Severe acute respiratory syndrome (SARS)

The right clinical information, right where it's needed
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## Disclaimer
Emerging infectious disease responsible for the first pandemic of the 21st century; there have been no reported cases since 2004.

Infection control precautions are of paramount importance; transmission is usually caused by direct contact with infected individuals through respiratory droplets.

Reverse-transcription polymerase chain reaction (RT-PCR) is the test of choice for confirming diagnosis.

Treatment is mainly supportive; neither specific therapy nor a vaccine is available.

Fatality rate is about 10% and death usually occurs due to severe respiratory failure.
**Definition**

Severe acute respiratory syndrome (SARS) is a viral pneumonia that rapidly progresses to respiratory failure.[1] It is an emerging, potentially fatal infectious disease.[2] A novel coronavirus (SARS-CoV), which is not closely related to any of the previously characterized coronaviruses, has been identified as the pathogen responsible for the disease.[3] This syndrome is associated with signs and symptoms of acute lower respiratory tract illness and radiologic evidence of consolidation following close contact with an infected person.[1]

**Epidemiology**

Early cases of SARS appeared to have originated in southern China (Guangdong province) as an unusual epidemic of severe pneumonia in November 2002. In 2003, an international outbreak developed involving 29 countries with 8098 cases of probable SARS and 774 (9.6%) deaths.[2] Most of what is known about the disease has been provided by this 2003 outbreak. The countries with the greatest number of reported cases included China, Hong Kong, Taiwan, Singapore, and Canada.

In the US there were 27 cases (13 female and 14 male, with a median age of 36 years), 8 of which had laboratory evidence of SARS coronavirus (CoV) infection. The probable date of onset of the last case was July 13, 2003, and all of those infected had traveled to parts of the world affected with SARS. The disease did not spread more widely within the community in the US and there were no reported deaths.

There are no known cases of SARS transmission in any part of the world. The last known case in North America was identified on June 22, 2003, in Toronto, and globally on July 15, 2003, in Taiwan. Since then, 7 additional sporadic cases in humans have been reported: 2 laboratory-acquired in Singapore and Taiwan in 2003, and a cluster of 5 confirmed cases in China in April 2004.

**Etiology**

The newly recognized SARS coronavirus (CoV) has been identified as the probable causal agent of SARS.[3] SARS-CoV is an enveloped, positive-strand RNA virus in the Coronaviridae family. Human coronaviruses such as OC43 and 229E have definitively been associated with upper respiratory tract illness, while the recently discovered agents NL63 and HKU1 are recognized as common causes of community-acquired respiratory infections.

The origin of SARS-CoV is still being investigated. The fact that SARS-like viruses have been identified in a number of different animals supports the hypothesis that SARS-CoV was first transmitted to humans from wild animals used for food, with subsequent person-to-person transmission.[6] Furthermore, genotypic evidence suggests that SARS-CoV evolved from a positive selective pressure acting on animal SARS-like viruses, finally leading to the emergence of the SARS-CoV genotype responsible for the pandemic of 2002-2003. While animal reservoirs of animal SARS-like viruses exist, human or animal reservoirs of SARS-CoV have not been found. Research laboratories are recognized as the only reservoirs of SARS-CoV, highlighting the importance of biosafety. Recent findings that horseshoe bats are the natural reservoir of a SARS-like CoV and that civet cats are the amplification host explain how these animals may serve as the source and amplification focuses for emerging infections.[7] [8]
Pathophysiology

SARS coronavirus (CoV) is transmitted primarily through droplets, entering the human body via the respiratory tract mucosa and causing viremia. Angiotensin-converting enzyme 2 (ACE2) has been identified as a functional receptor for SARS-CoV.[9] The incubation period is 2 to 10 days and the risk of transmission is greater during the second week of illness, which correlates with the timing of peak viral load.[10] [11] The possibility of fomite transmission and airborne transmission cannot be excluded, although the role of fecal-oral or fecal-respiratory spread seems to be of minor importance.[12] Although each SARS case is expected to infect 2 to 4 people,[13] it is thought that, in the pandemic of 2002-2003, a small number of infected individuals were responsible for a disproportionate number of transmissions in so-called "superspreading events," and that it was through this mechanism that the SARS outbreak disseminated globally.[14] [15]

There are 3 phases in the course of the disease: viral replication, inflammatory pneumonitis, and pulmonary fibrosis.[16] Pathologic findings of the lungs include diffuse alveolar damage, desquamation of pneumocytes, hyaline membrane formation, and inflammatory infiltrates.[17] The longer the course of the disease, the more extensive the fibrous organization of the lung tissue.

Clinical deterioration in some patients during the third week of illness, despite a fall in viral load, suggests that immune dysregulation may play a role.[18] [19] Furthermore, the HLA-B*4601 haplotype has been associated with the severity of SARS infection, suggesting the existence of a genetic predisposition.[20]
Primary prevention

Implementation and maintenance of appropriate control measures on the handling and trading of wild animals offered for human consumption in food markets is critical in the primary prevention of SARS.

Secondary prevention

As disease transmission appears to occur through close interactions with infected individuals, early recognition of new SARS cases is the cornerstone for preventing the spread of the disease.[91] [92] A high level of suspicion is required in the inter-epidemic period, especially when “unusual” cases of severe lower respiratory tract infection are identified. There are a number of strategies to reduce further transmission of the disease within both the hospital and the community setting.

- Healthcare workers or others exposed to SARS patients should be monitored for possible development of the disease.
- Individuals who have had unprotected contact with a confirmed or suspected case of SARS must be quarantined for 10 days after the potential exposure. No specific precautions are required for those sharing the household with a person in quarantine as long as that person remains asymptomatic.
- Implementation of infection control precautions should be immediate, with the initiation of triage strategies that ensure early recognition of possible cases. The healthcare infrastructure has to be examined and upgraded in order to handle efficiently a possible re-emergence of SARS.[93]
- Fever screening stations, triage of fever patients, separating SARS patients from other patients, separation of entrances and passageways between patients and healthcare workers, and increasing hand-washing facilities all demonstrated a protective effect for healthcare workers.[94]
- Healthcare workers should be adequately trained in and diligently adhere to infection control guidelines.[95]
- Healthcare workers must use protective masks, such as the N95,[96] or HEPA filter-containing respirators, long sleeve forms, impermeable gowns, and clean gloves.[97] If slash or spray of respiratory secretions or other body fluids is likely, protection of the eyes with goggles or a face shield is required. Good air ventilation in SARS wards may be effective in minimizing or preventing SARS transmission among healthcare workers in hospitals.[98]
- Labor and delivery of pregnant patients with suspected and probable SARS should be managed in a designated negative pressure isolation room, by personnel with specialized infection control preparation and protective gear. [99]
- Neonates of mothers with SARS should be isolated in a designated unit until the infant has been well for 10 days, or until the mother’s period of isolation is complete. The mother should not breastfeed during this period.[99]
**Case history**

**Case history #1**

A 34-year-old man presents to the emergency department with a 3-day history of fever, chills, headache, dry cough, myalgia, dyspnea, and diarrhea. He reports that he returned from an area with a recently documented cluster of SARS cases 5 days prior to the onset of his symptoms. He is hypoxic, and the initial chest x-ray reveals multifocal bilateral infiltrates. Laboratory findings show a moderate leukopenia (in particular, lymphopenia) and thrombocytopenia along with elevated creatinine kinase, lactate dehydrogenase, and aminotransferase levels. He is isolated in a negative pressure chamber and gradually improves over the next 4 days. On day 5, the fever and diarrhea relapse and subsequent chest x-rays reveal new infiltrations. The patient develops respiratory failure and hemodynamic instability. He is transferred to the ICU, where mechanical ventilation is initiated. As clinical deterioration continues, he progresses to acute respiratory distress syndrome (ARDS) and dies 6 days later.

**Other presentations**

The typical febrile response may be absent in older patients, who may present with malaise, loss of appetite, delirium, or even an episode of a fall with an associated fracture.[4] Infants and children present with milder symptoms and associated rhinorrhea in 50% of cases.

**Step-by-step diagnostic approach**

The clinical manifestations of SARS are nonspecific and mimic other causes of respiratory infection.[16] However, a combination of epidemiologic and clinical features increase the likelihood of a diagnosis of SARS, which is confirmed with viral testing. Maintaining a high index of suspicion, in case of a reemergence of SARS coronavirus (CoV) infection, is essential for the early diagnosis of the disease.

Although hematologic and radiologic findings are only suggestive of a diagnosis in a suspected case of SARS, these investigations are indicative of disease prognosis and are essential for the follow-up of treatment.

**Clinical history**

The aim of the history is to demonstrate epidemiologic and clinical features that will aid diagnosis.[21]

It should include questioning on the following epidemiologic factors.

- History of recent travel, within 10 days of the onset of symptoms, to a foreign or domestic location with documented or suspected recent transmission of SARS: raises suspicion of the infection.[21]
- History of close, prolonged contact with an individual suspected of or documented as being infected with SARS-CoV.[22]
- History of exposure to anyone with an unexplained respiratory illness who has recently traveled to a country affected by SARS.[21]
- History of contact with contaminated materials: of particular importance in relation to laboratory workers.[24]
The chronology of symptoms is also important.

- Prodromal symptoms are similar to those of other viral infections, with myalgia, malaise, and headache.
- These progress to the early symptoms of fever with associated chills (rapid onset and persistent), cough (usually nonproductive and develops 2 to 7 days from the onset of symptoms), and sore throat.
- Later symptoms include dyspnea (develops 8 to 12 days from the onset of symptoms), watery diarrhea (occurs in 20% to 25% of cases in the second week), chest pain, and pleurisy.\[4\] \[24\] Other less common symptoms include nausea and vomiting, abdominal pain, rhinorrhea, arthralgia, sputum production, dizziness, and seizure.

The typical febrile response may be absent in older adult patients, who may present with nonspecific symptoms such as malaise, loss of appetite, or delirium, or even an episode of a fall with an associated fracture.\[4\] Infants and children present with milder symptoms and associated rhinorrhea in 50% of cases.

**Physical exam**

On examination, the patient may be febrile with a temperature of 100.4°F (38°C) or more, with rigors, shortness of breath, tachypnea, tachycardia, and cyanosis.\[4\] Auscultation of the chest may reveal inspiratory crackles, rales, and/or bronchial breathing.

Less common findings in atypical cases include altered mental status, confusion, and delirium.

**Initial investigations**

First-line evaluation of a patient with suspected SARS should include routine laboratory tests, cultures, and a chest x-ray, with pulse oximetry and ABG measurement necessary in patients with respiratory distress and cyanosis.

**Blood tests**

- CBC: leukopenia is common, with lymphopenia reported in 98% of patients early in the disease.\[3\] Lymphopenia is due to reduced CD4 and CD8 cell counts. Thrombocytopenia is found in the presence of disseminated intravascular coagulation.
- LFTs: mild elevation of AST and ALT has been reported in 23% to 50% of SARS patients, although this result shows low specificity for diagnosis of the disease.\[19\]
- Lactate dehydrogenase: elevated.
- Creatine kinase: elevated.

**Blood and sputum cultures**

- All patients with signs of severe infection should receive blood and sputum cultures to rule out other causes of a lower respiratory tract infection, such as community-acquired pneumonia, especially those without a typical epidemiologic history for SARS.
- Blood cultures would be negative for a bacterial infection, and the sputum culture would not show growth of *Streptococcus pneumoniae* or other infecting bacteria in SARS.

**Tests for influenza virus**
**Severe acute respiratory syndrome (SARS)**

**Diagnosis**

- Nasopharyngeal virus culture and direct immunofluorescent antibody staining would be negative for influenza A and influenza B viruses in SARS.

**Chest x-ray**

[Fig-1]

- About 20% to 25% of cases have a normal chest x-ray on presentation.[24] [25]
- Examined for unilateral or bilateral infiltrates in the peripheries of the lower zones. Infiltrates manifest as patchy, confluent, or diffuse consolidation, or nodular shadowing.
- Cavitation, hilar lymphadenopathy, and pleural effusion are not typically seen.[26]
- Pneumomediastinum and pneumothorax often occur with assisted ventilation.[27]

**Further investigations**

**Pulse oximetry**

- Indicated in patients with respiratory distress and cyanosis.
- Reveals a low oxygen saturation (SpO2 <90%).

**ABG**

- Performed when the SpO2 measured with pulse oximetry is <90%.
- Reveals low partial oxygen pressure.

**Coagulation screen**

- Indicated in patients with spontaneous bleeding.
- Reveals a prolonged activated partial thromboplastin time (aPTT) and elevated D-dimers.

**High-resolution CT (HRCT)**

- Imaging of the thorax with HRCT should be undertaken in those with a normal chest x-ray on presentation and a high suspicion of SARS for the detection of lung opacities.
- Reveals ground glass opacities with interlobular septal thickening and, in some cases, subpleural consolidation.
- Abnormal in 67% of patients with an initially normal chest x-ray.[28]

**Specific viral testing**

**Reverse-transcription polymerase chain reaction (RT-PCR)**

- Detecting SARS-CoV-specific RNA directly using an RT-PCR assay is the mainstay of laboratory diagnosis and should be ordered in all suspected cases immediately.
- For a positive diagnosis based on PCR testing, the patient must have either 2 positive clinical specimens from different anatomic sites or positive specimens from the same site on 2 separate occasions.[29]
- Multiple specimen sources should be obtained. During the first week, nasopharyngeal, oropharyngeal, and serum/plasma specimens should be tested and, following this, nasopharyngeal, oropharyngeal, and stool specimens should be sampled.
Severe acute respiratory syndrome (SARS) Diagnosis

• Preferred samples are respiratory tract specimens (nasopharyngeal aspirate or throat swab) obtained in viral transport media. Stool specimens or whole blood samples in ethylene diamine tetra-acetic acid (EDTA) are also appropriate.
• Nasopharyngeal specimens, which are often negative during the first week of infection, have the highest positivity rates in the second week of illness, peaking at approximately day 10.
• The positivity rates on urine, nasopharyngeal aspirate, and stool specimen have been reported to be 42%, 68%, and 97%, respectively, on day 14 of illness.[11]
• The sensitivity of these tests, which is highly dependent on the type of specimen and increases the later the time of collection after the onset of symptoms, ranges from 83.3% to 100%. The specificities range from 94% to 100%.[30]
• Respiratory and stool specimens have the highest yield (between 80% and 90%) 10 to 14 days into the course of the disease.[31]
• Improved methods of specimen collection and real-time RT-PCR assays have improved the sensitivity of testing during the first few days of illness.[32]
• Quantitative measurement of blood SARS-CoV RNA with the technique of real-time RT-PCR has a detection rate of 80% as early as day 1 of the disease, with a subsequent drop to 45% on day 14.[32]

Serologic testing for SARS-CoV-specific antibodies

• Tested using an immunofluorescent antibody assay (IFA) or enzyme-linked immunosorbent assay (ELISA).
• Useful for epidemiologic surveillance and retrospective diagnosis.
• Serum specimens should be collected when the diagnosis is first suspected and at later times if indicated.
• Seroconversion usually occurs 1 to 4 weeks (>90% after day 28) after the onset of symptoms, with an antibody response (4-fold increase in SARS-CoV antibody) occasionally detected during the first week of illness, likely to be detected by the end of the second week of illness, but not normally detected until >28 days into the illness.[29] [33]

Viral culture

• Not recommended for routine detection.[29]
• Lacks sensitivity of RT-PCR.
• Given the potential risk of transmission, growth of the SARS-CoV virus should be restricted to biosafety level III (or IV) laboratories.[33]

Rapid immunoswab assay for SARS-CoV detection

• An emerging diagnostic test.
• The key feature of this simple immunoswab diagnostic assay is its ability to detect the presence of the SARS-CoV antigen (nucleocapsid protein) within 45 to 60 minutes following availability of the body fluid samples.[34]

Monoclonal antibodies

• An emerging diagnostic test.
• Five monoclonal antibodies against recombinant nucleocapsid protein of SARS-CoV were developed by hybridoma technology.
• Potentially ideal candidates for developing early and sensitive diagnostic assays for SARS-CoV.[35]
Severe acute respiratory syndrome (SARS)

Diagnosis

[VIDEO: Radial artery puncture animated demonstration ]

[VIDEO: Femoral artery puncture animated demonstration ]

Risk factors

Strong travel to affected area

• History of recent travel, within 10 days of the onset of symptoms, to a foreign or domestic location with documented or suspected recent transmission of SARS raises suspicion of the infection.[21]

close contact with infected individuals

• Risk of transmission is enhanced by close, prolonged contact with an infected individual.[22]

Transmission in hospitals was a major factor in the amplification of outbreaks, and a significant proportion of those affected were healthcare workers. Healthcare workers, especially those who are exposed to respiratory secretions of a SARS patient (for example, when intubating, suctioning, manipulating oxygen masks, or applying noninvasive ventilation), are at increased risk of infection. In addition, household members in close proximity to a SARS patient, such as those involved in direct patient care, have a higher risk of acquiring SARS.[23]

laboratory work on SARS coronavirus (CoV)

• Cases of SARS infection have been reported in research laboratories working on SARS-CoV.[24]

Providing guidelines for biosafety standards and maintaining continuous vigilance can minimize the risk of such transmission.

History & examination factors

Key diagnostic factors

hx of travel to affected area (common)

• History of recent travel, within 10 days of the onset of symptoms, to a foreign or domestic location with documented or suspected recent transmission of SARS raises suspicion of the infection.[21]

hx of close contact with infected individuals (common)

• Risk of transmission is enhanced by close, prolonged contact with an infected individual.[22]

hx of laboratory work on SARS coronavirus (CoV) (common)

• Cases of SARS infection have been reported in research laboratories working on SARS-CoV.[24]

fever (common)

• Rapid onset of a persistent temperature 100.4°F (38°C) or more is an early symptom and sign. Afebrile cases of SARS can occur in older adults.[4] [36]

cough (common)

• Common in the early respiratory phase (2-7 days from the onset of symptoms) of the disease. Usually nonproductive.
myalgia (common)
- Prominent in the prodromal phase of the disease. The patient complains of muscle aches.

dyspnea (common)
- Prominent later in the course of the disease (8-12 days from the onset of symptoms). Ranges from mild to severe.

Other diagnostic factors

chills or rigors (common)
- Usually associated with fever.

malaise (common)
- Present in the prodromal phase of the disease.

headache (common)
- Usually present in the prodromal phase of the disease.

watery diarrhea (common)
- Occurs in 20% to 25% of the patients, usually late in the course of the disease (second week) and together with recurrence of fever. Usually watery without blood or mucus.[11]

tachypnea (common)
- A respiratory rate of >20 breaths per minute is present in patients with respiratory distress.

tachycardia (common)
- Usually present in patients with fever and/or respiratory distress.

cyanosis (common)
- A low oxygen saturation is present in patients with respiratory failure progressing to ARDS.

nausea and vomiting (uncommon)
- Nonspecific symptom, present in many viral infections. Reported frequency up to 19.5%[1]

sore throat (uncommon)
- May be present early in the course of disease.

sputum production (uncommon)
- May be present, but cough is usually nonproductive.

chest pain (uncommon)
- If present, appears late in the course of the disease.

pleurisy (uncommon)
- If present, appears late in the course of the disease.

rhinorrhea (uncommon)
Severe acute respiratory syndrome (SARS)

Diagnosis

- Appears mainly in children and infants, who present with a milder course of the disease with associated rhinorrhea in 50% of cases.[37]

**dizziness (uncommon)**
- Nonspecific symptom, present in many viral infections. Reported frequency varies from 4.2% to 43%. [1]

**arthralgia (uncommon)**
- Common symptom of many viral infections. Reported frequency up to 10.4%. [1]

**abdominal pain (uncommon)**
- Reported frequency 3.5%. [1]

**seizure (uncommon)**
- A severe acute neurologic syndrome has been reported in patients who developed status epilepticus. SARS coronavirus (CoV) RNA has been detected in cerebrospinal fluid. [38]

**delirium (uncommon)**
- May be present in older adult patients, who often have an atypical presentation of symptoms. [39]

**rales (uncommon)**
- Present in less than one third of cases. Clinically less severe than would be expected from the radiologic findings. [3]

**inspiratory crackles (uncommon)**
- Auscultation of the chest may reveal inspiratory crackles.

**bronchial breathing (uncommon)**
- Auscultation of the chest may reveal bronchial breathing.
## Diagnostic tests

### 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CBC</strong></td>
<td>Leukopenia is common, with lymphopenia reported in 98% of patients early in the disease. Lymphopenia is due to reduced CD4 and CD8 cell counts. Thrombocytopenia is found in the presence of DIC.</td>
</tr>
<tr>
<td><strong>aminotransferases</strong></td>
<td>Mild elevation of AST and ALT has been reported in 23% to 50% of SARS patients, although this result shows low specificity for diagnosis of the disease.</td>
</tr>
<tr>
<td><strong>lactate dehydrogenase</strong></td>
<td>Common, nonspecific laboratory abnormality. Indicates liver injury or lysis of blood erythrocytes.</td>
</tr>
<tr>
<td><strong>creatine kinase</strong></td>
<td>Common, nonspecific laboratory abnormality. Indicates muscle or myocardium injury. Has also been related to left ventricular dysfunction.</td>
</tr>
<tr>
<td><strong>blood culture</strong></td>
<td>All patients with signs of severe infection should receive blood and sputum cultures to rule out other causes of a lower respiratory tract infection, especially those without a typical epidemiologic history for SARS.</td>
</tr>
<tr>
<td><strong>sputum culture</strong></td>
<td>All patients with signs of severe infection should receive blood and sputum cultures to rule out other causes of a lower respiratory tract infection, such as community-acquired pneumonia, especially those without a typical epidemiologic history for SARS.</td>
</tr>
<tr>
<td><strong>nasopharyngeal virus culture</strong></td>
<td>To rule out presence of influenza infection.</td>
</tr>
<tr>
<td><strong>direct immunofluorescent antibody staining</strong></td>
<td>To rule out presence of influenza infection.</td>
</tr>
<tr>
<td><strong>CXR</strong></td>
<td>About 20% to 25% of cases have a normal chest x-ray on presentation. Examine chest x-ray for unilateral or bilateral infiltrates in the peripheries of the lower zones. Infiltrates manifest as patchy, confluent, or diffuse consolidation, or nodular shadowing. Cavitation, hilar lymphadenopathy, and pleural effusion are not typically seen. Pneumomediastinum and pneumothorax often occur with assisted ventilation.</td>
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<tr>
<td><strong>pulse oximetry</strong></td>
<td>Indicated in patients with respiratory distress and cyanosis. Low oxygen saturation (SpO2 &lt;90%)</td>
</tr>
</tbody>
</table>
Severe acute respiratory syndrome (SARS)

**Diagnosis**

Test | Result
---|---
reverse-transcription polymerase chain reaction (RT-PCR) | positive for SARS coronavirus (CoV)-specific RNA
  - For a positive diagnosis based on PCR testing, the patient must have either 2 positive clinical specimens from different anatomic sites or positive specimens from the same site on 2 separate occasions.[40]
  - Multiple specimen sources should be sampled: nasopharyngeal, oropharyngeal, and serum/plasma specimens (during first week); nasopharyngeal, oropharyngeal, and stool specimens (after first week).
  - Preferred samples are a nasopharyngeal aspirate (often negative in first week of infection) or throat swab obtained in viral transport media. Dacron or rayon swabs with plastic shafts should be used rather than those with calcium alginate or wooden sticks. Specimens must be shipped in cold packs to keep the sample at 39.2°F (4°C).
  - Stool specimens or whole blood samples in ethylene diamine tetra-acetic acid (EDTA) are also appropriate.
  - Quantitative measurement of blood SARS coronavirus (CoV) RNA with the technique of real time RT-PCR has a detection rate of 80% as early as day 1 of the disease.[32]

**Other tests to consider**

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ABG</strong></td>
<td>low partial oxygen pressure</td>
</tr>
</tbody>
</table>
  - Performed when the SpO2 measured with pulse oximetry is <90%.
| **coagulation screen** | prolonged PT, elevated D-dimers |
  - Indicated in patients with spontaneous bleeding.
| **high-resolution CT (HRCT) of thorax** | ground glass opacities with interlobular septal thickening ± subpleural consolidation |
  - Imaging of the thorax with HRCT should be undertaken in those with a normal chest x-ray on presentation and a high suspicion of SARS for the detection of lung opacities.
  - Abnormal in 67% of patients with an initially normal chest x-ray.[28]
| **serologic testing for SARS coronavirus (CoV)-specific antibodies** | 4-fold increase in SARS-CoV antibody |
  - Tested using an immunofluorescent antibody assay (IFA) or ELISA.
  - Useful for epidemiologic surveillance and retrospective diagnosis.
  - Serum specimens should be collected when the diagnosis is first suspected and at later times if indicated.
  - Seroconversion usually occurs 1 to 4 weeks (>90% after day 28) after the onset of symptoms, with an antibody response (4-fold increase in SARS-CoV antibody) occasionally detected during the first week of illness, likely to be detected by the end of the second week of illness, but not normally detected until >28 days into the illness.[40] [33]
| **viral culture** | growth of SARS coronavirus (CoV) |
  - Not recommended for routine detection.[40]
  - Lacks sensitivity of RT-PCR.
  - Given the potential risk of transmission, growth of the SARS coronavirus (CoV) should be restricted to biosafety level III (or IV) laboratories.[33]
# Emerging tests

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>rapid immunoswab assay for SARS coronavirus (CoV) detection</td>
<td>detects presence of SARS-CoV antigen</td>
</tr>
<tr>
<td>• The key feature of this simple immunoswab diagnostic assay is its</td>
<td></td>
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<tr>
<td>ability to detect the presence of the SARS-CoV antigen (nucleocapsid</td>
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<tr>
<td>protein) within 45 to 60 minutes following availability of the body fluid samples. [34]</td>
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<td>monoclonal antibodies</td>
<td>detects presence of SARS coronavirus (CoV) with high specificity</td>
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<td>• Five monoclonal antibodies against recombinant nucleocapsid protein</td>
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<td>of SARS coronavirus (CoV) were developed by hybridoma technology,</td>
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<td>Potentially ideal candidates for developing early and sensitive</td>
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<tr>
<td>diagnostic assays for SARS-CoV. [35]</td>
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</tbody>
</table>
# Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Coronavirus disease 2019 (COVID-19)    | • Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset.  
• Signs and symptoms are similar so it may be difficult to differentiate between the conditions clinically.  
• The situation is evolving rapidly; see our COVID-19 topic for further information.                                                                                   | • Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for SARS-CoV-2 viral RNA.  
• It is not possible to differentiate COVID-19 from other causes of pneumonia on chest imaging.                                                                            |
| Middle East respiratory syndrome (MERS) | • Caused by MERS coronavirus (MERS-CoV).  
• Associated with history of travel in countries of the Arabian Peninsula.  
• Clinical features are similar to those of SARS, but progresses to respiratory failure much more rapidly than SARS.  
• Primarily affects older individuals, with a male predominance.  
• In contrast to SARS, about 75% of patients with MERS-CoV have at least 1 comorbid illness.[41]                                                                              | • Nasopharyngeal swabs (RT-PCR): positive for MERS-CoV.                                                                                                                                                                 |
| Community-acquired pneumonia           | • Lack of recent travel history to an affected area or of recent close contact with a person confirmed with or suspected of having SARS.                                                                                               | • Sputum and blood cultures: may be positive for *Streptococcus pneumoniae* or other bacterial pathogens.  
• CBC: leukocytosis and/or elevated neutrophil count. Clinical and radiologic improvement with proper antibiotic therapy.                                                                                     |
| Viral respiratory infections           | • Lack of history of recent travel to an affected area or of recent close contact with a person confirmed with or suspected of having SARS.  
• Unlikely to cause serious illness in young patients with no comorbidities.                                                                                                                                              | • Nasopharyngeal virus culture and direct fluorescent antibody/ELISA: may be positive for such pathogens as influenza viruses (A and B), respiratory syncytial virus, parainfluenza viruses, and adenovirus. |
<table>
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<td></td>
<td>respiratory symptoms are usually present.</td>
<td>Serology: useful for retrospective diagnosis.</td>
</tr>
<tr>
<td>Atypical pneumonia</td>
<td>• Lack of history of recent travel to an affected area or of recent close contact with a person confirmed with or suspected of having SARS. • Mild respiratory illness, often occurring in young people following exposure in close community settings.</td>
<td>Serology, PCR, or culture of nasopharyngeal swabs for <em>Chlamydia pneumoniae</em> and <em>Mycoplasma pneumoniae</em>. • Sputum culture or direct fluorescent antigen detection for <em>Legionella pneumophila</em>. • Rapid urinary <em>Legionella</em> antigen detection.</td>
</tr>
<tr>
<td></td>
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<tr>
<td>Avian influenza infection</td>
<td>• Difficult to distinguish from SARS based on symptomatology as both cause a febrile lower respiratory tract illness. Historical risk factors may prove useful as avian influenza is more commonly associated with travel to a country affected with avian influenza A (H5N1) virus or direct contact with poultry or birds that may be carriers of H5N1.</td>
<td>Pharyngeal swab: positive RT-PCR for H5-specific RNA. • Immunofluorescence antigen test: positive for antigen of H5N1 virus. • Viral culture: growth of H5N1. • Serologic testing: positive for H5N1-specific antibody.</td>
</tr>
</tbody>
</table>

**Diagnostic criteria**

**WHO case definitions of SARS in the post outbreak period[42]**

Clinical case definition requires all of the following:

- Fever (≥100.4°F [38°C])
- One or more symptoms of lower respiratory tract illness: cough, difficult breathing, SOB
- Radiologic evidence of lung infiltrates consistent with pneumonia or respiratory distress syndrome
- No alternative diagnosis that can fully explain the illness.

Laboratory case definition:

- Positive laboratory findings of SARS coronavirus (CoV), based on either or both of the following diagnostic criteria:
  - PCR positive from at least 2 different clinical specimens or the same specimen collected on 2 or more occasions during the course of the illness
  - Seroconversion between acute and convalescent phase sera and virus isolation.

**CDC updated interim case definition for SARS[21]**
Clinical criteria

• Early respiratory illness
  • Two or more of the following features: fever, chills, rigors, myalgia, headache, diarrhea, sore throat, rhinorrhea.
• Mild to moderate respiratory illness
  • Fever (≥100.4°F [38°C]) plus 1 or more symptoms of lower respiratory tract illness: cough, dyspnea, difficulty breathing.
• Severe respiratory illness
  • Mild to moderate respiratory illness plus radiologic evidence of lung infiltrates consistent with pneumonia or ARDS.

Epidemiologic criteria

• History of recent travel, within 10 days of the onset of symptoms, to a foreign or domestic location with documented or suspected recent transmission of SARS; or
• Close contact with a person confirmed with or suspected of having SARS.

Laboratory criteria

• Detection of serum antibodies to SARS-CoV; or
• Isolation in cell culture of SARS-CoV from a clinical specimen; or
• Detection of SARS-CoV RNA by reverse-transcription polymerase chain reaction (RT-PCR) testing with subsequent confirmation in a reference laboratory.

Probable case of SARS-CoV

• Patient meets the clinical criteria for severe respiratory illness and the epidemiologic criteria for likely exposure to SARS-CoV.

Confirmed case of SARS-CoV

• Patient has a clinically compatible respiratory illness (early, mild to moderate, or severe) that is confirmed by the laboratory.
Step-by-step treatment approach

There are currently no specific treatments shown to be effective against SARS. A variety of pharmacologic interventions have been used, but their efficacy remains inconclusive.[44] Therefore, treatment is focused on the alleviation of symptoms, the prevention and treatment of complications, and the aggressive support of vital functions if these are threatened or compromised.

Isolation procedures

Once a clinical suspicion of SARS has been established, all appropriate protective measures must be initiated to minimize the risk of transmission, with immediate implementation of the strict contact and airborne precautions set out by the CDC.[40] These measures must be further intensified when diagnostic or therapeutic aerosol-generating procedures are carried out.

An assessment of the clinical severity allows the most appropriate location for management to be established. The CDC advises that patients with SARS coronavirus (CoV) disease who do not require hospitalization for medical reasons may be isolated at home.[40] Stable patients should be placed in isolation and nursed in a negative pressure room where one is available. More severe cases (i.e., those presenting with or developing acute respiratory failure) should be admitted to the ICU or an intermediate care unit under airborne transmission precautions.

Supportive care

Supportive care is the mainstay of treatment. This includes administration of adequate supplemental oxygen to correct hypoxemia, replacement of fluid deficits caused by diarrhea or fever, correction of electrolyte disturbances, and antipyretics and analgesics to control fever and pain.

Impending or established respiratory failure

Patients with impending or established respiratory failure should be admitted to the ICU or an intermediate care unit. About 14% to 26% of all SARS cases and about 50% to 85% of patients admitted to the ICU will require either invasive (preferred) or noninvasive mechanical ventilation.[19] [24] [25] [36] [45] [46] [47] Intubation and mechanical ventilation are instituted if the patient is clinically deteriorating and cannot maintain an SaO2 >90% with spontaneous ventilation despite maximal oxygen therapy.[B]Evidence

Noninvasive mechanical ventilation[48]

- The role of noninvasive positive pressure ventilation (NIPPV) is controversial.
- Although it appears to reduce mortality and the need for intubation, there are concerns regarding the possibility of viral transmission.
- High rates of pneumothorax as well as subcutaneous and mediastinal emphysema are also noted with NIPPV.

In order to decrease the risk of transmission during mechanical ventilation, the following precautions must be taken.

- Avoidance of nebulized humidity and utilization of Venturi masks without humidification.[49]
- Avoidance of bag-mask ventilation and utilization of masks that permit filtration of exhaled gas.
- Utilization of adequate sedation during intubation.
• Utilization of closed suction systems and submicron filters in the exhalation outlet of mechanical ventilators.
• Utilization of sedation or paralysis to minimize coughing.
• Turning ventilator to standby and PEEP to off when disconnecting the circuit.
• Avoidance of bronchoscopy if possible.

**Empiric therapy for community-acquired pneumonia ± influenza**

Due to the initial uncertainty regarding diagnosis, empiric antibiotic therapy against both typical (including drug-resistant strains) and atypical community-acquired respiratory pathogens is a prudent first-line therapy.

An appropriate beta-lactam combined with a quinolone or a macrolide represent a reasonable option. Possible intravenous combinations in hospitalized patients include ceftriaxone and azithromycin, or ertapenem and azithromycin. Monotherapy with levofloxacin or moxifloxacin is an alternative.[50] Antibiotic therapy should be discontinued as soon as a definite diagnosis of SARS is documented.

When epidemiologically indicated (i.e., during a seasonal epidemic of influenza), influenza virus should also be covered with a 5-day course of either zanamivir or oseltamivir.

**Antiviral therapy upon confirmation of the diagnosis**

RCT data on the efficacy of antivirals in the treatment of SARS are limited, although the consensus is that antiviral therapy should be given to all confirmed cases as early as possible. The combination of the antiproteases lopinavir/ritonavir should be given for 14 days.[51]

Although not effective as a monotherapy, ribavirin can be given with the antiprotease lopinavir/ritonavir combination.[16]

**Severe infection**

In addition to the above measures, patients with severe infection (deteriorating radiographic consolidation, increasing oxygen requirement [SpO2 <90%/Oxygenation Index <300 mmHg/PaO2 <10 kpa], and a respiratory rate of ≥30 breaths/minute) should receive corticosteroids with the possible addition of immunoglobulin, interferon, and convalescent plasma.

Corticosteroids have been reported to have some efficacy in severe cases (critical SARS).[52] Although various regimens have been tried, the most commonly used is 3 to 6 days of pulsed methylprednisolone. Corticosteroids added to lopinavir/ritonavir and/or ribavirin early in the course of the infection have been shown to reduce the progression to ARDS as well as the death rate.[16]

Immunoglobulin, interferon, or convalescent plasma should be added in patients who do not show a favorable response to treatment with pulsed methylprednisolone and ribavirin.

• Although not available in the US or the UK, a 5-day course of IgM-enriched immunoglobulin (pentaglobin®), has been found to be beneficial in the treatment of SARS in other countries.[53]
• Interferon has shown promising results in in vitro and animal models. Interferon alfa-2b has been shown to inhibit growth of SARS in vitro.[54]
• The efficacy of convalescent plasma administration as a treatment of SARS has not been documented.[55] [56]
Psychological support and counseling

Patients, as well as their relatives, may require consultation with a specialist in psychological therapy and counseling for specialized treatment.

In addition, healthcare workers report higher levels of burn-out, psychological distress associated with quarantine, fear of contagion, concern for family, and perceived stigma as well as post-traumatic stress, which limit their ability to provide high-quality patient care. Psychological and moral support for healthcare workers should be established in the acute phase and, ideally, in the prepandemic period in order to provide adequate preparation for future outbreaks. [57]

Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Initial</th>
<th>(summary)</th>
</tr>
</thead>
<tbody>
<tr>
<td>suspected SARS</td>
<td>1st isolation procedures plus supportive care</td>
</tr>
<tr>
<td></td>
<td>adjunct mechanical ventilation</td>
</tr>
<tr>
<td></td>
<td>plus empiric therapy for community-acquired pneumonia</td>
</tr>
<tr>
<td></td>
<td>adjunct empiric therapy for influenza</td>
</tr>
<tr>
<td>mild-moderate infection</td>
<td>1st isolation procedures plus supportive care</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------------------------------------------</td>
</tr>
<tr>
<td></td>
<td>plus lopinavir/ritonavir upon confirmation of diagnosis</td>
</tr>
<tr>
<td></td>
<td>adjunct ribavirin</td>
</tr>
<tr>
<td></td>
<td>adjunct psychological therapy and counseling</td>
</tr>
<tr>
<td>severe infection</td>
<td>1st isolation procedures plus supportive care</td>
</tr>
<tr>
<td></td>
<td>plus lopinavir/ritonavir upon confirmation of diagnosis</td>
</tr>
<tr>
<td></td>
<td>plus corticosteroid</td>
</tr>
<tr>
<td></td>
<td>adjunct ribavirin</td>
</tr>
<tr>
<td></td>
<td>adjunct interferon</td>
</tr>
<tr>
<td></td>
<td>adjunct convalescent plasma</td>
</tr>
<tr>
<td></td>
<td>adjunct psychological therapy and counseling</td>
</tr>
</tbody>
</table>
Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Initial suspected SARS

1st isolation procedures plus supportive care

» Once a clinical suspicion of SARS has been established, all appropriate protective measures must be initiated to minimize the risk of transmission, with immediate implementation of the strict contact and airborne precautions set out by the CDC. These measures must be further intensified when diagnostic or therapeutic aerosol-generating procedures are carried out.

» The CDC advises that patients with SARS coronavirus (CoV) disease who do not require hospitalization for medical reasons may be isolated at home. Stable patients should be placed in isolation and nursed in a negative pressure room where one is available. More severe cases (i.e., those presenting with or developing acute respiratory failure) should be admitted to the ICU or an intermediate care unit under airborne transmission precautions.

» Supportive care involves administration of adequate supplemental oxygen to correct hypoxemia, replacement of fluid deficit caused by diarrhea or fever, correction of electrolyte disturbances, and antipyretics and analgesia for the control of fever and pain.

adjunct mechanical ventilation

Treatment recommended for SOME patients in selected patient group

» Patients with impending or established respiratory failure should be admitted to the ICU or an intermediate care unit. Intubation and mechanical ventilation are instituted if the patient is clinically deteriorating and cannot maintain an SaO2 above 90% with spontaneous ventilation despite maximal oxygen therapy. Evidence

» Noninvasive positive pressure ventilation (NIPPV) is associated with the risk of viral transmission and high rates of pneumothorax as well as subcutaneous and mediastinal emphysema.

» To decrease the risk of transmission during mechanical ventilation, the following precautions must be taken: avoidance of nebulized humidity and utilization of Venturi masks without humidification, avoidance of bag-mask ventilation and utilization of masks that permit filtration of exhaled gas, utilization of adequate sedation during intubation, utilization of closed suction systems and submicron filters in the
Severe acute respiratory syndrome (SARS)

Treatment

**Initial**

Exhalation outlet of mechanical ventilators, utilization of sedation or paralysis to minimize coughing, turning ventilator to standby and PEEP to off when disconnecting the circuit, and avoidance of bronchoscopy if possible.

**plus**

Empiric therapy for community-acquired pneumonia

Treatment recommended for ALL patients in selected patient group

**Primary options**

- **ceftriaxone**: 1-2 g intravenously every 24 hours
- **azithromycin**: 500 mg intravenously every 24 hours

OR

- **ertapenem**: 1 g intravenously every 24 hours
- **azithromycin**: 500 mg intravenously every 24 hours

OR

- **levofloxacin**: 750 mg intravenously every 24 hours

OR

- **moxifloxacin**: 400 mg intravenously every 24 hours

**adjunct**

Empiric therapy for influenza

Treatment recommended for SOME patients in selected patient group

**Primary options**
<table>
<thead>
<tr>
<th>Initial</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>zanamivir</strong>: 10 mg (2 inhalations) twice daily for 5 days</td>
</tr>
<tr>
<td><strong>oseltamivir</strong>: 75 mg orally twice daily for 5 days</td>
</tr>
</tbody>
</table>

When epidemiologically indicated (i.e., during a seasonal epidemic of influenza), influenza virus should also be covered with a 5-day course of either zanamivir or oseltamivir.
Treatment

Acute confirmed SARS

- **mild-moderate infection**
  - 1st isolation procedures plus supportive care
    - Mild-moderate infection is denoted by fever (≥100.4°F [38°C]) plus 1 or more symptoms of lower respiratory tract illness: cough, dyspnea, difficulty breathing.[21] The following are absent: deteriorating radiographic consolidation, increasing oxygen requirement, and a respiratory rate of ≥30 breaths/minute.
    - Once a clinical suspicion of SARS has been established, all appropriate protective measures must be initiated to minimize the risk of transmission, with immediate implementation of the strict contact and airborne precautions set out by the CDC.[29] These measures must be further intensified when diagnostic or therapeutic aerosol-generating procedures are carried out.
    - The CDC advises that patients with SARS coronavirus (CoV) disease who do not require hospitalization for medical reasons may be isolated at home.[29] Stable patients should be placed in isolation and nursed in a negative pressure room where one is available. More severe cases (i.e., those presenting with or developing acute respiratory failure) should be admitted to the ICU or an intermediate care unit under airborne transmission precautions.
    - Supportive care involves administration of adequate supplemental oxygen to correct hypoxemia, replacement of fluid deficit caused by diarrhea or fever, correction of electrolyte disturbances, and antipyretics and analgesia for the control of fever and pain.

- **adjunct** mechanical ventilation
  - Treatment recommended for SOME patients in selected patient group
    - Patients with impending or established respiratory failure should be admitted to the ICU or an intermediate care unit. Intubation and mechanical ventilation are instituted if the patient is clinically deteriorating and cannot maintain an SaO2 above 90% with spontaneous ventilation despite maximal oxygen therapy.[B]Evidence
      - Noninvasive positive pressure ventilation (NIPPV) is associated with the risk of viral transmission and high rates of pneumothorax as well as subcutaneous and mediastinal emphysema.
Acute

» To decrease the risk of transmission during mechanical ventilation, the following precautions must be taken: avoidance of nebulized humidity and utilization of Venturi masks without humidification,[49] avoidance of bag-mask ventilation and utilization of masks that permit filtration of exhaled gas, utilization of adequate sedation during intubation, utilization of closed suction systems and submicron filters in the exhalation outlet of mechanical ventilators, utilization of sedation or paralysis to minimize coughing, turning ventilator to standby and PEEP to off when disconnecting the circuit, and avoidance of bronchoscopy if possible.

plus lopinavir/ritonavir upon confirmation of diagnosis

Treatment recommended for ALL patients in selected patient group

Primary options

» lopinavir/ritonavir: 400/100 mg orally twice daily

» Mild-moderate infection is denoted by fever (≥100.4°F [38 °C]) plus 1 or more symptoms of lower respiratory tract illness: cough, dyspnea, difficulty breathing.[21] The following are absent: deteriorating radiographic consolidation, increasing oxygen requirement, and a respiratory rate of ≥30 breaths/minute.

» RCT data on the efficacy of antivirals in the treatment of SARS are limited, although it would appear that antiviral therapy should be given to all confirmed cases as early as possible.

» The combination of lopinavir/ritonavir should be given for 14 days.[51]

adjunct ribavirin

Treatment recommended for SOME patients in selected patient group

Primary options

» ribavirin: consult specialist for guidance on dose

» Mild-moderate infection is denoted by fever (≥100.4°F [38 °C]) plus 1 or more symptoms of lower respiratory tract illness: cough, dyspnea, difficulty breathing.[21] The following are absent: deteriorating radiographic consolidation, increasing oxygen requirement, and a respiratory rate of ≥30 breaths/minute.
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adjunct</th>
<th>Psychological therapy and counseling</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjunct</strong></td>
<td>Psychological therapy and counseling</td>
<td>Treatment recommended for SOME patients in selected patient group</td>
</tr>
<tr>
<td><strong>Mild-moderate infection</strong></td>
<td></td>
<td>Infection is denoted by fever ((\geq 100.4^\circ F / 38 ^\circ C)) plus 1 or more symptoms of lower respiratory tract illness: cough, dyspnea, difficulty breathing. The following are absent: deteriorating radiographic consolidation, increasing oxygen requirement, and a respiratory rate of (\geq 30 \text{ breaths/minute}).</td>
</tr>
<tr>
<td><strong>Severe infection</strong></td>
<td>Isolation procedures plus supportive care</td>
<td>Severe infection is denoted by deteriorating radiographic consolidation, increasing oxygen requirement (SpO2 &lt;90%, Oxygenation Index &lt;300 mmHg/(\text{PaO}_2 &lt; 10 \text{ kpa})), and a respiratory rate of 30 or more.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Once a clinical suspicion of SARS has been established, all appropriate protective measures must be initiated to minimize the risk of transmission, with immediate implementation of the strict contact and airborne precautions set out by the CDC. These measures must be further intensified when diagnostic or therapeutic aerosol-generating procedures are carried out.</td>
</tr>
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<td></td>
<td></td>
<td>The CDC advises that patients with SARS coronavirus (CoV) disease who do not require hospitalization for medical reasons may be isolated at home. Stable patients should be placed in isolation and nursed in a negative pressure room where one is available. More severe cases (i.e., those presenting with or developing acute respiratory failure) should be admitted to the ICU or an intermediate care unit under airborne transmission precautions.</td>
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<td></td>
<td></td>
<td>Supportive care involves administration of adequate supplemental oxygen to correct hypoxemia, replacement of fluid deficit caused by diarrhea or fever, correction of electrolyte disturbances, and antipyretics and analgesia for the control of fever and pain.</td>
</tr>
</tbody>
</table>

### 1st isolation procedures plus supportive care

**Adjunct** Mechanical ventilation

Treatment recommended for SOME patients in selected patient group
Patients with impending or established respiratory failure should be admitted to the ICU or an intermediate care unit. Intubation and mechanical ventilation are instituted if the patient is clinically deteriorating and cannot maintain an SaO2 >90% with spontaneous ventilation despite maximal oxygen therapy.1 Evidence

Noninvasive positive pressure ventilation (NIPPV) is associated with the risk of viral transmission and high rates of pneumothorax as well as subcutaneous and mediastinal emphysema.

To decrease the risk of transmission during mechanical ventilation, the following precautions must be taken: avoidance of nebulized humidity and utilization of Venturi masks without humidification,[49] avoidance of bag-mask ventilation and utilization of masks that permit filtration of exhaled gas, utilization of adequate sedation during intubation, utilization of closed suction systems and submicron filters in the exhalation outlet of mechanical ventilators, utilization of sedation or paralysis to minimize coughing, turning ventilator to standby and PEEP to off when disconnecting the circuit, and avoidance of bronchoscopy if possible.

plus lopinavir/ritonavir upon confirmation of diagnosis

Treatment recommended for ALL patients in selected patient group

Primary options

lopinavir/ritonavir: 400/100 mg orally twice daily

Severe infection is denoted by deteriorating radiographic consolidation, increasing oxygen requirement (SpO2 <90%/Oxygenation Index <300 mmHg/PaO2 <10 kpa), and a respiratory rate of 30 or more.

RCT data on the efficacy of antivirals in the treatment of SARS are limited, although it would appear that antiviral therapy should be given to all confirmed cases as early as possible.

The combination of lopinavir/ritonavir should be given for 14 days.[51]

plus corticosteroid

Treatment recommended for ALL patients in selected patient group

Primary options
## Severe acute respiratory syndrome (SARS)

### Treatment

#### Acute

**Primary options**

- **methylprednisolone**: 250-500 mg intravenously once daily for 3-6 days

- Reported to have some efficacy in severe cases (critical SARS) presenting with deteriorating radiographic consolidation, increasing oxygen requirement (SpO2 <90%/Oxygenation Index <300 mmHg/PaO2 <10 kpa), and a respiratory rate of 30 or more.[52]

- Although various regimens have been tried, the most commonly used is 3 to 6 days of pulsed methylprednisolone.

- Corticosteroids added to lopinavir/ritonavir and/or ribavirin early in the course of the infection have been shown to reduce the progression to ARDS as well as the death rate.[16]

**adjunct ribavirin**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **ribavirin**: consult specialist for guidance on dose

- Severe infection is denoted by deteriorating radiographic consolidation, increasing oxygen requirement (SpO2 <90%/Oxygenation Index <300 mmHg/PaO2 <10 kpa), and a respiratory rate of 30 or more.

- Although not effective as a monotherapy, ribavirin can be given with lopinavir/ritonavir.[16]

**adjunct interferon**

Treatment recommended for SOME patients in selected patient group

**Primary options**

- **interferon alfa 2b**: consult specialist for guidance on dose

- Severe infection is denoted by deteriorating radiographic consolidation, increasing oxygen requirement (SpO2 <90%/Oxygenation Index <300 mmHg/PaO2 <10 kpa), and a respiratory rate of 30 or more.

- Can be given to patients who do not show a favorable response to treatment with pulsed methylprednisolone and ribavirin.

- Interferon alfa-2b has been shown to inhibit growth of SARS in vitro.[54]
<table>
<thead>
<tr>
<th>Adjunct</th>
<th>Convalescent Plasma</th>
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</thead>
<tbody>
<tr>
<td>Treatment recommended for some patients in selected patient group</td>
<td></td>
</tr>
<tr>
<td>Severe infection is denoted by deteriorating radiographic consolidation, increasing oxygen requirement ($\text{SpO}_2 &lt; 90%$, Oxygenation Index $&lt; 300$ mmHg/ PaO$_2 &lt; 10$ kpa), and a respiratory rate of 30 or more.</td>
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<tr>
<td>Can be given to patients who do not show a favorable response to treatment with pulsed methylprednisolone and ribavirin.</td>
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</tr>
<tr>
<td>The efficacy of convalescent plasma administration as a treatment of SARS has not been documented. [55] [56]</td>
<td></td>
</tr>
<tr>
<td>Adjunct</td>
<td>Psychological Therapy and Counseling</td>
</tr>
<tr>
<td>Treatment recommended for some patients in selected patient group</td>
<td></td>
</tr>
<tr>
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<td></td>
</tr>
<tr>
<td>Patients, as well as their relatives, may require consultation with a specialist in psychological therapy and counseling for specialized treatment.</td>
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</tbody>
</table>
Emerging

Fusion inhibitors
Inhibitors of HR1-HR2 complex formation prevent entry of the virus into target cells. Although extensive experimental data are available, no clinical trials or documentation of efficacy in humans have been reported.[58]

Nitric oxide and nitric oxide donors
These compounds, which inhibit the SARS coronavirus (CoV) replication cycle, have been used as salvage therapy in a few SARS patients, and it has been suggested that nitric oxide has a degree of clinical efficacy against the infection.[59]

Neutralizing human monoclonal antibodies
These offer passive protection and should ideally be used in the postinfection period. Although a substantial number of experimental studies exist, there is a lack of clinical data to show efficacy of neutralizing human monoclonal antibodies in humans.[60]

Chinese herbs
There is weak evidence that Chinese herbs combined with Western medicines may improve symptoms, quality of life, and absorption of pulmonary infiltration, and decrease the corticosteroid dosage for SARS patients. No difference in decreasing mortality was proved with Chinese herbs combined with Western medicines versus Western medicines alone.[61]

Niclosamide
An anthelmintic drug that inhibits SARS-CoV replication. Only in vitro data exist for niclosamide.[62]

Valinomycin
A cyclodepsipeptide insecticide that acts as a potassium ion transporter, inhibiting viral replication. It is perhaps the most potent agent against SARS-CoV in vitro.[63]

Small interfering RNAs (siRNAs)
These act via post-transcriptional regulation of viral mRNA and are a promising intervention, with no adverse effects observed in animal models.[64]

Aurintricarboxylic acid
This compound inhibits SARS-CoV replication inside host cells. No clinical trials or documentation of efficacy in humans have been reported.[65]

RNA interferon inducer (ampligen)
In animal models, this RNA interferon inducer appears to inhibit virus titers in the lungs. No clinical trials or documentation of efficacy in humans have been reported.[66]

Glycopeptide antibiotics
Various semisynthetic derivatives of glycopeptide antibiotics have shown inhibitory activity against SARS-CoV. No clinical trials or documentation of efficacy in humans have been reported.[67]
Hesperetin
A phenolic compound that inhibits the cleavage activity of 3CLpro. 3CLpro mediates the proteolytic processing of the replicase polypeptides 1a and 1ab into functional proteins required for the existence of the SARS-CoV virus. Only in vitro data exist for hesperetin.[68]

Diterpenoids
Only in vitro data exist of the inhibitory effects of these compounds on SARS-CoV.[63]

Calpain inhibitors
A class of cellular cysteine proteinases that inhibit SARS-CoV replication. There is a lack of clinical data to show efficacy of calpain inhibitors in humans.[69]

Plant lectins
The activity of these compounds against coronaviruses is based on their interference of 2 targets in the viral replication cycle. Only in vitro data exist for plant lectins.[70]

Glycyrrhizin
An active component of licorice root shown to inhibit the replication of SARS-CoV in vitro. There is a lack of clinical data to show efficacy of glycyrrhizin in humans.[71]

Chloroquine
This antimalarial drug appears to be able to negatively influence virus-receptor binding. It is suggested that chloroquine prevents viral spread in cell culture.[72]

Nelfinavir
This compound has been found to have anti-SARS-CoV activity in experimental models. No clinical trials or documentation of efficacy in humans have been reported.

Vaccines
Peripheral memory B-cell responses are undetectable in recovered SARS patients. In contrast, specific T-cell anamnestic responses can be maintained for at least 6 years. These findings have applications in preparation for the possible re-emergence of SARS.[73] Several candidate vaccines are under development, including inactivated virus vaccine, protein-based vaccine (RBD-Fc), recombinant adeno-associated virus vector vaccine (RBD-rAAV), and attenuated virus vaccine. Immunization against SARS-CoV, although not available for clinical use at present, appears to be possible.[74] [75]
Recommendations

Monitoring

In patients with persistent dyspnea, pulmonary function testing and a chest x-ray and/or high-resolution CT of the thorax are used for the monitoring of residual deficits in physiologic and structural lung function.

Psychiatric and psychological support is indicated in patients facing psychobehavioral problems. These include psychological distress with the inability to concentrate, poor memory, depression, and anxiety and are frequently reported in patients who have recovered from SARS.[82]

Patient instructions

Hospitalized patients should limit their activities to the isolation chamber and avoid any unnecessary contact with other patients, family members, or healthcare personnel. For those isolated at home, outdoor activities should be avoided. All patients should be instructed to avoid the contamination of inanimate objects with respiratory secretions.
Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>respiratory failure</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Almost 20% of patients develop worsening respiratory distress with persistent or progressive hypoxia requiring ICU admission.[46] [47] [78] [81] Most of these patients require intubation and mechanical ventilatory support.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARDS</td>
<td>short term</td>
<td>high</td>
</tr>
<tr>
<td>Radiologic evidence of ARDS in the presence of a mild to moderate respiratory illness is a marker of severe respiratory illness in SARS, and ARDS is a common cause of death in patients with SARS. Antiprotease combinations (e.g., lopinavir/ritonavir) added to corticosteroids and/or ribavirin early in the course of SARS coronavirus (CoV) infection have been shown to reduce the progression to ARDS as well as the death rate.[16] A low-tidal volume strategy for the protection of the lungs has been used for the ventilation of SARS patients developing ARDS.[1][B]Evidence</td>
<td></td>
<td></td>
</tr>
<tr>
<td>spontaneous or iatrogenic barotrauma</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Pneumomediastinum and pneumothorax, often spontaneous but also during positive-pressure ventilation, complicate extensive disease.[11] [47] Air leakage is usually caused by rupture of subpleural cysts formed by diffuse alveolar damage and fibrosis. Signs and symptoms of barotrauma during mechanical ventilation include worsening of hypoxemia, tracheal deviation, and hypotension. Chest x-ray confirms the presence of pneumothorax or pneumomediastinum. Treatment includes drainage with insertion of a chest tube.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>secondary sepsis</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Critically ill patients are often complicated with superimposed bacterial infections resulting in sepsis and sepsis-induced organ dysfunction or tissue hypoperfusion. Treatment includes antibiotics and supportive therapy to prevent multiple organ failure.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>multiple organ failure</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Renal and cardiac compromise, along with respiratory failure, are common manifestations of multiple organ failure complicating severely ill patients with SARS. Treatment involves specific supportive therapy for each organ affected.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>death</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>About 10% of patients die as a result of severe respiratory failure, sepsis, ARDS, multiple organ failure, and complications related to hospital admission.[47] [81]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death usually occurs during the third week of illness. [47] [81]</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td><strong>persistent muscle weakness</strong></td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>May be present up to 1 year after infection. [85] It is probably related to prolonged bed rest, systemic effects of the acute disease, or exposure to high doses of corticosteroids. [82] [85] Rehabilitation programs may improve this symptom.</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>Chronic post-SARS syndrome is characterized by chronic fatigue, diffuse myalgia, weakness, depression, and sleep disturbance. [86]</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td><strong>psychobehavioral problems</strong></td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>Psychological distress with the inability to concentrate, poor memory, depression, and anxiety are frequently reported in patients who have recovered from SARS. [82]</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>Important decrements in mental health, with reduced quality of life as well as notable utilization of psychiatric and psychological services, were reported in the 1-year follow-up period. [85]</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td>During the illness, many patients experience stress due to quarantine and isolation, fear for their physical health, and concern about the possibility of transmission to their family. In addition, there may be stress related to social stigmatization, the loss of anonymity through the media, the death of relatives, and the inability to attend funerals of close relatives due to strict quarantine rules. [85]</td>
<td>long term</td>
<td>high</td>
</tr>
<tr>
<td><strong>pancytopenia</strong></td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Hematologic changes such as lymphopenia, thrombocytopenia, and, occasionally, leukopenia and anemia are common in the acute phase. A notable drop in CD4 and CD8 lymphocyte counts occurs early in the course of the syndrome. [80] A mild degree of anemia is commonly seen at the early follow-up period. [79]</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Few patients in critical condition develop frank DIC with signs of spontaneous bleeding.</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Treatment is symptomatic and includes fresh frozen plasma and blood transfusion when required.</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td><strong>abnormal lung function</strong></td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Pulmonary function testing following hospital discharge reveals mild or moderate restrictive ventilatory defects with a mild decrease in carbon monoxide diffusion capacity. These findings are consistent with fibrotic lung changes. [82] [87]</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td>Lung function and radiologic abnormalities tend to improve spontaneously over time. [82]</td>
<td>variable</td>
<td>medium</td>
</tr>
<tr>
<td><strong>neuromuscular disorders</strong></td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>Axonopathic polyneuropathy, myopathy, rhabdomyolysis with associated renal failure, and large artery ischemic stroke with poor prognosis have been described in SARS patients. [88]</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>Treatment is symptomatic with hemodialysis for renal failure.</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td><strong>perinatal complications</strong></td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td>In women infected during pregnancy, spontaneous miscarriage, preterm delivery, and intrauterine growth restriction are frequent complications. [89]</td>
<td>variable</td>
<td>low</td>
</tr>
<tr>
<td><strong>corticosteroid-related adverse effects</strong></td>
<td>variable</td>
<td>low</td>
</tr>
</tbody>
</table>
Avascular necrosis of the femoral head has been reported in some SARS patients and is strongly associated with corticosteroid use.[90]

Treatment is surgical and includes decompression with bone grafting, arthroplasty, or replacement of the femoral head.

**Prognosis**

**Poor prognostic factors**

Prognostic factors associated with a poor outcome (intensive care unit admission or death) include advanced age and the presence of comorbidities such as diabetes mellitus, hepatitis B infection, and heart disease.[11] [24] [25] [78] [79]

An increased LDH level, elevated CRP, and high neutrophil count on presentation[24] [78] as well as low counts of CD4 and CD8 lymphocytes[80] are also associated with an independent increased risk of death.

**Morbidity and mortality**

Clinical deterioration requiring intubation and mechanical ventilation occurs at a median of 8 days after the onset of symptoms.[1] Death is most often attributed to sepsis, ARDS, and multiple organ failure.[81]

The case-fatality rate during the 2003 SARS outbreak was 9.6% and ranged between 0% and 40%.[2] The mortality rate in patients over 65 years of age exceeds 50%.

A residual decrease in lung function and persistent radiologic abnormalities, as well as prolonged psychological sequelae and muscle weakness, are frequently observed in the survivors of SARS, although these tend to improve over time.[82]

**Children (<12 years of age)**

Children have a milder and shorter clinical course resembling that of the common cold.[37] [83] [84]

Prognosis is thus more favorable than in adults, and no death has been reported in young children infected by SARS coronavirus.
# Diagnostic guidelines

## International

### Severe acute respiratory syndrome (SARS) [43]

**Published by:** World Health Organization  
**Last published:** 2004

## Treatment guidelines

## International

### Infection prevention and control for clinical office practice [76]

**Published by:** The College of Physicians and Surgeons of Ontario  
**Last published:** 2015

### Antiviral agents for the treatment and chemoprophylaxis of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP) [77]

**Published by:** Centers for Disease Control and Prevention  
**Last published:** 2011

### Clinical issues and research in respiratory failure from severe acute respiratory syndrome [49]

**Published by:** National Heart Lung and Blood Institute; Centers for Disease Control and Prevention; National institute of Allergy and Infectious Diseases  
**Last published:** 2005

### Severe acute respiratory syndrome (SARS) [43]

**Published by:** World Health Organization  
**Last published:** 2004

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1. Mortality and ventilator-free days: there is medium-quality evidence that mechanical ventilation utilizing a low tidal volume of 6 mL/kg of predicted body weight in patients with acute lung injury (ALI) or ARDS seems to be more effective compared with conventional or high tidal-volume mechanical ventilation at reducing duration of ventilation and mortality in the longer term.

**Evidence level B:** Randomized controlled trials (RCTs) of <200 participants, methodologically flawed RCTs of >200 participants, methodologically flawed systematic reviews (SRs) or good quality observational (cohort) studies.
Key articles


References


Abstract


Abstract

Abstract


Severe acute respiratory syndrome (SARS)


Figure 1: CXR of a SARS patient showing multifocal opacities

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