



Review article

Asian Pacific Journal of Tropical Medicine

journal homepage: www.apjtm.org



doi: 10.4103/1995-7645.254934

Impact factor: 1.634

SARS and its treatment strategies

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ARTICLE INFO

Article history:

Received 30 June 2018

Received in revised form 20 December 2018

Accepted 10 February 2019

Available online 27 March 2019

Keywords:

iRT-ABCDEF

SARSr-CoV

Severe acute respiratory syndrome

Treatment

ABSTRACT

This paper briefly review severe acute respiratory syndrome, a devastating disease which broke out 15 years ago, and its treatment strategies. With the newly discovered SARSr-CoV strain in Yunnan, China, and the help of new technologies such as RNA interference, DNA vaccines, CRISPR technology and base editing, and intervention of RT-ABCDEF (iRT-ABCDEF), a standardized comprehensive program, people can better fight severe acute respiratory syndrome and other major virus-communicable diseases like highly pathogenic avian influenza and dengue fever with these powerful tools in the future.

1. Introduction

It has been 15 years since the first outbreak of severe acute respiratory syndrome (SARS). After a novel SARS-like coronavirus (SARS-CoV) was isolated in Saudi Arabia five years ago[1], strong evidence was found that Chinese horseshoe bats are natural reservoirs of SARS-CoV[2], and that intermediate hosts may not be necessary for direct human infection. Recently, Chinese scientists have found the origin and evolution of the deadly SARSr-CoV in a remote cave in Yunnan[3]. As cardiologists in the battle against SARS, a review and perspective strategies of SARS treatment will help gather some experience and highlight the necessity of preparedness for future emergence of SARS-like diseases.

2. SARS, SARS–CoV and treatments

The SARS epidemic has received worldwide attention since 2003, when *Science* reported several cases of SARS in Asia[4–6], especially in China. SARS, caused by a CoV variant, is called acute infectious atypical pneumonia in China. The disease was first reported in Guangdong province in November, 2002, and SARS became a new type of acute respiratory infection that seriously affected human health after its outbreak in the spring of 2003.

SARS research teams in Hong Kong and Mainland China have found that CoV isolated from patients may be the main pathogen[7].

Subsequently, the World Health Organization named it SARS-CoV and confirmed that it was mainly carried by civets and raccoons. Teams on SARS investigation from the United States, Canada, Hong Kong and Mainland China reported typical clinical symptoms, complete genomic sequence, and genotypes of the SARS-CoV. High structural similarity to the human SARS-CoV nonstructural protein 3 (nsp3) is present, the “SARS-unique” region is not unique but is conserved among several different phylogenetic groups of CoV[8].

Physicians in Hong Kong first reported the successful treatment of SARS. Except for routine therapy such as oxygen inhalation and corticosteroid therapy, its treatment mainly included “anti-virus drug ribavirin + a large dose of steroid hormone”. Mechanical ventilation was confirmed to be very important in the treatment of SARS. A large dose of a steroid hormone was effective at the earlier stage of SARS-CoV infection. However, disadvantages of a large dose of a steroid hormone also appeared when follow-up was done, including bone osteonecrosis.

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How to cite this article: Hu CS, Tkebuchava T. SARS and its treatment strategies. Asian Pac J Trop Med 2019; 12(3): 95-97.

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Dr. S. C. Jiang first used the recovery serum of patients with SARS to cure himself from the infection[9], which confirmed that passive immunity for SARS therapy was effective at the earlier stage, but needed to be combined with other strategies. After the epidemic and causes of SARS in Guangdong were determined, experts from Mainland China had accumulated rich clinical experience[10], in which they combined traditional Chinese medicine such as Ginseng, Lianhuaqingwen capsules and other medicinal herbs.

Real-time quantitative polymerase chain reaction (RT-qPCR) test for SARS-CoV offers a rapid, sensitive method for early diagnosis. Sino-US scientists found that 3C-like proteinase was involved in SARS-CoV genome expression, and they have already carried out biosynthesis, purification and substrate specificity of the proteinase as well as its crystal structures and determined a 3D model. This created an opportunity for the development of anti-SARS-CoV drugs or inhibitors. Chinese scientists also established a related cell-filter-model and a series of drugs for SARS-CoV were developed.

The first SARS case in the winter of 2003 drew attention worldwide. Treatment with the strategy of “protease inhibitor + serum recovery” has achieved good clinical outcome in a short period of time. On the one hand, this strategy used protease inhibitors instead of commonly used ribavirin. The former is less toxic and does not cause obvious side effects, hence maintaining the physical strength of the patient. Protease inhibitors are a class of HIV drugs in AIDS cocktail therapy. After use, the antiviral effect is remarkable. The reason that patients can be cured in a short time is related to the application of the anti-AIDS drugs protease inhibitors. Most importantly, 3C-like proteinase is involved in the expression of the SARS-CoV genome. Therefore, protease inhibitors are ideal anti-SARS drugs or inhibitors. It can be inferred from this that if the SARS-CoV is treated as HIV and also treated by cocktail therapy, things seem much simpler and easier. Other types of drugs that can replace protease inhibitors, such as efavirenz (Sustiva) [11,12], a non-nucleoside reverse transcriptase inhibitor developed

by DuPont Pharmaceuticals, have the same effect and similar price as protease inhibitors. On the other hand, psychotherapy and humanistic care also have positive effects. In conclusion, in this case, the use of antiviral therapy, enhanced immune function and immunosuppression can achieve good results and reflect the spirit of the new “5 P” medical model[13].

In-situ hybridization study of SARS autopsy tissue indicates that SARS-CoV invades different human organs. The pathophysiological changes in the human body are not only caused by SARS-CoV itself that may impair the myocardium also by a cytokine mediated immune response. A subclinical diastolic injury was found in SARS patients without involvement of systole. This is a reminder that protecting heart and lung function is very important to avoid the occurrence and increase of death from multiple organ dysfunction syndrome.

At the same time, people also tried to use a strategy by RNA interference to inhibit SARS-CoV infection and replication[14,15]. The 80R human monoclonal antibody may be an effective inhibitor of SARS-CoV invasion. Since the receptor binding domain of the coronavirus spike (S) protein is a key factor in determining the viral tropism and transmission capacity[16], it is also a potential target for developing subunit vaccines and drugs. The development of nucleic acid-based vaccines (DNA and mRNA vaccines) as new approaches should be continued due to the high mortality of SARS-CoV[17]. Therefore, the inactivated SARS viral vaccine is very promising and should be tested in clinical trials.

Since SARS coronavirus infection can induce acute lung injury and rapid pulmonary fibrosis, which is negatively correlated with lung function, it is important to assay serum levels of associated inflammatory cytokines in patients with severe respiratory virus infection[18,19]. Follow-up of SARS patients showed significant functional and psychological abnormalities, including pulmonary fibrosis and vascular necrosis, and it was important to continue to track the long-term or lifelong consequences of these patients.

Table 1. iRT-ABCDEF for major virus-communicable diseases (mVCDs).

No.	Pathogen	Spreading pathways	Related mVCDs	Tips of iRT-ABCDEF
1	Human immunodeficiency virus	Sexual contact, blood	Acquired immunodeficiency syndrome	Follow-up
2	Ebola-virus	Blood, saliva, sweat, secretions	Ebola	Examination (comprehensive or targeted)
3	SARS-related coronaviruses	Air, subject contact	Severe acute respiratory syndrome	Disease & risk factors control
4	Avian influenza viruses, including H5N1, H7N7, H7N9	Respiratory tract, subject contact	Highly pathogenic avian influenza	Cut spreading pathways & change unhealthy lifestyle
5	Cox A16, EV 71	Digestive tract, respiratory tract, subject contact	Hand-foot-mouth disease	Biohazard control
6	High-risk human papilloma virus	Sexual contact	Cervical carcinoma	Antagonistic treatment
7	Hepatitis A/B/C/D/E virus (HAV, HBV, HCV, HDV, HEV)	Subject contact, blood, saliva, sweat, secretions	A/B/C/D/E virus-related hepatitis	Intervention of routine, right, and reversible treatments
8	African Zika virus (ZIKV) (MR-766), Asian ZIKV (MEX1-44)	<i>Aedes aegypti</i> mosquito, <i>Aedes albopictus</i> (“Asian tiger”) mosquito	Zika fever, Guillain-Barre syndrome, microcephaly and other severe fetal brain defects	
9	Dengue virus (DENV1, DENV2, DENV3)	Aquatic mosquitoes (eggs, larvae and pupae), adult mosquitoes (susceptible, exposed and infectious) and human hosts (susceptible, exposed, infectious and recovered)	Dengue fever	
10	MERS coronavirus	Air, respiratory tract	Middle East respiratory syndrome	

3. iRT-ABCDEF for SARS and other mVCDs

Due to the new SARS-CoV strain found in Yunnan[3], China, the mystery of SARS prevention and management will be further revealed by the application of intervention of RT-ABCDEF (iRT-ABCDEF) (Table 1), which is applicable not only to major non-communicable diseases, for example, chronic heart failure[20], but also to major viral infectious diseases. Here, iRT-ABCDEF originated from previous RT-ABCDE[21], and means follow-up (F), examination (comprehensive or targeted) (E), disease & risk factors control (D), cut spreading pathways & change unhealthy lifestyle (C), biohazard control (B), antagonistic treatment (A). This program should be used as an intervention of routine, right, and reversible treatments (iRT). iRT-ABCDEF will be a new standardized comprehensive program to detect and control the threat of emerging infectious diseases in the future. It is also worth developing new vaccines or discovering new anti-inflammatory molecules as new biotherapeutics[22].

4. Prospects

With the help of powerful tools, especially the rapid development of small science[23], new technologies such as the “molecular scissors”, CRISPR and base editing[24], can be expected to have better prospects in the fight against SARS in the future. It will help fight dengue fever in southern China[25-27].

Conflict of interest statement

The authors declared that they have no conflict of interest.

Acknowledgements

There is an ethical approval on May 25, 2018 granted by Jiangxi Academy of Medical Science, Nanchang University.

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