

Advances in clinical diagnosis and treatment of severe acute respiratory syndrome

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Abstract

It has been proved that severe acute respiratory syndrome (SARS) is caused by SARS-associated coronavirus, a novel coronavirus. SARS originated in Guangdong Province, the People' s Republic of China at the end of 2002. At present, it has spread to more than 33 countries or regions all over the world and affected 8 360 people and killed 764 by May 31, 2003. Identification of the SARS causative agent and development of a diagnostic test are important. Detecting disease in its early stage, understanding its pathways of transmission and implementing specific prevention measures for the disease are dependent upon swift progress. Due to the efforts of the WHO-led network of laboratories testing for SARS, tests for the novel coronavirus have been developed with unprecedented speed. The genome sequence reveals that this coronavirus is only moderately related to other known coronaviruses. WHO established the definitions of suspected and confirmed and probable cases. But the laboratory tests and definitions are limited. Until now, the primary measures included isolation, ribavirin and corticosteroid therapy, mechanical ventilation, etc. Other therapies such as convalescent plasma are being explored. It is necessary to find more effective therapy. There still are many problems to be solved in the course of conquering SARS.

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INTRODUCTION

On 12 March 2003, the World Health Organization (WHO) issued a global alert on the atypical pneumonia, also called severe acute respiratory syndrome (SARS), after reports from the Department of Health of Hong Kong of an outbreak of pneumonia in one of its public hospitals. At about the same time, WHO received reports of the syndrome from China, Singapore, Vietnam, Thailand, Indonesia, Taiwan, and the Philippines, as well as from countries in other continents including Canada, the United States, and Germany. The disease

originated in Guangdong Province at the end of 2002 and has affected 8 360 people and killed 764 by May 31, 2003. Dr. Carlo Urbani reported the disease first in a Vietnam French Hospital of Hanoi^[1]. WHO took prompt measures to avoid wider spread of SARS according to his alarm. It has been proved that a novel coronavirus is associated with SARS (SARS-CoV), and that this virus plays an etiologic role in SARS^[2-9]. Because of the death of Dr. Carlo Urbani (46 years old, an expert of infectious diseases, Italian) from SARS, Ksiazek and his colleagues proposed that their first isolate be named the Urbani strain of SARS-associated coronavirus.

On 17 March 2003, WHO called upon 11 laboratories in 9 countries to join a collaborative multi-center research project on SARS diagnosis. This network took advantage of modern communication technologies to share outcomes of investigation of clinical samples from SARS cases in real time. Clinicians from China, Hong Kong and the USA introduced their own experience of treatment on SARS. Scientists have made great progress in the clinical diagnosis and treatment of SARS. However, there are still many difficulties and problems to be solved in the course of conquering SARS.

DIAGNOSIS

Identification of SARS causative agent and development of a diagnostic test are of paramount importance. Detecting disease in its early stage, understanding its pathways of transmission and implementing disease specific prevention measures are dependent upon swift progress and results in aetiological and diagnostic research.

Clinical presentations

Booth *et al*^[10] reported that features of the clinical examination most commonly found in the patients at admission were self-reported fever (99 %), documented elevated temperature (85 %), nonproductive cough (69 %), myalgia (49 %), and dyspnea (42 %). The reports from Zhong^[11] and Chan-Yeung *et al*^[12] were similar to this.

Laboratory tests

Due to the efforts of the WHO-led international multi-center collaborative network of laboratory testing for SARS, tests for the novel coronavirus have been developed with unprecedented speed^[13].

Early in the course of the disease, the absolute lymphocyte count is often decreased. Overall white blood cell counts are generally normal or decreased. At the peak of the respiratory illness, approximately 50 % of patients have leukopenia and thrombocytopenia or low platelet counts within normal range. Early in the respiratory phase, elevated creatine phosphokinase levels (as high as 3 000 IU/L) and hepatic transaminases (two to six times of the upper limits of normal) have been noted. In the majority of patients, renal function is normal. Common laboratory features include elevated lactate dehydrogenase (87 %), hypocalcemia (60 %), and lymphopenia (54 %). Only 2 % of patients have rhinorrhea^[10] (Tables 1 and 2).

Table 1 Earliest symptoms of SARS^a

Symptom	No. (%) of patients (n=144)
Fever (n=106)	
Alone	33(23)
With prodrome	33(23)
With prodrome and cough or dyspnea	16(11)
With cough or dyspnea	15(11)
With other combinations	9(6)
Prodrome alone	19(13)
Cough or dyspnea alone	13(9)
Symptom reported first	
Prodrome	74(52)
Fever	106(74)
Cough or dyspnea	51(35)
Diarrhea	9(6)

^aProdrome includes headache, malaise, or myalgia.

Table 2 Laboratory features of SARS at admission and during hospitalization

	At admission		During hospitalization ^a	
	Median (IQR)	No./Total(%) Abnormal ^b	Median (IQR)	No./Total(%) Abnormal ^b
Lymphocytes, / μ L	900 (700-1300)	104/122 (85)	500 (400-800)	106/120 (88)
Lactate dehydrogenase, U/L	396 (219-629)	86/99 (87)	630 (363-1156)	115/123 (94)
Creatine kinase, U/L	157 (70-310)	43/109 (39)	370 (208-959)	64/118 (54)
Potassium, mEq/L	3.7 (3.4-4.0)	36/137 (26)	3.2 (2.9-3.4)	60/140 (43)
Calcium, mg/dL ^c	8.52 (8.2-9.16)	53/89 (60)	8.1 (7.76)	71/101 (70)
Magnesium, mg/dL	1.94 (1.7-2.19)	12/68 (18)	1.43 (0.97-1.51)	55/96 (57)
Phosphorus, mg/dL	3.10 (2.76-3.69)	17/64 (27)	2.17 (1.83-2.48)	41/78 (53)

Abbreviations: IQR, interquartile range; SI conversions: To convert calcium to mmol/L, multiply by 0.25. To convert magnesium to mmol/L, multiply by 0.411. To convert phosphorus to mmol/L, multiply by 0.323. ^aThe most abnormal value recorded used. ^bDefined as lymphocytes <1 500/ μ L; lactate dehydrogenase >190 U/L; creatine kinase >240 U/L for men and >190 U/L for women; potassium <3.5 mEq/L; calcium <8.8 mg/dL; magnesium <1.70 mg/dL; phosphate <2.79 mg/dL. ^cCalcium values have been corrected for serum albumin.

Radiographic findings of SARS

Wong *et al*^[14] found that initial chest radiographs were abnormal in 108 of 138 (78.3 %) patients and showed air-space opacity. Lower lung zone (70 of 108, 64.8 %) and right lung (82 of 108, 75.9 %) were more preferably involved. In most patients, peripheral lung involvement was more common (81 of 108, 75.0 %). Unifocal involvement (59 of 108, 54.6 %) was more frequent than multifocal or bilateral involvement.

Molecular test (PCR)

Sequencing of the about 30000-base genome of the SARS-associated coronavirus has completed^[15-21]. The genome sequence revealed that this coronavirus was only moderately related to other known coronaviruses, including two human coronaviruses, HCoV-OC43 and HCoV-229E. A valid positive PCR result indicated that there was genetic material (RNA) from the SARS-CoV in the sample. However, it does not mean the virus present is infectious, or that it is present in a large

enough quantity to infect another person. Negative PCR results do not exclude SARS. Besides the possibility of obtaining false-negative test results, specimens may not have been collected at a time when the virus or its genetic material was present.

The SARS-CoV-specific RNA can be detected in various clinical specimens such as blood, stool, respiratory secretions or body tissues by PCR. A number of PCR protocols developed by members of the WHO laboratory network are available on a WHO website^[22].

Despite their high sensitivity, the existing PCR tests cannot rule out the presence of the SARS virus in patients on account of possible false negative results. On the other hand, contamination of samples in laboratories may lead to false positive results.

SARS-CoV isolation

The presence of the infectious virus can be detected by inoculating suitable cell cultures (e.g. Vero cells) with patient's specimens (such as respiratory secretions, blood or stool) and propagating the virus *in vitro*. Once isolated, the virus must be identified as SARS-CoV using further tests. Cell culture is a very demanding test, but is currently (with the exception of animal trials) the only means to show the existence of a live virus. Positive cell culture results indicate the presence of live SARS-CoV in the sample. Negative cell culture results do not exclude SARS.

Antibody detection

Various methods provide a means for the detection of antibodies produced in response to infection with SARS-CoV. Different types of antibodies (IgM or IgG) appear and change in level during the course of infection. They can be undetectable in the early stages of infection. IgG usually remains detectable after resolution of the illness. It was reported that IgG would reach peak value 60 days after obvious symptoms and then keep it, while IgM would reach peak value on day 14 after onset of apparent symptoms. Enzyme-linked immunosorbent assay (ELISA), immunofluorescence assay (IFA), neutralisation test are being developed, but are not yet commercially available.

WHO CASE DEFINITION^[23]

The definitions of suspected and confirmed and probable case according to the WHO Case Definition are as follows:

Suspect case

A person presenting after 1 November 2002, with history of: high fever (>38 °C) and cough or breathing difficulty, and one or more of the following exposures during the 10 days prior to onset of symptoms: (1) close contact, with a person who is a suspect or probable case of SARS; (2) history of travel, to an area with recent local transmission of SARS; (3) residing in an area with recent local transmission of SARS. Close contact means having cared for, lived with, or had direct contact with respiratory secretions or body fluids of a suspect or probable case of SARS.

A person with an unexplained acute respiratory illness resulting in death after 1 November 2002, but on whom no autopsy has been performed, and one or more of the following exposures during the 10 days prior to onset of symptoms: (1) close contact with a person who is a suspect or probable case of SARS; (2) history of travel to an area with recent local transmission of SARS, and (3) residing in an area with recent local transmission of SARS.

Probable case

(1) A suspect case with radiographic evidence of infiltrates

consistent with pneumonia or respiratory distress syndrome (RDS) on chest X-ray (CXR). (2) A suspect case of SARS that is positive for SARS coronavirus by one or more assays. See Use of laboratory methods for SARS diagnosis. (3) A suspect case with autopsy findings consistent with the pathology of RDS without an identifiable cause.

Exclusion criteria

A case should be excluded if an alternative diagnosis can fully explain their illness.

Reclassification of cases

As SARS is currently a diagnosis of exclusion, the status of a reported case may change over time. A patient should always be managed as clinically appropriate, regardless of their case status. (1) A case initially classified as suspect or probable, for whom an alternative diagnosis can fully explain the illness, should be discarded after carefully considering the possibility of co-infection. (2) A suspect case who, after investigation, fulfils the probable case definition should be reclassified as "probable". (3) A suspect case with a normal CXR should be treated, as deemed appropriate, and monitored for 7 days. Those cases in whom recovery is inadequate should be re-evaluated by CXR. (4) Those suspect cases in whom recovery is adequate but whose illness cannot be fully explained by an alternative diagnosis should remain as "suspect". (5) A suspect case who died, on whom no autopsy was conducted, should remain classified as "suspect". However, if this case is identified as being part of a chain transmission of SARS, the case should be reclassified as "probable". (6) If an autopsy was conducted and no pathological evidence of RDS was found, the case should be "discarded".

The surveillance period began on 1 November 2002 to capture cases of atypical pneumonia in China now recognized as SARS. International transmission of SARS was first reported in March 2003 for cases with onset in February 2003. The Centers for Disease Control and Prevention have added laboratory criteria for evidence of infection with SARS-CoV to the interim surveillance case definition^[24]. Using the new laboratory criteria, a SARS case is laboratorily confirmed if one of the following is met: detection of the SARS-CoV antibody by indirect fluorescent antibody (IFA) or enzyme-linked immunosorbent assay (ELISA), isolation of SARS-CoV in tissue culture, detection of SARS-CoV RNA by reverse transcriptase-polymerase chain reaction (RT-PCR), which must be confirmed by a second PCR test. Negative laboratory results for PCR, viral culture, or antibody tests obtained within 21 days of illness do not rule out SARS-CoV infection. In these cases, an antibody test of a specimen obtained more than 21 days after the onset of illness is needed to determine infection. Unless PCR confirms the initial suspicion of SARS infection, the diagnosis of SARS is based on the clinical findings of an atypical pneumonia not attributed to any other cause as well as a history of exposure to a suspect or probable case of SARS, or to their respiratory secretions or other body fluids. The initial diagnostic testing for suspected SARS patients should include chest radiography, pulse oximetry, blood cultures, sputum Gram stain and culture, and testing for viral respiratory pathogens, obviously influenza A and B and respiratory syncytial virus. A specimen for Legionella and pneumococcal urinary antigen testing should also be considered.

Clinicians should save any available clinical specimens (respiratory, blood, and serum) for additional testing until a specific diagnosis is made. Acute and convalescent (greater than 21 days after the onset of symptoms) serum samples should be collected from each patient who meets the definition criteria for SARS. Specific instructions for collecting specimens from suspected SARS patients are available on the Internet.

In the early stages, SARS may be hard to differentiate from other viral infections, and diagnostic delays may contribute to the spread of the epidemic. Nevertheless, until standardized reagents for virus and antibody detection become available and methods have been adequately tested, the diagnosis of SARS remains based on clinical and epidemiological findings. The revised case definition for the first time includes laboratory results: a suspected case of SARS, that is positive for SARS-CoV in one or more assays, should be reclassified as a probable case. At present there are no defined criteria for SARS-CoV test results to confirm or reject the diagnosis of SARS.

Positive laboratory test results for other known agents that are able to cause atypical pneumonia such as Legionella pneumophila, influenza and parainfluenza viruses, mycoplasma pneumoniae etc. may serve as exclusion criteria; according to the case definition, a case should be excluded if an alternative diagnosis can fully explain the illness. However, the possibility of dual infection must not be ruled out completely. According to our clinical experience and correlative papers, we think that exact diagnosis of a confirmed case must need a history of close contact and persistent symptoms (fever or influenza-like symptom). To observe the chest x-ray of patient continuously is also necessary.

TREATMENT

From initial clinical experience, SARS can develop in stages, including acute constitutional symptoms, acute viral pneumonitis, acute lung injury, and even acute respiratory distress syndrome, evolving over 1 to 2 weeks. Initial infection followed by a hyperactive immune response appears to underlie the severe manifestations of SARS. Therefore, corticosteroids can be used to dampen excessive lung damage due to an inflammatory response.

Ribavirin and glucocorticoid therapy

A series of 31 patients with probable SARS were treated according to a treatment protocol consisting of antibacterials and a combination of ribavirin and methylprednisolone in Hong Kong^[25]. One patient recovered by antibacterial treatment alone, 17 showed rapid and sustained responses, and 13 achieved improvements with step-up or pulsed methylprednisolone. Four patients required short periods of non-invasive ventilation. No patient required intubation or mechanical ventilation. There was no mortality or treatment morbidity in this series. The following is the standard protocol.

Antibacterial treatment

(1) Levofloxacin 500 mg once daily intravenously or orally;
(2) Or clarithromycin 500 mg twice daily orally plus coamoxiclav (amoxicillin and clavulanic acid), 375 mg three times daily orally if patient is <18 years old, pregnant, or suspected to have tuberculosis.

Ribavirin and methylprednisolone

Combination treatment with ribavirin and methylprednisolone when: (1) Extensive or bilateral chest radiographic involvement; (2) Or persistent chest radiographic involvement and persistent high fever for 2 days; (3) Or clinical, chest radiographic, or laboratory findings suggestive of worsening; (4) Or oxygen saturation <95 % in room air.

Standard corticosteroid regimen for 21 days

(1) Methylprednisolone 1 mg/kg every 8 h (3 mg/kg daily) intravenously for 5 days; (2) Then methylprednisolone 1 mg/kg every 12 h (2 mg/kg daily) intravenously for 5 days; (3) Then prednisolone 0.5 mg/kg twice daily (1 mg/kg daily) orally

for 5 days; (4) Then prednisolone 0.5 mg/kg daily orally for 3 days; (5) Then prednisolone 0.25 mg/kg daily orally for 3 days; (6) Then off.

Ribavirin regimen for 10-14 days

(1) Ribavirin 400 mg every 8 h (1 200 mg daily) intravenously for at least 3 days (or until condition becomes stable); (2) Then ribavirin 1 200 mg twice daily (2 400 mg daily) orally.

Pulsed methylprednisolone

(1) Give pulsed methylprednisolone if clinical condition, chest radiograph, or oxygen saturation worsens (at least two of these), and lymphopenia persists; (2) Give methylprednisolone 500 mg twice daily intravenously for 2 days, then back to standard corticosteroid regimen.

Mechanical ventilation

Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 ml per kilogram of body weight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network therefore conducted a trial. The mean tidal volumes on days 1 to 3 were 6.2 ± 0.8 and 11.8 ± 0.8 ml per kilogram of predicted body weight. They found that in patients with acute lung injury and acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than traditionally used resulted in decreased mortality and increased number of days without ventilator use^[26-29].

Cordingley *et al*^[30] suggests that reduced mortality may be achieved by using a strategy that aims at preventing overdistension of the lungs. There is no clinical evidence to support the use of specific FiO_2 thresholds, but it is common clinical practice to decrease FiO_2 below 0.6 as quickly as possible. SaO_2 values of around 90 % are commonly accepted. PaCO_2 is allowed to rise during lung protective volume and pressure limited ventilation. PaCO_2 levels of 2-3 times 3 normal seem to be well tolerated for prolonged periods. Renal compensation for respiratory acidosis occurs over several days. Many clinicians infuse sodium bicarbonate slowly if arterial pH falls below 7.20, Set PEEP at a relatively high level such as 15 cm H_2O in patients with ARDS. It is common practice during pressure control ventilation to increase the I:E ratio to 1:1 or 2:1 (inverse ratio ventilation) with close monitoring of intrinsic PEEP and haemodynamics.

Other therapies being studied

At present, serum therapy is being studied for SARS patients. 40 patients were divided into two groups in the Medical College of Hong Kong Chinese University. One group was treated with convalescent plasma and another group not. The effect was obviously different among two groups after one month, the therapy group died no patients while another group 3 patients, but it needs more clinical trial to be proved. In their opinion, to use convalescent plasma within earlier two weeks will shorten the in-hospital period and fever time and reduce mortality. Serum therapy was used to dying patients and aged patients with other severe or chronic disease and pregnant women.

As to another trial in Hong Kong^[31], treatment of a SARS patient followed by 200 ml convalescent plasma donated by SARS patients in their convalescent phase. No adverse reaction occurred after administration of convalescent plasma. The fever subsided, chest X-ray showed further resolution of basal lung infiltrates, and she made an uneventful recovery. Although no probable SARS case has been ascribed to transmission by labile blood products or blood derivatives, there is a theoretical risk

of transmission of the SARS virus through transfusion of labile blood products, since low viraemia has been detected up to approximately 10 days after the onset of symptoms from probable SARS patients^[32].

Moller *et al*^[33] reported that bovine surfactant therapy in severe ARDS improved oxygenation immediately after administration. This improvement was sustained only in the subgroup of patients without pneumonia but with an initial $\text{PaO}_2/\text{FIO}_2$ ratio higher than 65. The SARS studies on antisense oligonucleotide drug, polypeptide, and vaccine will benefit the treatment of this disease.

It has been proved that a novel coronavirus is the cause of SARS with strong infectivity. Up to now, we have only understood the preliminary pathogenesis and epidemiology of SARS. After all SARS is a disease seen never before in human. To control and defend human being from this disease, further studies are needed, such as: (1) origin, mutation, life cycle, transmission pathways of SARS-CoV; (2) the mechanisms of SARS-CoV replicating and coming into the host cell; (3) pathogenesis of acute lung injury and abnormal immune response; (4) rapid diagnosis and vaccine, and (5) effective medicine such as inhibitory polypeptide. With rapid progress in the basic studies of the disease all over the world, more effective drugs and treatment measures will be discovered in the days to come and SARS will be put under complete control by mankind soon.

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