acute inflammation, by activating the body defense system to secrete proteolytic enzymes for the mucus dissolution. Meanwhile, the enzymes would also dissolve the tissue antigens of the shell, and make the virus resume its infectivity to other individuals. This clear-cut route of transmission is characterized by SARS-CoV. It has been proposed that SARS be liable to transmit among the family members because of the same type of HLA. The second is that different strains of bacteria in the sewage are able to produce proteolytic enzymes and dissolve the shell protein of SARS-CoV, and promote its infectivity to others. This mechanism might explain why SARS outbreak occurred in Amoy Garden, as well as in sporadic individuals who had been

to the epidemic regions, without direct contact with the patients. This virus can enter the human body via any part of mucosa, including respiratory tract, oral cavity, and genital tract. Owing to the higher concentration of proteolytic enzymes in the lung, SARS patients have a strong infectivity even at the early stage of the disease. Although the above hypotheses could explain some phenomena in SARS epidemiology, they need to be further confirmed.

Susceptible population

The ordinary population is very susceptible to SARS, the healthcare workers who have close contacts to the patients during the treatment and nursing, are the high-risk group. Anyone who has a history of close contact to the patients is a high-risk individual, and may exist the occult infection. In view of professions, healthcare workers are the most easily infected persons. Compared with other infectious diseases, the rate of SARS infection was very high in medical professionals, accounting for 20-30 % in some areas. It might be due to the insufficient protective measures in the early epidemic stage of SARS. But in Beijing, the rate of infection was relatively low in healthcare workers both at hospitals and at CDC. It is suggested that personal protection plays an important role in prevention of SARS among the healthcare workers. In order to protect the doctors and nurses, the Chinese Government has taken almost all the necessary preventive measures to strengthen sterilization and ventilation in the wards and to forestall medical staffs to be overworked. This is why the incidence of SARS has been kept at a lower level in the healthcare workers.

Distribution characteristics in epidemic areas

There are four kinds of SARS epidemic situation in China: (1) Epidemic area of SARS (in Zhujiang Delta of Guangdong Province, China, there was no direct relationship among the primary cases in different cities). (2) Imported SARS cases, which caused local spreading (as in Shanxi Province and Beijing, etc.). (3) Imported SARS cases, which did not cause local spreading (as in Hunan Province and Sichuan Province, etc.), and (4) no SARS cases reported.

Epidemiological statistical analysis and prediction

How will the SARS epidemic situation develop? How to control SARS effectively? Are there any scientific ways to predict the SARS epidemic situation? According to the current actual SARS epidemic situation in the world, the Center of Geosystem Science and the Key Laboratory of Geodynamics of the Chinese Academy of Sciences have studied the relationship between SARS epidemic situation and its development based on their accumulated experience for years, established the systemic dynamics model of SARS contagion, and calculated the relationship between the control of SARS epidemic situation and its development in detail. The results were identical with the current actual SARS situation in the world, and the model could predict the SARS epidemic situation. The successful establishment of this model is important to evaluate and predict SARS epidemic situations. The task group of "SARS Epidemic Trend and Control System" in Xi' an Jiaotong University made use of computers to make computing simulation with the data and theories by using the statistical methods and parameters confirmed in the epidemic transmission, and then composed the software by modifications and got the predicting cuve to meet the actual demand. They finally put forward the epidemic patterns and trend of SARS. The predicted number of increasing cases of SARS was basically identical with that publicized by the Ministry of Public Health every day.

According to the data of the diagnosed, suspected and dead cases of SARS in the world, the task group of mathematical epidemiology in the University of Science and Technology of China has established the epidemic spatial statistical model of SARS, and predicted on June 10, 2003, that the number of SARS inpatients in Beijing would be decreased below 60[12].

There are so many problems which need to be further studied. For example, our understanding of the source of SARS infection remains on the conditions of SARS patients, and little is known about its effect on sub-clinical SARS patients and animals, as well as the blood transmission and fecal-mouth transmission ,except for the short distance transmission of droplets from respiratory tract and transmission by close contacts. The reason why the incidence rate is high in young people and low in children and elderly people is not clear. What are the influence factors of the superior infectors?

ETIOLOGY

At the beginning of the study conducted by the Chinese scientists, chlamydia-like and coronavirus-like granules were found by electron microscopy in the dead bodies of SARS patients in Guangdong Province, China. Though chlamydia was thought to be the possible pathogen of SARS, it could not be confirmed in foreign laboratories due to the limited specimens for assay. Furthermore, there was not much possibility that chlamydia was the pathogen of SARS according to the clinical manifestations and therapeutic efficacy of SARS patients. Thus it might be due to the secondary infection. After the outbreak of SARS in Hong Kong, researchers isolated the avian influenza virus from a symptomatic child in Hong Kong, which was soon excluded to be the pathogen of SARS. Not long after, paramyxovirus was found in many SARS patients, but not in all the SARS patients in the further studies. However, all these findings could not be further confirmed.

The Pei Weishi Research Group of Hong Kong incubated the blood and tissue samples from SARS patients in cell lines which are not usually used to culture and isolate viruses. The genes of infected tissues were randomly screened in order to find the DNA fragments which could provide useful clues. On March 17, 2003, the cultured tissues isolated from two SARS patients could kill the cell line which is usually used to culture hepatitis A virus. In order to find the relationship between it and SARS, we observed the different reactions occurred when serum in the early and recovery stages was used to culture the tissues. Antibody reaction occurred in the former, while it did not occur in the latter. It was obvious that there was something in the culture, which was related to SARS. Nicols is the first who has found and isolated coronavirus in the tissue samples by electron microscopy. In the following days, three foreign laboratories including that in Hong Kong have confirmed almost at the same time that the pathogen of SARS is a novel kind of coronavirus.

On March 23, 2003, the Institute of Microbiology and Epidemiology, Academy of Military Medical Sciences of China, successfully isolated coronavirus from the pulmonary tissues of SARS patients and established its animal model. Based on the model, the pathogen was isolated by cell culture of samples from pulmonary tissues of the dead bodies and nasopharyngeal swabs. Coronavirus granules were found by electron microscopy in the pathological cells and their culture supernatant. The results of SARS patient serum detected by immunofluorescence staining showed that the isolated virus was closely related to SARS virus, which could induce infection of SARS in mice. The coronavirus-like granules were also found in the pulmonary tissues of mice. The cDNA fragments were amplified with RT-PCR, respectively from the pulmonary tissues of SARS dead bodies, the infected mice, and the infected

cell culture isolations. The whole genome of coronavirus was sequenced at 11pm, on April 15,2003. The sequence had 60 % homogeneity with the known coronavirus, and was about 30 000 bp long, which was identical with the results reported in Canada and USA, suggesting that it is a novel kind of coronavirus closely related with the epidemic of SARS, and may be the major pathogen of SARS.

Hong Kong University has found that some gene fragments have different sequences by comparing "6 SARS samples" from different regions (2 from Hong Kong, 2 from Guangzhou, China, 1 from Canada and 1 from USA), indicating that the "6 viruses" are different members of one family. However, it is not quite sure which one is their "mother". The inclination of the researchers is that one of the two samples from Hong Kong was similar with the two samples from Canada and USA respectively, the other one from Hong Kong was similar with the two from Guangdong, China. Further study is needed to clarify whether the members of such a family exist or they are deprived of a variety of SARS viruses.

Shanghai Institute of Life Science, Chinese Academy of Sciences, has successfully cloned the 6 main protein genes of S, M, N, E, RNA polymerase and proteinase (3CL), and found the expression samples of proteins E, N, and 3CL in the experiment of expression, isolation and purification of the important protein genes. The expression samples passed the drug virtual screening. This achievement is of great importance in the study of biological functions of SARS virus and in seeking after the vaccines and drugs against SARS virus.

The survival time of SARS virus in different conditions varies greatly. It can survive for a long time in 3 human discharges (sputum, feces, and urine) and in blood at 24 ℃, for 5 days in sputum and feces, for 10 days in urine, and for 15 days in blood, respectively. In the indoor condition, it can survive for 3 days on the surface of filter paper, cotton, wood block, soil, metal, plastic, glass, etc. SARS virus is sensitive to temperature. Its survival rate decreases with increasing temperature. It can survive for 4 days in the culture condition without serum at 37 ℃, and can be inactivated at 56 ℃ for 90 minutes, at 75 ℃ for 30 minutes, respectively.

PATHOLOGY

Macroscopically, the pulmonary tissue is swollen and extensively consolidated. The surface blood vessels are dilated and hyperemic, dot or sheet necrosis and hemorrhagic infarct can be found. Thrombi are formed in the pulmonary artery, and wine liquid flows out from the cut section.

Light microscopy

Chronic inflammatory cell infiltration can be found in trachea and bronchioles, and some necrosis tissues and a few inflammatory cells in the duct and some shed mucous epithelia. The pathology in the lung shows severe acute interstitial exudation, pulmonary interstitial and alveolar septum capillaries are severely dilated and congested, and there is a medium amount of lymphocytes, macrophages and polymorphonuclear white cells infiltrated. Some red blood cells are exudated into the alveolar septum and cavity. Pale and red fluids are exudated in most alveolar cavities, and hyaline membrane is formed in about 20-30 % alveolar cavities, but no inflammatory cells infiltrate into alveolar cavities, and focal compensatory emphysema can be seen. Diffuse alveolar epithelial cell injuries are manifested as pyknosis of chromatin to mass in alveolar epithelial cells which are distributed along the karyotheca, apoptosis of alveolar epithelial cells, vacuolar changes of nuclei in some alveolar epithelial cells. The necrosis in pulmonary tissue is not obvious and the phenomenon of lymphocytes attacking alveolar epithelial cells is not found. Regional proliferation is very active in the H type alveolar epithelial cells. Under light microscopy, some virus inclusion bodies-like structures can be observed in alveolar intraepithelial cells. The surface of pleura is smooth, subpleura stroma is edematous and loose, capillaries are dilated and congested with lymphocytes infiltrated.

Many superficial and deep lymph nodes show extensive or large regional hemorrhage and necrosis which are significant in the subcapsular region. Cell proliferation is obvious around the necrosis tissues and the phenomenon of red blood cells phagocytosed by macrophages . Hemosiderin is deposited in the cytoplasm. The lymphocyte infiltration is decreased , the lymphoid follicle structure can hardly be seen. The vascular and splenic sinusoids are greatly dilated and congested, the white pulp is decreased . Extensive and fused hemorrhage and necrosis as well as cell reactive hyperplasia are easily found.

Vacuolation can be found in a few cardiac myocytes, there are interstitial infiltration of a few lymphocytes and mild vascular dilation. The structure of hepatic lobule remains integrated. Mildly mixed hepatocellular fatty degeneration and mildly hydropic degeneration can be seen in the lobules, focal hemorrhagic inflammation and apoptotic body can be occasionally found. Liver sinusoid is dilated and congested, mild reactive hyperplasia occurs in Kupffer cells, and infiltration of lymphocytes is observed. Bilateral adrenal gland also shows focal hemorrhagic inflammation and lymphocyte infiltration which are obvious in the medulla. The structure of glomerulus is almost normal, the capillaries are dilated and congested, but no hyaline thrombus and fibrinoid necrosis can be found. Renal tubular epithelial cells are swollen, with few protein casts and tubular necrosis, there are focal hemorrhage and interstitial lymphocyte infiltration[8]. The structure of the walls of stomach and intestinal tract remains its integrity with a few lymphocytes infiltrated in the lamina propria mucosae and submucosa. Vasodilatation and congestion can also be seen. The intestinal tract shows segmental hemorrhage, and the rest changes are the same as in the stomach.

Transmission electron microscopy

The structure of pulmonary tissue remains very well, intracellular mitochondria and endoplasmic reticulum in alveolar epithelial cells and some endothelial cells of capillaries are swollen, the matrix is very loose, degranules can be found in some rough endoplasmic reticula. Chromatin in the nucleus is changed into mass shape and is not well distributed and is accumulated under the nuclear membrane. Type I alveolar epithelial cells show proliferation which is characterized by increased number, abundant chromatin, intracytoplasmic lamellar bodies, widened interspace of capillaries in the alveolar septum and increased pinocytosis vesicles in the endothelial cells. It is observed that there are many virus-like particles in most of the type II alveolar epithelial cells, bronchioles epithelial cells and intracytoplasma of some endothelial cells of capillaries in the alveolar septum which has an envelope with halation or in the shape of garland and is about 100-150 μm in size with low density in the centre, and these kinds of virus-like particles can also be seen in the dilated endoplasmic reticulum. In addition, chlamydia-like inclusion bodies at different stages which have reticular bodies, midbodies and elementary bodies can be seen in very few alveolar epithelial cells and endothelial cells. In the edema fluid of alveolar cavity, virus-like particles can be found. Proliferation of macrophages in which virus-like particles can also be found is mainly seen in the alveolar septum and alveolar cavity[19].

Many virus-like particles can be found in a few cardiac myocytes which are the same as in the lung tissues. Mild swelling of mitochondrion and endoplasmic reticulum is found in the hepatocytes, and lipid droplet with moderate electron

density is also found, and chlamydia-like inclusion bodies at different stages are seen in the cytoplasm. Some renal tubular epithelial cells show swelling and no villi, virus-like and chlamydia-like particles are also found in them. The injured immune organs mainly include the spleen, lymph nodes and bone marrow. Deposited plasma protein can be seen in the central arteries of splenic corpuscle, massive necrosis can be found in the white medulla and marginal sinus lymph tissues. Some remaining lymphocytes are at the apoptotic state. Blood vessels in the lymph nodes are severely dilated and congested, and lymphoid nodules are atrophied and disappeared, a lot of monocytes are found in the lymphatic sinus, the lymph tissue shows focal necrosis and lymphocytes show apoptosis. Hematopoietic area of myeloid tissue is decreased, granulocyte and macrophage systems are relatively inhibited, polychromatophil erythroblasts show little focal proliferation[20,21].

Tissues around the venules and the vascular walls of lung, heart, liver, kidneys, adrenal gland and striated muscles show swelling, and there are monocytes, lymphocytes, plasmocytes and neutrophilic granulocytes infiltrated.

After the nude mouse is inoculated with SARS virus, and onset of SARS occurs. The main lesions are found in the lung and liver, the alveolar cavity is microscopically very narrow even atelectatic, the alveolar septum is widened, bronchioles epithelial cells are shed. Swollen hepatocytes show hydropic degeneration and vacuolation and some hepatocyes show pyknosis and necrosis. And other anomalies include myocardial hyperemia and increased multinuclear giant cells in the spleen.

In the culture medium of Vero E6 cells infected with SARS virus, virus particles can be found under electron microscope with negative staining which is in the shape of ball with coronally arrayed processes, the end of the process is also a round shape and there is a wide interspace between processes. The diameter of the virus is about 80-120 μm. The viruses detected from the culture medium of cells infected with viruses from Beijing and Guangdong are similar.

PATHOGENESIS

The mechanism of the injury caused by SARS virus is unknown. It is suspected that there are auto-antibodies developed after the infection of SARS virus which induces the autoimmunity reaction, and the current studies cannot explain it.

The reasons why T cells of SARS patients are quickly declined in a short time after the onset of SARS are probable as following: (1) SARS virus directly attacks T cells and causes them splitting and to be destructed quickly which results in the sharp decrease of the count of T cells. (2) After the infection of SARS, SARS virus has no effect on the immune system and results in the abnormal distribution and leads to the decrease of T cells in the peripheral blood. (3) SARS virus, or its productions or its components act as a super-antigen and polyclonally activate T cells and lead the activated T cells to death and decrease of T cells in the peripheral blood.

CLINICAL MANIFESTATIONS

The analysis of the blood samples of SARS patients has shown that the latent period of SARS is at least 4 days and the longest is 17 days. This is related to the load of virus and individuality. The one who has been infected but without symptoms has no infectivity, no such cases have been reported so far.

After the patient is infected with SARS, he will have a high fever and dry cough without the symptoms of influenza such as nasal mucus, pharyngalgia, spitting white or yellow sputum. But sometimes there is some blood in the sputum, and the patient will feel short of breath, and even develop ARDS. Generally, the count of white blood cells will increase when a patient has a fever, but it is normal or below it when the SARS patient has a fever. The most prominent phenomenon is that the X-ray characteristics are not disassociated with its clinical situations. The patient with common pneumonia usually has very severe clinical manifestations and then the changes in the X-ray films can be found. But the X-ray films of SARS patients have very significant changes when the patient of SARS is not very severe, which show floccule shadows and have the trend of quick development[29-31].

The symptoms of SARS include high fever (more than 38 ℃), dry cough, shortness of breath, headache, anorexia, malaise, skin eruption and diarrhea without the common symptoms of influenza such as nasal mucus, pharyngalgia, spitting white or yellow sputum. But sometimes there is some blood in the sputum and the patient will feel short of breath, and even develop ARDS. About 7 % patients of SARS need artificial breathing. The clinical manifestations in different areas in China are shown in Table 2.

The manifestations of chest radiograph of SARS include patchy consolidation or reticular consolidation. Some patients' conditions develop very fast, large patchy consolidation is shown in the chest film and multiple lobes or bilateral lung are involved. The absorbance of the patchy consolidation is very slow. The sites and scope of pulmonary lesions in SARS patients are shown in Table 3.

Table 2 Clinical manifestations in different areas of China

	Fever (%)	Dry cough (%)	Shortness of breath (%)	Chest pain (%)	Bloody sputum (%)	Diarrhea (%)	Headache (%)	Muscle pain (%)	Inertia (%)
Guangzhou[22]	100	72.2	31.2	1.9	11.5	24.2	25.8		24.6
Guangzhou[23]	97.7	81.2	20	22.3		22.3	63.5	41.2	74.1
Guangzhou[24]	100	92		22	13	24	61	60	92
Beijing[25]	97.8	68.9	53.3		9.8	26.7		26.7	60
Beijing[26]	100	87.8	12.2						
Henan[27]	100	67	29	17		17		50	83
Hongkong[28]	100	62	20			10	20	54	

Table 3 Sites and scope of pulmonary lesions in SARS patients

	Superior lung field	Medial lung field	Inferior lung field	Hilum of lung	Multiple lobes	Total
Pachy-lung markings, small shadow	3(2.5)	5(4.2)	10(8.5)	2(1.7)	0(0)	20(16.9)
Unilateral inflammation	8(6.8)	11(9.3)	16(13.6)	0(0)	0(0)	35(29.7)
Bilateral inflammation	3(2.5)	7(5.9)	15(12.7)	0(0)	37(31.4)	62(52.5)
Total	14(11.9)	23(19.5)	41(34.7)	2(1.7)	37(31.4)	117(99.2)

The count of white blood cells of SARS patients is normal or below it, and CD4+ and CD8+ T lymphocytes are also decreased, but all these will be in the normal range after patients are fully recovered.

LABORATORY EXAMINATION

Theoretically, there are three ways to diagnose SARS: cell culture, RT-PCR and detection of antibody. All these ways are mature, so progress in the detecting techniques can be achieved in the work of prevention and cure of SARS easier than that in the study of vaccines and drugs. But cell culture and detection of antibody have no effect at the early stage of clinical diagnosis. Cell culture needs very high requirements of laboratory conditions and experienced operators, it takes a long time to isolate viruses or bacteria, and its positive rate is low. The time of the generation of antibody against SARS virus in the body is at least 10 days, and the time of the generation of IgG is at least 15-20 days. The antibody has interactions with the *in vivo* immune system, the mechanism of the generation of antibody is not clear. Whether all SARS patients have antibody after 3 weeks of infection needs to be further studied. RT-PCR is the simple and easy diagnostic method of SARS at the early stage[33-35]. Although there are many kinds of RT-PCR kits in China, it needs further improvement for its clinical use. It is needed to explore how to get the best virus nucleic acid and the best sampling time. Till today, the diagnosis still depends on the epidemiology and clinical symptoms, no methods have been found to be effective in the prevention and cure of SARS. The natural immunity adhesive function of red blood cells in two SARS cases in China was detected, and it was found that its adhesive function was lowered with aggravation of SARS. It is thought that it may be a good index indicating the degrees of the conditions of SARS patients.

Laboratory examinations, points for attention and evaluation of data

The Ministry of Public Health of PRC proposed the precautions on June 7, 2003 for guidance in practice and applications of tests supposed to be of diagnostic value for SARS.

Virus isolation by cell culture The method is used to isolate SARS virus from human respiratory secretion, blood, urine, stool and autopsy tissue samples. The positive result is considered as a reliable evidence for the presence of replicating SARS virus, and for the diagnosis of the disease or a virus-carrier status in combination with the clinical symptoms. The test must be performed by specialists in a BSL-3 laboratory. Thus, it is difficult at present to be widely used. Another weak point is that this assay is laborious and time-consuming, thereby not suitable for the quick diagnosis. Usually, the positive rate of this assay is not high, and the negative result cannot be regarded as a reliable evidence to exclude SARS. For these reasons, it is not a routine examination in clinical laboratories of most medical centers.

Detection of viral nucleic acid by polymerase-chain reaction following reverse transcription (RT-PCR) The procedure can be used for detection of SARS virus from human respiratory secretion, blood, serum, urine, stool and autopsy tissue samples. It is a quick and convenient method.

Up to date, it is not clear what time is best for sampling and what samples are optimal for the assay. Its sensitivity remains to be improved. The possibility of false negativity is considerably high. In addition, inappropriately handling of the samples often leads to laboratory pollution by the viral nucleic acids and false negative results. When the virus is detected in different samples from the same individual, or the amplification product is demonstrated repeatedly in the same sample, the positivity is established, meaning that the sample contains nucleic acids of SARS virus. For the clinically suspected patients, the positive reaction is a diagnostic parameter for SARS. For apparently healthy individuals, the positive result is a reliable evidence for the establishment of their virus-carrier status. Apparently, a negative reaction cannot be regarded as an evidence to exclude SARS or the suspected either.

Immunofluorescence test and enzyme-linked immunosorbent assay (ELISA) for antibodies to SARS virus The procedures are used to demonstrate specific SARS virus antibody from the serum. The antibody is detectable in a majority of samples from asymptomatically infected individuals and SARS patients for about 10 days, or even later for some cases, after being infected or onset of the disease.

The assays are used mainly for verification of the clinical diagnosis and for epidemiological surveys. A positive reaction obtained using sera from the convalescent suspected patients, or a four-time increase in its titer during recovery compared to that in the acute stage can be regarded as a diagnostic parameter for SARS. Occurrence of the antibody is also found in healthy individuals, reflecting the past infection of SARS virus. As for the replicating virus and its nucleic acids as described above, the antibody is not always detectable in SARS patients. A negative result, therefore, cannot be regarded as a reliable evidence to exclude the possibility of SARS.

Laboratory approaches for assays of SARS in China

A chip covering genomic sequences of all the reported coronaviruses, including SARS virus, was prepared and the detection has been established based on the microarray, as declared by Benyuan-Zhengyang Gene Technology Company Limited, China and its partner organizations in May 2003. The genotyping, conducted based on this system and similar assays, may be useful for determination of pathogenic factors and monitoring of mutations in the genomes of these viruses from different geographic areas, possibly providing some clues to the origin of SARS virus. Moreover, this system and database were designed to be an open platform, allowing the online processing and analysis of data by customers through Internet. In addition, the online exchange and management of detection data from all registered customers can provide an opportunity for the related administrations to obtain statistic information about the disease epidemics on time[37].

The virus-collecting facility, prepared by a group in Wu Jianxiong Laboratory, Dongnan University allows collection and concentration of viral particles from air, claiming to be able to process 30 liters of air per minute. According to the manufacturer, its collection efficiency can be as high as 90 %, as tested using protein particles and the inactivated viral particles. It can be used for sampling from air and viral particle concentration. In combination with PCR, the device may be applied for the detection of SARS virus contamination of the air, providing timely and dynamic data of the viral load.

A preliminary observation was made on dynamic changes of circulating T cells and serum immunoglobulin contents in 124 SARS patients by the Beijing Group of the National Emergent and Technological Action on SARS Prevention and Treatment. A marked decrease was found for all subsets of T lymphocytes examined, including those expressing CD3, CD4 and CD8, with their cell counts reduced to about one third of those of healthy individuals. This shows that the immune functions of SARS patients are severely impaired. The counts of CD4- and CD8-positive T cells were found to decrease quickly at the same time, the change was more pronounced during the period between the 10^{th} day and the 14^{th} day. This is in accordance with the disease course for most cases, its levels going up gradually two weeks after the onset with the recovery

of the patients. It appears reasonable to consider T cells to be involved in the pathogenesis of SARS.

Another apparatus, invented by Gene Company Limited and the Molecular Medical Diagnosis Center in Hong Kong based on the fast DNA hybridization, was claimed to allow the detection of SARS-associated coronavirus in patients' samples and identification of the mutated viruses within 15 minutes. Rong-An Tan, the technical spokesman of the diagnosis center, declared that the system could be used to detect SARS-associated virus from blood, saliva and secretion samples. According to him, the times requested for the detection range from 1 to 15 minutes, with 5 or 6 mutated viruses demonstrated as conducted in Guangzhou, Taiwan and Hong Kong for separate cases.

A seroassay for circulating antibody to SARS virus, namely immuno-chromatography test (ICT), is now being established in Taiwan University Hospital. As claimed by the laboratory, it is possible to determine the diagnosis of SARS at the 7th or 8th day by this assay, much earlier than RT-PCR that cannot show the positive result till the 21st day after the disease onset. The project, currently, is reported to arrive at the ultimate stage of sensitivity assessment. ICT is hoped to be an assay faster than RT-PCR by 13 days[27].

Dalian Institute of Chemistry and Physics, the Chinese Academy of Sciences, recently claimed to have established an early detection system for the virus-induced respiratory diseases with fever based on a controlled micro-current chip. They have finished the preparation of the chip and established the system. Currently, the system is under the evaluation using 9 primer pairs for the amplification following RT, with the SARS virus and parainfluenza virus RNA samples as the templates and a negative control, respectively. The system is characterized by its early detection of viral RNA even if the target sequence contained in samples is minimal in quantity. The controlled micro-current chip is also known as a chip laboratory, which is greatly different from the ordinary gene chips regarding their principles, preparation and applications. It is characterized by high-throughout and large-scale integration. Several fundamental units, involving sample preparation, biological and chemical reactions, isolation and detection, are integrated onto a single chip as small as several cm, being able to finish different reactions and to characterize their minimal-amount products[39].

Recently, artificial virus-like particles were prepared, with the SARS coronavirus nucleic acid enveloped within liposome, by a group in the Laboratory of Clinical Chemistry, Beijing Hospital under the Ministry of Public Health. The reagent may prompt technical improvement, standardization and quality control of the RT-PCR for SARS, as the kits currently available are not stable enough and require further clinical verification. The virus-like particles have been characterized by two properties: safety (non-infectious) and stability. This is of application value for the quality control of RT-PCR for SARS virus in clinical laboratories of medical centers, as well as for evaluation of new diagnostic reagents for the disease[40].

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Criteria for clinical diagnosis of SARS proposed by Ministry of Public Health of PRC

Epidemiological history The history evidences indicative for SARS include close contact with the patient, individuals from an infected group, having infectivity to others, and a tourist back, or a resident moving away from the epidemic regions two weeks before onset of the disease where there are SARS patients reported and the secondary infection has taken place.

Symptoms and signs The onset of the disease is acute. Fever is the first symptom, with the body temperature above 38 ℃ for most cases and chilling as one of the complaints occasionally. Headache, joint pain, fatigue and diarrhea may also be the complaints. Usually respiratory catarrh symptom is not evident. Coughing may be the manifestation, mostly a dry cough with very little sputum. Occasionally, little blood is present in the sputum. Chest distress is common, with the quick respiration, short ness of breath and even breathing difficulty in unfavorable cases. Signs of the lung disorder are usually not obvious, with some moist rales heard or pulmonary consolidation found in some cases. In a small number of the patients, fever is not the first symptom. This is particularly true for those cases operated recently or having some accompanying diseases.

Laboratory tests Usually, the count of peripheral blood leukocytes is not increased, or even decreased. The count of lymphocytes decreases in most cases examined.

Chest roentgenological examination There are various degrees of pulmonary infiltration, with many small pieces of lungs involved or in a meshwork pattern. In the fast progressing cases, massive shadows are present frequently, with multiple or bilateral lobes involved. Their resolution is usually slow. Occurrence and resolution of the roentgenological changes are not necessarily in accordance with the related symptoms and signs. For the cases not showing the changes, reexamination should be performed one or two days later.

Response to antibiotics Treatment with various antibiotics is not effective.

Diagnotic criteria For suspected cases: With positive findings in the epidemiological history + symptoms and signs + laboratory tests, or the epidemiological history + symptoms and signs + laboratory tests, or the symptoms and signs + laboratory tests + X-ray examination.

For cases with a clinical diagnosis of SARS: With positive findings in the epidemiological history + symptoms and signs + X-ray examination , or more, or the symptoms and signs + X-ray examination + no response to antibiotics , or the history + symptoms and signs + laboratory tests + X-ray examination.

For cases under medical observation: With findings in the symptoms and signs + laboratory tests.

For severe cases of SARS: SARS cases with one of the following findings: (1) a breathing difficulty, with respiratory rate exceeding 30 times per minute; (2) hypoxemia even during O_2 inhalation at 3-5 L/min, with PaO_2 below 70 mmHg and SpO_2 below 93 %, or having acute lung injury (ALI) or acute respiratory distress syndrome (ARDS); (3) multiple-lobe lesions involving more than one third of the lungs in area, or enlargement of the pulmonary lesion by more than 50 % within 48 hours as shown by chest roentgenograms; (4) shock or multiple organ dysfunction syndrome (MODS); (5) with a severe accompanying disease or a complicating infection, or with the age exceeding 50 years.

Differential diagnosis

Attention should be paid to the exclusion of other diseases or clinical syndromes such as infection of the upper respiratory tract, influenza, bacterial or fungous pneumonia, pulmonary infection complicating AIDS, legionnaires disease, pulmonary tuberculosis, epidemic hemorrhagic fever, pulmonary neoplasms, non-infectious interstitial pulmonary diseases, pulmonary edema, atelectasis, pulmonary embolism, pulmonary eosinophilic pneumonia and pulmonary vasculitis.

TREATMENT

Patients under the medical observation should receive treatment and observation in the appointed isolation ward or hospital, or under isolation observation in their homes. For the later case, the patients should live in a well-ventilated room and avoid

any close contact with other family members. They should be still under the observation of the disease-control department with their body temperature measured every day during the period. The patients, whose conditions are found to progress and to meet the criteria for SARS or the suspected during the observation, should be sent immediately to the appointed hospital by the special vehicles for isolation and treatment.

The key procedures of prevention and treatment of SARS are early detection, report, isolation and early treatment.

Treatment protocol for SARS and its suspected cases recommended by Chinese Center for Disease Control and Prevention (China CDC)

General therapy The general treatment includes adequate rest and supplement of nutrients such as fluid and vitamins, avoidance of intense and vigorous coughing. The patient' s condition should be observed intensively, since the onset of SARS within 14 days probably belongs to the progressive period in the majority of patients. Regular reexamination of chest x-rays and the functions of heart, liver and kidney are also necessary. The interval for the reinspection of chest x-rays in early phase of SARS should not be more than 3 days. SpO_2 should be checked daily.

Expectant treatment (1) Antipyretic analgesics should be used for patients with fever more than 38.5 ℃ and systemic prominent soreness. For the patients with hyperpyrexia, cooling measures should be applied such as ice compress and sponge bath with alcohol. (2) Antibechic and expectorant should be given when the patients suffer from cough and expectoration. (3) Corresponding measures should be taken when dysfunctions of multiple organs such as heart, liver and kidney take place. (4) Persistent oxygen inhalation by nasal tube should be applied early to the patients with obvious tachypnea and mild hypoxemia. (5) Aspirin medication should be avoided in children for fear of resulting in Reye syndrome.

Antibacterial treatment It is recommended to use antibiotics such as macrolides, fluoroquinolones, β-lactams and tetracyclines early in the course of SARS. Vancomycin or norvancomycin should be chosen as the preferable therapy when the infection caused by antimicrobial-resistant cocci is evidenced either clinically or experimentally.

Glucocorticoid therapy The following indications for the use of corticosteroids are proposed: Patients with severe toxic reaction and persistent high fever, and those with rapid deterioration of the chest film by increased infiltration progressing to a critical condition. The drug should be given regularly with the doses matching the actual condition of the disease and should be used with caution in children.

Selective therapy Selective therapy includes the use of antiviral agents, immunopotentiators and Chinese herbs.

Treatment of critical cases (1) Intensive care and monitoring should be applied to the patients with severe dyspnea or those who meet the criteria of a critical case. (2) Noninvasive and positive pressure ventilation is recommended for those with SaO_2 less than 93% while the oxygen inspiration is at 3-5 L/min and breath rate $\geqslant$ 30/min, in which CPAP with nasal mask is preferable. Routine level of inspiratory positive airway pressure should be set at 4-10 cmH_2O. Selection of adequate breathing masks, and persistent use of noninvasive ventilation that is interrupted no more than 30 min including hora decubitus till the disease remission are required. (3) For patients with severe dyspnea and hypoxemia, SaO_2 < 90 % or oxygenation index < 200 mmHg at 5 $L \cdot min^{-1}$ of oxygen inhalation, failure to tolerate or respond to noninvasive ventilation should be promptly followed by invasive ventilation after intubation. (4) Timely therapeutic measures should be taken once shock or MODS takes place in SARS patients and consultations of relevant experts are indicated when the treatment is limited by professional skill or poor medical equipments.

Standard treatment protocol for SARS (suspected and probable) in adult patients in Hong Kong[41]

Antibacterial treatment Levofloxacin 500 mg is given once daily intravenously or orally, or clarithromycin 500 mg is given twice daily orally plus co-amoxiclav (amoxicillin and clavulanic acid) 375 mg three times daily orally if patient is younger than 18 years, or pregnant, or suspected to have tuberculosis.

Ribavirin and methylprednisolone Combination treatment with ribavirin and methylprednisolone is given when the patient has extensive or bilateral chest radiographic involvement, or persistent chest radiographic involvement and persistent high fever for 2 days, or clinical and chest radiographic or laboratory findings suggestive of worsening, or oxygen saturation < 95 % in room air.

Standard corticosteroid regimen for 21 days Methylprednisolone 1 mg/kg is given every 8 h (3 mg/kg daily) intravenously for 5 days, then methylprednisolone 1 mg/kg is given every 12 h (2 mg/kg daily) intravenously for 5 days, followed by prednisolone 0.5 mg/kg twice daily (1 mg/kg daily) orally for 5 days, prednisolone 0.5 mg/kg daily orally for 3 days, prednisolone 0.25 mg/kg daily orally for 3 days, withdrawal of drugs.

Ribavirin regimen for 10-14 days Ribavirin 400 mg is given every 8 h (1 200 mg daily) intravenously for at least 3 days (or until condition becomes stable), followed by ribavirin 1 200 mg twice daily (2 400 mg daily) orally.

Pulsed methylprednisolone Pulsed methylprednisolone is given if clinical condition, chest radiograph, or oxygen saturation worsen (at least two of these), and lymphopenia persists, followed by methylprednisolone 500 mg twice daily intravenously for 2 days, and then standard corticosteroid regimen.

Ventilation

Non-invasive ventilation or mechanical ventilation should be considered if oxygen saturation < 96 % while O_2 > 6 L per min or if the patient complains of increasing shortness of breath.

Indications for intubation: (1) Failure to respond to non-invasive ventilation, SaO_2 less than 93 % while oxygen inspiration with facial/nasal mask at 5 L/min and progressive deterioration on chest radiography. (2) Failure to tolerate noninvasive ventilation while with severe dyspnea and hypoxemia. (3) With serious toxic reaction and rapid deteriorating conditions[42-46].

One of the important principles that should be noted in mechanical ventilation is the permission of hypercapnia that is usually performed when there are extensive pulmonary consolidation, poor compliance, and possible pneumothorax. In this way, the tidal volume and oxygen supply per minute could be reduced at the moment. SaO_2<90 % and positive end expiratory pressure (PEEP) at 10-15 cmH_2O may prevent atrophy of pulmonary alveoli and improve oxygen supply.

Academician Zhong Nanshan has recently emphasized 4 important therapies for SARS, including paying attention to fever and myalgia at the acute onset with a combination of traditional Chinese and Western medicine, prompt medication with large-dose of corticosteroids to prevent development of pulmonary fibrosis, timely application of nasal (facial) mask ventilation to improve the supply of oxygen, preventing alveolar collapse thus reducing the need for intubation and timely treatment of complications (especially super infections).

Therapeutic approaches in research

The SARS therapy with convalescent sera was firstly proposed

and used for himself by Dr. Su-Chun Jiang. Later, It was also used for the critically ill patients by Hong Kong scholars and achieved some beneficial effects[48]. However, detailed information about it has not been available.

Theoretically, the therapy is specific, but ineffective when used before severe and irreversible pathological changes take place. On the other hand, it should be screened for the pathogens that are probably transmitted via blood such as HBV, HCV and HIV in patients before the sera are used. Meanwhile, more attention should be paid to the possibility of serum sickness reaction[49, 50]. Other drugs such as protease inhibitors[51] and pulmoalveolar surfactant[52] have been under research and development.

Immunomodulators or immunopotentiators such as thymosin or thymopeptide and glutamine dipeptides have been proposed to be used in the treatment of SARS, though the current evaluation of these approaches remains absent. The therapy is based on the finding that the number of peripheral blood T lymphocytes, especially subgroups of CD4+ and CD8+, is significantly decreased in acute phase of SARS patients, suggesting that impairment of cellular immunity does occur in the early stage of SARS.

The therapies described above are the components of the whole treatment protocol for SARS. Their effectiveness and safety have not been systemically evaluated by prospective, randomized and controlled clinical trials. Therefore, it is hard to conclude which is better. SARS, a disease coming all of a sudden, is highly contagious. The researchers working in the first line of anti-SARS battle are engaged in clinical therapeutic activities. Meanwhile, they are also facing the risk to be infected. Under the circumstances, it is more difficult to perform a well and strictly designed clinical trial, and further more, plenty of concrete problems such as ethnics, research time, and lack of investigators and experimental control may also exist. Therefore it is difficult to make sure the effectiveness and safety of different therapies used in the coming months and years, if well designed trials are not performed. Notwithstanding these difficulties and problems, a reasonably designed clinical trial for SARS therapy remains to be very necessary[53].

Development of new anti-SARS drugs in China

Sivelestat sodium is the first newly developed anti-SARS drug in China that has been approved to enter clinical trials on May, 19, 2003, by State Food and Drug Administration of China. It is also the first one that has been approved to be tested in clinical trial since the rapid ratification program for anti-SARS drugs came into operation. It is an injection of chemical medicine used mainly to prevent and alleviate acute lung injury induced by PMN elastase via a mechanism of inhibiting systemic inflammatory response, with an attempt to improve pulmonary function, shorten the period of ventilation, decrease ventilator-related lung injury and other complications.

On May 21, 2003, the researchers in the Fourth Military Medical University discovered 3 polypeptides that exhibit prominent inhibitory effects on SARS virus *in vitro*, which may lay a solid foundation for the development of new polypeptide-type anti-SARS drugs. They found that a corona-like ring existed in the periphery of SARS virus and there were 4 constitutive proteins within this structure, in which the protein S plays a central role in the virus replication and invasion to human cells. These polypeptides were observed to be able to prevent coronavirus from invading the cells. Currently, these polypeptides have acquired the identification from Institute for Viral Disease Control and Prevention of China CDC. On May 15, State Intellectual Property Office of China has accepted the patent application for these findings.

A research group in the Second Military Medical University currently developed a kind of suspension containing porcine pulmoalveolar surfactant for SARS therapy, which has been approved to enter clinical trial by State Food and Drug Administration of China. It has been demonstrated by the animal study that its primary actions are to reduce pulmoalveolar surface tension, improve pulmonary ventilation and gas exchange, as well as prevent the formation of atelectasis and pulmonary edema. Furthermore, the safety, simplicity, sufferingless of this therapy make it possible to be applied in county or even in rural hospitals[54].

National Center for Drug Screening and Shanghai Institute of Materia Medica have received a considerable variety of pharmaceutical compounds, totally more than 4 000 samples, from more than 50 institutes of drug research in more than 20 domestic provinces and municipalities, as well as from that in USA and South Korea for screening new anti-SARS drugs. Co-operations among National Center for Drug Screening, Shanghai Institute of Materia Medica, Shanghai Municipal Center for Disease Control and Prevention and Academy of Military Medical Sciences have made more than 400 samples screened, in which 3 compounds, namely ZZ-I natural unity compound, an empirical prescription of Chinese medicine "Jieduwan" (detoxicating pill) and 5-hydroxytryptamine receptor antagonist DDDC-AS-001, were found to be the most powerful agents in anti-SARS efficiency among those currently screened all over the world.

TRADITIONAL CHINESE MEDICINE

The clinical characteristics of SARS are mainly manifested as prominent symptoms due to noxious heat and pathogenic dampness in most cases, which may lead to the rapid exhaustion of yin-qi and body fluids, and severe complications. Accordingly, the preventive strategy against SARS is to clear away the lung heat and toxic substances, to remove the pathogenic dampnes' s by aromatics and to supplement qi and promote the production of body fluids.

Prevention and treatment protocol for SARS and suspected cases by State Administration of Traditional Chinese Medicine of China

In order to improve the curative effects on the basis of recommended treatment protocol for SARS or suspected cases and discharge criteria by Ministry of Public Health, the following therapeutic approaches of the traditional Chinese medicine are proposed to be used in the anti-SARS treatment. It is recommended that the therapeutic principles of traditional Chinese medicine, namely diagnosis and treatment based on an overall analysis of the illness and the patient' s condition, should be performed in the treatment of SARS and suspected cases. Meanwhile, the treatment protocols should be adjusted as the patient' s condition changes.

In the early phase, the SARS patients are characterized by the impairment of pulmonary function due to noxious heat and stagnation of damp-heat, which are symptomatically categorized into 3 types of pulmonary impairment due to noxious heat, stagnation of damp heat and exterior cold and interior heat with dampness. For the cases manifested as pulmonary impairment due to noxious heat, it is suitable to promote pulmonary function by eliminating toxic heat via activating superficial channels and choosing a modified prescription of Yinqiao Powder plus Maxing Shigan Decoction. For the patients displaying stagnation of damp-heat, it is recommended to disperse the pathogenic factor out of the body by a revised recipe of Sanren Decoction plus Shengjiang Powder. When the condition is dominated by more dampness and less heat in these cases, Huopu Xialing Decoction should be adopted. For those with a manifestation of exterior cold

and interior heat, the therapeutic strategy is to clear the interior heat and ventilate the lung to get rid of toxic heat, which can be achieved by a modified prescription of Maxing Shigan Decoction plus Shengjiang Powder.

In the metaphase of SARS, the manifestations of the patients are displayed as the invasion of lung by epidemic pathogenic factors, abundant heat both in exterior and interior, accumulation of noxious heat, obstruction of Shaoyang by pathogenic factors and excessive epidemic pathogenic factors both in exterior and interior. For these patients, it is suitable to clear away heat and toxic materials, expell the lung heat and suppress the pathogenic factors with Qingfei Jiedu Decoction. A modified prescription of Ganlu Xiaodu Pill can exert the function of clearing away heat and toxic materials, eliminating dampness and keeping away filthiness, which is favorable for those with accumulated toxic heat. For patients with obstruction of Shaoyang by toxic heat, the therapeutic principles are to clear away the toxic heat at Shaoyang channel and to remove the damp-heat and a modified recipe of Haoqin Qidan Decoction should be adopted. For the patients with predominating toxic heat, pathogenic heat should be removed from blood and excessive heat should be purged. For this purpose, a modified recipe of Qiwen Baidu Decoction should be used.

In the critical phase, SARS cases are manifested as excessive accumulation of toxic heat with impaired body resistance, consumption of both qi and yin, and loss of consciousness and collapse. Accordingly, they are divided into accumulation of phlegm damp-heat blocking pulmonary vessels, stagnation of excessive pathogenic heat with deficiency of both qi and yin, excessive damp-heat weakening body resistance and blockage of breath. For the accumulation of phlegm toxic damp-heat blocking pulmonary vessels, it is helpful to invigorate qi for detoxication, eliminate phlegm for dispersing toxic damp-heat and remove blood heat for activating the channels. To achieve this purpose, Huoxie Xiefei Decoction should be used. For the patients with pulmonary stagnation of damp-heat with deficiency of both qi and yin, it is beneficial to clear away heat and promote diuresis, and to invigorate qi and nourish yin. Under the circumstances, Yifei Huazhuo Decoction is indicated. For the patients with hyperpyrexia weakening body resistance and blockage of breath, the preferable choice is to invigorate qi for restoring the vitality, dredge channels for promoting resuscitation, and choose Shenfu Decoction for getting the therapeutical purpose.

In the recovery phase, the symptoms of deficiency of both qi and yin, and deficiency of the lung and spleen, and the stagnant damp-heat are noted as the primary characteristics of SARS cases. For the former, it is recommended to nourish qi and yin, dispel pathogenic dampness to activate the channels, and to choose a modified prescription of Lishi Qinshu Yiqi Decoction. For the latter, it is reasonable to nourish qi and invigorate the spleen, which can be achieved by a modified prescription of Shenglin Baishu Powder plus Gegen Qinlian Decoction.

PROBLEMS AND COGITATION[55-57]

(1) The SARS cases reported in domestic medical literatures are all diagnosed on the basis of clinical experience without pathogenic evidences. (2) It is not worthwhile to advocate that the same contents are repeatedly reported by several papers or the same paper are repeatedly published by different journals. (3) Researches are lack of creative and constructive results or even simply repeat what have been performed overseas. (4) Most of the papers published are empty in contents with no substantive conclusions. Besides, some clinical reports are published by different journals. (5) The reasons why such inferior papers have been published are the insufficient collection of data and a lack of experience. (6) The achievements of SARS related research are exaggerated sometimes in certain domestic media, which mislead the public and should be prohibited. (7) Co-operations and communications in SARS research are seldom carried out among domestic research institutes, which deeply impressed the author when he was working in Beijing Xiaotangshan Hospital.

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