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Review

Clinical management and infection control of SARS: Lessons learned

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ABSTRACT

The outbreak of severe acute respiratory syndrome (SARS) in 2003 was the first emergence of an important human pathogen in the 21st century. Responding to the epidemic provided clinicians with extensive experience in diagnosing and treating a novel respiratory viral disease. In this article, we review the experience of the SARS epidemic, focusing on measures taken to identify and isolate patients, prevent the transmission of infection to healthcare workers and develop effective therapies. Lessons learned from the SARS epidemic will be especially important in responding to the current emergence of another highly pathogenic human coronavirus, the agent of Middle East respiratory syndrome (MERS), and to the recently emerging H7N9 influenza A virus in China. This paper forms part of a symposium in *Antiviral Research* on "From SARS to MERS: 10 years of research on highly pathogenic human coronaviruses."

Contents

1. Introduction

It has been 10 years since the outbreak of severe acute respiratory syndrome (SARS) caused by a novel coronavirus which was subsequently named SARS coronavirus (SARS-CoV) (Peiris et al., 2003b). SARS-CoV is phylogenetically diverged from other known coronaviruses associated with human infections including human coronavirus (HCoV)-OC43, HCoV-229E, HCoV-NL63 and Middle East respiratory syndrome coronavirus (MERS-CoV), but closely related to the civet and the bat SARS-CoVs, a group of lineage B betacoronaviruses found in civets, raccoon dogs, ferret badgers and Chinese horseshoe bats (*Rhinolophus sinicus*) in Guangdong Province of South China (Chan et al., 2013c) The Chinese horseshoe bat appears to be the natural reservoir of the ancestral SARS-CoV, because the Ka/Ks ratios (rate of nonsynonymous mutation/rate of synonymous mutation) of the S, orf3a, and nsp3 genes were low, while those of the civet strains in both the 2003 and the minor 2004 outbreaks were high, suggesting a rapidly evolving process of gene adaptation in the animals (Lau et al., 2005b; Li et al., 2005a).

SARS emerged as an outbreak of atypical acute, community-acquired pneumonia in late 2002. The initial cases were animal handlers in Guangzhou Province having regular contact with wild game food animals, suggesting that civets could serve as an

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intermediate amplification host, and later the patients' close household and hospital contacts. The human SARS-CoV subsequently evolved and was capable of person-to-person transmission. The epidemic was rapidly and globally disseminated when a medical professor from a teaching hospital in Guangzhou, who was considered as a "super-spreader" of SARS, came to Hong Kong on 21 February 2003. During his stay in hotel M, he transmitted the infection to other residents, and the secondary cases spread the disease to hospitals in Hong Kong, and to other countries including Vietnam, Singapore, and Canada. Eventually, a total of 8096 patients were infected in over 30 countries among 5 continents and 774 (9.5%) of them died (Cheng et al., 2007a).

As there were no known effective antiviral agents for SARS, supportive care and the use of broad-spectrum antibiotics to cover secondary bacterial infection were the key treatment regimen. The use of existing antiviral therapies including conventional ones like ribavirin, interferon alpha (Infacon), and convalescent plasma, or those with inhibitory effects on SARS-CoV such as lopinavir/ritonavir, with or without corticosteroid use has been reported in non-randomized clinical trials (Cheng et al., 2004b). Since the clinical efficacy of these antiviral agents were found to be uncertain in retrospective analysis (Leong et al., 2004), effective public health and infection control measures including contact tracing and quarantine of close contacts played an important role in preventing further transmission of SARS in the communities and hospitals (Pang et al., 2003; Svoboda et al., 2004).

International collaboration, uniting laboratories with different technologies and capacities, allowed research laboratories to rapidly fulfill all postulates for establishing SARS-CoV as the cause of SARS. The epidemic came to an end when there was no further transmission of SARS in Taiwan on 5 July 2003 (Cheng et al., 2007a). However, there was a brief reemergence (Che et al., 2006), from accidental laboratory exposures in Singapore, Taiwan, and Beijing, and from recurrent animal-to-human transmissions in Guangzhou in late 2003 and early 2004 (Liang et al., 2004; Lim et al., 2004; Normile, 2004a, b), which posed a potential threat to public health.

2. Clinical features

The incubation period of SARS is generally 2–14 days with occasional cases of up to 21 days in a family cohort in Hong Kong (Chan et al., 2004c). Most patients were admitted to hospitals 3–5 days after onset of symptoms (Donnelly et al., 2003). The typical clinical presentation includes fever, chills, rigors, cough, headache, myalgia, fatigue and malaise, whereas sore throat, rhinorrhea, dizziness, and chest pain are less frequently seen (Table 1). However, symptoms may be milder in children, and an atypical presentation without fever may occur in elderly patients (Chow et al., 2004; Fisher et al., 2003; Kwan et al., 2004) but rarely in healthy young adults (Woo et al., 2004). Diarrhea at presentation occurred in 12.8% and 23.2% of patients in Asia and North America respectively, but in up to 73% of patients after a mean of 7.5 days after onset of symptoms in a community cohort (Peiris et al., 2003a), which was positively correlated with a higher mean viral load in nasopharyngeal specimens (Cheng et al., 2004a).

Higher initial viral load is independently associated with worse prognosis in SARS (Chu et al., 2004c). Rapid respiratory deterioration was observed one week after the onset of illness, with 20% of patients progressing to acute respiratory distress syndrome (ARDS) which required mechanical ventilation (Peiris et al., 2003a). The radiographic features of SARS were similar to viral pneumonia, but ground-glass opacities and focal consolidations as demonstrated in chest radiographs predominantly involved the peripheral and subpleural regions of the lower zones (Grinblat et al., 2003; Hsieh et al., 2004; Lai et al., 2005a). Spontaneous pneumomediastium was found in about 12% of cases (Chu et al., 2004b), whereas 26% of patients developed barotrauma during mechanical ventilation (Gomersall et al., 2004).

Table 1
Clinical features of probable and laboratory-confirmed cases of SARS, Cases in Asia include 1693 reported from Beijing, 575 from Hong Kong, 190 from Guangzhou, 159 from Taiwan, 118 from Singapore and 62 from Vietnam, of which 606 (21.7%) were healthcare workers. Cases in North America include 168 reported from Canada, of which 87 (51.8%) were healthcare workers. NM, not mentioned. References for SARS in Asia are (Chen et al., 2006; Fan et al., 2006; Hsu et al., 2003; Jang et al., 2004; Lee et al., 2003; Liang et al., 2004; Peiris et al., 2003a; Peiris et al., 2003b; Rainer et al., 2003; So et al., 2003; Tsang et al., 2003a; Tsang et al., 2003b; Vu et al., 2004; Yeh et al., 2005; Zhao et al., 2003). References for SARS in North America are (Avendano et al., 2003; Booth et al., 2003; Poutanen et al., 2003).

Clinical symptom	Number/total (% with sign or symptom)	
	SARS in Asia (n = 2797)	SARS in North America (n = 168)
Fever	2708/2797 (96.8%)	130/168 (77.4%)
Chills	554/934 (59.3%)	NM
Rigors	411/804 (51.1%)	NM
Cough	1373/2797 (49.1%)	116/168 (69.0%)
Sore throat	85/445 (19.1%)	21/154 (13.6%)
Rhinorrhea	65/492 (13.2%)	3/144 (2.1%)
Headache	335/822 (40.8%)	61/168 (36.3%)
Dizziness	201/753 (26.7%)	6/144 (4.2%)
Dyspnea	460/2477 (18.6%)	68/154 (44.2%)
Chest pain or tightness	404/2208 (18.3%)	18/154 (11.7%)
Fatigue or malaise	437/653 (66.9%)	60/168 (35.7%)
Nausea or vomiting	79/564 (14.0%)	32/168 (19.0%)
Diarrhea	349/2725 (12.8%)	39/168 (23.2%)
Myalgia	459/944 (48.6%)	84/168 (50.0%)
Arthralgia	NM	15/144 (10.4%)

In addition to upper and lower respiratory tract disease, extrapulmonary manifestations were also reported for SARS. These included liver and renal impairment (Chau et al., 2004; Chu et al., 2005c), bradycardia and hypotension due to diastolic cardiac dysfunction (Li et al., 2003), pulmonary arterial thrombosis (Ng et al., 2005), rhabdomyolysis (Wang et al., 2003b), neuromuscular disorder (Tsai et al., 2004), and an acute neurological syndrome with status epilepticus (Lau et al., 2004d). Lymphopenia, leucopenia, thrombocytopenia were commonly observed (Lee et al., 2003).

3. Diagnosis of SARS

The diagnostic criteria for SARS were based on a list of clinical features suggested by the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) during the initial phase of the epidemic. According to the WHO criteria, a suspected case was defined as a person presenting after 1 November 2002 who had a history of fever >38 °C, with cough or difficulty breathing, and had close contact with a person who was a suspected or probable case of SARS, or had a history of traveling to or residing in an area with transmission of SARS within 10 days before the onset of symptoms. In addition, a person with an unexplained acute respiratory illness resulting in death, with epidemiological exposure similar to that described above, but on whom no autopsy was performed, also fulfilled the clinical criteria of suspected SARS.

A probable case of SARS was defined as a suspected case with chest X-ray evidence of infiltrates consistent with pneumonia or acute respiratory distress syndrome, with a positive test result for SARS-CoV by one or more laboratory diagnostic assays, and/or with autopsy findings consistent with the pathology of ARDS, without an identifiable cause (WHO, 2003b). The overall accuracy of the WHO guidelines for identifying suspected SARS was found to be 83% with an negative predictive value of 86% (Rainer et al., 2003).