Clinical, Laboratory, and Radiologic Manifestation of SARS

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Severe acute respiratory syndrome (SARS) is a highly contagious and predominantly pneumonic illness caused by a novel coronavirus now commonly known as SARS-CoV. This article describes the key diagnostic clinical features, radiologic features, and investigation profiles of affected patients. We summarize our understanding from anecdotal experience and limited published data on the use of antiviral and corticosteroid therapy in the management of this highly contagious disease.

Introduction
Severe acute respiratory syndrome (SARS), a new emerging disease, was first described in a patient in November 2002 in Foshan, Guangdong, a province in southern China [1]. In February 2003, the World Health Organization (WHO) received a report of 305 cases from that province [1]. The disease spread very rapidly and by April 30th, 2003, 5663 cases were reported globally from countries on four continents [2]. At the end of July 2003, SARS had spread to 30 countries and had affected more than 8000 people, resulting in almost 774 deaths worldwide [3•]. It took an economic toll of at least 30 billion dollars. The causative microorganism for the disease has been identified to be a novel coronavirus [4••,5,6]. The disease is transmitted by droplets and direct contact, although airborne and oral-fecal route transmission cannot be excluded.

Epidemiology
The early cases of SARS probably occurred in southern China. In November 2002, there were many cases of severe pneumonia of unknown etiology in Guangdong Province in southern China, with a high rate of transmission to health care workers [1]. A 64-year-old physician from southern China, who visited Hong Kong on February 21, 2003 and died 10 days later of severe pneumonia, is thought to have been the source of infection, causing subsequent outbreaks of SARS in Hong Kong, Vietnam, Singapore, and Canada [7•,8,9]. The index patients of these cities had been exposed to the Guangdong physician while they were visiting China or had been staying on the same floor of the same hotel. By May 21, 2003, 1719 patients in Hong Kong had SARS, and 20% were health care workers. Two hundred and fifty-five patients died during this period.

SARS appears to spread by close person-to-person contact through droplet transmission or fomite. The high level of infectivity of this viral illness is highlighted by the fact that 158 patients were hospitalized with SARS within 2 weeks as a result of exposure to one patient in a general medical ward in Hong Kong. The use of a jet nebulizer for administering bronchodilators to the index case, who presented clinically with community-acquired pneumonia, could have increased the droplet load around the patient and, with the overcrowding condition in the hospital ward, contributed to this major hospital outbreak [10••].

SARS-associated Coronavirus
Coronaviruses are large enveloped viruses with a positive-sense RNA genome ranging in size from 27 to 30 kb. Clinically speaking, coronaviruses are usually associated with the common cold in humans, but in animals the virus can cause highly virulent respiratory, enteric, and neurologic diseases and hepatitis. The detection of the virus in sputum and feces indicates more than one tissue tropism with protean clinical presentation. The full sequence of the SARS coronavirus (SARS-CoV) was recently reported by a Canadian collaborative group [11,12]. With 29,751 bases, the genome, denoted Tor-2, possesses a classic coronavirus complement of 11 open-reading frames, spike (S), membrane (M), and small envelope (E) glycoproteins, and the matrix, replicase, and nucleocapsid (N) proteins. However, at the amino acid level, SARS-CoV has minimum homology with any of the three classes of coronavirus; thus, SARS-CoV is in its own group. In a separate study comparing full-length genome sequence analysis of 14 SARS-CoV isolates, a remarkable genetic conservation of the virus was found since the outbreak was first documented in February 2003.
Clinical and Laboratory Profiles of SARS

Most patients with SARS initially present with fever (> 38 °C for more than 24 hours) and chills. Approximately 50% of the patients also complain of nonproductive cough, dyspnea, malaise, and headache during diagnosis [7-10,16]. Very few patients report upper respiratory tract symptoms such as rhinorrhea, nasal obstruction, sneezing, sore throat, or hoarseness. There usually is an interval of 3 to 7 days from the onset of fever to experiencing dyspnea [7,16]. Physical examination of the chest usually is normal initially, but signs of consolidation, including crinkles and dullness on percussion, occur in later stages of the disease [7]. Watery diarrhea has been reported in a subgroup of patients 1 week through the clinical course. This was reported in a cohort infected in a community outbreak that has been linked to a faulty sewage system, presumably caused by involvement of the gastrointestinal tract through the fecal-oral route [17]. However, it also is possible that diarrhea could be secondary to antibiotic therapy in some patients.

Whereas leukocytosis, leukopenia, and thrombocytopenia are uncommon, lymphopenia (< 1500 cells/mm³) is almost always seen at disease onset [7]. Lymphopenia is caused by the destruction of CD4 and CD8 lymphocytes. Transaminases, including aspartate aminotransferase (AST) or alanine aminotransferase (ALT), are elevated slightly in 40% to 60% of our patients, and these tend to normalize simultaneously with clinical and radiologic recovery [7]. Features of low-grade disseminated intravascular coagulation (ie, thrombocytopenia, prolonged activated partial thromboplastin time, and elevated D-dimer levels), and elevated lactate dehydrogenase levels (reflecting lung injury) and creatinine kinase levels (reflecting myositis), are common laboratory features of SARS. Renal function, as reflected by serum creatinine levels, usually is normal on admission [7,16]. However, late-onset acute renal failure occurred in 6% of patients in a recent retrospective analysis of 267 patients with SARS [17].

The pathologic picture of SARS appears to follow a triphasic pattern in severe cases. Phase 1 (viremia and viral replication) is associated with increasing viral load and is clinically characterized by fever, myalgia, and other systemic symptoms that generally improve after a few days. Phase 2 (immunopathologic damage) is characterized by the recurrence of fever, oxygen desaturation, and radiologic progression of pneumonia with decreases in viral load. Most patients will respond to treatment with a combination of antiviral agents and steroids, but 20% of patients may progress to phase 3, which is characterized by acute respiratory distress syndrome (ARDS) necessitating ventilatory support [18]. SARS seems to run a less aggressive clinical course in younger children than in adults or teenagers; no children in any case studies required supplemental oxygen [19].

Radiologic Findings

The radiographic appearances of SARS share features with other causes of pneumonia. At fever onset, almost 80% of patients with SARS have abnormal chest radiographs, all of which show airspace consolidation. All patients will eventually develop airway opacities during the course of the disease. The opacities occupy a peripheral or mixed peripheral and axial location in more than 80% of patients [20]. The predominant involvement of the lung periphery and the lower zone, in addition to the absence of cavitation, hilar lymphadenopathy, or pleural effusion at diagnosis, are the more distinctive radiographic features of SARS [20]. Radiographic progression from unilateral focal airspace opacity to multifocal or bilateral involvement during the second week of the disease course, followed by radiographic improvement with treatment, is commonly encountered. The radiologic appearances of SARS have been described as similar to those of bronchiolitis obliterans with organizing pneumonia, which include the peripheral appearance of lung opacities, lower lobe predominance, and a mixture of ground-glass opacities and consolidation (Fig. 1a). Contrary to bronchiolitis-organizing pneumonia, there is no lymphadenopathy or pleural effusion in SARS [7,21]. In one report, 12% of patients developed spontaneous pneumomediastinum, and 20% of patients developed evidence of ARDS over a period of 3 weeks [18]. In general, the incidence of barotrauma in intensive care unit (ICU) admissions seems higher than expected despite treatment with low-volume and low-pressure mechanical ventilation, yet excessive hyperinflation or bullous lung disease is not commonly encountered. Our study quantifying the severity of lung abnormalities on chest radiographs correlates with clinical and laboratory parameters [22]. There are significant relationships among radiographic parameters, oxygen supplementation, and treatment response [23].
High-resolution computed tomography (CT) scanning of the thorax is useful in detecting lung opacities in patients with unremarkable chest radiograph findings (Fig. 1b). Common findings include ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening (Fig. 2), with predominantly peripheral and lower lobe involvement. The characteristic peripheral alveolar opacities similar to those found in patients with bronchiolitis obliterans–organizing pneumonia are best characterized on CT scanning.

Daily radiographic assessment is essential for monitoring of this potentially rapidly progressive pneumonic illness. Invasive procedures, such as bronchoscopy and associated specimen collection, impose a prohibitory high infection risk to the operators. Initial radiographs might be normal. Rapid progression of ground-glass opacification, sometimes even overnight, despite potent antibiotic therapy, is probably the most helpful diagnostic clue. Air-space opacification often progresses in size, extent, and severity within a few days. In severe cases, diffuse opacification suggestive of ARDS develops despite intensive treatment. Very rarely, nodules not dissimilar to those seen in miliary tuberculosis also appear in a background of ground-glass opacification, and this necessitates invasive investigations, such as transbronchial biopsies, because miliary tuberculosis and fungal infections have to be excluded. This is particularly important during later stages of the disease, when patients might develop secondary infection of the lung after receiving considerable doses of corticosteroids.

Establishment of the Diagnosis
The initial diagnosis of SARS is based on clinical, epidemiologic, and laboratory criteria that have been outlined by the US Centers for Disease Control and Prevention (CDC) and the WHO [24,25]. The clinical criteria include: asymptomatic or mild respiratory illness; moderate respiratory illness (ie, temperature > 100.4 ° F or 38 ° C) and at least one respiratory feature (ie, cough, dyspnea, difficulty breathing, or hypoxia); and severe respiratory illness (features of the second criterion and radiographic evidence of pneumonia, the presence of respiratory distress syndrome, autopsy findings consistent with pneumonia, or the presence of respiratory distress syndrome without an identifiable cause). The epidemiologic criteria include travel (including transit in an airport) within 10 days of the onset of symptoms to an area with current, recently documented, or suspected community transmission of SARS, or close contact within 10 days of the onset of symptoms with a person known or suspected to have SARS infection. Laboratory criteria include: the detection of an antibody to SARS-CoV in specimens obtained during acute illness or 21 days after illness onset; the detection SARS-CoV RNA by reverse transcriptase polymerase chain reaction (RT-PCR) that was confirmed by a second PCR assay by using a second aliquot of the specimen and a different set of PCR primers; or the isolation of SARS-CoV. Since the last case of SARS infection in July 2003, the epidemiologic criterion of travel may not be applicable. The case definitions proposed by the WHO and the CDC are designed more toward disease surveillance than making bedside clinical diagnosis for SARS.

Despite the availability of several RT-PCR techniques since March 2003, these remain to be validated. Molecular assays currently available for detection of SARS-CoV have low sensitivity and specificity during the early stage of the illness [25,26]. Recently, by combining the modified RNA
extraction method and real-time quantitative PCR technology, one laboratory reported a positive detection rate of 80% (40 of 50 samples) in the nasopharyngeal aspirate samples by the real-time RT-PCR assay [27]. Although sensitivity of 80% might seem acceptably high, there is a highly significant proportion of patients who would be “missed” by this test if used as a lone diagnostic criterion, as it is commonly and perhaps erroneously perceived. The specificity of these RT-PCR assays also is unknown, thus making these tests unqualified as gold standard diagnostic tests. These findings must be validated by other laboratories and in larger sample numbers. Serologic testing of the detection of specific immunoglobulin-G against SARS-CoV is very specific, but it takes 30 days for just over 90% of patients to show a significant increase (fourfold) in titer [18]. It does not help in establishing the diagnosis at early and key phases of an outbreak, and the sensitivity and specificity of SARS serologic tests also are unknown. The periods during which SARS-CoV infection is confirmed by molecular or serologic testing are summarized in Table 1. Even the pathologic findings of SARS-related ARDS, readily recognizable on autopsy and open-lung biopsies as diffuse alveolar damage, are still regarded as nonspecific [28].

Although the most recently established diagnostic criteria from the CDC and the WHO require laboratory proof of SARS-CoV infection (RT-PCR detection of SARS-CoV, serologic proof of a significant increase in specific antibody titer, or positive viral culture yielding SARS-CoV) to diagnose SARS, this process largely remains a clinical decision. This diagnostic process is usually made after carefully and repeatedly reviewing the clinical features, radiologic findings, and hematologic and biochemical profiles of a patient. More importantly, the diagnosis should be made only after considerable efforts are made to exclude background pneumonia, especially that caused by atypical organisms (e.g., Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila), and other mimicking diseases (especially bronchiolitis-organizing pneumonia).

When we are considering the resurgence of SARS, there are five prerequisites for diagnosis of confirmed SARS: clinical symptoms of respiratory illness (temperature > 100.4° F or 38° C) and at least one respiratory feature (cough, dyspnea, difficulty breathing, or hypoxia); the presence of radiologic evidence of consolidation; failure to demonstrate a clinical or radiologic response to potent antibiotic therapy; otherwise unexplained and persistently abnormal lymphopenia and increased AST and ALT; and a molecular or serologic confirmation of SARS-CoV infection. History of contact with suspected or confirmed patients with SARS or history of travel to at-risk areas also is helpful. Once SARS is suspected, these patients must be admitted to designated isolation wards while waiting for confirmation of SARS-CoV infection.

**Management of SARS**

Proper isolation is mandatory to prevent cross-infection within the hospital because the disease is transmitted by droplets and direct contact. An outbreak in a hospital or health care institution results in community outbreaks and must be prevented by stringent infection control strategies [10]. Wards are designated for "triage" (i.e., all initial admissions), "suspected or confirmed SARS," and "step down" (i.e., non-SARS). "Triage" and "suspected or confirmed SARS" wards are isolation single- or double-bed wards with negative pressure and double-door facilities. Each bed is separated from the next by 6 feet. An air exchange rate of 12 times per hour and a temperature of 20° C are maintained in these wards. Patients are required to wear a surgical mask at all times except during meals, and visitation by family or friends is not permitted. All staff entering these wards are required to follow strict and stepwise gowning and degowning procedures. Standard personal protection equipment includes a disposable surgical paper cap, N95 mask, reusable eye goggles, and reusable green cotton neck-to-heel surgical gown. Gloves and clear plastic face shields are worn for patient care or specimen collection procedures and must be immediately disposed of afterwards. The adoption of frequent effective hand-washing and use of diluted bleach to wipe work surfaces and the floor is essential. The use of nebulizer therapy...
was considered as the cause of a major hospital outbreak in Hong Kong and is thus avoided for patients with suspected or probable SARS [10••].

The initial treatment of patients with SARS starts with the use of potent antibiotics to target bacterial pathogens incriminated in the etiology of severe community-acquired pneumonia. This usually includes a combination of intravenous cefepime (2 g three times daily) and oral clarithromycin (500 mg two times daily), or intravenous levofloxacin (500 mg/day) in the event of allergies [7•]. Most patients with non-SARS community-acquired pneumonia would have radiologic resolution and resolution of fever, even if partial. Diagnosis of SARS in these patients could effectively be excluded, although they should be monitored for at least 10 more days in hospital isolation initially and home quarantine later. For a typical case of SARS, high fever, lymphopenia, and AST/ALT abnormalities usually persist, with radiographic deterioration, with or without high-resolution CT evidence of more widespread changes. During the SARS crisis between March and June 2003, these patients would then be considered for an empirical “anti-SARS” therapy, which is usually administered between 2 and 11 days after hospitalization. Often, there is difficulty for the more indolent cases that neither progress nor improve clinically or radiologically within the first few days after admission, particularly if the epidemiologic link is not explicit.

Anecdotal experience using a combination of ribavirin and steroids has been described by three studies in Hong Kong [10••,29,30••]. Ribavirin (1.2 g three times daily orally or 400 mg every 8 hours intravenously) and corticosteroids (prednisolone, 1 mg/kg per day) were prescribed as combination “specific anti-SARS.” When there was radiologic progression of pneumonia and/or hypoxemia, in most cases, intravenous high-dose methylprednisolone (0.5 g daily for up to 6 doses) was administered to prevent immunopathologic lung injury, with the rationale that progression of the pulmonary disease may be mediated by the host inflammatory response [18•]. Most of these patients (70% to 80%) appeared to have a favorable response to the combination treatment, with resolution of fever and lung opacities within 2 weeks, whereas approximately 23% of the same cohort required ICU admission, and 14% required invasive ventilatory support [10••]. However, the use of ribavirin therapy in patients with SARS is associated with significant toxicity, including hemolysis (76% of patients) and a decrease in hemoglobin of 2 g/dL (49% of patients), elevated transaminase levels (40% of patients), and bradycardia (14% of patients) [9]. The other reservation is that ribavirin exhibits no in vitro efficacy against SARS-CoV. This raises the question of whether the improvement could be caused by the immune defense of the patient rather than the antiviral effect of ribavirin. Another drawback of early introduction of corticosteroid was the possible link between its use and avascular necrosis of bone, detected in at least 10% of patients by routine magnetic resonance imaging scanning criteria (Unpublished data).

With better understanding of the pathogenesis, it is now more rational to test other antiviral agents during the early viremic phase in established SARS, sparing the initial use of corticosteroid. One of the promising agents is Kaletra (lopinavir/ritonavir; Abbott Laboratories, Abbott Park, IL), an antiprotease designed against HIV. In a recent retrospective analysis of patients from Hong Kong, it was shown that the addition of Kaletra as initial treatment was associated with a significant reduction in the overall death rate (2.3%) and intubation rate (0%), compared with a matched cohort that received the aforementioned standard treatment (15.6% and 11%, respectively) [31], and a lower rate of use of methylprednisolone rescue therapy at a lower mean dose. However, the subgroup that had received Kaletra as rescue therapy showed no difference in overall death rate and rates of oxygen desaturation. In vitro studies reveal lopinavir exhibits in vitro activity against the prototype SARS-CoV and acts in synergism with ribavirin [32]. Yet with the toxicity of ribavirin, any treatment regimen for SARS needs to be tested with a randomized placebo-controlled design. Other potential therapeutic agents, based solely on in vitro studies, are the α- and β-interferons [33] and thus have less clinical basis to be used as the preferred first-line therapy.

Because the immunopathologic damage of the lung (phase 2) and ARDS (phase 3) appear to be mediated through an enhanced immune response resulting in inflammatory injury in SARS, immunomodulating therapy is a logical treatment. Experimental and SARS-related ARDS are characterized by pulmonary infiltration of macrophages releasing macrophage migration inhibitory factor (MIF) that finally causes severe alveolar damage [28,34]. Experimental acute lung injury or ARDS is effectively ameliorated by corticosteroid of anti-MIF treatment [34]. Thus, the use of corticosteroid in phase 2 or 3 of SARS infection is an appropriate therapeutic approach based on animal studies of ARDS. A recent study has shown the superiority of pulse steroid over nonpulse steroid in the treatment of SARS-induced ARDS [30••]. Despite similar cumulative steroid dosage, ICU admission, mechanical ventilation, and hematologic and biochemical parameters in both groups after 21 days,
patients in the pulse steroid group had less oxygen requirement, better radiographic outcome, and less likelihood of requiring rescue-additional pulse steroid therapy than did their counterparts. Thus, initial use of pulse methylprednisolone therapy appears to be a more efficacious and an equally safe steroid regimen compared with regimens with lower dosage, and should be considered the preferred steroid regimen in the treatment of SARS, pending data from future randomized controlled trials.

Anti-MIF therapy is effective in ameliorating the pulmonary injury in the experimental ARDS model, but the supply limits clinical use in humans. Because MIF induces tumor necrosis factor (TNF)-α and interferon-γ production in macrophages through an amplifying proinflammatory loop [35], the use of anti-TNF-α (available commercially) also may be considered as an adjuvant immunomodulatory agent as demonstrated in other pathological conditions [36]. Convalescent serum from patients who recovered from SARS has been suggested as an alternative immunomodulatory treatment [10••]. Nevertheless, its use is limited by the supply of serum from donors and risk that the viral infection may even be aggravated by the antibody-dependent enhancement

Prognosis/Outcome
The calculation of case fatality rates in the situation of an emerging epidemic is difficult, but it has been estimated to be 13.2% (95% confidence interval [CI] = 9.8–16.8) for patients aged younger than 60 years and 43.3% (95% CI = 35.2–52.4) for patients aged 60 years or older [10••]. The prognostic factors associated with a poor outcome (ie, ICU admission or death) include age [10••, 18•, 37], chronic hepatitis B treated with lamivudine [18•], high peak lactate dehydrogenase [10••], high neutrophil count during diagnosis [10••], or presence of diabetes mellitus or other comorbid conditions [9].

Conclusions
With the recent onset of the SARS epidemic worldwide, research on the development of diagnostic tests and an effective treatment is urgently needed. We hope that the availability of the genome sequence of the SARS-CoV will facilitate efforts to develop new and rapid diagnostic tests, antiviral agents, and vaccines. SARS patients who have recovered from the acute illness should be monitored carefully for the possibility of continued viral shedding and the potential development of pulmonary fibrosis or long-term complications. The prevention of spreading the illness is most important for this highly infectious disease. Isolation facilities, strict precautions against droplet exposure among health care workers managing patients with SARS, the avoidance of the use of nebulizers in a general medical ward, contact tracing, and quarantine isolation for close contacts are all important measures.

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