72. Pediatric and Adult SARS

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Outline

INTRODUCTION

Severe acute respiratory syndrome (SARS) is an often fatal infectious respiratory disease with prominent systemic symptoms. It is caused by a novel coronavirus, SARS coronavirus (SARS-CoV), which was responsible for a global outbreak from November 2002 to July 2003. SARS-CoV probably has its origin in Southern China and is a zoonosis that initially affected wild animals, possibly bats, and subsequently spread to exotic animals. The virus can be identified by reverse transcriptase polymerase chain reaction (RT-PCR) in blood, plasma, respiratory secretions, and stool. Specific antibody is detected in acute and convalescent sera from patients by indirect fluorescent antibody (IFA) testing and enzyme-linked immunosorbent assay (ELISA) targeting the surface spike (S) protein.

EPIDEMIOLOGY

During the 2002–2003 SARS outbreak, a cumulative total of 8096 probable cases, with 774 deaths, were reported from 29 countries and areas. A global case-fatality rate of 9.6% was recorded at the end of the outbreak. The total number of health care workers affected was 1706 (21.1% of all probable cases). Interestingly, the severity of the syndrome appears to have been greater in adults and adolescents than in young children. No mortality was reported in children worldwide.

The incubation period of SARS generally ranged from 2 to 10 days. The primary mode of transmission appears to be direct mucous membrane (eyes, nose, and mouth) contact with infectious respiratory droplets and/or through exposure to fomites. The majority of SARS cases had a history of direct contact with another SARS case, though transmission rates were low in the community and screening for SARS-CoV antibodies in asymptomatic direct contacts showed near zero positive rates. Subclinical infection was rare even among health care workers. Nosocomial and household contacts were most common. Transmission to casual and social contacts occurred only occasionally in cases of intense exposure to an index case (in workplaces, airplanes, or taxis) or in high-risk transmission settings, such as health care institutions and patients' homes. Children with SARS are apparently less infectious than their adult counterparts.

Risk Factors for SARS

Risk factors for SARS include:

- health care workers, especially those involved in aerosol-generating procedures
- household contact with a probable case of SARS
- increasing age
- male sex
- presence of comorbidities
- environmental contamination

CLINICAL FEATURES

Most patients infected with SARS-CoV present with sudden onset of fever, though there are cases with distinct presentations, especially among the elderly. Symptoms such as malaise, chills, myalgia, headache, and cough are common in affected adults and children (Tables 72.1 and 72.2), though cough and sputum production may be absent even with radiographic evidence of pulmonary involvement. Upper respiratory symptoms of coryza and sore throat are present in about 25% of adult patients and 40% of children. In more advanced cases, patients may present with dyspnea and/or tachypnea.

Nausea, vomiting, and diarrhea are the main gastrointestinal symptoms of SARS. Diarrhea is common during the course of illness and is reported in 38–73% of adult patients, but it is more frequent in the first week. In studies on pathologic intestinal specimens, light microscopy findings were unremarkable with minimal inflammatory changes. Electron microscopy showed virus particles in the endoplasmic reticulum and on the luminal surface of microvilli, suggesting viral shedding into the gut lumen. Diarrhea is thus a significant infection control problem.

Involvement of most organ systems has been reported with SARS-CoV infection. Reactive hepatitis is a common complication, and patients with associated severe hepatitis had

Table 72.1 Clinical Features: SARS

Organism	SARS coronavirus (SARS-CoV)
Incubation Period	2–10 days (range 1–14 days, mean 4–6 days, median 4–5 days)
Signs and Symptoms	• Fever • Malaise, chills, myalgia, headache, and dizziness • Cough, coryza (in children), sore throat, and shortness of breath • Nausea, vomiting, and diarrhea
Laboratory and Radiologic Findings	• CXR: airspace opacification in the lower zones and periphery of lungs • HRCT findings: ground glass infiltration with or without consolidation, with septal and interstitial thickening • Lymphopenia, thrombocytopenia, prolonged aPTT, and elevated ALT and D-dimer levels • As disease progresses – elevation of CK and LDH levels occur

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; CK, creatine kinase; CXR, chest x-ray; HRCT, high-resolution computed tomography; LDH, lactate dehydrogenase.

Table 72.2 Presenting Clinical Features of SARS in Adults and Children

	Adult Series		Pediatric Series (Combined)
	Donnelly et al. (2003)	**Booth et al. (2003)**	**Leung et al. (2004) and Chiu et al. (2003)**
Number of patients	1425	144	64
Fever (%)	94	99	97
Chills (%)	65	28	33
Malaise (%)	64	NR	56
Myalgia (%)	51	49	28
Headache (%)	50	35	28
Dizziness (%)	31	NR	19
Sore throat (%)	23	13	11
Coryza (%)	25	2	41
Cough (%)	50	69	56
Sputum production (%)	28	5	30
Shortness of breath (%)	31	NR	9
Nausea with or without vomiting (%)	22	NR	20
Diarrhea (%)	27	24	17

NR, not reported.

worse clinical outcome. Subclinical diastolic cardiac dysfunction without systolic impairment has been reported in SARS patients and was reversible in those who recovered. There is one case report of generalized seizures in a pregnant woman with SARS whose cerebrospinal fluid (CSF) was positive for SARS-CoV antibody by RT-PCR.

Acute renal impairment, uncommon in SARS infection, is likely related to multiorgan failure rather than representing renal tropism of the virus. Not surprisingly, the development of acute renal impairment is a poor prognostic indicator.

PATHOGENESIS

The primary site of attack by SARS-CoV is the respiratory tract but other organs are also seeded by early viremia. Thus, SARS is a systemic disease with extrapulmonary dissemination. The tissue tropism of SARS-CoV includes the lungs, gastrointestinal tract, liver, spleen, lymph nodes, pancreas, heart, kidneys, adrenals, skeletal muscles, sweat glands, parathyroid glands, pituitary gland, and cerebrum. Viral shedding occurs in respiratory secretions, stool, urine, and possibly sweat. The tissue and organ damage is likely the result of both viral replication and host inflammatory response.

The natural history of untreated SARS in both adults and children remains unclear. SARS is probably a triphasic disease in adults. The first week of illness (viral replication phase) is characterized by fever, myalgia, and other prodromal systemic symptoms that generally improve after a few days. In the second week, the immune system attacks the virus and infected cells, releasing inflammatory cells and mediators. This immune hyperactive phase is characterized by recrudescence of fever, increasing respiratory symptoms and lung consolidation, and the development of respiratory failure and acute respiratory distress syndrome (ARDS) in many adult patients. The final pulmonary damage phase is associated with varying degrees of residual lung injury in survivors (Figure 72.1).

In children, SARS is milder and follows a biphasic pattern. The separation of prodromal and pneumonic phases of the disease may be less distinct in comparison with adults.

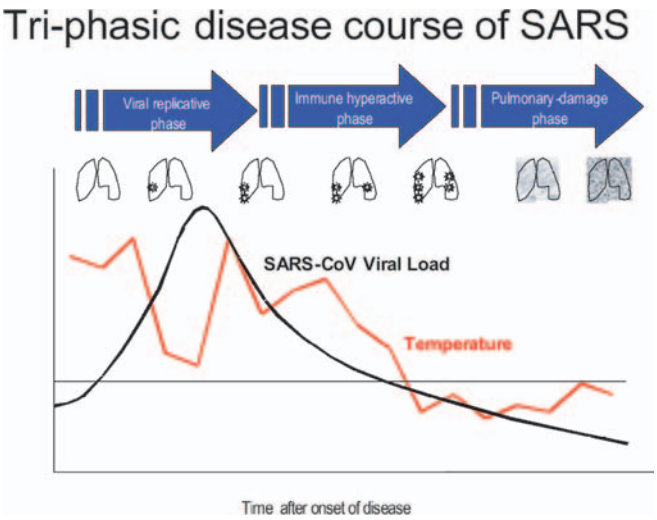


Figure 72.1 Clinical phases of SARS in adult patients. From Sung JY, Yuen KY. Clinical presentation of the disease in adults. In: Peiris M, Anderson L, Osterhaus AD, et al., eds, Severe acute respiratory syndrome. Oxford, UK: Blackwell, 2005.

Progression to ARDS is only seen in a very small number of pediatric patients, predominantly adolescents.

DIFFERENTIAL DIAGNOSIS

Early disease mimics influenza and other respiratory infections. Thus, the differential diagnosis includes most causes of community-acquired pneumonia or upper respiratory tract infections. These include:

- Acute bacterial pneumonia
- Acute viral respiratory infections:
  - influenza A virus (including avian influenza H5, H7, and H9)
  - influenza B virus
  - parainfluenza viruses 1, 2, 3, and 4
  - respiratory syncytial virus
  - adenoviruses
  - human metapneumovirus
- Community-acquired pneumonia caused by atypical respiratory pathogens:
  - *Chlamydophilae (*formerly *Chlamydia) pneumoniae*
  - *Chlamydophilae psittaci*
  - *Mycoplasma pneumoniae*
  - *Legionella pneumophila*

Key features that may help to distinguish SARS from other causes of pneumonia are:

- History of close contact with a patient with suspected or confirmed SARS
- Failure of clinical response after 48 hours of empiric broad-spectrum antibiotic therapy for presumed community-acquired pneumonia

LABORATORY AND RADIOGRAPHIC FINDINGS

Most SARS patients had normal or low leukocyte counts and lymphopenia at the time of presentation (Table 72.3), and lymphopenia may persist during the course of disease. Thrombocytopenia is also a common presenting feature. Prolonged activated partial thromboplastin time (aPTT) and elevated D-dimer levels were documented in one report, but were not accompanied by clinically significant bleeding.

Of adult and pediatric SARS patients, 23–35% and 10–16%, respectively, have elevated alanine aminotransferase (ALT) levels at presentation. Moreover, 76% and 24–48% of adult and pediatric patients, respectively, developed liver dysfunction during the course of illness. The peak ALT or bilirubin levels correlated with pathologic chest radiographic findings.

Elevation of creatine kinase and lactate dehydrogenase levels may occur and persist with disease progression. Three cases of acute rhabdomyolysis associated with probable SARS have been reported in adults.

The predominant chest radiographic finding is airspace opacification in the lower zones and in the periphery of the lungs (Figure 72.2). Chest radiography is the primary tool for diagnosis and for follow-up of pulmonary disease progression and response to therapy. When the initial chest radiograph is negative and clinical suspicion persists, high-resolution computed tomography (HRCT) may aid early diagnosis (Figure 72.3). Common HRCT findings include ground-glass opacification with or without consolidation, and interlobular, septal and intralobular interstitial thickening (Figure 72.4).

Although the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) have promulgated clinical case definitions for SARS, final diagnosis of the disease requires laboratory confirmation. A confirmed case of SARS is a person who has a clinically compatible disease (i.e., fever with constitutional symptoms *and/or* lower respiratory symptoms *plus* an epidemiologic link) that is laboratory confirmed.

Rapid laboratory diagnosis can be accomplished by detecting the virus, viral antigens, or viral nucleic acid in respiratory secretions, blood, plasma, or stool specimens obtained during the acute illness. The most sensitive rapid diagnostic test is the real-time quantitative RT-PCR assay of either plasma or respiratory secretions (e.g., nasopharyngeal aspirate) obtained

Table 72.3 Key Laboratory Findings of SARS in Adults and Children at Presentation

	Adult Series					Pediatric Series	
	Choi et al. (2003)	Booth et al. (2003)	Lee et al. (2003)	Peiris et al. (2003)	Vu et al. (2004)	Leung et al. (2004)	Chiu et al. (2003)
Number of patients	267	144	138	75	62	44	21
Leukopenia (%)	27	NR	34	7	19	34	24
Lymphopenia (%)	73	85	70	75	79	77	57
Thrombocytopenia (%)	50	NR	45	37	40	27	24
Hyponatremia (%)	NR	NR	20	NR	30	NR	NR
Elevated ALT (%)	31	NR	23	29	35	16	10
Elevated CK (%)	19	39	32	36	NR	7	NR
Elevated LDH (%)	47	87	71	NR	NR	55	NR

ALT, alanine aminotransferase; CK, creatine kinase; LDH, lactate dehydrogenase; NR, not reported.

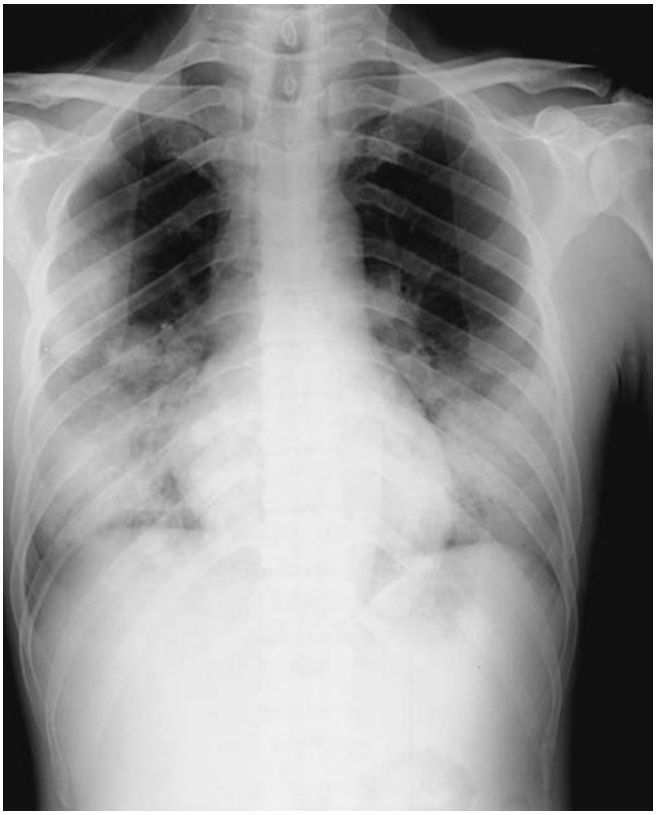
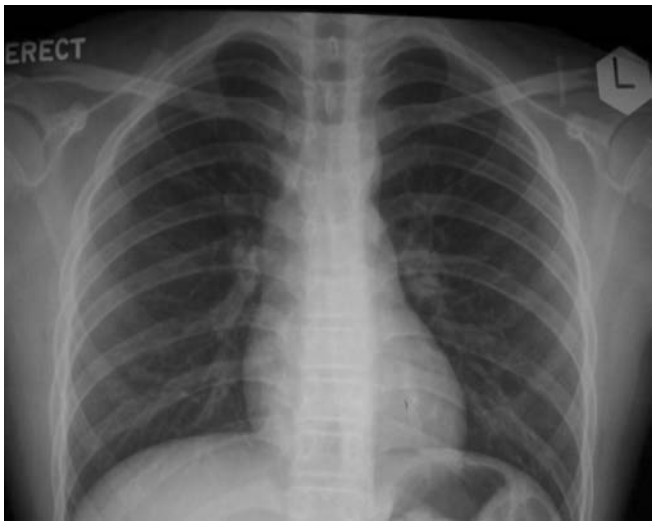


Figure 72.2 Chest radiograph showing bilateral multifocal consolidation in both lower zones.



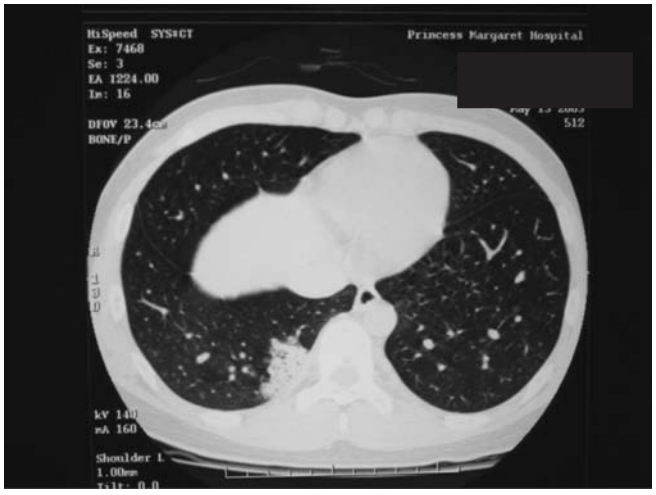


Figure 72.3 High-resolution computed tomography of thorax showing peripheral, subpleural, focal consolidation of the right lower lobe that was not evident on the admission chest radiograph.

during the first week of illness. When performed in the first 3 days of illness on nasopharyngeal aspirate, the preferred specimen, the sensitivity of RT-PCR approaches 80% and the specificity 100%. The overall diagnostic yield can be further improved to over 80% in the second week of illness when stool specimens are also examined. In the United States, the test is available from the CDC and related public health facilities, and research laboratories.

The gold standard of laboratory diagnosis is a rise in SARS-CoV specific antibody titer during illness. A negative antibody test on acute serum followed by positive antibody test on convalescent serum *or* a fourfold or greater rise in antibody titer between acute and convalescent phase sera tested in parallel is confirmatory. Seroconversion is documented by IFA or ELISA assay, and the absence of SARS-CoV specific IgG beyond 28 days from onset of symptoms practically excludes the diagnosis.

Isolation of SARS-CoV from specimens inoculated in appropriate cell cultures is hazardous, technically demanding, and limited by low sensitivity. The requirement for Biosafety Level 3 (infectious agents that may cause serious or potentially lethal diseases as a result of exposure by the inhalation route) containment precludes its application for routine clinical practice.

TREATMENT

The best treatment strategy for SARS is still unknown. Current recommendations include both anti-viral therapy and immunomodulatory agents to combat the abnormal inflammatory response (Table 72.4), though there is concern that immunomodulation could compromise viral clearance by the host immune system. Listed below are suggested treatment regimens based on small numbers of patients. Patients and physicians should be advised that no randomized controlled studies have been performed with these agents. All regimens should include coverage for severe bacterial community-acquired pneumonia. Supportive care such as assisted ventilation is commonly required.

Antivirals

Because SARS-CoV triggers a vigorous immune response, the best approach is to halt the early viral replication to diminish the peak viral load, tissue spread, and ensuing immunopathologic damage.

Ribavirin was chosen for use empirically in the initial outbreak because of its broad-spectrum antiviral coverage. The use of ribavirin has generated considerable criticism because of its relative lack of in vitro activity against the SARS-CoV and its association with a number of adverse effects such as hemolytic anemia, bradycardia, elevated serum aminotransferase levels, and teratogenic effects. Limited studies in adult

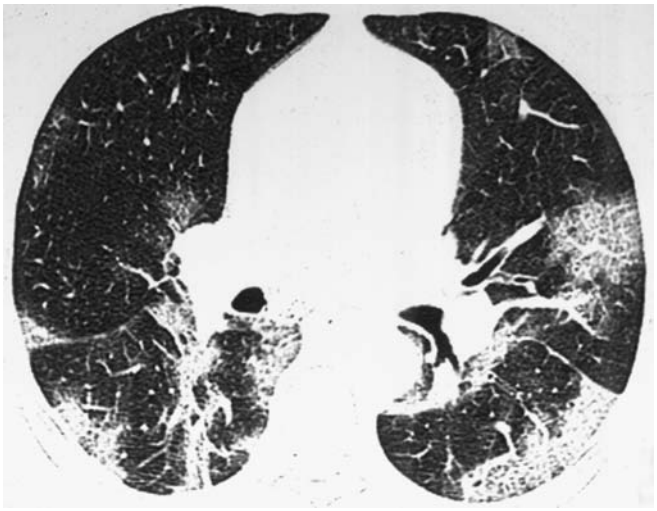


Figure 72.4 High-resolution computed tomography of thorax showing ground-glass opacification of the basal segments of both lower lobes.

patients suggest that Kaletra (a mixed formulation of the protease inhibitors lopinavir and ritonavir), in combination with ribavirin, reduces the intubation and overall death rates and improves the clinical, biochemical, virologic, and radiographic parameters.

The suggested regimen for adults is:

1. Ribavirin: 2.4 g oral loading followed by 1.2 g bid orally for a total of 10 days
2. Kaletra: 3 tablets bid orally (each tablet containing 400 mg of lopinavir and 100 mg of ritonavir) for a total of 10 days

Corticosteroids

It is hypothesized that the tissue damage during SARS is caused by the exaggerated systemic inflammation or cytokine storm during the second immunopathological phase of SARS. *Corticosteroids should not be used in the early stage of SARS because they may compromise viral clearance*. They should only be considered if there is evidence of acute lung injury, defined by a PaO_2/FiO_2 ratio of 200–300 mm Hg (26.7–40.1 kPa) plus worsening chest radiographic findings not due to heart failure or other causes.

The suggested regimen for adults is:

1. Start with methylprednisolone 1 mg/kg q8h intravenously (IV) for 5 days, then 1 mg/kg q12h IV for 5 days, then prednisolone 0.5 mg/kg bid orally for 5 days, then 0.5 mg/kg qd orally for 3 days, then 0.25 mg/kg qd orally for 3 days.
2. In patients suffering from "critical SARS" defined as a PaO_2/FiO_2 ratio of less than 200 mmHg (<26.7 kPa) and progressive chest radiographic deterioration, the use of pulse corticosteroid and choice of regimen is at the discretion of the clinician. The suggested dosage for pulse corticosteroid therapy is methylprednisolone at 0.5 g per day IV for 3 days, followed by a tapering course starting at 3 mg/kg/day. The cumulative dose of methylprednisolone should preferably not exceed 2 g.

Table 72.4 Treatment*

Standard Treatment for Severe Community-Acquired Pneumonia	• Broad-spectrum antibiotics (third- or fourth-generation cephalosporin plus macrolide) if not penicillin allergic (e.g., cefotaxime plus erythromycin or clarithromycin at standard dosages for adults and children) • Antipneumococcal quinolones for penicillin-allergic patients (e.g., levofloxacin at standard dosages) • General supportive care
Antiviral Treament Against SARS-CoV	Suggested regimen for adults: • Dosage of ribavirin: 2.4 g oral loading followed by 1.2 g bid orally for a total of 10 days • Dosage of Kaletra: 3 tablets bid orally (each tablet containing 400 mg of lopinavir and 100 mg of ritonavir) for a total of 10 days
Corticosteroids	Suggested regimen for adults: • Start with methylprednisolone 1 mg/kg q8h IV for 5 days, then 1 mg/kg q12h IV for 5 days, then prednisolone 0.5 mg/kg bid orally for 5 days, then 0.5 mg/kg qd orally for 3 days, then 0.25 mg/kg qd orally for 3 days • In patients suffering from "critical SARS" defined as a PaO_2/FiO_2 ratio of <200 mm Hg (<26.7 kPa) and progressive chest radiographic deterioration, the use of pulse corticosteroid and choice of regimen is at the discretion of the clinician. The suggested dosage for pulse corticosteroid therapy is methylprednisolone at 0.5 g per day IV for 3 days, followed by a tapering course starting at 3 mg/kg/day. The cumulative dose of MP should preferably not exceed 2 g.
Immunoglobulin	Salvage therapy

*The best treatment strategy for SARS is still unknown.

Convalescent Plasma

Convalescent plasma, obtained from patients who recovered from SARS, was used as salvage therapy in patients who deteriorated irrevocably during the SARS outbreak despite pulse methylprednisolone. Preliminary data suggest that its use may be associated with a shorter hospital stay and lower mortality but the clinical efficacy remains to be confirmed.

Immunoglobulin

Another form of salvage therapy that may be considered for patients who have a deteriorating course is intravenous immunoglobulin (IVIG). However, the use of IVIG must be balanced against the risk of hemolytic anemia and venous thrombosis.

Noninvasive Positive Pressure Ventilation

There have been anecdotal reports of the efficacy of noninvasive positive pressure ventilation (NIPPV) such as bilevel positive airway pressure (BiPAP) and continuous positive

Table 72.5 Clinical Outcome and Prognostic Factors in Adult SARS Patients

Study	Number of Patients	Median or Mean (SD) Age	Case Fatality Rate (%)	ICU Care (%)	Assisted Ventilation (%)	Adverse Outcomes	Clinical Correlates of Adverse Outcomes	Odds Ratio or Relative Risk (95% CI)
Tsui et al. (2003)	323	41 (14)	NR	21	13	Death or ICU care	Age (per 10-year increase) Admission neutrophil count (per 1×10^9/L increase) Initial LDH level (per 100 international units/L increase)	1.57 (1.26–1.95) 1.28 (1.13–1.46) 1.35 (1.11–1.64)
Choi et al. (2003)	267	39	12 (3 months)	26	21	Death	Age >60 LDH > 3.8 μkat/L at presentation	5.1 (2.3–11.31) 2.2 (1.03–4.71)
Booth et al. (2003)	144	45	6.5 (21 days)	20	13.9	Death, ICU care, or assisted ventilation	Diabetes mellitus Other comorbid conditions	3.1 (1.4–7.2) 2.5 (1.1–5.8)
Lee et al. (2003)	138	39 (16.8)	3.6 (21 days)	23.2	13.8	Death or ICU care	Advanced age (per 10-year increase) High absolute neutrophil count at presentation High peak LDH level	1.8 (1.16–2.81) 1.6 (1.03–2.5) 2.09 (1.28–3.42)
Chan et al. (2003)	115	41 (14.8)	10 (21 days)	34	26	Death	Age >60 Diabetes mellitus or heart disease Another coexisting condition	3.5 (1.2–10.2) 9.1 (2.8–29.1) 5.2 (1.4–19.7)
Peiris et al. (2003)	75	40 (12.2)	7 (25 days)	NR	NR	Development of ARDS	Age 60–81 Positive test for hepatitis B surface antigen	28.0 (3.1–253.3) 18.0 (3.2–101.3)

ARDS, acute respiratory distress syndrome; CI, confidence interval; LDH, lactate dehydrogenase; NR, not reported.
From Princess Margaret Hospital SARS Study Group: Lee PO, Tsui PT, Tsang TY, et al. Severe acute respiratory syndrome: clinical features. In: Schmidt A, Wolff MH, Weber O, eds, Coronaviruses with special emphasis on first insights concerning SARS. Basel, Switzerland: Birkhäuser, 2005:71–99.

airway pressure (CPAP) in SARS patients with respiratory decompensation in China and Hong Kong. Institution of NIPPV resulted in the avoidance of intubation in 70% of treated subjects, as well as shorter length of intensive care unit (ICU) stay and lower chest radiography scores, compared with the intubated group. NIPPV initially was banned in Hong Kong because of the fear of aerosol generation and viral dissemination via mask leakage. However, evidence shows that NIPPV is a useful and safe treatment option for SARS patients with respiratory failure, and it should be considered if acute lung injury develops. The procedure must be performed under respiratory precautions with appropriate personal protective equipment in a suitable setting (single room with negative pressure and air changes of 12 cycles or more per hour).

Invasive Mechanical Ventilation

When patients fail to improve or deteriorate after 1–2 days of NIPPV, or if NIPPV is contraindicated, endotracheal intubation and mechanical ventilation must be considered. The plateau pressures are kept lower than 30 cm H_2O in intubated adults owing to the high susceptibility to barotrauma.

INFECTION CONTROL

Basic Considerations

SARS-CoV is present in respiratory secretions, blood, saliva, urine, and feces of patients. The virus is stable in the environment for up to 2 days at room temperature and longer at lower temperatures. Its survival in stool ranges from up to 4 days in alkaline, diarrheal stool to 3–6 hours in normal stool. The virus is inactivated by exposure to commonly used disinfectants (e.g., hypochlorite and alcohol) and by exposure to a temperature of at least 56°C for 15 minutes. The principal modes of transmission occur through droplets, aerosolized respiratory secretions, and direct contact with patients' secretions, excreta, and fomites.

Infection Control of SARS in the Hospital

Four specific measures are important in the infection control practice for SARS: hand washing and the wearing of masks, gowns, and gloves. The quantity of exposure is related to the duration of hospital stay of SARS patients. A longer exposure results in higher chance for procedural lapses to occur, which can result in nosocomial spread.

Specific risk assessment should include:

1. Patient-related risk (exposure to a confirmed or suspected SARS case, superspreading events, triage areas, patient with fever of unknown origin, etc.)
2. Procedure-related risk (ICU, procedure room such as bronchoscopy room or x-ray department, area serving SARS patients, dirty utility room, etc.)
3. Direct patient contact or activities with risk of exposure to blood, body fluids, secretions, excreta, and contaminated items.

In addition, procedures with high risk of generating aerosols (e.g., resuscitation, high-flow oxygen) and involving prolonged very close contact with affected patients require:

- N95 respirator (surgical mask may suffice for non-aerosol generating procedures)
- a linen or disposable gown
- full-face shield or eye shield
- latex gloves (only for procedures with exposure to blood and body fluid, secretion, excreta, and contaminated items)
- goggles (only for aerosol-generating procedures)
- disposable cap (optional)

PROGNOSIS

Young children affected by SARS generally have an excellent prognosis: respiratory failure is uncommon, and no deaths have been reported in patients under 18 years of age. The principal immediate morbidity of SARS in adults is acute respiratory failure. Some 20% of adult patients develop ARDS, while 20–34% require intensive care unit admission, and 13–26% require assisted ventilation.

The case fatality rate (CFR) is widely variable in different regions. According to WHO, the global CFR was 9.6% and ranged from 7% to 17%. The rates were between 3.6% and 12% in the major published series. The figures must be interpreted with caution. The patient population, length of follow-up, and case definition were all different in the various reports. The premorbid risk factors of patients, such as older age and multiple comorbidities, may affect the CFR substantially.

Risk stratification and management planning in SARS patients depends very much on the identification of prognostic factors. Different studies have established that advanced age, especially over 60, and concurrent medical illness, particularly diabetes mellitus, are independent prognostic indicators for adverse clinical outcomes including intensive care unit admission, need for assisted ventilation, and death (Table 72.5). In addition, high neutrophil counts, elevated initial lactate dehydrogenase level, low CD4 and CD8 lymphocyte counts, hypoxemia, and thrombocytopenia are associated with poor clinical outcomes. High initial viral load by quantitative PCR of nasopharyngeal aspirate is also a poor prognostic factor in adult patients. One report found that initial chest radiographic score was also an independent prognostic factor.

PEARLS AND PITFALLS

1. An epidemiologic link such as close contact with a SARS patient appears to be the single most important clue leading to diagnosis.
2. Though lobar pneumonia usually suggests a bacterial cause, especially pneumococcal, pneumonia in SARS may present as lobar consolidation instead of patchy infiltration.
3. SARS patients are generally most infectious shortly after hospitalization and pose significant risk to health care workers.
4. Stringent infection control measures and constant vigilance for procedural lapses are critical to preventing nosocomial transmission of SARS.
5. Chronic hepatitis B carriers should be given lamivudine to prevent the hepatitis flare that may occur on corticosteroid withdrawal.

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