Epidemic and Emerging Coronaviruses (Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome)

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KEYWORDS

• SARS-CoV • MERS-CoV • Respiratory tract infections • Clinical features • Pathogenesis • Treatment

KEY POINTS

- Bats are the natural reservoirs of severe acute respiratory syndrome (SARS)-like coronaviruses (CoVs) and are likely the reservoir of Middle East respiratory syndrome (MERS)-CoVs.
- The clinical features of SARS-CoV infection and MERS-CoV infection are similar but patients with MERS-CoV infection progress to respiratory failure much more rapidly than those with SARS.
- Although the estimated pandemic potential of MERS-CoV is lower than that of SARS-CoV, the case fatality rate of MERS is much higher and likely related to older age and presence of comorbid illness among the sporadic cases.
- Although dromedary camels have a high seroprevalence of MERS-CoV antibody and some camels have been found to have positive nasal swabs by reverse transcription (RT)–polymerase chain reaction (PCR), the transmission route and the possibility of other intermediary animal sources remain uncertain among many sporadic primary cases.
- The more feasible clinical trial options for MERS-CoV infection at present include monotherapy and combination therapy with lopinavir/ritonavir, interferon (IFN)-β1b, passive immunotherapy with convalescent plasma, or human monoclonal or polyclonal antibody.

INTRODUCTION

CoVs (order Nidovirales, family Coronaviridae, subfamily Coronavirinae) are a group of highly diverse, single-stranded, enveloped, positive-sense, RNA viruses that may cause respiratory, hepatic, gastrointestinal, and neurologic diseases of varying severity in a wide range of animal species, including humans. There are 4 genera of CoVs: αCoV, βCoV, γCoV, and δCoV.[1] Before the SARS epidemic, the main CoVs causing respiratory tract infection in humans were human CoV-OC43 and human CoV-229E. A novel group, 2b βCoV, was discovered in March 2003 as the causative agent responsible for SARS-CoV infection.[2–4] Both SARS-CoV and MERS-CoV are βCoV and belong to lineages B and C, respectively.[1] In this article, the clinical features, laboratory aspects, pathogenesis, and potential treatment modalities of SARS-CoV infection and MERS-CoV infection are reviewed.

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SEVERE ACUTE RESPIRATORY INFECTION–CORONAVIRUS INFECTION

SARS-CoV first emerged in November 2002 in the Guangdong province in the southern part of China before spreading to Canada, Singapore, and Vietnam by travelers through Hong Kong (HK) in February 2003 and March 2003.[5,6] In November 2002, there was an unusual epidemic of atypical pneumonia in Foshan, Guangdong province, in China, with a high rate of nosocomial transmission to health care workers (HCWs).[7,8] A retrospective analysis of 55 patients hospitalized with atypical pneumonia in Guangzhou between January 2003 and February 2003 revealed positive SARS-CoV in their nasopharyngeal aspirates whereas 48 (87%) patients had positive serology to SARS-CoV in their convalescent sera. Genetic analysis showed that the SARS-CoV isolates from Guangzhou shared the same origin with those in other countries, with a phylogenetic pathway that matched the spread of SARS-CoV to other parts of the world.[9]

The Origin of the Virus

In March 2003, a novel CoV was confirmed as the causative agent for SARS and thus was referred to as SARS-CoV. A retrospective serologic survey suggested that cross-species transmission of SARS-CoV or its variants from animal species to humans might have occurred frequently in the wet market where a high seroprevalence of 16.7% was detected among asymptomatic animal handlers.[10] It was initially thought that masked palm civets might have contributed to transmission of SARS-CoV to humans after detection of a close variant of SARS-CoV from palm civets in Dongmen market, Shenzhen, in 2003.[11] During the small-scale SARS-CoV infection outbreaks in late 2003 and early 2004 in China, 3 of the 4 patients had direct or indirect contact with palm civets.[12,13] Viral genomic sequence analysis showed, however, that the SARS-CoV–like virus had not been present among masked civets in markets for long. CoVs highly similar to SARS-CoV were isolated in horseshoe bats in 2005.[14,15] These bat SARS-like CoVs shared 88% to 92% sequence homology with human or civet isolates and the data suggest that bats could be a natural reservoir of a close ancestor of SARS-CoV.[16]

Pathogenesis

SARS-CoV infects humans through the respiratory tract, mainly via droplet transmission. Although human intestinal cells were proved susceptible to SARS-CoV replication, the role of the intestinal tract as a portal of entry remains uncertain.[17] The surface envelope spike protein (S protein) of SARS-CoV plays an important role in establishing infection and determining the cell and tissue tropism. Entry of the virus requires receptor binding, followed by conformational change of the S protein and then cathepsin L–mediated proteolysis within the endosome.[18] The angiotensin-converting enzyme 2 (ACE2) is the host receptor mediating the entry of SARS-CoV[19] and is expressed on a wide variety of body tissues.

Several mechanisms of direct injury in infected lungs with SARS have been revealed. The ACE2 probably contributes to the diffuse alveolar damage (DAD). ACE2 is a negative regulator of the local renin-angiotensin system and data from animal study support that the DAD seen in SARS is mediated by S protein–ACE2-renin-angiotensin pathway.[20] In addition, the SARS-CoV–encoded 3a and 7a proteins were shown a strong inducer of apoptosis in cell lines derived from different organs, including lungs, kidneys, and liver.[21,22]

Activation of helper T (T_H1) cell–mediated immunity and hyperinnate inflammatory response might be responsible for disease progression in SARS-CoV infection,[23,24] as shown by marked increases in the levels of the T_H1 and inflammatory cytokines (IFN-γ, interleukin [IL]-1, IL-6, and IL-12) and marked increases in chemokines, such as T_H1 chemokine IFN-γ–inducible protein 10 (IP-10), neutrophil chemokine IL-8, and monocyte chemoattractant protein-1 (MCP-1) in patients with SARS-CoV infection for more than 14 days after illness onset.[25] In mice infected with SARS-CoV, T cells played an important role in SARS-CoV clearance whereas a reduced T-cell response contributed to severe disease.[26] In another study of mice infected with SARS-CoV, robust virus replication accompanied by delayed type I IFN (IFN-I) signaling was observed orchestrating inflammatory responses and lung immunopathology with reduced survival.[27] Case-control studies have suggested that genetic variants of IL-12 receptor B1 predispose to SARS-CoV infection,[28] whereas Mannose-binding lectin deficiency is a susceptibility factor for acquisition of SARS-CoV infection.[29]

Lung histopathology in patients with severe SARS-CoV infection include DAD, denudation of bronchial epithelia, loss of cilia, squamous metaplasia, and giant cell infiltrate, with a marked increase in macrophages in the alveoli and the interstitium. Hemophagocytosis, atrophy of the white pulp of the spleen, hyaline membranes, and secondary bacterial pneumonia were also noted.[4,5,23,30] Although DAD was the main pulmonary feature,[4,5,23] lesions in subpleural locations