Clinical and Epidemiological Aspects of SARS

Chapter Contents

This document is subject to revision and will be updated as new information becomes available.

Introduction

With the world currently in the recovery phase of the 2003 SARS emergency, a number of global gatherings have occurred to further the knowledge on the clinical and epidemiological aspects of SARS to further inform public health practice. These included a global meeting on epidemiology of SARS in May 2003, a SARS Clinical Management Workshop in June and a Scientific Research Advisory Committee meeting on October 21, 2003. This most recent meeting brought together more than 30 leading SARS researchers to identify the specific research most urgently needed to understand the disease better and prepare for its possible recurrence.

Diagnosis of SARS is difficult. Mild SARS cases and cases with atypical symptoms could be initially missed and all currently available laboratory tests have limitations. At present, there is no single "gold standard" that can be recommended for laboratory testing.

This chapter summarizes recent documentation from various sources on the clinical and epidemiological aspects of SARS and will be updated as further information comes to light and additional research sheds more light on this and other severe respiratory infections.

Clinical Aspects of SARS

While much has been learned about this syndrome since March 2003, including its causation by a new coronavirus (SARS-CoV), knowledge about the epidemiology and ecology of SARS coronavirus infection and of this disease remains limited. The non-specific clinical features of SARS, the lack of a current rapid diagnostic test that can reliably detect SARS-CoV in the first few days of illness, and the seasonal occurrence of other respiratory diseases, including influenza, may confound any surveillance for SARS or demand a level of quality and intensity which few health care system worldwide can sustain. Even with the most sophisticated surveillance systems, the first case of SARS in the post-outbreak period may escape early detection.

The WHO and CDC have provided guidance, as outlined below, to clinicians on the clinical presentation, laboratory and radiological findings to assist in diagnosis of SARS and in decisions to implement transmission-based infection control.

Aetiology

- Severe acute respiratory syndrome (SARS) is a disease caused by SARS coronavirus (SARS-CoV).

Epidemiology

- Nosocomial transmission of SARS CoV has been a striking feature of the SARS outbreak. The majority of the cases are adults. Children are rarely affected.
- The mean incubation period is 5 days with a range of 2-10 days although there are isolated reports of longer incubation periods (up to 14 days). There have been no reports of transmission occurring before the onset of symptoms.

Natural History of the Disease

- **Week 1 of illness**
    - Patients initially develop influenza-like prodromal symptoms. Presenting symptoms include fever, malaise, myalgia, headache, and rigors. No individual symptom or cluster of symptoms has proven specific. Although history of fever is the most frequently reported symptom, it may be absent on initial measurement. Fever may resolve prior to onset of respiratory symptoms.
- **Week 2 of illness**
    - Respiratory symptoms often begin 3-7 days after symptom onset and peak in the second week; 30% have respiratory symptoms at onset. Up to 25% may have symptoms of an upper respiratory tract infection. Severe cases develop rapidly progressive

respiratory distress and oxygen desaturation with about 20% requiring intensive care.

- Diarrhoea may be present in the first week but is more commonly reported in the second week of illness. The diarrhoea has been described as large volume and watery without blood or mucus.

Symptoms commonly reported by patients presenting with SARS:

SYMPTOM	RANGE (%)
Fever	95-100
Cough	57-100
Dyspnoea	20-100
Chills/Rigor	73-90
Myalgias	20-83
Headache	20-70
Diarrhoea	10-67
Nausea/Vomiting	10-24
Rhinorrhoea	5-25
Sore throat	5-25

Clinical Findings

Physical examination is nonspecific. Rales or rhonchi have been reported in 38-90% of patients. Hypoxia is apparent in 60-83% of cases.

Haematological and Biochemical Findings

- There are no haematological or biochemical parameters specific for SARS; however, studies have consistently highlighted the following:
- **Haematological findings**
  - Lymphopenia is common on presentation and progresses during the course of the illness. Sometimes thrombocytopenia and prolonged APTT are observed.
- **Biochemical findings**
  - LDH is frequently high and some reports have suggested association with poor prognosis. ALT, AST and CPK elevation are less frequently reported. Abnormal serum electrolytes have also been reported on presentation or during hospitalization including hyponatraemia, hypokalaemia, hypomagnesaemia and hypocalcaemia.

Common laboratory findings in patients with SARS:

FINDING	RANGE (%)
Laboratory	
Leukopenia	17-34
Lymphopenia	70-95
Thrombocytopenia	30-50
Prolonged aPTT	40-60
Increased ALT	20-30
Increased LDH	70-94
Increased CPK	30-40

Radiographic Features of SARS:

- Infiltrates develop on chest radiograph (CXR) in nearly 100% of laboratory confirmed cases
- CXR may be normal at presentation in up to 30%
    - 66% are abnormal by Day 3, 97% by day 7 and 100% by Day 10
- The infiltrates are initially focal, often involving the peripheral lobes
    - Usually interstitial, but sometimes consolidated
    - 75% progress to involve multiple lobes or both lungs over several days
- Computed tomography is more sensitive than conventional radiography and may show ground glass opacification in the peripheral lower lobes

Treatment of persons SARS

- At the present time, there is no proven effective therapy for SARS. Therefore, in addition to antibiotics and/or antiviral agents for other viral illnesses (e.g. influenza) as indicated, supportive care should be optimized.
- Some agents currently under investigation for the treatment of SARS include cystine proteinase inhibitors, interferons and corticosteroids or SARS Co-V specific immune globulin. Loutfy (Loutfy, 2003) et al recently reported that interferon alfacon-1 and steroids were safe and of potential benefit in a small uncontrolled sample of SARS patients.

Elderly and Paediatric Cases and SARS in Pregnancy

- The **elderly** are more likely to have atypical presentations such as afebrile illness or concurrent bacterial sepsis/pneumonia. In addition, underlying chronic conditions and the more frequent use of health facilities in the elderly have both contributed to initially unrecognized nosocomial transmission events.
- SARS occurred less frequently and was observed to be a milder illness in the **paediatric** population.

- There is a suggestion of increased fetal loss with SARS infection in early **pregnancy** and maternal mortality in later pregnancy.

Clinical outcomes

- Based on an analysis of data from Canada, China, Hong Kong SAR, Singapore, Viet Nam and the United States the case fatality ratio (CFR) of SARS is estimated to range from 0% to more than 50% depending on the age group affected, with an overall CFR estimate of approximately 11%. Higher mortality has also been associated with male sex and presence of co-morbidity in various studies.

Epidemiological Aspects of SARS

There are still considerable gaps in knowledge of the global epidemiology of SARS. In May 2003, the World Health Organization held the first global meeting on the epidemiology of SARS to produce a consensus document on current understanding of epidemiology of SARS as it informs public health practice. Participants at the meeting included representatives of the seven areas* that experienced outbreaks of SARS and leading international experts in the fields of public health and communicable disease epidemiology, mathematical modeling and clinical virology.

The discussion focused on the following topics and are summarized in this document:

- Key epidemiological distributions,
- Routes of transmission, exposure dose and risk factors for transmission,
- The presence and significance of subclinical infection,
- Reproduction number in different transmission settings and under different control strategies,
- Animal and environmental reservoirs

Key Epidemiological Distributions

The global epidemiology of SARS

- The first cases of SARS emerged in Guangdong Province, China in mid-November 2002.
- A cumulative total of 8422 probable cases, with 916 deaths, were reported from 29 countries during the outbreak (as of Aug 7, 2003).
- WHO announced that the last chain of human transmission was broken on July 5, 2003.
- A global case-fatality ratio of 11% was recorded at the end of the outbreak. In Canada, the attack rate was 5.1 per 100,000.

Incubation Period

- The estimates for the incubation period for SARS are starting to converge. Most countries report a median incubation period of 4-5 days and a mean of 4-6 days.
- 4 of the 7 areas stated that the maximum observed incubation period was 10 days. There was considerable discussion about the range of the incubation period and the effect of "outliers" at the upper end of the incubation period on existing recommendations on the isolation of cases and their contacts. It was agreed that a detailed investigation of "outliers'

* Canada; People's Republic of China; China, Hong Kong SAR; China Taiwan; Singapore; Viet Nam; WHO European Region

is needed before public health policy is changed to extend the incubation period beyond 10 days.

- It remains unclear whether the route of transmission influences the incubation period.

Infectious Period

- Transmission appears to be greatest from severely ill patients or those experiencing rapid clinical deterioration, usually during the second week of illness.
- Maximum virus excretion from the respiratory tract occurs on about day 10 of illness and then declines.
- There are no reports of transmission beyond 10 days of fever resolution consistent with the total period of isolation following defervescence recommended by WHO.
- There is an urgent need for well-defined virus shedding studies linked to the clinical progression of disease. Virus shedding studies are underway in Singapore, Hong Kong SAR, Canada and China.

Case-fatality Ratios

- The case-fatality ratio of SARS is estimated to range from 0% to more than 50% depending on the age group affected, with an overall CFR estimate of approximately 15%.
- Given that in some areas, most SARS deaths occurred in the elderly, there is a need to distinguish between SARS as the direct cause of death and dying with an intercurrent SARS infection. Gender differences also need further investigation.
- The crude CFR in Canada was 16.7% in probable cases and 9.3% in probable and suspect cases combined. The median age of SARS deaths was 75 years, 83% over 60 years.

Routes of Transmission Exposure, Dose and Risk Factors for Transmission

Routes of Transmission

- A basic reproduction number (R_0) of approximately 3 is consistent with a disease spread by direct contact or larger virus-laden droplets that travel only a few meters rather than by lighter airborne particles.
- The **primary mode of transmission** appears to be direct mucous membrane contact with infectious respiratory droplets and/or through exposure to fomites.
- Aerosolizing procedures in hospitals that promote aerosolization of infectious respiratory droplets or other potentially infectious materials in hospitals or other settings may amplify transmission.

- While the role of faecal-oral transmission is unknown, there is no current evidence that this mode of transmission plays a key role in the transmission of SARS. However, given viral excretion in stool, diarrhea could still remain important for infectivity.
- Under certain circumstances, such as in health care settings, contamination of inanimate materials or objects by infectious respiratory secretions seems to occasionally play a role in disease transmission.

Risk Factors for Transmission

Risk factors for SARS

- Health care workers, especially those involved in procedures generating aerosols, accounted for 21% of all cases.
- Other risk factors include household contact with a probable case of SARS.
- Limited transmission was associated with air travel.
- Transmission in Metropole Hotel (Malaysia) and Amoy Gardens (Hong Kong SAR) has been attributed in part to environmental contamination.

Special populations requiring investigation

- The WHO has recommended serological studies among children for evidence of transmission in settings where virus has been circulating and a global collaborative study on SARS in pregnancy.

Airline transmission

- WHO has verified reports of 40 flights on which one or more probable SARS cases traveled while symptomatic (a total of 37 potential source cases).
- A total of 29 secondary cases have been linked to probable cases of SARS who traveled while symptomatic.
- A crude estimate from the verified flights of March is that 6.5 passengers per million traveled as symptomatic probable SARS cases in March 2003 having departed from locations with local transmission of SARS.

The Presence and Significance of Subclinical Infection

- The presence and epidemiological significance of asymptomatic infection needs to be further investigated. Studies are ongoing in different countries to determine the presence and extent of asymptomatic infection, including serologic testing of asymptomatic contacts.

- There are currently no reports of the transmission of SARS from asymptomatic individuals.

Reproduction Number in Different Transmission Settings and Under Different Control Conditions

- The basic reproduction number, R_0, is the average number of secondary infectious cases produced by an infectious case. It determines the potential for epidemic spread in a totally susceptible population in the absence of specific control measures.
- Various modeling approaches yield similar results, i.e. R_0 is approximately 3 in the absence of specific public health measures.

Animal and Environmental Reservoirs

Animal Reservoirs

- There is considerable speculation about whether there is an animal reservoir for the SARS-CoV and if SARS is a zoonotic infection that has successfully crossed the species barrier.
- There is evidence that natural infection with SARS-CoV may occur in a number of animal species indigenous to China and parts of South-East Asia.
- A number of studies of both domestic and wild animals are underway and/or planned. Information on the potential role of animals in the transmission of SARS is important to the overall understanding of SARS
- Studies indicate that the SARS virus exists outside a human host; however, many questions remain. The eradication of SARS-CoV is unlikely if the infection is zoonotic.

Food Safety

- Food has not been shown to be infective for SARS-CoV. However, symptomatic patients with febrile illnesses of any sort should not handle or prepare food for others.
- WHO is developing recommendations for food safety, given the trade and marketing implications if food and food handling were to be associated with the transmission of SARS.

Stability and Resistance of the SARS Coronavirus

- The virus is stable in faeces and urine at room temperature for at least 1-2 days; it is stable for up to 4 days in stool from patients with diarrhea because of its higher pH compared to normal stool.
- Data from a number of areas indicate that SARS-CoV has been isolated on a variety of environmental surfaces.
- The virus loses infectivity after exposure to different commonly used disinfectants and fixatives. In addition, heat at 56°C rapidly kills approximately 10,000 units of SARS-CoV per 15 minutes.

References

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