Severe acute respiratory distress syndrome (SARS): A critical care perspective

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Objective: **To review the epidemiology, clinical features, etiology, diagnosis, and management of severe acute respiratory syndrome (SARS) from a critical care perspective.**

Data Sources: **A MEDLINE search was performed using the following terms: severe acute respiratory syndrome and SARS virus. Additional information and references were obtained from the Web sites for the Centers for Disease Control and Prevention, World Health Organization, and Health Canada.**

Study Selection: **Recent case series were used to develop a review of the epidemiology, clinical features, outcomes, and management of patients with SARS from an intensive care unit (ICU) perspective. This was supplemented by epidemiology information obtained from other Web-based sources. Recent published studies describing the etiology of SARS were also included.**

Data Synthesis: **SARS has rapidly spread from Southeast Asia to numerous countries, including Canada and the United States. A new coronavirus has been isolated and detected from many affected patients. The mortality rate worldwide is approximately 10.5%. From five cohorts, the ICU admission rate ranged from 20% to 38%. Fifty-nine percent to 100% of the ICU patients required mechanical ventilatory support. The mortality rate of SARS patients admitted to the ICU ranged from 5% to 67%. The most common clinical symptoms and signs are fever, cough, dyspnea, myalgias, malaise, and inspiratory crackles. Common laboratory abnormalities included mild leukopenia, lymphopenia, and increased aspartate transaminase, alanine transaminase, lactic dehydrogenase, and creatine kinase. The chest radiograph pattern ranged from focal infiltrates to diffuse airspace disease. Management consisted of isolation, strict respiratory and contact precautions, ventilatory support as needed, empiric broad-spectrum antibiotics, ribavirin, and corticosteroids. Predictors of mortality included advanced age, the presence of comorbidities, and a high lactic dehydrogenase or high neutrophil count at admission.**

Conclusions: **SARS is a highly contagious, infectious process that can advance to significant hypoxemic respiratory failure requiring ICU monitoring and support. Early recognition is critical for effective management and containment of this disease. (Crit Care Med 2003; 31:2684–2692)**

KEY WORDS: severe acute respiratory syndrome; SARS; coronavirus; mechanical ventilation; critical care

Severe acute respiratory syndrome (SARS) is a new, highly virulent respiratory infection. Originally described as an outbreak of a severe atypical pneumonia in the Guangdong Province of southern China in late 2002, it has rapidly spread through Southeast Asia, Europe, and North America. The international spread of the disease has been traced back to a few individuals who were in contact with the index case of a healthcare worker staying in the same hotel in Hong Kong. By March 2003, the World Health Organization (WHO) issued a worldwide alert for surveillance for this respiratory syndrome. As of June 26, 2003, there have been 8,456 probable cases worldwide, predominately in Hong Kong, China, Southeast Asia, Canada, and the United States, with 809 deaths (1) (Table 1). The worldwide case fatality proportion is currently reported at 10.5%.

In Canada, two outbreaks were identified. A larger one in Toronto, Ontario, and a smaller one in Vancouver, British Columbia. Both were related to exposure to the index case in a Hong Kong hotel. In Ontario, the transmission of the disease was initially limited to close contacts with the original index family in Toronto (2). These included healthcare workers and patients in close proximity to the index patient. Subsequent cases in the community have also been linked to the index family. In Vancouver, transmission of the disease was limited to healthcare workers and other close contacts.

SARS is currently classified as either a suspected case or a probable case. Patients with a fever (>38°C), with symptoms of cough or dyspnea, and with a history of close contact with a suspected or probable case of SARS, who traveled to an affected area, or who live in an affected area are defined as a suspected case. A probable case is defined by the presence of a suspected case associated with chest radiograph changes consistent with pneumonia or respiratory distress syndrome. As of June 26, 2003, there were 442 cumulative cases in Canada, probable and suspected (1) (Table 2). This gives a Canadian case fatality proportion of 8.6%. All deaths occurred in the Toronto cluster in those with probable cases, giving a case fatality proportion of 15.1% for those with probable SARS.

In the critical care setting, healthcare workers are at particular risk. Patients managed in the intensive care unit (ICU) have a more severe illness that may be partly related to a higher viral burden and, therefore, more likely to be infective. Procedures associated with a higher risk of transmission of respiratory droplets (a proposed vector for transmission) include the use of nebulization, noninvasive ventilation, endotracheal intubation, suctioning, and bronchoscopy. This was

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Table 1. Cumulative Number of Severe Acute Respiratory Distress Syndrome Cases[a] and Deaths: November 1, 2002 to June 26, 2003

Country	No. of Cases	No. of Deaths
Australia	5	0
Brazil	3	0
Canada	251	37
China, mainland	5327	348
China, Hong Kong Special Administrative Region	1755	296
China, Macao Special Administrative Region	1	0
China, Taiwan	682	84
Colombia	1	0
Finland	1	0
France	7	0
Germany	10	0
India	3	0
Indonesia	2	0
Italy	9	0
Japan	1	0
Kuwait	1	0
Malaysia	5	2
Mongolia	9	0
New Zealand	1	0
Philippines	14	2
Republic of Ireland	1	0
Republic of Korea	3	0
Romania	1	0
Russian Federation	1	0
Singapore	206	32
South Africa	1	1
Spain	1	0
Sweden	3	0
Switzerland	1	0
Thailand	9	2
United Kingdom	4	0
United States	74	0
Vietnam	63	5
Total	8456	809

[a]Only probable cases are being reported by all countries. Source: *http://www.sars.ca/* (accessed June 26, 2003).

Table 2. Cumulative Number of Severe Acute Respiratory Distress Syndrome Cases Reported in Canada: June 26, 2003

	Persons Meeting the Criteria for		
Province/Territory	Probable Case	Suspect Case	No. of Deaths
British Columbia	4	46	0
Alberta	0	6	0
Saskatchewan	0	1	0
Manitoba	0	0	0
Ontario	247	132	38[a]
Quebec	0	0	0
Nova Scotia	0	0	0
Newfoundland	0	0	0
New Brunswick	0	2	0
Prince Edward Island	0	4	0
Nunavut	0	0	0
North West Territories	0	0	0
Yukon	0	0	0
Total	251	191	38

[a]Thirty-seven of 38 deaths were probable cases, and one was a suspect case. Source: *http://www.sars.ca/* (accessed June 26, 2003).

highlighted by the transmission of SARS to a number of healthcare workers during difficult intubations of SARS patients in three different hospitals in the Toronto region (3). In Vancouver, two healthcare workers in a large community hospital became infected while taking care of a patient with probable SARS, despite taking what was believed to be proper protective measures at the time (except for eye protection). In two outbreaks described in Hong Kong, 28% to 54% of those affected were healthcare workers (4, 5). In a recently described Toronto cohort, 51% were healthcare workers (6). Diligent respiratory and contact precautions must be taken in this high-risk setting.

SARS also carries a significant economic burden for all countries affected. In Canada, the public health costs associated with screening, isolation measures both at home and in hospitals, tracing cluster breakouts, and medical management rose rapidly. Indirectly, the social and economic burden has extended beyond the healthcare arena, significantly impacting the travel and tourism industry and loss of time from work in many other fields.

As the number of cases of SARS increases worldwide, SARS will become a significant respiratory illness and part of our differential diagnosis of atypical community-acquired pneumonia and hypoxemic respiratory failure in the ICU. Early recognition is key in both the management and containment of this infectious process. This article will review the most recent literature to provide a composite picture of severe acute respiratory syndrome.

Etiology

The rapid spread of the disease, the lack of a response to antibiotics, and the absence of culture or pathologic evidence of a bacteria infection suggest that SARS is virally mediated. In five cohorts described in the literature, extensive testing for bacterial, fungal, and viral studies were largely negative (2, 4–7).

The causative pathogen is a new human coronavirus (5, 8, 9). Investigators for the Centers for Disease Control and Prevention (CDC), using virus cell cultures, reverse transcription-polymerase chain reaction (RT-PCR), and/or indirect immunofluorescence, demonstrated the virus in 19 patients (8). Twelve patients in whom they were able to amplify a viral RNA fragment by RT-PCR had the same viral genome sequence. This was also identical to the sequence from the coronavirus isolated in five patients from the Canadian cohort (2). Drosten et al. (9) described isolating the same coronavirus from a physician and a relative who were in close contact. This index Frankfurt

case was a Singapore-based physician who treated a patient from Hong Kong with SARS. The role of the novel coronavirus was further supported by finding positive RT-PCR results for this virus in five of five (100%) probable SARS patients, three of 13 (23%) suspected SARS patients, and zero of 21 (0%) in healthy contacts from Hanoi, Vietnam. Peiris and colleagues (5) in Hong Kong isolated a coronavirus from two patients, one from an open lung biopsy specimen and the other from a nasopharyngeal aspirate. Using RT-PCR, 22/44 (50%) nasopharyngeal samples and 10/18 (56%) stool samples were positive for the virus. In addition, 35/50 (70%) serum samples showed evidence of an antibody to the newly discovered coronavirus, with a significant rise in antibody titers between acute and convalescent sera. None of the control patients (those with respiratory disease other than SARS or healthy blood donors) had positive results.

The coronavirus is from the coronaviridae family, which are large positive-stranded RNA viruses with a distinctive "crown-like" appearance on electron microscopy. Three antigenic groups (I, II, III) exist. Mammalian forms of the virus are found in groups I and II. Coronaviruses involved in avian infections are found in group III.

The two human coronaviruses, 229E and OC43, belong to groups I and II, respectively. Both cause mild, self-limited upper respiratory tract infections similar to the rhinoviruses and are often associated with the common cold. It has also been described as a cause of viral diarrhea in children. Immunocompromised individuals are at risk for more severe forms of respiratory and gastrointestinal infections, although this is uncommon (10).

The SARS-related coronavirus was recently sequenced by scientists in Vancouver, British Columbia (http://www.bcgsc.ca/bioinfo/SARS/), and confirmed by scientists at the CDC (11, 12). The nucleotide and inferred amino acid sequence of fragments of this coronavirus differed from the other known human and animal coronaviruses by 26% to 46% (5, 8, 9, 11, 12). Phylogenetic analysis places this SARS-related coronavirus between groups II and III, providing evidence that this virus is significantly different from the other groups. This information will greatly enhance the understanding of the nature of this virus and aid in the development of a rapid diagnostic tests and therapies (13).

It is believed that respiratory transmission from direct contact with respiratory particles is the main route of spread of this infection. However, demonstration of evidence of viral shedding in stool samples suggests other possible modes of transmission (5, 8). Recently, a large cluster of severe cases emerged from an apartment block in Hong Kong, suggesting the possibility of a common environmental source (14).

Diagnosis

Currently, diagnosis is based on clinical and epidemiologic features as per the WHO and CDC criteria for surveillance of SARS cases and the exclusion of other known infectious and noninfectious processes that can mimic this syndrome.

Recently, the case definitions have been expanded to include the results of SARS coronavirus laboratory tests. The latest WHO guidelines still retain the original case definitions for suspected and probable cases but have added positive SARS coronavirus assays to the probable case definition (Table 3). The CDC case definition also maintains the suspected and probable case classification but emphasizes the spectrum of clinical presentation and the need for laboratory testing (Table 4).

A variety of diagnostic tests are currently being evaluated (Table 5). A positive serologic or RT-PCR test or isolation of the virus in association with clinical and epidemiologic features suggests a SARS coronavirus infection. Caution must be observed for negative antibody tests <21 days after the onset of symptoms. A negative result at this stage does not exclude the disease. In the prospective study, Peiris et al. (14) showed that immunoglobulin G seroconversion occurred in 70/75 (93%) patients at an average of 20 days. RT-PCR was positive in 24/75 (32%) patients from nasopharyngeal aspirates at initial presentation of the disease, which increased to 68% by

Table 3. Severe Acute Respiratory Distress Syndrome (SARS) Case Definition (World Health Organization Case Definition for Surveillance as of May 1, 2003)

Suspect case
1. A person presenting after November 1, 2002 with a history of
   —High fever (>38°C)
   and
   —Cough or difficulty breathing
   and one or more of the following exposures during the 10 days before the onset of symptoms
   —Close contact[a] with a person who is a suspect or probable case of SARS
   —History of travel to an area with recent local transmission of SARS
   —Residing in an area with recent local transmission of SARS
2. A person with an unexplained acute respiratory illness resulting in death after November 1, 2002 but on whom no autopsy has been performed and one or more of the following exposures during 10 days before onset of symptoms
   —Close contact with a person who is a suspect or probable case of SARS
   —History of travel to an area with recent local transmission of SARS
   —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 radiograph
2. A suspect case of SARS that is positive for SARS coronavirus by one or more assays
3. A suspect case with autopsy findings consistent with the pathology of RDS without an identifiable cause

Exclusion criteria
1. A case should be excluded if an alternative diagnosis can fully explain the illness

[a]Close contact: having cared for, lived with, or had direct contact with respiratory secretions or body fluids of a suspect or probable case of SARS. Source: Case Definition for Surveillance of Severe Acute Respiratory Syndrome (SARS), WHO, Geneva. *http://www.who.int/csr/sars/casedefintion/en/print.html* (accessed May 16, 2003).

Table 4. Centers for Disease Control and Prevention Updated Interim U.S. Case Definition for Severe Acute Respiratory Syndrome (SARS) (May 20, 2003)

Clinical criteria
- Asymptomatic or mild respiratory illness
- Moderate respiratory illness
  - Temperature of >100.4° F (>38°C), and
  - One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia)
- Severe respiratory illness
  - Temperature of > 100.4° F (>38 °C), and
  - One or more clinical findings of respiratory illness (e.g., cough, shortness of breath, difficulty breathing, or hypoxia), and
  - Radiographic evidence of pneumonia, or
  - Respiratory distress syndrome, or
  - Autopsy findings consistent with pneumonia or respiratory distress syndrome without an identifiable cause

Epidemiologic criteria
- Travel (including transit in an airport) within 10 days of onset of symptoms to an area with current or recently documented or suspected community transmission of SARS, or
- Close contact within 10 days of onset of symptoms with a person known or suspected to have SARS infection

Laboratory criteria
- Confirmed
  - Detection of antibody to SARS-CoV in specimens obtained during acute illness or >21 days after illness onset, or
  - Detection of SARS-CoV RNA by RT-PCR confirmed by a second PCR assay, by using a second aliquot of the specimen and a different set of PCR primers, or
  - Isolation of SARS-CoV
- Negative
  - Absence of antibody to SARS-CoV in convalescent serum obtained >21 days after symptom onset
- Undetermined: laboratory testing either not performed or incomplete

Case classification
- Probable case: meets the clinical criteria for severe respiratory illness of unknown etiology with onset since February 1, 2003, and epidemiologic criteria; laboratory criteria confirmed, negative, or undetermined
- Suspect case: meets the clinical criteria for moderate respiratory illness of unknown etiology with onset since February 1, 2003, and epidemiologic criteria; laboratory criteria confirmed, negative, or undetermined

Source: *http://www.cdc.gov/ncidod/sars/casedefinition.htm* (accessed May 20, 2003).

Table 5. Diagnostic Tests for Severe Acute Respiratory Distress Syndrome (SARS) Coronavirus

Test	Description	Interpretation of Test
PCR	Polymerase chain reaction (PCR) can detect genetic material of the SARS-CoV in various specimens. PCR tests are very specific but lack sensitivity (i.e., a negative test does not rule out the disease)	Positive—there is genetic material (RNA) of the SARS-CoV in the sample. This does not mean that there is live virus present or that it is present in a quantity large enough to infect another person Negative—does not exclude SARS
ELISA antibody test	Test detecting a mixture of IgM and IgG antibodies in the serum of SARS patients yields positive results around day 21 after the onset of illness	Positive antibody test—indicates a previous infection with SARS-CoV. Seroconversion from negative to positive or a four-fold rise in antibody titer from acute to convalescent serum indicates recent infection
IFA antibody test	Test detecting IgM antibodies in serum of SARS patients yields positive results after about day 10 of illness. This test format is also used to test for IgG	Negative antibody test—no detection of antibody after 21 days from onset of illness seems to indicate that no infection with SARS-CoV took place
Cell culture	Inoculating cell cultures and growing the virus. Once isolated, the virus must be identified as the SARS virus with further tests. Cell culture is a very demanding test but currently only means to show the existence of a live virus	Positive—indicates the presence of live SARS-CoV in the sample tested Negative—does not exclude SARS

ELISA, enzyme-linked immunosorbent assay; Ig, immunoglobulin; IFA, immunofluorescence assay; SARS-CoV, SARS coronavirus.

Adapted from: Severe Acute Respiratory Syndrome (SARS): Laboratory diagnostic tests: 29 April 2003. Geneva: WHO, 2003 (accessed May 21, 2003, at *http://www.who.int/csr/sars/diagnostictests/en/*).

day 14. In this cohort in which diarrhea was common, the SARS coronavirus RNA was detected in stool samples by RT-PCR in 65/75 (97%) patients at day 14. As demonstrated by this observation, the sensitivity of RT-PCR is dependent on the type of specimen and the timing in relation to the duration of the disease. More research is necessary to better determine the sensitivity, specificity, and predictive values of these diagnostic tests, especially early in the disease process to help identify (or exclude) patients with SARS. Local public health laboratories should be consulted on the availability of these tests.

Clinical Findings

The incubation period for SARS ranges from 2 to 7 days but has been described to be as long as 14 days (7, 15). Six cohorts of adult SARS-affected patients were identified in the literature (2, 4–7, 14). The larger Canadian cohort by

Booth et al. (6) also included the ten patients reported by Poutanen et al (2). The development of SARS as described from the Canadian and Hong Kong cohorts revealed similar clinical features that were fairly nonspecific for the disease (Table 6). Universal to all cohorts was the presence of a fever of >38°C, which is part of the case definition. Other common symptoms included nonproductive cough, dyspnea, malaise, and myalgias. In a large cohort of 1,425 cases in Hong Kong, a similar pattern of symptoms was observed (15). The most common physical examination finding was the presence of inspiratory crackles.

The hematologic findings at the time of presentation varied. Mildly reduced to normal leukocyte counts occurred commonly. Lee et al. (4) reported finding increased neutrophil counts in some patients. Lymphopenia was common in all cohorts, which persisted during the hospital course (6, 14). Other common laboratory abnormalities included mild elevations in aspartate transaminase, alanine transaminase, lactic dehydrogenase, and creatine kinase. Booth et al. (6) also described electrolyte abnormalities in their cohort both at admission and during hospitalization.

Chest radiograph abnormalities were observed in most patients during the course of the disease. Typically, chest radiographs varied from unilateral focal airspace process to unilateral multifocal and bilateral multifocal airspace patterns. In general, in patients who had deterioration, the chest radiograph appearance progressed to diffuse bilateral infiltrates consistent with acute respiratory distress syndrome. Both Poutanen et al. (2) and Tsang et al. (7) reported predominately lower lung zone predominance. Lee et al. (4) described mainly peripheral predominance. In ten patients reported by Poutanen et al. (2), subtle interstitial patterns at presentation were described before progressing to a more diffuse airspace pattern. Pleural effusions were not seen in any of the cohorts. On chest computed tomography, peripheral airspace consolidation was observed, typically subpleural with surrounding ground glass opacification (4, 14, 16).

A case series of ten hospitalized pediatric patients described similar clinical features (17). All presented with a fever. Younger patients presented with milder symptoms compared with teenagers, who had symptoms similar to that of the adults. Lymphopenia and chest radiograph abnormalities were also a common finding during the course of the disease.

Pathology

Patients that had a lung biopsy or autopsy lung specimen (ranging from 8 to 24 days after the onset of illness) for examination revealed features of diffuse alveolar damage with varying degrees of severity (4, 7, 8, 18). In those with samples obtained early in the course of the illness (<10 days), there was evidence of edema, hyaline membrane formation, and pneumocyte proliferation. In addition, there were cellular "fibromyxoid" organizing exudates in the airspaces. There was also evidence of lymphocytic interstitial infiltrates (4, 7, 8). Although there was no clear evidence of direct viral involvement, such as viral inclusion bodies, multinucleated and vacuolated pneumocytes were observed (4, 8, 18). The significance of this finding is unknown.

Management

Patients with significant hypoxemic respiratory failure were managed in the ICU. A progressive regimen of oxygen (nasal cannula to high-flow masks) and intubation and ventilation was instituted for severe acute hypoxemic respiratory failure. A description for ventilation management was only reported by Poutanen et al. (2) for two of the patients who died. Both patients had high F_{IO_2} requirements and low Pa_{O_2}/F_{IO_2} ratios. The tidal volumes ranged from 500 to 750 mL. PEEP requirements ranged from 5 to 15 cm H_2O. Peak inspiratory pressures observed between both patients ranged from 17 to 42 cm H_2O but were reported to be below 35 cm H_2O for the majority of the time.

Given the unknown cause of the disease process in SARS and the severity of the illness, all cases described were treated empirically with broad-spectrum antibiotics. With the hypothesis that this disease is virally mediated, most were also given combinations of ribavirin, oseltamivir, and corticosteroids.

Soon after a local outbreak of SARS within a hospital setting in Hong Kong, Lee et al. (4) used combinations of cefotaxime and clarithromycin (or levofloxacin) for coverage for a community-acquired pneumonia, plus oseltamivir for possible influenza. If the fever persisted for >48 hrs, oral ribavirin (1.2 g three times a day) and corticosteroids (prednisolone, 1 mg/kg once daily) were added. For those with worsening symptoms, the ribavirin was given intravenously (400 mg every 8 hrs), along with pulse corticosteroids (prednisolone, 0.5 g intravenously (IV) once daily for 2–3 days).

Tsang et al. (7) used a combination of β-lactam and macrolide antibiotics initially. Because no improvement was noted in their patients with antibiotics, ribavirin (8 mg/kg IV every 8 hrs or 1.2 g by mouth every 8 hrs) and corticosteroids (hydrocortisone, 4 mg/kg IV every 8 hrs, tapering to 200 mg IV every 8 hrs, or methylprednisolone, 240–320 mg IV once daily) were added after 4 days.

Peiris and colleagues (5), also in Hong Kong, used various combinations of antibiotics along with ribavirin and corticosteroids, empirically similar to that of Tsang et al (7).

In the Canadian cohort as described by Booth et al. (6), almost all the patients received empiric antibiotic coverage. Corticosteroids were used in 40%, but at lower doses compared with the other cohorts (hydrocortisone, 20–50 mg/day). Ribavirin was used in 88% of the patients at higher doses than the other cohorts (loading dose of 2 g, then 1 g every 6 hrs for 4 days, then 500 mg every 8 hrs for 4–6 days). Oral oseltamivir was also used early in the outbreak but was quickly stopped after it was determined that influenza was not involved. The use of ribavirin was associated with toxicity in many patients. A significant drop in hemoglobin was observed in 49% of the patients using ribavirin, of which 76% of these patients had evidence of hemolysis. Elevations in aspartate transaminase and alanine transaminase were observed in 40% of patients receiving ribavirin.

The efficacy of ribavirin and corticosteroids is unknown. Anecdotal evidence suggests that there may be a benefit with corticosteroid use. Preliminary *in vitro* testing suggests that ribavirin is ineffective against the SARS coronavirus (19). Further research is required to determine the effect of ribavirin on outcomes in patients with confirmed SARS.

Outcomes

The overall worldwide case fatality rate is approximately 10.5%. Given that the SARS epidemic is ongoing, the true case fatality rate may likely be higher as cases determined not to be SARS are excluded and the outcomes of hospitalized patients are known. For example, if it is true that only 23% of suspected cases

Table 6. Summary of Clinical and Pathologic Features

Cohort	Booth et al. (6) (Toronto)		Tsang et al. (7) (Hong Kong)		Lee et al. (4) (Hong Kong)		Peiris et al. (5) (Hong Kong)		Peiris et al. (14) (Hong Kong)	
No. of Patients	144 Hospitalized		10 Hospitalized		138 Hospitalized		50 Hospitalized		75 Hospitalized	
Age	Median	45	Median	53.5	Mean	39.3	Median	42	Mean	39.8
	Interquartile range	34–57	Range	37–72	SD	16.8	Range	23–74	SD	12.2
Male:female	1:1.6		1:1		1:1.1		1:1.3		1:0.92	
Clinical features, %	Fever	99	Fever	100	Fever	100	Fever	100	Fever	100
	Cough	69	Rigors	90	Rigors	73	Rigors	74	Myalgias	68
	Myalgias	49	Cough	80	Myalgias	60	Cough	62	Chills	65
	Dyspnea	42	Malaise	70	Cough	60	Myalgias	54	Rigors	56
	Headache	35	Headache	70	Headache	55	Malaise	50	Cough	29
	Malaise	31	Dyspnea	60	Sore throat	23	Coryza	24	Headache	15
	Chills	28	Myalgias	50	Coryza	23	Sore throat	20	Sore throat	11
	Diarrhea	24	Pleurisy	30	Nausea	20	Dyspnea	20	Dyspnea	4
	Vomiting	19	Rhinnorrhea	10	Vomiting	20	Headache	20	Diarrhea	1
	Sore throat	13			Diarrhea	20	Anorexia	20		
	Arthralgia	10					Diarrhea	10		
	Chest Pain	10								
	Rhinorrhea	2								
	Inspiratory crackles	26	Inspiratory crackles	90			Inspiratory crackles	38		
Laboratory findings, %	Lymphopenia	85	Leukopenia	20	Leukopenia	34	Leukopenia	26	Leukopenia	7
			Lymphopenia	70	Lymphopenia	70	Lymphopenia	68	Lymphopenia	75
			↓ Platelets	20	↓ Platelets	44	↓ Platelets	40	↓ Platelets	37
			Anemia	40			Anemia	18	Anemia	8
	↑ LDH	87	↑ AST	86	↑ LDH	71	↑ ALT	34	↑ AST	29
	↑ CK	39	↑ ALT	40	↑ ALT	23	↑ CK	26	↑ ALT	32
					↑ CK	32	↓ Albumin	68	↑ CK	36
Chest radiograph at presentation, %	Abnormal	75	Abnormal	90	Abnormal	78	Abnormal	100	Abnormal	71
	Bilateral infiltrate	29	Bilateral airspace	30	Unilateral focal airspace	54	Focal infiltrate	72	Bilateral infiltrate	21
	Unilateral infiltrate	46	Focal consolidation	20	Unilateral or bilateral multifocal	46	Multifocal infiltrate	26	Unilateral infiltrate	49
			Patchy consolidation	30			Diffuse	2		
Additional features	Lower lung predominance (Poutanen et al.)		Lower lung predominance		Peripheral pattern				Lower lung predominance	60
CT chest			Subpleural focal consolidation with areas of ground glass		Subpleural/peripheral consolidation with adjacent areas of ground glass				Varied between ground-glass and consolidation	
Histopathology	Diffuse alveolar damage (Poutanen et al.)		Diffuse alveolar damage		Diffuse alveolar damage		Interstitial inflammation			
					Vacuolated and multinucleated pneumocytes		Scattered alveolar pneumocytes with cytomegaly			
	No viral cytopathic effects		No viral inclusions		No viral inclusions		No viral inclusions			

have coronavirus-related SARS as reported by Drosten et al. (9), this observation will influence the mortality rate for SARS in Canada. Taking 251 probable cases and 44 suspected cases that may truly have SARS, it is possible that the crude mortality rate is 38/295 (12.9%).

The mortality rate between the reported cohorts varied (Table 7). In the Canadian cohort, 20% required admission to the ICU, with most requiring mechanical ventilation (6). The overall mortality rate was 5.5%. The ICU mortality rate was much higher, 35%. In a multivariate analysis, the presence of diabetes or other comorbid diseases was associated with an increased risk for developing a poor outcome (ICU admission or death) (Table 8). Age older than 60 yrs showed a moderate association but was not statistically significant.

In the Tsang et al. (7) cohort of ten patients, three of the ten patients required admission to the ICU. Two patients died, giving an overall mortality rate of 20% and an ICU mortality rate of 67%. Unlike the Canadian cohort, none of the patients had significant comorbidities.

In the first cohort reported by Peiris et al. (5), 19 of 50 (38%) patients required ICU admission. All ICU patients required mechanical ventilation. Lower than the other cohorts, there was only a 2% overall mortality rate but a 5% ICU-related mortality rate.

In the second cohort described by Peiris et al. (14) of an outbreak of SARS in an apartment complex, 24 of 75 (32%) of those hospitalized required ICU admission, with 15 (63%) ICU patients requiring mechanical ventilation for ARDS. The overall mortality rate was 7%, with an

Table 7. Adult Patients Requiring Intensive Care Unit (ICU) Admission and Mechanical Ventilatory Support

Cohort	No. of Patients	ICU Admission		Mechanical Ventilation		ICU Mortality	
		No.	%	No.	% of ICU	No.	%
Booth et al. (6)	144	29	20	20	69	7[a]	35
Tsang et al. (7)	10	3	30	3	100	2	67
Peiris et al. (5)	50	19	38	19	100	1	5
Peiris et al. (14)	75	24	32	15	63	5	21
Lee et al. (4)	138	32	23	19	59	5	16
Total	417	107	26	76	71	20	19

[a]One patient died at home without entering the ICU.

Table 8. Factors Influencing a Poor Outcome

Booth et al. (6) (Toronto)	Tsang et al. (7) (Hong Kong)	Lee et al. (4) (Hong Kong)	Peiris et al. (5) (Hong Kong)	Peiris et al. (14) (Hong Kong)
Univariate analysis Increased age Male sex Increased neutrophil count Increased CK Increase urea Hyponatremia Multivariate analysis Diabetes Other comorbid diseases	No significant factors found	Multivariate analysis Advanced age Increased LDH Increased neutrophil count	Increased age Severity of lymphopenia Increase in ALT Delay in starting ribavirin and corticosteroids after deterioration	Univariate analysis Increased age Male sex Chronic hepatitis B carriage Increased creatinine Recurrence of fever Multivariate analysis Increased age Recurrence of fever

CK, creatine kinase; LDH, lactic dehydrogenase; ALT, alanine transaminase; HBsAg, hepatitis B surface antigen.

ICU mortality rate of 21%. All five patients died between 13 and 25 days after the onset of their illness. Only two factors, age >60 yrs and hepatitis B surface antigen positive, were independent predictors for the development of ARDS.

Finally, in the cohort of Lee et al. (4) in Hong Kong, 32 of 138 (23%) patients required ICU admission for respiratory failure, of which 19 patients required mechanical ventilator support (59% of those requiring ICU admission). The overall mortality was 3.6%, and the ICU mortality rate was 15.6%. Of the five patients who died, all had comorbidities ranging from myleodysplastic syndrome, congestive heart failure, and liver disease. In a multivariate analysis, only increased age, increased lactic dehydrogenase, and increased neutrophil count at admission were independent predictors of adverse outcomes and/or death.

Pooling the results among the five cohorts, the overall mortality is 4.8%. A total of 76 patients required mechanical ventilation in the ICU for severe hypoxemic respiratory failure. This gives a mortality rate of 26% for mechanically ventilated patients, lower than the 31% reported by the ARDS Network low tidal ventilation trial (20). However, it should be noted that the mortality rate for mechanically ventilated patients in the five cohorts ranged from 5% to 67%. Additional studies are required to provide a more accurate estimate of ICU outcomes related to SARS.

Variability in Outcome

The differences in mortality rates observed between the cohorts may be due to many factors that can influence outcome. Cohorts with a younger age have a lower mortality rate. In the cohort of Lee et al. (4), the mix of suspected and probable cases may be a factor influencing the outcome observed. Length of follow-up in each cohort varies, which also greatly influences the mortality rates reported.

The epidemiology and clinical features identified thus far describe a spectrum of SARS ranging from mild disease to respiratory failure and death. Risk factors identified from limited epidemiologic studies for poor outcomes and death include older age, the presence of diabetes or other comorbidities, and neutrophilia and increased lactic dehydrogenase at presentation (Table 7). Estimated case fatality rates from 1,425 patients with SARS in Hong Kong varied significantly with age (15). The estimated case fatality rate was 6.8% for those <60 yrs of age and 55% for those >60 yrs of age. This is also supported by examining the distribution of the age of those reported to have died from SARS in Canada (Fig. 1). Most patients were in their 70s and had coexisting illnesses.

Many close contacts of SARS patients with probable SARS either do not develop the disease or have an attenuated form of SARS. In the original Toronto report of SARS in a family, nonrelated family members in close contact with cases did not develop the disease (2). In the Hong Kong cohort, the wife of a patient who developed SARS had the same exposure as her husband (in a hotel) but did not develop the disease (8). However, young, otherwise healthy patients have also died of SARS. We suggest that variations in the host immune response to an infection, which is known to be governed by genetic variability, influences the outcome (21, 22). The combination of the intensity of exposure to the virus, the virulence, and patient-related factors including genetic susceptibility likely influence the outcome of an individual who is infected with the SARS-related pathogen.

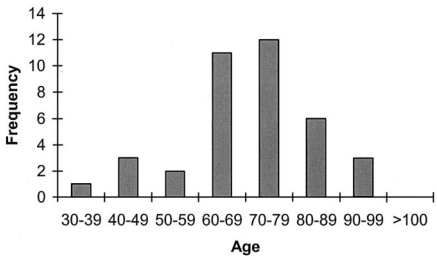

Figure 1. Distribution of severe acute respiratory distress syndrome deaths in Canada by age, as of June 26, 2003. Source: http://www.health.gov.on.ca/

Recommendations for Management of SARS Patients in the ICU

Recognizing the limited information currently available in the literature about this disease, important features of SARS that have been observed thus far can be used to guide critical care physicians, nurses, and other healthcare workers to care for SARS patients.

1. In the absence of a well-validated diagnostic test, a low clinical threshold is required to identify potential SARS patients as per the surveillance criteria of the WHO and the CDC. Web sites for these organizations and other public health Web sites for the respective local regions should be monitored frequently for any updates in the diag-

The critical care management of SARS should focus on providing adequate oxygen and ventilatory support similar to patients with acute respiratory distress syndrome, along with general intensive care unit support.

nosis, classification, and management of SARS patients.

2. Strict isolation and contact precautions must be taken when managing a patient with SARS. This includes isolation of suspected patients in (in order of preference) negative pressure rooms, single rooms, or an area with an independent air supply/exhaust system. Personal protective equipment for contact precautions include disposable gowns, gloves, eye protection, and appropriate respiratory protection using NIOSH-certified disposable respirators, with a filtering efficiency of at least 95% (N95, N99, or N100 masks). However, even in this setting, it should be recognized that the risk of transmission still exists (23). Healthcare workers should be trained in the use and the proper removal of personal protective equipment. Contact with SARS-affected patients should be limited to the fewest number of healthcare workers to maintain appropriate patient care. Each healthcare facility with the potential of managing a SARS patient should have a strategic plan to implement these procedures. Examples of an approach to the development of such a plan can be found at the Ontario Medical Association Web site: http://www.oma.org/phealth/sars.htm. For the most recent guidelines on infection control procedures, consult the CDC (http://www.cdc.gov/ncidod/sars/) and the WHO (http://www.who.int/csr/sars/en/) Web sites.
3. Investigations should be performed to eliminate other possible causes that mimic SARS. In coordination with local microbiology or public health laboratories, samples such as nasopharyngeal aspirates, bronchial lavage/tracheal aspirates, stool samples, and blood samples for acute and convalescent sera should be obtained to be used for emerging diagnostic tests and research purposes.
4. High-risk procedures in the ICU such as nebulization, noninvasive positive pressure ventilation (e.g., BiPAP), high-frequency oscillatory ventilation, and bronchoscopy should be minimized and avoided if possible. If bronchoscopy or intubation is required, powered air purification respirator hoods should be used. In addition, adequate sedation is necessary. Paralysis to reduce coughing during the procedure should be considered. Additional recommendations for precautions in the ICU are available at: http://www.oma.org/phealth/sars/june17/DIRECTIVEhighriskproceduresAcuteCareJune16.pdf (24) and in a recent review on ICU management of SARS patients (25).
5. SARS patients in the ICU requiring mechanical ventilation should be managed with ventilatory strategies similar to that of the ARDS Network low-tidal volume strategy (20). Severe hypoxemic respiratory failure associated with the SARS-related pathogen is a form of acute lung injury/acute respiratory distress syndrome, both clinically and pathologically.
6. It is difficult to determine at this time whether the addition of antivirals such as ribavirin or the use of corticosteroids influences outcome. The current practice includes the empiric use of ribavirin in the dose ranges as described above, although *in vitro* data suggest it may not be effective. Ribavirin is also associated with significant adverse effects. Oseltamivir is not recommended. Corticosteroids can be considered, using the dose ranges as described above. All patients should be covered with broad-spectrum antibiotics based on current guidelines for the management of community-acquired pneumonia until the results of bacterial cultures of initial respiratory samples are available (26, 27).

CONCLUSIONS

SARS appears to be a highly contagious, rapidly spreading viral respiratory infection caused by a new coronavirus not previously seen. Clinical features range from mild to severe acute hypoxemic respiratory failure, to death. Diagnostic tests including RT-PCR and antibody sera are emerging but await further testing. The critical care management of SARS should focus on providing adequate oxygen and ventilatory support similar to patients with acute respiratory distress syndrome, along with general ICU support. The use of ribavirin and corticosteroids is common but not yet based on evidence of efficacy in SARS. Adherence to strict isolation and contact protocols for infection control is essential in the critical care setting where there is a high risk for transmission. The risk factors for poor outcome include increased age, the presence of comorbidities, and perhaps genetic susceptibility to infection of the human host.

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