SEVERE ACUTE RESPIRATORY SYNDROME (SARS):

Clinical Features, Epidemiology, Diagnosis and Management.

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In February 2003, the WHO notified the world of the emergence of a highly contagious respiratory community acquired pneumonia.[1]

This outbreak was initially reported in Southern China, Hong Kong and Vietnam. It soon spread to other nations, within five months of the disease over eight thousand (8000) cases had been reported worldwide, of which over 800 people had died.[2] The WHO estimates that the case fatality ratio of SARS range from 0% to 50% depending on the age group affected: less than 1% in persons aged 24 years or younger; 6% in persons aged 2544 years, 15% years in persons aged 4564 years; and greater than 50% in persons aged 65 years and older.[3]

With increasing recognition of the unusual infection, the U.S centers for disease control and prevention termed the condition Severe Acute Respiratory Syndrome (SARS).[4]

The aetiological agent of SARS has been identified as a corona virus.[5,6]
The primary mode of transmission is by close contact with respiratory droplets. Studies have suggested that the responsible viral agents can be found in urine and feaces from infected individuals.[7]

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Unprotected health care workers like physicians and nurses are at the highest risk of infection. In the out break in Hong Kong, Infection control investigations revealed that out of the total of 156 subjects admitted between 11 and 25 March 2003 for SARS, sixty nine (69) were health care workers and 16 were medical students who had examined index cases. The others were individuals who had visited patients in the index ward.[8]

Although after July only one case of SARS infection has been reported. The situation may not be all over. About mid September 2003 there was a new SARS alert in Hong Kong as eight elderly patients were hospitalized. There is fear that the disease may be endemic in China. Also the fear of another out break still looms ahead especially of the infected individual is a 'super spreader'. In this article I will concentrate on the clinical presentation and outcome of this disease. I shall also discuss the approach to the management of this condition.

CASE DEFINITION

The diagnosis of SARS is difficult. The WHO definitions were established to assist in the

definition of hospital cases.[9]

In the WHO case definition, patients are classified into two main categories: suspect case and probable case (See Table 1)

The WHO definition has been found to have a sensitivity of 26% and a negative predictive value of 86%, in the detection of non-hospitalized patients defined by seroconversion.[10]

The center for disease control and prevention in US has added laboratory criteria for evidence of infection with the SARS, associated corona virus (SARS COV) to the case definition. The updated interim surveillance case definition for Severe Acute Respiratory Syndrome was published July 18 2003.[11]

The CDC definition for probable and suspect case is as follows:

- Probable case: meets the clinical criteria for severe respiratory illness of unknown etiology and epidemiologic criteria for exposure; laboratory criteria confirmed or undetermined.

Suspect case: meets clinical criteria for moderate respiratory illness of unknown etiology, and epidemiologic criteria for exposure; laboratory criteria confirmed or undetermined.

CLINICAL FEATURES
SIGNS AND SYMPTOMS

Patients with SARS have two forms of clinical presentation. (The typical and atypical). Typically patients present with fever with a body temperature of >38oC (1000F) after an incubation period of 58 days. Fever is a major criteria in the current WHO case definition for suspected or probable SARS. Fever is usually associated with chills, rigors, dry cough, headaches, dizziness, malaise and myalgia. Productive sputum and coryza are uncommon.

These symptoms resemble that of patients presenting with other forms of atypical pneumonia. (See Table 11)

(Table II shows the frequency of symptoms in different cohorts)
Clinical symptoms at presentation (in %)

	Lee et al.[8] n=138	Peiris et al.[5] n=50	Donnelly et al.[12] n>1250	Booth et al[13] n=144	Poutanen et al[14] n=10
Fever	100	100	94	99	100
Chills or rigors	73	74	65*	28*	N.A
Cough	57	62	50	69	100
Myalgia	61	54	51	49	20
Malaise	N.a	50	64	31	70
Runny nose	23	24	25	2	N.A
Sore throat	23	20	23	12	30
Shortness of breath	N.a	20	31	N.a	80
Diarrhea	20	10	27	24	50
Headache	56	20	50	35	30
Vomiting	N.a	N.a	N.a	N.a	10

*Chills

N.a = not available

Some patients may also present atypically, in a group of twenty patients with SARS from Singapore dry cough has been reported to be very uncommon (75%) while chills and rigors are relatively rare (15%).15

In most patients sore throat, nausea, vomiting are less common. Diarrhea is also less frequently reported. Although this was a prominent symptoms in Amory Gardens outbreak in Hong Kong16. In that study 55 out of the 75 patients (73%) had watery diarrhea. However within the other cohorts published diarrhea was less frequent.

Table III

Characteristics of four Patients with atypical presentations of SARS*

	Patient 1	**Patient 2**	**Patient 3**	**Patient 4**
Age (years)	71	43	78	63
Time to Isolation (h)	3	8	4	12
Temperature on Admission 0C	38.7	37.3	36.3	36.0
WBC (109/l)	4.5	19.3	11.2	9.3
Lymphocytes (109 L)	0.78	0.94	0.69	0.63
LDH (IU/L)	747	2513	1032	1770
Initial diagnosis	Possible congestive cardiac failure	Pneumonia bilateral possibly bilateral	exacerbation of chronic lung disease possible congestive cardiac failure	congestive cardiac failure
Co-morbidities	Diabetes, Ischemic heart disease	Hypertension	connective tissue disease on steroids, Ischemic heart disease	Ischemic heart disease
Outcome	Survived	Died	Died	Died

***MODIFIED FROM FISHER ET AL 17**

Fisher et al17 describes four patients with atypical presentations of disease; the patients did not have the SARS related fever. This raises the question about the sensitivity of temperature monitoring as a screening tool for the diagnosis of SARS15. Although most patients who are initially febrile became febrile during the course of the illness. Patients who typically present without fever often have co-mortalities that may impair their ability to mount a febrile response to the disease.

Physical examination usually reveals a high swinging fever. Auscultation of the chest shows inspiratory crackles at the base. Wheeze, bronchial breath sounds are generally not found. However in the Canadian study14 three patients were noted to have bronchial breath sounds and egophony.

CHEST RADIO GRAPHICAL ABNORMALITIES

The chest x-ray shows predominately involvement of the peripheral zone. This is initially unilateral however, as the disease progresses it may become bilateral with multi lobar involvement.

Airspace opacities eventually develop during the course of the disease in patients who deteriorate clinically airspace opacity may increase in size, extent and severity.

Rapid radiological progression is associated with the deterioration of clinical condition and respiratory failure.

Wong et al18 in a large study focused on radiological appearances and the pattern of progression. Within this cohort four patterns of radiological progression were recognized.

Type 1 - initial radiological deterioration to a peak level followed by improvement in 70.3%

Type 2- fluctuating radiological changes in 17.4%

Type 3 - static radiological appearance in 7.3% and

Type 4 - progressive radiological deterioration in 5.1% these findings are in keeping with acute respiratory distress syndrome.

Computerized Tomography Scan

This should be considered in patients with symptoms and signs consistent with SARS but who have a normal chest radiograph.

The typical finding of the CT is indistinguishable from other forms of severe pneumonia such as pneumonia of bronchiolitis obliterans and acute interstitial pneumonia.19, 20

The lesions tend to be peripheral and small in the early stage of the disease progressing to central perihilar regions and larger (3cm) lessons.

Majority of the lesions are contained an area of ground-glass opacification with or without

consolidation. Severe disease is evident by intralobular, thickening and features of bronchiectasis; honeycombing is not a feature of SARS.21

Hematological Manifestation

The typical finding in patients with SARS is lymphopenia and thrombocytopenia. Studies by Wong et al22 showed that lymphopenia was found in 98% of patients reaching its lowest form in the second week. The lymphocyte counts commonly recovers by the third week although about 30% are still lymphopenic at the fifth week of SARS. Fifty-two percent (52%) of patients develop a self-limiting thrombocytopenia. The degree of thrombocytopenia is usually mild except for about 2% of patients.

Transient leukopenia occurs in over two-third of patients during the first week. However this is usually reversed by the second week. This laboratory finding may partially be due to the use of steroid in this condition with leukocytosis being the prominent feature.

The CD4 and CD8 counts are usually characteristically low during the early phase of the illness and there may portend an adverse outcome for the disease. As the disease progresses about 50% patient may develop features in keeping with disseminated intravascular coagulation demonstrated by deranged prothrombin time, activated partial thromboplastin time, increase international normalized ratio and D-dimer.8

Electrolyte / Biochemical Abnormalities

Patients with SARS often have elevated level of LDH, creatine kinase (of muscular origin) asparate and alaine amino transferences. The high LDH levels may be partially due to extensive lung injury or as complication of ribavirin therapy. In a multi-variate analysis elevated LDH was an independent factor for poor outcome of SARS.8

A large number of patients demonstrate low calcium, magnesium, sodium, potassium and phosphorus levels. These findings may reflect the natural course of the disease or may be due to compilations with Ribavirin or steroid therapy.

Table IV

Compares the laboratory findings in three cohorts

Laboratory findings at presentation (in %)

	Lee, et al. n=138	Peiris, et al. n=50	Poutanen et al. n=10
Leukopenia (<3.5x109/l)	34	26	22
Lymphopenia (<1.0x109/l)	70	68	89
Thrombocytopenia	45	40	33
Alanine aminotransferase	23	34	56
Creatine Kinase	32	26	56
LDH	71	n.a	80
Hyponatremia	20	n.a	n.a
Hypokalemia	25	n.a	n.a
D-dimer level	45	n.a	n.a
Prolonged activated partial-thromboplatin time	43	n.a	n.a

N.a = not available

CLINICAL COURSE

The first prospective study on clinical course was published in May 24 2003 by Peiris et al.16 Two retrospective studies from Canada 14 and Hong Kong demonstrated a comparable outcome.

Patients develop a triphasic pattern of presentation. The initial phase or onset period is mainly characterized by fever, myalgia, dry cough and other constitutional symptoms.

After the initial phase, in week 1 patient may develop progressive pneumonia and increasing oxygen dependency. Most patients may become a febrile within 48 hrs after a standard treatment protocol. In week 2 the patient's frequently have recurrence of fever, onset of diarrhea and oxygen desaturation. They may be shifting radiological infiltrates with deterioration. Patient may progress to severe clinical worsening with the development ARDS and death.

It is thought that this deterioration is caused by immuno-pathological dysregulation and uncontrolled activation of cytokine system resulting in lung damage.

The third phase of illness or week 3 is

characterized by ARDS necessitating ventilatory support several patients develop severe nosocomial sepsis and end organ damage with severe lymphopenia an average of about 25% of adult patients require intensive care and 15% need mechanical ventilation.

In the study by Peiris et al 16 32% of patients required intensive care at a mean of 11.0 days after onset of symptoms of which 79% had to be intubated at a mean of 12.9 days. The mean length of stay for 75 patients where 22.1 days whereas for the 15 patients who developed ARDS, the mean length of stay was 26.8 days. The total mortality in this cohort was 7%.

In the cohorts from Canada14 and Hong Kong8 20-23% were admitted in the intensive care unit with 5969% requiring mechanical ventilation mortality ranged from 3-6% (See Table V)

PROGNOSTIC FACTORS

A number of studies have consistently revealed that older age, co-morbid conditions were independent predictors of both mortality and poor outcome5,8,12,13,14. These factors are similar to the risk factors identified in patients presenting with severe atypical bacteria pneumonia.23

In a study by Chan et al24 the clinical features of 115 patients with SARS admitted to a single hospital in Hong Kong, beginning March 2003 were reviewed, using univariate cox proportional hazard model they showed that the mortality risk was 6.8 times higher in those aged above 60. The presence of co-morbidities increase the mortality risk with cardiac disease and diabetes mellitius being the most important co-morbidities other factors that significantly affected mortality include prolonged thromboplastin time, increased urea level and raised lactate dehydrogenase levels.

They also showed that diabetes, cardiac disease and age are strongly predictive of adverse outcome. This was similar to the previous study by Peiris et al16 in a smaller study of patient in the Amroy Gardens housing block in Hong Kong. In that study 40% of these with ARDS (n = 15) had chronic hepatitis B infection compared with 5% of the 60 patients who did not develop ARDS Lee et al8 in their study of 138 patients identified advanced age, a high peak level of LDH and a high absolute neurophill count at presentation as the three independent predictive factors for a poor outcome (ICU admission or death).

These observations raises a question while some patients develop mild disease and survive others become very ill and die. The presence of co-morbid condition in elderly patients may have hightened the immune responses that augment the immuno-pathological response to SARS and lead to more severe pulmonary infiltration, ARDS and death.20, 25 It could also be speculated that immunological traits that lead to chronic disease may also adversely influence the immuno pathological response to SARS. A number of patients have been

reported to have developed various degree of pulmonary fibrosis following recovery. The pathophysiological mechanism of this phenomena remains unknown.

Table VI

Summary of factors affecting mortality and adverse outcome in patients with SARS

1. Age > 60 yrs
2. Presence of co-morbid conditions
   E.g. Cardiac diseases
   - 0 Diabetes mellitus
   - 0 Chronic viral hepatitis B
3. High serum urea
4. High latate dehydrogenenase (LDH)
5. Low CD4 and CD8 counts
6. Severe lymphopenic
7. High Neurophill Count
8. Impaired Alaine Amino Transferase

Table VII

RISK FACTORS ASSOCIATED WITH CLINICAL DETERIORATION

AUTHORS	N	RISK FACTORS
Lee et al	138	Old age, high neutrophil count, high LDH peak
Peiris et al	50	Old age, severe lymphopenia, impaired alanine amino transferase, delayed starting of ribavirin and steroids
Booth et al	144	Diabetes mellitus and other comorbid conditions (trend for old age)
Wong et al	157	Old age, high LDH
Chan et al	115	Diabetes mellitus, cardiac disease and old age.
Poutanen et al	10	Advanced age co-morbid Conditions Tobacco Smoking

MANAGEMENT

The first principle in the treatment of SARS is to establish the diagnosis of SARS and rule out other causes of atypical pneumonia. Patients presenting with SARS must undergo thorough diagnostic investigations which should include chest x-ray, CT Scan (if possible) pulse oximetry, blood culture, sputum/Gramstain and culture, tests for viral respiratory pathogen, legionella and pneumococcal urinary antigen testing.

The Center for disease control and prevention (CDC) in the USA has advised clinicians to save many available clinical specimens (respiratory, blood, serum) for additional testing until specific diagnosis is made.26

Acute and convalescent serum samples should be collected from each patient who meets the SARS diagnosis criteria, paired sera and other clinical specimen should be forwarded through the state and local health department for testing possible to the CDC or any other specialized center. Strict and specific procedures should be adopted in collecting and transporting specimens.

The treatment of SARS still remains controversial no standard protocol has been established. All patients with SARS should be treated with broad spectrum antibiotics covering for both atypical and typical community acquired pneumonia Ribavirin an antiviral drug has been used by various centers in treating SARS. Ribavirin is a nucleoside analogue first synthesized in the early 1970s. It has activity against a wide variety of DNA and RNA viruses including influenza A and B.27

In addition to Ribavirin, steroids have been extensively used in the treatment of SARS.

The treatment protocol used in Hong Kong is oral Ribavirin (loading dose of 2.4g followed by 1.2g three times a day) and a low dose Corticosteroid (prednisolone 0.5 / mg / kg / day)28

Those with progressive dyspnea and hypoxia are treated with intravenous Ribavirin 400mg very 8 hours combined with hydrocortisone (100mg every 6 hours). Pulses of high dose methyl prednisone (0.5g daily for 3 days are given to patients who continue to have fever and progressive clinical and radiographical deterioration.

Similar treatment protocols have been used in other hospitals in Hong Kong and Canada. Although the dose of steroids used in Canada was much lower than that used in Hong Kong.8, 14, 29 There has also been a controversy on the use of these agents in the treatment of SARS. 30,31

The convalescent serum obtained from patients who have recovered from SARS has been used for selected patients who continue to deteriorate despite treatment of ribavirin and steroids27.

However there are no randomized trials to evaluate the effectiveness of convalescent serum in patients with SARS.

Patients who have been treated with ribavirin and steroids have reported various side effects of the drugs 27, 32. The most commonly reported has been haemolytic anaemia for ribavirin and myopathy for steroids.

Patients who continue to deteriorate as demonstrated by increased diffuse infiltrates in the lungs, hypoxaemia without left ventricular failure will need to be mechanically ventilated.

The best approach for ventilating patients with SARS is not known, but a lung protective strategy shown to reduce mortality in patients with ARDS33 possibly by preventing multiorgan dysfunction syndrome may be adopted.34,35

Physicians managing patients with SARS should observe strict infection control strategy. The disease is highly contagious and health practitioners and those closely associated with the index case are at high risk.

Patients with SARS should be transferred to centers that have specifically trained staff and good isolation facilities to prevent the spread of infections. As much as possible use of nebulizers and non-invasive positive pressure ventilation should be minimized or avoided.

Visitors should not be allowed to see patients. Details of infection control measures are available in WHO and related websites9, 25. Public health and quarantine measures are extremely important in controlling the spread of the infection in the community. Clinicians evaluating cases should observe both airborne precautions (e.g. use of the N. 95 respirator) and the contact precautions (e.g. gowns and gloves), as recommended by the CDC36 to avoid infecting themselves or spreading the infection.

SARS has proved true the saying, where there is a will, there is a way. The manner of response of WHO, Center for disease control and prevention in the USA and other health authorities to the outbreak of this disease is vastly responsible for the success in controlling its spread. To the developing countries, SARS poses a great threat, with malnutrition, HIV / AIDS and tuberculosis already compromising the immune system coupled with the fragile economy, poverty and poor health facilities. The additional burden of SARS would cause a havoc of untold magnitude. There is the need for improvement in surveillance strategies and training of health practitioners to help them effectively manage the disease if ever an epidemic breaks out.

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