# 222 Human Coronaviruses

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Coronaviruses are included in the Coronaviridae family under the order Nidovirales. They are enveloped, nonsegmented, single-stranded, positive-sense RNA viruses named after their corona-like or crown-like surface projections seen on electron microscopy that correspond to large surface spike proteins (Figs. 222.1 and 222.2). They are host specific and can infect humans and a variety of animals.[1]

Four genera of coronaviruses have been described. Human coronaviruses (HCoVs) are part of the *Alphacoronavirus* and *Betacoronavirus* genera[1,2] (Table 222.1).

## EPIDEMIOLOGY

In the 1930s, coronaviruses were recognized as animal pathogens.[3] Thirty years later, coronaviruses were identified as human respiratory pathogens. The first recognized HCoV strains included 229E and OC43. Strains such as B814, OC16, OC37, and OC48 also were described but were not characterized further.[4–6] Coronavirus-like particles have been detected in stool, primarily in infants with gastroenteritis and necrotizing enterocolitis, but further characterization has not been completed.[7–9]

In 2003, severe acute respiratory syndrome (SARS) CoV was identified as a novel respiratory pathogen responsible for a global outbreak of SARS. First emerging in 2002 in China, the outbreak lasted 9 months and resulted in 8098 people infected and 774 deaths.[10–14] Data suggest that SARS CoV evolved from SARS CoV–like viruses in horseshoe bats, with civet cats and other wild market animals serving as intermediate hosts.[15–20]

Renewed interest in CoV research let to the discovery of two novel HCoVs 2 years later: NL63 (also known as NL or NH) and HKU1.[21–23]

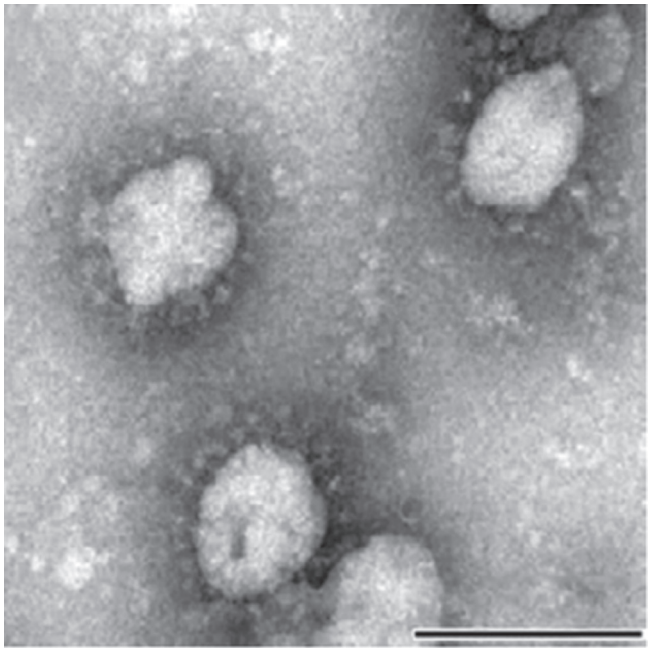

**FIGURE 222.1** Negative-contrast electron micrograph of severe acute respiratory syndrome coronaviruses shows the typical crown-like spike proteins on the surface of the coronavirus particles (bar = 100 nm). (From Kuiken T, Fouchier RA, Schutten M, et al. Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. Lancet 2003;362:263–270.)

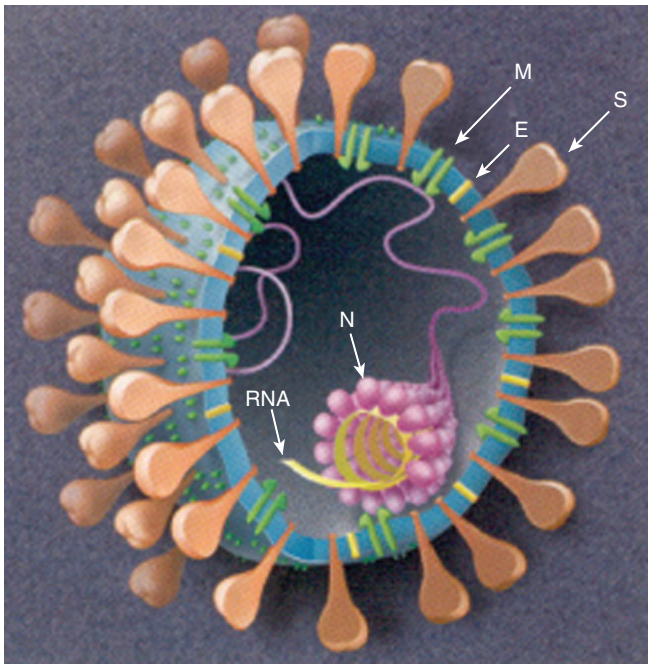


**FIGURE 222.2** Organization of the spike (S), membrane (M), and envelope (E) glycoproteins in a typical coronavirus is shown for a typical coronavirus. The RNA is protected by the nucleocapsid proteins (N). (From Holmes KV, Enjuanes L. The SARS coronavirus: a postgenomic era. Science 2003;300:1377–1378.)

HCoV-NL63 has been detected in human respiratory samples from as early as 1981.[24] It is unclear how HCoV-NL63 and HCoV-HKU1 relate to the HCoV strains originally described in the 1960s (i.e., B814, OC16, OC37, and OC48) or to the enteric coronavirus-like particles detected in stool.[25]

In 2012, the Middle East respiratory syndrome (MERS) CoV (also called hCoV-EMC) was identified as a novel CoV responsible for an epidemic of respiratory illness in the Kingdom of Saudi Arabia.[26,27] Data suggest that MERS CoV likely evolved from bat CoV, with camels acting as intermediate hosts.[28] A total of 1733 cases and 678 deaths were associated with MERS CoV as of May 2016.[29]

HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1 are found worldwide and cause disease predominantly in winter and spring months in temperate climates.[24,30] Seroprevalence data suggest that exposure is common in early childhood.[31,32] SARS CoV has not been identified since 2004, when 4 sporadic community-acquired cases of SARS were identified in China[33] and 13 cases linked to laboratory biosafety practice breaches were identified in Southeast Asia.[34–36] During the 2002–2003 outbreak, most SARS CoV transmission occurred within hospitals from patients with unrecognized illness.[37] MERS CoV cases continue in the Middle East, primarily linked to exposure to camel or camel products or close contact with unrecognized cases in hospitalized patients.[38–40] Household transmission also has occurred.[41] In 2015, a large outbreak of MERS CoV in South Korea, affecting 186 cases and associated with 36 deaths, was traced to an individual who returned from travel in the Middle East.[28,29,42]

Modes of transmission for HCoV other than SARS CoV and MERS CoV have not been well studied. Based on studies of other respiratory viruses, transmission likely occurs primarily by a combination of spread by droplet and direct and indirect contact.[43–45] The possible role of aerosol spread needs further study. Droplet spread and direct contact likely are the most common modes of transmission for SARS CoV, although evidence for spread by indirect contact and aerosol also

**TABLE 222.1** Human Coronaviruses

| Genus | Species | Acronym | Host | Associated Diseases |
|---|---|---|---|---|
| ***Alphacoronavirus*** | Human CoV-229E | HCoV-229E | Human | Respiratory tract infection |
| | Human CoV-NL63 | HCoV-NL63 | Human | Respiratory tract infection |
| ***Betacoronavirus*** | | | | |
| Subgroup A | Human CoV-OC43[a] | HCoV-OC43 | Human | Respiratory tract infection |
| | Human CoV-HKU1 | HCoV-HKU1 | Human | Respiratory tract infection and possibly gastroenteritis |
| Subgroup B | SARS CoV | SARS CoV | Human | Respiratory tract infection |
| Subgroup C | MERS CoV | MERS CoV | Human | Respiratory tract infection |
| Subgroup D | No human CoV identified | — | — | — |
| ***Deltacoronavirus*** | No human CoV identified | — | — | — |
| ***Gammacoronavirus*** | No human CoV identified | — | — | — |

[a]This species has been abolished according to the International Committee on Taxonomy of Viruses. It is now considered part of the species *betacoronavirus 1*.[1] However, because the name HCoV-OC43 is still commonly used, the species is referred to as HCoV-OC43 in this chapter.
CoV, coronavirus; HCoV, human coronavirus; MERS, Middle East respiratory syndrome; SARS, Severe acute respiratory syndrome.

exists.[46–53] There is no evidence of vertical transmission of SARS CoV.[54,55] Transmission of MERS CoV is thought to occur through droplet, contact, and possibly aerosol routes.[40,41,56]

HCoV-229E and HCoV-OC43 are most likely transmitted during the first few days of illness, when symptoms and respiratory tract viral load are maximal.[57,58] Further study is needed to confirm if this also is the case for HCoV-NL63 and HCoV-HKU1. SARS CoV and MERS CoV are most likely transmitted during the second week of illness, when symptoms and viral load in the respiratory tract peak.[59–62] Supershedding events have been associated with SARS CoV and MERS CoV.[39]

The incubation period for HCoV-229E is 2 to 5 days (median, 3 days).[58,63] Further study is needed to confirm the incubation periods for HCoV-OC43, HCoV-NL63, and HCoV-HKU1. The incubation period for SARS CoV is 2 to 10 days (median, 4 days).[59] The incubation for MERS CoV is 2 to 15 days (median, 5 days).[40]

## PATHOGENESIS AND IMMUNITY

The pathogenesis of HCoVs has been best described for HCoV-229E, SARS CoV, and MERS CoV. For SARS CoV, most evidence is from infections in adults because few children were affected by the 2002–2003 outbreak.[64]

**Human Coronavirus 229E.** HCoV-229E infections are initiated through inoculation of respiratory tract mucosal surfaces. Nasal mucosal plasma exudation and increased interferon γ (IFNγ) levels in nasal lavage specimens correlate with symptom severity.[65,66] Respiratory tract viral loads peak within the first 3 days after infection and drop off dramatically at 1 week, correlating with development and improvement in symptoms.[57,67] Antibodies can be detected at 1 week, correlating with the drop in viral load, and they reach maximal levels approximately 1 week later and decline thereafter.[68]

Immunity is not complete, and reinfection is common.[68,69] Higher circulating antibody levels, especially levels of specific IgA anti-HCoV, correlate with reduced symptoms and reduced virus shedding on re-exposure.[68,70]

**Severe Acute Respiratory Syndrome Coronavirus.** SARS CoV infection is initiated through inoculation of the respiratory tract mucosa using angiotensin-converting enzyme 2 acting as the functional receptor for cell entry.[71] Viremia and replication in the lung and gastrointestinal tract follows.[72,73] Replication at other sites likely occurs given the wide distribution of SARS CoV in tissues examined at autopsy.[74,75]

Peak viral loads in nasopharyngeal specimens are detected during the second week of symptoms.[60,73] A rise in SARS CoV–specific antibodies typically is seen at the same time. Increasing antibody titers and symptomatic improvement during the second and third week are associated with a decrease in SARS CoV viral loads.[60,76] Paradoxically, despite a fall in viral load and a rise in SARS-specific antibodies, clinical deterioration is observed in some patients.[60] The host immune responses likely contribute to clinical deterioration in these patients. Elevated levels of IFNγ, inflammatory cytokines interleukin-1 (IL-1), IL-6, and IL-12; neutrophil chemokine IL-8; monocyte chemoattractant protein 1; and IFNγ-inducible protein-10 have been detected, with levels of IL-6 correlating with severity of disease.[77,78]

**Middle East Respiratory Syndrome Coronavirus.** MERS CoV infection most likely is initiated through inoculation of the respiratory tract mucosa mediated by dipeptidyl peptidase 4 (DDP4) (i.e., CD26) acting as the functional receptor.[79,80] Viral loads are highest in lower respiratory tract specimens, but real-time polymerase chain reaction (rt-PCR) evidence of MERS CoV also can be found in the upper respiratory tract, serum, stool, and urine.[62] Autopsy data from a single patient did not show extrapulmonary MERS CoV dissemination, but because DPP4 is widely distributed in different tissues, extrapulmonary dissemination is thought to be possible.[79]

## CLINICAL MANIFESTATIONS

**Human Coronaviruses 229E, OC43, NL63, and HKU1.** HCoVs 229E, OC43, NL63, and HKU1 are commonly associated with the common cold, which is typically characterized by rhinorrhea, nasal congestion, sore throat, sneezing, and cough that may be associated with fever.[22,24,67,81–84] Together, the HCoVs are the second most common cause of the common cold after rhinoviruses.[85,86]

Based on data for HCoV-229E, symptoms typically peak on day 3 or 4 of illness and are self-limited.[67,87] HCoVs also may be associated with acute otitis media or exacerbations of asthma.[24,82,84,88,89] Less frequently, these viruses are associated with lower respiratory tract infections, including bronchiolitis and pneumonia, primarily in infants and immunocompromised children and adults.[23,82,84,90–98]

Compared with other HCoVs, HCoV-NL63 more frequently is associated with croup and is the second most common cause after parainfluenza virus type 1.[99,100] A possible association of HCoV-NL63 with Kawasaki disease was not substantiated.[101,102]

HCoV-HKU1 has been associated with symptoms of gastroenteritis, including vomiting and diarrhea, which typically occur along with respiratory symptoms.[84,89,103] HCoV-HKU1 also appears to be more frequently associated with febrile seizures compared with other HCoVs.[84,89]

**Severe Acute Respiratory Syndrome Coronavirus.** SARS CoV is associated with severe symptoms.[104–106] SARS CoV disproportionately affects adults, who typically manifest fever, myalgia, headache, malaise, and chills, followed by a nonproductive cough and dyspnea 3 to 5 days later. Approximately 25% develop watery diarrhea. Respiratory distress progresses and requires intubation and ventilation in 25% of cases. The overall associated mortality rate is approximately 10%, with most deaths occurring in the third week of illness.[105] The case-fatality rate for persons older than 60 years of age approaches 50%.[107]

Typical laboratory abnormalities include lymphopenia and increased serum lactate dehydrogenase (LDH) and creatine kinase levels.[108,109] Most patients have progressive unilateral or bilateral, ill-defined airspace infiltrates on chest imaging.[108,110–112] Pneumothoraces and other signs of barotrauma are common in patients receiving mechanical ventilation.[105]

Infants and children younger than 12 years of age who develop SARS typically have fever, cough, rhinorrhea, and milder symptoms compared with adolescents and adults. Associated lymphopenia is less severe, and radiographic changes are milder and usually resolve more quickly than in adolescents and adults. No infants or children died of SARS CoV infection in the 2002–2003 outbreak.[64,113–116] Adolescents who developed SARS had clinical courses more closely resembling that of adults, including fever, myalgia, headache, and chills, and they were more likely to have dyspnea, hypoxemia, and worsening chest radiographic findings.

Women infected with SARS CoV during pregnancy who survive have an increased risk of spontaneous miscarriage, preterm delivery, and intrauterine growth restriction.[54,55,117] Two neonates born to mothers with SARS in the 2002–2003 outbreak developed gastrointestinal complications (e.g., jejunal perforation, necrotizing enterocolitis with ileal perforation) soon after birth, but neither had clinical evidence of SARS CoV infection.[55] It is unclear whether these findings related to complications of maternal SARS or treatments for SARS, such as ribavirin and corticosteroids, used during pregnancy.

**Middle East Respiratory Syndrome Coronavirus.** MERS CoV infection is associated with severe symptoms similar to those seen with SARS CoV, although a spectrum of disease, including asymptomatic infections and mild disease, can occur.[27] Most cases have been identified in male adults with comorbidities. Infected children typically have milder symptoms.[27] Fever, myalgia, and chills are followed a few days later by a nonproductive cough and dyspnea. Approximately 25% of patients also have vomiting, diarrhea, or abdominal pain.[27] Rapid deterioration of oxygenation with progressive unilateral or bilateral airspace infiltrates on chest imaging may follow, requiring mechanical ventilation and often associated with acute renal failure.[118]

Laboratory abnormalities include thrombocytopenia, lymphopenia, and an elevated LDH level.[27] The case-fatality rate is high, estimated at 36%.[28]

## DIAGNOSIS

Some laboratories offer comprehensive rt-PCR for respiratory tract specimens, which may include detection of HCoVs 229E, OC43, NL54, and HKU1.[84,119] Public health laboratories offer rt-PCR and antibody testing for SARS CoV and MERS CoV testing.[120,121]

Upper and lower respiratory tract specimens are the most appropriate samples for viral detection when testing is available.[62,73,82,84,122] Stool

samples frequently are positive for patients with SARS and have been positive for some with MERS CoV[62] and HCoV-HKU1 infection.[73,89,103,122] Serum samples also may be positive by rt-PCR for patients with SARS CoV and MERS CoV infection.[62] For cases of HCoV-299E and HCoV-OC43 infection, specimens are most likely to be positive during the first few days of illness[57]; whether this also is true for HCoV-NL63 and HCoV-HKU1 needs further study. For SARS CoV infection, serum samples for RT-PCR testing are most likely to be positive in the first week of illness,[72,123] but respiratory and stool specimens may not be positive until the second week of illness, when symptoms and viral loads peak.[60,73] Infants and children with SARS CoV infections are less likely to have positive specimens, consistent with the milder symptoms and presumed correspondingly lower viral loads in children.[113,114] For cases of MERS CoV infection, specimens for rt-PCR should be collected from the lower respiratory and upper respiratory tract along with serum and stool samples.[62,124]

Laboratory guidance for SARS CoV and MERS CoV diagnostic testing is available on the Centers for Disease Control and Prevention (CDC) website.[124,125] Because of the potential for false-positive results and the associated public health implications, testing for SARS CoV in the absence of known person-to-person transmission should be done only in consultation with public health departments and when there is a high degree of clinical suspicion. Similarly, testing for MERS CoV should be done only in consultation with public health officials and in the context of known risk factors for MERS CoV infection.

## TREATMENT

Because of the self-limited nature of infection with HCoV strains 229E, OC43, NL63, and HKU1, few treatment studies have been performed. Care typically is supportive.

SARS CoV infections are more serious. Corticosteroids, type 1 IFN agents, convalescent plasma, ribavirin, and lopinavir or ritonavir have been used to treat SARS.[108,126–129] For many of these agents, anecdotal reports suggest benefit, and in vitro assays and animal models offer supportive data,[108,126–138] with the exception of ribavirin, for which in vitro studies do not support efficacy.[135,139,140]

Since the SARS outbreak, viral entry– and protease-inhibiting agents, RNA-interfering agents, and glycyrrhizin have been tested in vitro and appear promising.[140,141] However, no definitive conclusions can be drawn. If SARS CoV re-emerges, clarification of the effectiveness of these treatments through controlled clinical trials will be needed. For MERS CoV, preliminary data suggest several treatments may be useful, but no definitive recommendations can be made at this time.[142]

## PREVENTION

Practicing good hand and respiratory hygiene is the most useful control measure to curb the spread of all respiratory viruses, including HCoVs.[143,144] Prophylactic intranasal IFNα has reduced the duration and severity of HCoV-229E infection in research settings, but it has not been used clinically.[145,146] A proprietary extract of the roots of North American ginseng (*Panax quinquefolium*) can reduce the number of colds and the severity and duration of cold symptoms in adults when taken daily, presumably due to immune stimulation.[147–150] Efficacy for a decrease in the number of colds specifically due to HCoVs has not been studied.

Healthcare personnel should use a gown, gloves, mask, and eye protection for the duration of illness when caring for children hospitalized with signs and symptoms of a respiratory tract infection.[151] The same precautions, with the replacement of the mask by a respirator if available, and negative-pressure isolation are recommended for patients with SARS CoV infection for the duration of illness or 10 days after resolution of fever, provided respiratory symptoms are absent or improving.[151] The same precautions recommended for SARS CoV are recommended for MERS CoV except the duration of precautions should be decided in conjunction with public health authorities.[152]

Standard disinfectants should be used to clean and disinfect environmental surfaces that are frequently touched by infected persons. This can decrease the potential for indirect transmission of HCoVs by fomites.[153]

The control of the 2002–2003 SARS outbreak is credited to the rapid identification of cases and early implementation of infection control and public health measures, including contact tracing and quarantine. If SARS CoV re-emerges, all measures should be

**Key Points:** Epidemiology, Clinical Manifestations, Diagnosis, and Treatment of Human Coronavirus (HCoV) Infections

### EPIDEMIOLOGY

- Human coronaviruses (HCoVs) 229E and OC43 (identified in the 1960s) and NL63 and HKU1 (identified in 2004) are found worldwide. Exposure is common in early childhood; in temperate climates, it primarily causes infections in the winter and spring months.
- Severe acute respiratory syndrome coronavirus (SARS CoV) was identified in 2003 as responsible for the 2002–2003 global outbreak of SARS.
- SARS CoV has not been associated with disease since 2004, and the possibility or probability of a large-scale re-emergence of SARS is unknown.
- Middle East respiratory syndrome coronavirus (MERS CoV) was identified in 2012 as responsible for an epidemic of respiratory illness in the Kingdom of Saudi Arabia. Transmission is ongoing and is primarily limited to countries in the Middle East.
- Risk factors include exposure to camels or camel products or close contact with persons infected with MERS CoV.
- The most common modes of transmission are through droplet and direct and indirect contact.

### CLINICAL MANIFESTATIONS

- HCoV strains 229E, OC43, NL63, and HKU1 are associated with the common cold, acute otitis media, asthma exacerbations, and less frequently, bronchiolitis and pneumonia.
- HCoV-NL63 is also associated with croup. HCoV-HKU1 is associated with vomiting and diarrhea and frequently with respiratory tract symptoms; it appears to be associated more frequently with febrile seizures compared with other HCoVs.
- SARS CoV causes SARS, with an attendant mortality rate of 10%, which primarily affects adults and adolescents. Children younger than 12 years of age who develop SARS typically have less severe manifestations (i.e., fever, cough, and rhinorrhea).
- MERS CoV is associated with a spectrum of disease, ranging from asymptomatic and mild disease to severe respiratory disease with an associated mortality rate of 36%.
- MERS CoV primarily affects male adults with comorbidities; children with MERS typically have milder symptoms.

### DIAGNOSIS

- Upper and lower respiratory tract specimens can be tested by HCoV real-time polymerase chain reaction.
- Stool samples frequently are positive for patients with SARS CoV and have been positive for some patients with MERS CoV and HCoV-HKU1 infection; antibody tests also are available for SARS CoV and MERS CoV infection.
- Serum samples may be positive for patients infected with SARS CoV and MERS CoV.

### TREATMENT

- Infections with HCoV strains 229E, OC43, NL63, and HKU1 require supportive care.
- SARS CoV and MERS CoV infections have no definitive treatment recommendations because of a lack of controlled trials.

implemented urgently in an attempt to prevent a recurrent worldwide outbreak.[28,154,155]

Transmission of MERS CoV within hospitals and households can be averted with the use of infection control precautions,[55] but preventing the transmission from camels to humans is more challenging given the prevalent use of camels for transport, meat, and milk. Recommendations to reduce the likelihood of transmission include regulation of camel movement, enforcing the use of personal protective precautions while handling camels, and educating the public about the risks of consuming unpasteurized camel milk and urine.[156] Given the challenges of following these recommendations, it is likely that sporadic transmission will continue until an effective MERS CoV vaccine is found.[28,157]

*All references are available online at www.expertconsult.com.*

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