Severe acute respiratory syndrome (SARS)

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Severe acute respiratory syndrome was first recognized in November 2002. An international outbreak involving 26 countries, 8098 cases, and 774 deaths subsequently developed, ending in July 2003. Since then, two isolated cases of SARS and one cluster of 11 cases including one death have been identified, resulting from the "escape" of SARS-associated coronavirus (CoV) from research laboratories. In addition, four isolated cases of SARS with no secondary cases were identified in December 2003 and January 2004. Aside from these scenarios, to date there has been no evidence of a large-scale reemergence of SARS. Regardless, much interest and research continues into better understanding SARS in order to be prepared for its possible reemergence and/or the emergence of other similar pathogens.

Etiologic agent

With unprecedented speed after the recognition of SARS, a newly identified coronavirus, SARS-CoV, was pinpointed as the causal agent of the disease. Coronaviruses are enveloped, single-stranded RNA viruses that cause a variety of diseases in animals. Prior to the discovery of SARS-CoV, only two coronaviruses were recognized as causing human disease, coronavirus OC43 and 229E, both associated with the common cold. In general, coronaviruses can be divided into three groups based on their genetic and protein content. However, SARS-CoV does not readily fit into any of these three groups and has been placed into a new fourth group.

While the origins of SARS-CoV are still being investigated, data suggest that SARS-CoV evolved from animal SARS-like viruses that are closely related to SARS-CoV. SARS-like viruses have been identified in a number of different animals, including most frequently Himalayan palm civets found in food markets and eaten as a delicacy in Guangdong Province of the People's Republic of China. Genotypic evidence suggests that cases early in the outbreak were infected with viruses more closely resembling animal SARS-like viruses than SARS-CoV and that SARS-CoV evolved from positive selective pressure acting on animal SARS-like viruses, ultimately culminating in the emergence of the predominant SARS-CoV genotype responsible for the 2002–2003 outbreak.

There is evidence to suggest that animal SARS-like viruses existed and were transmitted to humans, remaining clinically undetected, at least 2 years predating the 2002–2003 outbreak. In addition, it appears that such transmission likely is ongoing today. For example, in Hong Kong 1.8% of frozen sera from 938 adults collected in 2001 were positive for antibodies against animal SARS-like viruses. More recently, at least one of the four isolated cases of SARS that occurred in December 2003 was due to a virus more closely resembling animal SARS-like

viruses than SARS-CoV. Present data, while sparse, suggest that human infection due to animal SARS-like viruses is milder and associated with less human-to-human transmission than infection with SARS-CoV.

Epidemiology

Whether or not SARS will reemerge as it did in the 2002–2003 outbreak is up for debate. At the time of this writing, the only known reservoirs of SARS-CoV are laboratories in which live SARS-CoV is being handled. While animal reservoirs of animal SARS-like viruses exist, human or animal reservoirs of SARS-CoV have not been found. Thus the only likely ways for SARS to reemerge are for the circumstances that permitted the selection and purification of SARS-CoV from animal SARS-like viruses to be repeated or for laboratory accidents exposing workers to SARS-CoV to occur. The risk of the former is difficult to predict until more is understood about the circumstances that permitted the selection of SARS-CoV to have occurred in the first case. The risk of the latter will be reduced by continued vigilance and reinforcement of the importance of appropriate biosafety standards to be used in laboratories in which research with SARS-CoV is being conducted. Despite the fact that it is not clear whether or not new outbreaks of SARS will occur, it is important to be prepared for the possibility that they may.

Transmission

SARS-CoV is typically transmitted by direct contact with people with SARS or by mucous membrane exposure to respiratory droplets from infected people. Some evidence suggests that airborne transmission, or transmission via fomites (inanimate contaminated objects) may occur, but only very rarely. Transmission appears not to occur before the onset of symptoms, and is most common from severely ill people in the second week of illness. In the 2003 outbreaks, transmission was almost entirely limited to households, hospitals, and immediate prehospital care.

Pathogenesis

The mechanisms by which SARS-CoV causes disease are still being investigated. Angiotensin-converting enzyme 2, predominantly found in heart and kidney tissues, has been identified as a cellular receptor for SARS-CoV. However, given that SARS-CoV is found in highest numbers in lung and gastrointestinal tissue, other unidentified receptors likely also play a role. Based on clinical, epidemiologic, and virologic data, it appears that SARS-CoV, after entry via the respiratory system, is first associated with viremia (presence of viral particles in the blood), followed by predominant replication in the lung and gastrointestinal tract. However, dissemination to and replication in other organs likely also occurs, given that SARS-CoV ribonucleic acid (RNA) has been found in a wide range of organs at autopsy. Viral replication is thought to be maximal during the second week of symptoms, a time during which SARS-CoV can be most readily detected in tissues and most efficiently transmitted to others. It has been postulated that the immune response to SARS-CoV replication in the lung is primarily responsible for the worsening of respiratory symptoms seen in some patients, typically during the third week of illness. The associated lymphopenia (a reduction of lymphocutes in the circulating blood) observed in many patients suggests

that lymphocytes play a role in either fighting the infection or possibly in being infected themselves. Further study is needed to better understand the pathogenesis of and immune response to SARS.

Clinical manifestations

Patients infected with SARS-CoV may be asymptomatic, may have only mild nonspecific symptoms that do not progress, or may develop typical SARS. Patients with typical SARS usually present two to ten days following exposure with nonspecific symptoms including fever, myalgia (muscle pain), headache, malaise, and chills. Three to five days later, these patients develop a nonproductive (dry) cough and dyspnea (difficult or labored breathing) with approximately 25% developing watery diarrhea. Approximately 20% of patients subsequently develop worsening respiratory distress requiring admission to an intensive care unit. Overall 15% of patients require tracheal intubation (insertion of a tube into the trachea to maintain an airway and permit suction of the respiratory tract) and mechanical ventilation support. Approximately 10% of all patients die from progressive respiratory distress or complications of their hospital admission, typically during the third or fourth week of symptomatic illness.

Typical laboratory abnormalities at the time of presentation include a normal total white blood cell count, lymphopenia, and increased levels of the enzymes lactate dehydrogenase and creatinine kinase (most likely due to associated lung tissue injury). However, such laboratory abnormalities are not uncommon in patients with community-acquired pneumonia due to causes other than SARS-CoV, so that a diagnosis of SARS cannot accurately be made based on clinical or laboratory features alone. Approximately 75% of patients present with infiltrates on a chest radiograph (that is, the appearance of ill-defined opacities on a chest x-ray) but virtually all infected patients will eventually develop chest infiltrates, usually in the second week of illness. Multifocal infiltrates (opacities in more than one lung zone) with ground-glass appearance are more common in SARS than bacterial pneumonia. High-resolution computerized tomography may detect ground-glass opacities not detected by standard radiography. Both laboratory abnormalities and infiltrates usually progress after admission and peak at, or just after, the end of the second week of disease.

Increased age, comorbidity (having a concurrent but unrelated disease), elevated levels of lactate dehydrogenase, and elevated neutrophil (large granular white blood cell) counts at the time of presentation have been associated with an increased risk of death; the case fatality rate in persons over the age of 60 approaches 50%. Infants and children appear to be protected against acquiring the infection and typically have a milder course; associated rhinorrhea (mucous discharge from the nose) is seen in 50% of those who develop symptoms.

Diagnosis

Multiple assays for the diagnosis of SARS have been developed. Reverse transcription–polymerase chain reaction (RT-PCR), which detects SARS-CoV RNA in specimens of blood, stool, and respiratory secretions taken from

patients, and serologic tests, which detect SARS-CoV antibodies in the serum produced after infection, have become the mainstay of laboratory diagnosis. Viral culture appears to be less sensitive.

Seroconversion (development of antibodies to a particular antigen) occurs in patients with SARS from 1 to 4 weeks after symptom onset. The majority of patients do not develop either immunoglobulin G (IgG) or IgM antibodies until the third or fourth week of illness.

Treatment

During the 2002–2003 outbreak many antiviral agents, such as ribavirin and lopinavir/ritonavir (which inhibit viral replication), and immunomodulatory durgs, such as interferon, steroids, and intravenous immunoglobulin (which modify the immune response to an infection), were used in varying doses and combinations in different regions of the world. Essentially, all of these treatments have had some reports of associated anecdotal clinical improvement. However, no definitive conclusions regarding the efficacy of any of these treatments can be made.

Many other treatments have shown promise in in-vitro or animal models. These include antiviral agents specifically directed against viral entry into cells and agents directed against expression of viral genes. Further in-vitro and in-vivo studies are needed to better determine the potential role of each of these agents as prophylaxis or treatment for SARS.

Prevention

Many candidate SARS vaccines are currently in the process of being developed, including vaccines based on inactivated virus, recombinant subunits of virus, DNA, and viral vector delivery. Preliminary work based on the immunization of animals has been published showing the ability of many of these vaccines to induce immune responses to SARS-CoV. Much more is expected to be understood about the possible usefulness of these candidate vaccines in the future.

Until effective vaccines are available for human use, the key components to prevention include early identification of cases, rapid implementation of control measures including isolation, contact tracing, and, possibly, quarantine.

Lessons learned

Many lessons learned from the 2002–2003 SARS outbreak can be used toward improving preparedness nationally and internationally for other emerging infectious diseases. The international cooperation of laboratory and clinical working groups during SARS sets a new standard for collaboration. Progress was also made in sharing information across international boundaries that may permit greater transparency and better international collaboration in the management of future outbreaks.

Syndromic surveillance systems, now being piloted in emergency departments and health units in several countries, will likely be useful in the detection of new infectious disease outbreaks. Having a prepared communications system in place to enable real-time communication between health care institutions, front-line physicians, emergency health care workers, public health and other health care workers is also important, as is an overall outbreak public communication plan based on the science of risk communication.

See also: ANIMAL VIRUS; INFECTIOUS DISEASE; RESPIRATORY SYSTEM DISORDERS; VACCINATION; VIRUS.

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