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Coronaviruses

From Common Colds to Severe Acute Respiratory Syndrome

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Coronaviruses were first identified in the 1960s, causing respiratory and enteric diseases in humans and domestic animals (Table 1). Human coronaviruses OC43 and 229E cause one-third of common colds each winter.¹ The name coronavirus reflects the electron microscopic (EM) appearance of viral particles studded with spike glycoproteins that project out like a crown or a “corona.”¹ When virus particles from patients with severe acute respiratory syndrome (SARS) in 2003 were visualized by EM, the classic “crown” on the virus particles helped researchers rapidly identify the responsible agent.² The application of knowledge from previous studies of animal and human coronaviruses has led to rapid progress toward development of diagnostics, therapeutics and potential vaccines for SARS.

A BRIEF HISTORY OF SARS

In November 2002, an atypical pneumonia emerged in Guangdong

Province, mainland China.³ In February 2003, at least 9 individuals at a hotel in Hong Kong likely came into contact with a man from Guangdong with the atypical pneumonia.² After the 9 returned home from Hong Kong, the disease spread to Singapore, Vietnam, Canada and elsewhere. Dr. Carlo Urbani, a physician in Vietnam who subsequently died after contracting the atypical pneumonia, was one of the first to alert the World Health Organization (WHO) to the new illness. On March 12, 2003, WHO issued a global alert for the new disease SARS.² International cooperation led to rapid identification of a novel coronavirus as the causative agent of SARS, and the virus was designated SARS-CoV. Within weeks, the complete sequence of this agent was determined and shown to be similar to but genetically distinct from all other known coronaviruses.²

The presence of SARS-CoV was demonstrated by reverse-transcription polymerase chain reaction (RT-PCR) and the isolation of virus from respiratory secretions, feces, urine and tissue specimens from lung biopsy.^{2,4} The virus is not confined to the respiratory tract, and fecal contamination may contribute to spread of the disease. Experimental infection of cynomolgus macaques,⁵ ferrets and cats⁶ with some clinical signs in macaques and ferrets indicated that SARS-CoV is necessary

and sufficient for causation of SARS. Whether cofactors such as coinfection, environmental or genetic factors enhance the severity or transmissibility of the disease remains unclear.

THE SOURCE OF SARS

Initial reports from Vietnam, Hong Kong and Toronto suggested that SARS was a previously undescribed severe pneumonia.² Where did this disease come from? Analysis of sera from patients and controls indicated that SARS-CoV had not been endemic in humans before 2002.² One possible explanation for the emergence of SARS is a “jump” of an animal virus to humans. Furthermore there were reports of SARS patients with occupational exposure to live animals used as exotic “game food” in southern China.⁷ Guan et al⁷ analyzed sera and fecal samples from animals sold in wildlife markets for the presence of SARS-CoV and isolated a SARS-like coronavirus from Himalayan palm civets and a raccoon dog. They also found that workers involved in wild animal trading had a higher seroprevalence of antibodies to SARS-CoV than workers in the vegetable market or unrelated controls.⁷ These findings support the hypothesis that SARS-CoV is a zoonotic infection from animals to humans and then spread from person to person.

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TABLE 1. Human Coronaviruses and Representative Animal Coronaviruses

Group	Virus	Name	Disease
1	HCoV-229E	Human coronavirus 229E	Common cold
	HCoV-NL	Human coronavirus—Netherlands	URI/pneumonia
	TGEV	Transmissible gastroenteritis virus of pigs	Gastroenteritis
2	HCoV-OC43	Human coronavirus OC43	Common cold
	BCoV	Bovine coronavirus	Respir/enteric
	MHV	Mouse hepatitis virus	Respir/enteric/neuro
3	IBV	Infectious bronchitis virus of chickens	Respir/enteric
4	SARS-CoV	Severe acute respiratory syndrome-CoV	SARS

Respir indicate respiratory; neuro, neurologic; URI, upper respiratory infection.

TRANSMISSION OF SARS-COV

The emergence and subsequent control of the 2002–2003 SARS epidemic showed that SARS-CoV is sufficiently transmissible to cause an epidemic, but not so contagious that it cannot be contained by rigorous public health measures.² The incubation period is estimated to be between 2 and 10 days. Transmission of SARS-CoV is currently thought to be predominantly by close contact with an infected person during the symptomatic phase of illness.^{2,8} However, study of the Amoy Gardens outbreak in Hong Kong implicated airborne transmission of SARS-CoV particles possibly spread by virus-laden aerosol plumes generated by flushing the toilets at the high rise apartment complex.⁹ RT-PCR analysis shows that SARS-CoV particles are present in feces of infected patients. The role of fecal contamination in the spread of SARS is unclear. Regarding respiratory transmission, aerosol-generating procedures may have amplified the early SARS outbreak in hospitalized patients.² However, implementation of strict infection control measures was ultimately successful in controlling the SARS-CoV outbreak of 2002–2003.

SARS IN ADULTS AND CHILDREN

A striking finding of the SARS epidemic was the age dependence in severity of disease.¹⁰ In SARS patients >65 years of age, the mortality rate exceeded 50%. Comorbid illnesses like diabetes mellitus and heart disease are independent risk factors for need for intensive care and death

from SARS-CoV. In contrast, SARS-CoV infection of children <12 years of age was associated with a relatively uneventful course and a good outcome.¹¹ To date, no evidence implicates asymptomatic individuals in SARS-CoV transmission.

FUTURE DEVELOPMENTS

Currently there are no approved diagnostics, vaccines or therapeutics for any human coronavirus infection. For detecting infection with SARS-CoV, fecal samples may be best for early detection of the virus by RT-PCR.⁹ The SARS-CoV viral load peaks around the 10th day of illness, with subsequent decrease in viral load and appearance of antibody to the virus,^{2,4} suggesting that early therapeutic intervention may reduce the viral load and disease severity. Pegylated interferon- α protects against SARS-CoV infection in macaques,¹² and a synthetic antibody to the spike glycoprotein neutralizes SARS-CoV.¹³ Agents to block SARS-CoV fusion¹⁴ and the SARS-CoV 3C-like protease^{14,15} are also being studied. Candidate SARS-CoV vaccines also have been developed. A DNA vaccine expressing the SARS-CoV spike glycoprotein elicits neutralizing antibodies and protective immunity in mice.¹⁶ Similar protection of mice was shown with a vaccinia virus expressing the SARS-CoV spike.¹⁷ Vaccine studies in macaques or other appropriate animal models will be critically important for evaluating potential vaccine candidates.

Are there other clinically important coronaviruses besides SARS-CoV? Approximately 20% of respiratory tract

infections are of unknown origin. Uncharacterized coronaviruses may be responsible for at least some of these infections. Recently 2 groups from the Netherlands independently isolated a new human coronavirus from children with upper respiratory tract infections; this new agent was designated HCoV-NL.^{18,19} van der Hoek and coworkers isolated HCoV-NL from a 7-month-old child in 2003 and then from clinical specimens from other individuals with respiratory illness.¹⁸ Fouchier et al¹⁹ had isolated essentially the identical virus from an 8-month-old boy in 1988, indicating that this coronavirus has been circulating in humans for many years. Future studies are needed to determine the role of HCoV-NL in respiratory illnesses.

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