



Trends-in-Medicine

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Quick Pulse

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SEVERE ACUTE RESPIRATORY SYNDROME (SARS) IN NORTH AMERICA

As of April 3, 2003, most of the cases of SARS continue to be in China/Hong Kong, but the disease has spread to North America and is starting to cause great concern. Canada has become the No. 3 site for SARS with 178 cases (69 probable and 109 suspected), and the U.S. is No. 5. Seven people have died of SARS in Canada. The vast majority of these cases (111 – 53 probable and 58 suspect) are in Ontario, particularly Toronto, which has a large Asian population. According to Health Canada, the Canadian health authority, all the Canadian cases have occurred in people who traveled to Asia or had contact with SARS cases in the household or in a healthcare setting. A Canadian expert said the Canadian cases “may represent the tip of an iceberg.”

Reported SARS Cases as of April 3, 2003

Location	Number of Cases	Deaths
People's Republic of China	1,190	46
Hong Kong	734	17
Canada	178	7
Singapore	98	4
U.S.	85	0
Vietnam	49	4
Europe	20	0
Taiwan	14	0
Thailand	7	2

So far, the World Health Organization and the U.S. State Department have not issued any warnings against travel to Canada, but the American Association for Cancer Research, a major medical meeting which expected more than 16,000 attendees was cancelled just three days before the meeting was to start on April 5, 2003. In addition, the U.S. State Department on April 3^d announced it was allowing non-essential diplomats and all family members in China to depart because of the SARS virus. The same advisory was previously issued for the consulate in Hong Kong.

THE DISEASE

Experts believe SARS is caused by a corona virus, but the CDC has not officially made that conclusion yet. A U.S. infectious disease expert said, "The U.S. isolates are all corona virus. Serum from Hong Kong patients neutralizes the isolates." A Canadian corona virus expert, Dr. Gary Levy, Director of the Multi Organ Transplant Program at Toronto General Hospital, said, "The best bet is that it's a corona virus, but no one knows for sure. We are working with the CDC (Centers for Disease Control) to help them come up with an assay. Serum reacts with it, suggesting cross-reactivity...Our best guess is that SARS jumped from a chicken to a human, probably in Guandong province in China. Recombination took place, which happens with corona viruses, and it moved from the chicken to a human...Corona virus is usually very self-limited."

According to the CDC, the early manifestations of SARS have included influenza-like symptoms such as fever (generally >100.4°F), myalgias, headache, sore throat, dry cough, shortness of breath, or difficulty breathing. Patients also may have an overall feeling of discomfort and body aches. In some cases these symptoms have been followed by hypoxia, pneumonia, acute respiratory distress (requiring mechanical ventilation) or even death. Lab findings may include thrombocytopenia and leukopenia.

The CDC advises that the incubation period for SARS is typically two to seven days but may be as long as 10 days. Health Canada is advising Canadians that symptoms begin within 10 days of direct exposure with a SARS patient.

Experts believe SARS is spread by close contact between people. The CDC believes it is most likely spread when someone sick with the disease coughs droplets into the air and someone else breathes them in, but the CDC admits it is possible that SARS also can spread more broadly through the air or from touching objects that have become contaminated.

TREATMENT

The World Health Organization (WHO) and the CDC are offering little concrete advice to doctors as to how to treat patients with SARS. The CDC website's advice to clinicians on treatment says: "Because the etiology of these illnesses has not yet been determined, no specific treatment recommendations can be made at this time."

However, WHO advises doctors and hospitals to:

- Isolate probable SARS cases.
- Take samples to exclude standard causes of pneumonia (including atypical causes).
- Take samples for: white blood cell count, platelet count, creatinine phosphokinase, liver function tests, urea and electrolytes and CRP.

- Pay particular attention to therapies/interventions which may cause aerolization, such as the use of nebulizers with a bronchodilator, chest physiotherapy, bronchoscopy, gastroscopy, any procedure/intervention which may disrupt the respiratory tract.
- Use antibiotics at time of admission for the treatment of community-acquired pneumonia with atypical cover.

Canadian health officials are advising people who suspect they have been exposed to SARS to quarantine themselves in their homes for 10 days. This includes anyone who was not wearing a protective mask and has:

- Been in close contact with anyone with SARS;
- Visited Scarborough Hospital, Grace Division, in the last 10 days;
- Visited York Central Hospital in Richmond Hill, in the last 10 days.

A Canadian doctor said, "When we have patients with an upper respiratory infection and maybe headache and fever, but the chest xray doesn't show any infiltrates in the lung, we send them home, tell them to take their temperature twice a day, and we follow them twice a week. We tell them if they have any shortness of breath to come back. It's almost like AIDS and HIV; you can have HIV for years and not have AIDS."

Failed treatments: Antibiotics and antivirals

World-wide doctors have tried numerous medications to treat SARS that failed. A U.S. infectious disease expert said these include Roche's Tamiflu (oseltamavir), the herpes drugs, and interferon. Dr. Levy said Canadian doctors have tried a variety of drugs, "At first we used a broad cocktail of antibiotics -- gram positive, gram negative, antivirals like penicillin derivatives, cephalosporins, a whole series of antibiotics up through gancyclovir, etc. We even included ribavirin because it might have been an organism like hepatitis C."

ViraPharma's Picovir (pleconaril) is unlikely to be effective in SARS. An expert explained that it works against a different virus (the picornavirus), and it uses a different receptor.

Current Treatments: Ribavirin plus steroids

North American doctors are using ribavirin and steroids to treat SARS. WHO advises: "Ribavirin with or without use of steroids has been used in an increasing number of patients. But, in the absence of clinical indicators, its effectiveness has not been proven. It has been proposed that a coordinated multicentered approach to establishing the effectiveness of ribavirin therapy be examined."

Dr. Levy said, "At the moment we are using IV ribavirin plus or minus steroids because of a belief that part of the picture is due to a host inflammatory response. Steroids will shut that

inflammatory response off. Many patients get inflammatory lesions in the lungs. Just one shot of steroids is used, not weeks of steroid therapy. It is not good idea to give steroids long term (for SARS) because this is a virus and steroids suppress the immune system. When there is virus plus fever, shortness of breath and infiltrates by chest x-ray, then we put the patient on IV ribavirin."

Why ribavirin? Dr. Levy said, "In our (mouse) work on corona viruses, we showed that ribavirin inhibits the growth of the corona virus and also had the side effect of augmenting the antiviral immune system – promoting the Th1CTL antiviral response."

Canadian doctors are not using oral ribavirin, just the IV formulation. Dr. Levy explained, "Initially, ribavirin was given by inhalation for respiratory syncytial virus (RSV), and inhalation would be the preferred way for these patients, but inhaled ribavirin make you cough and spit, and that spreads the disease and would endanger the healthcare workers. So, instead, we give it by IV to give a high concentration. Oral ribavirin is taken up by liver on first pass, so it is better to give it IV because it goes directly to the lungs, though the best way would be inhalation...We think ribavirin is having a positive effect, but we don't know...The inhibitory effect of ribavirin on corona virus growth itself is very poor. It does inhibit 90%, but it doesn't eliminate the virus."

Therapies being considered

A U.S. infectious disease expert said that, in the near future, a controlled study will be launched comparing oral ribavirin to placebo for early disease, with patients switched to IV ribavirin if the disease progresses with or without steroids.

Interferon alpha is not being used in North America, but it is under consideration. An expert said, "Interferon makes you sick. It is being contemplated but not being done. At the moment, no one is using interferon, but Rebetrone [Schering Plough's combination of Rebetol (ribavirin) and Intron-A (interferon alfa-2b)] may be tried in some patients."

Interferon gamma does not appear to be an option. An expert explained, "Gamma interferon would make it worse. You could argue that gamma interferon would work, but I don't think so, and alpha interferon does have an inhibitory effect on viruses...So, I think we might try either Schering's Rebetrone or Roche's Pegasys."

Another thing doctors are looking at is neutralizing antibodies. It is possible antibodies against the human corona virus might be used like antibodies for hepatitis B. Dr. Levy, the corona virus expert, explained, "There are at least 2 known human corona viruses...There is a receptor for corona viruses...so maybe we could give antibodies against the receptor."

People who develop SARS and then recover do not suffer permanent lung damage. They may develop some immunity to SARS for the future, but it is unlikely to be permanent. Dr. Levy said, "They should make a full recovery, and they should develop immunity, both T-cell and B-cell against that strain. But this is a virus that mutates."

THE FUTURE

SARS is not a one-time event, and it is not likely to be a limited crisis like Ebola outbreaks. Rather, it may become a cyclical event, sweeping through the world every year like the flu. Dr. Levy said, "Now that this has happened, we will enter the SARS arena. It will be recurring, like West Nile virus. In the spring and the fall, there will always be the concern that SARS will come back...Now that this has happened, it may evolve into a situation like the flu. Corona has a high recombination (mutation) rate...and we probably will see multiple strains emerging. It may be that this will become a yearly event for us...Most viruses (except West Nile) don't like hot weather, but this is transmitted by colds and coughs...and we tend to see these more in the spring."

In the future, it is possible Americans may have to get a yearly SARS vaccine along with a flu vaccine. Dr. Levy said, "You have to be vaccinated every year against the flu, so it may be that you will have a flu-type vaccine for SARS in the future...The starting point each year for SARS probably will be China because of the living conditions there, so we will get a head start in making a vaccine for whatever strain is coming that year...We may be able to develop a vaccine against this strain, but I'm not sure. It is theoretically possible that we can develop a yearly SARS vaccine."

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