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.

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 (TH1) 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 TH1 and inflammatory cytokines (IFN-γ, interleukin [IL]-1, IL-6, and IL-12) and marked increases in chemokines, such as TH1 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

resembling bronchiolitis obliterans organizing pneumonia were also seen.[31]

Epidemiology

A 64-year-old nephrologist who came from southern China to HK on February 21, 2003, was the index case causing subsequent outbreaks of SARS-CoV infection in HK, Singapore, and Toronto.[5,6,32,33] Sixteen hotel guests/visitors were infected by the physician while staying or visiting friends on the same floor of the Hotel M, where the physician had stayed. Through international air travel, these visitors spread the infection to 29 countries/regions, with a total of 8098 cases and a mortality rate of 774 (9.6%) by the end of the epidemic in July 2003.[34]

SARS seems to have spread by close person-to-person contact via droplet transmission or contact with fomite.[35] The superspreading event was a hallmark of SARS-CoV infection, as reflected by the nosocomial outbreak at a major teaching hospital in HK where 138 subjects (many HCWs and previously healthy) were infected within 2 weeks after exposure to 1 patient (a visitor of Hotel M), who was hospitalized with community-acquired pneumonia to a general medical ward.[5,36] This superspreading event was likely caused by several factors including the use of a jet nebulizer for delivering bronchodilator to the index case, overcrowding, and poor ventilation in the hospital ward.[5,36] In addition, the temporal-spatial spread of SARS-CoV among inpatients in the index medical ward of the hospital in HK was consistent with airborne transmission.[37] Apart from respiratory secretions, SARS-CoV was detected in feces, urine, and tears of infected individuals.[38]

In addition, SARS-CoV might have spread by opportunistic airborne transmission in a major community outbreak involving more than 300 residents in a private residential complex, Amoy Gardens, in HK.[39,40] Drying up of water inside the U-shaped bathroom floor drain and backflow of contaminated sewage (from a SARS patient with renal failure and diarrhea) related to negative pressure generated by the toilet exhaust fans might have created infectious aerosols that moved upward through the warm airshaft of the building. Based on analysis of the distribution of all confirmed cases, airborne spread was the most likely explanation in the Amoy Gardens outbreak and the SARS-CoV could have spread more than 200 m to nearby residential complexes.[41] Air samples obtained from a hospital room in Toronto occupied by a SARS patient and swab samples taken from frequently touched surfaces in rooms and in a nurses' station in Toronto were positive by PCR testing.[42] These data suggest the possibility of airborne transmission and stress the importance of taking appropriate respiratory protection apart from strict surface hygiene practices.

Clinical Features

The estimated mean incubation period of SARS was 4.6 days (95% CI, 3.8–5.8 days) whereas the mean time from symptom onset to hospitalization varied between 2 days and 8 days, decreasing over the course of the epidemic. The mean time from onset to death was 23.7 days (95% CI, 22.0–25.3 days).[43]

The major clinical features of SARS-CoV infection on presentation include persistent fever, chills/rigor, myalgia, dry cough, headache, malaise and dyspnea. Sore throat, rhinorrhea, sputum production, nausea and vomiting, and dizziness were less common.[5,6,32,33] Watery diarrhea became prominent in 40% to 70% of patients with SARS one week from illness onset during the clinical course of the illness.[44,45] In 2 patients who presented with status epilepticus, SARS-CoV was detected in the cerebrospinal fluid and serum samples.[46,47] Elderly subjects might not develop fever but present with decrease in general condition, delirium, poor feeding, and fall/fracture.[48] Teenagers tended to follow a clinical course similar to those of adults whereas young children (<12 years of age) often ran a benign clinical course.[49] There was no reported fatality in young children and teenage patients,[49] but SARS in pregnancy carried a significant risk of mortality.[50] Asymptomatic infection seems uncommon because a meta-analysis has shown overall seroprevalence rates of 0.1% for the general population and 0.23% for HCWs, although the true incidence of asymptomatic infection remains unknown.[51]

There was a typical pattern for the clinical course of SARS[5,24,52,53]: phase 1 (viral replication) was associated with increasing SARS-CoV load and characterized by fever, myalgia, and other systemic symptoms that generally improved after a few days; phase 2 (immunopathologic injury) was characterized by recurrence of fever, hypoxemia, and radiologic progression of pneumonia with falls in viral load whereas approximately 20% of patients progressed into acute respiratory distress syndrome (ARDS), necessitating invasive mechanical ventilatory support.[5,53] Because there was peaking of viral load on day 10 of illness followed by progressive decrease in rates of viral shedding from nasopharynx, stool, and urine from day 10 to day 21 after symptom onset, clinical worsening during phase 2 was likely the result

of immune-mediated lung injury due to an overexuberant host response.[24]

Laboratory Features

Lymphopenia, disseminated intravascular coagulation, elevated lactate dehydrogenase, and creatinine kinase were common laboratory features of SARS.[5] The CD4 and CD8 T-lymphocyte counts fell early in the course of SARS, whereas low counts of CD4 and CD8 at presentation were associated with adverse clinical outcome.[54]

Radiologic Features

Although nonspecific, common radiographic features of SARS included the predominant involvement of lung periphery and the lower zone in addition to absence of cavitation, hilar lymphadenopathy, or pleural effusion.[5,55] Radiographic progression from unilateral focal air-space opacity to either multifocal or bilateral involvement occurred during the second phase of the disease, followed by radiographic improvement with treatment.[5,55] In 1 case series, spontaneous pneumomediastinum occurred in 12% of patients whereas 20% of patients developed ARDS over a period of 3 weeks.[24] Common high-resolution CT features included ground-glass opacification, sometimes with consolidation, and interlobular septal and intralobular interstitial thickening, with predominantly a peripheral and lower lobe involvement.[5,55]

Treatment

Ribavirin, a nucleoside analog, was widely used for treating SARS patients in 2003 but ribavirin alone had no significant in vitro activity against SARS-CoV,[56] and it caused significant hemolysis in many patients.[5,33] Lopinavir and ritonavir in combination is a boosted protease inhibitor regimen widely used for treatment HIV infection. In vitro activity against SARS-CoV was demonstrated for lopinavir and ribavirin at 4 μg/mL and 50 μg/mL, respectively, whereas inhibition of in vitro cytopathic effects was achieved down to a concentration of 1 μg/mL of lopinavir combined with 6.25 μg/mL of ribavirin.[57] A retrospective analysis showed that the addition of lopinavir (400 mg)/ritonavir (100 mg) as initial therapy was associated with lower overall death rate (2.3% vs 15.6%) and intubation rate (0% vs 11%) than a matched historical cohort who received ribavirin alone as the initial antiviral therapy.[58] The outcome of a subgroup who had received lopinavir/ritonavir as late rescue therapy after receiving pulsed methylprednisolone for worsening respiratory symptoms, however, was not better than the matched cohort.[57,58]

IFN-Is are produced early as part of the innate immune response to virus infections. There are in vitro and limited animal and observational data that IFN, in particular early use, has efficacy against SARS-CoV.[56,59,60] In experimentally infected cynomolgus macaques, prophylactic treatment with pegylated IFN-α significantly reduced viral replication and excretion, viral antigen (Ag) expression by type I pneumocytes, and lung damage versus untreated macaques, whereas postexposure treatment with pegylated IFN-α yielded intermediate results.[61] Use of IFN-α1 plus systemic corticosteroids was associated with improved oxygen saturation, more rapid resolution of radiographic lung opacities, and lower levels of creatinine kinase than systemic corticosteroids alone in another study of SARS patients.[62]

During the second week of SARS illness, there was evidence of bronchiolitis obliterans organizing pneumonia radiologically[5] and histopathologically in some cases[31] whereas the progression of the pulmonary disease was mediated by the host inflammatory response.[24] Systemic corticosteroids in the form of pulsed methylprednisolone significantly reduced IL-8, MCP-1, and IP-10 concentrations from 5 to 8 days after treatment in 20 adult SARS patients in an uncontrolled study.[25] Induction of IP-10 is thought to be a critical event in the initiation of immune-mediated lung injury and lymphocyte apoptosis.[63] The use of rescue pulsed methylprednisolone during clinical progression was associated with favorable clinical improvement in some patients with resolution of fever and radiographic lung opacities within 2 weeks.[5,64] A retrospective analysis showed, however, that theuse of pulsed methylprednisolone was associated with an increased risk of 30-day mortality (adjusted odds ratio [OR] 26.0; 95% CI, 4.4–154.8).[65] In addition, disseminated fungal disease and avascular osteonecrosis occurred after prolonged systemic corticosteroids therapy.[66,67] A randomized placebo-controlled study showed that plasma SARS-CoV RNA concentrations in the second and third weeks of illness were higher in patients given initial hydrocortisone (n = 10) intravenously than those given normal saline as control (n = 7) during early clinical course of illness. Despite the small sample size, the data suggest that systemic corticosteroid given in the earlier phase might prolong viremia.[68]

Convalescent plasma, donated by patients, including HCWs, who had recovered from SARS, contained high levels of neutralizing antibody and seemed clinically useful for treating other SARS patients. In a study comparing patients with SARS-CoV infection who did and did not receive convalescent plasma, 19 patients who received such therapy had better survival rate (100% vs

66.2%) and discharge rate (77.8% vs 23.0%) compared with 21 controls.[69] Among 80 non-randomized patients with SARS who were given convalescent plasma at the Prince of Wales Hospital (Shatin, Hong Kong) the discharge rate at day 22 was 58.3% for patients (n = 48) treated within 14 days of illness onset versus 15.6% for those (n = 32) treated beyond 14 days.[70] An exploratory post hoc meta-analysis of studies of SARS-CoV infection and severe influenza showed a significant reduction in the pooled odds of mortality after convalescent plasma versus placebo or no treatment (OR 0.25; 95% CI, 0.14–0.45).[71]

Hospital Infection Control Aspects

A case-control study involving 124 medical wards in 26 hospitals in HK and Guangzhou has identified 6 independent factors of super-spreading nosocomial outbreaks of SARS-CoV infection: performance of resuscitation, minimum distance between beds less than 1 m, staff working while experience symptoms, and SARS patients requiring oxygen therapy or noninvasive ventilation whereas availability of washing or changing facilities for staff was a protective factor (Box 1).[72] A systematic review has shown that 4 aerosol-generating procedures would increase the risk of nosocomial SARS transmission to HCWs, including tracheal intubation, noninvasive ventilation, tracheotomy, and manual ventilation before intubation (Box 2).[73] Thus it is important for HCWs to take airborne precaution before carrying out aerosol-generating procedures.

MIDDLE EAST RESPIRATORY SYNDROME–CORONAVIRUS INFECTION

MERS-CoV was first reported in September 2012 when a novel βCoV was isolated from a male patient who had died of severe pneumonia and multiorgan failure in Saudi Arabia in June 2012.[74] MERS-CoV infection has spread to 27 countries since its discovery in 2012. Globally, from September 2012 to June 29, 2016, the World Health Organization has been informed of 1769 laboratory-confirmed cases of infection with MERS-CoV, with at least 630 deaths.[75] The case definitions of suspected and confirmed cases of MERS-CoV infection are shown in Box 3.[76]

The Virus and Its Origin

Although the natural reservoir of MERS-CoV is still unclear, bats may be one possible reservoir for the virus. In a study screening fecal specimens of bats from Ghana and 4 European countries for βCoVs, viruses related to the novel human βCoV (EMC/2012, which was later renamed MERS-CoV) were detected in 46 (24.9%) of 185 *Nycteris* bats and 40 (14.7%) of 272 *Pipistrellus* bats.[77] Of 1100 bat samples tested in another study, 1 fragment of MERS-CoV was found in 1 *Taphozous* bat with close matching to a human isolate of MERS-CoV.[78] Their genetic relatedness indicates that MERS-CoV has originated from bats.

Dromedary camels are an important natural host for the maintenance and diversification of

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Box 1
Independent factors associated with increased risk of superspreading[a] events of severe acute respiratory syndrome–coronavirus infection in the health care setting

Performance of resuscitation (OR 3.81; 95% CI, 1.04–13.87; *P* = .04)

Staff working while experiencing symptoms (OR 10.55; 95% CI, 2.28–48.87; *P* = .003)

SARS patients requiring oxygen therapy at least 6 L/min (OR 4.30; 95% CI, 1.00–18.43; *P* = .05)

SARS patients requiring noninvasive positive pressure ventilation (OR 11.82; 95% CI, 1.97–70.80; *P* = .007)

Minimum distance between beds <1 m (OR 6.94; 95% CI, 1.68–28.75; *P* = .008)

Washing or changing facilities for staff (OR 0.12; 95% CI, 0.02–0.97; *P* = .05)

[a] A superspreading event was defined as 1 patient who could infect at least 3 others.
Data from Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? Clin Infect Dis 2007;44:1017–25.

Box 2
Respiratory procedures reported to present an increased risk of transmission of severe acute respiratory syndrome–coronavirus to health care workers (n; pooled OR [95% CI])

Tracheal intubation (n = 4 cohort; 6.6 [2.3, 18.9], and n = 4 case-control; 6.6 [4.1, 10.6])

Noninvasive ventilation (n = 2 cohort; 3.1 [1.4, 6.8]),

Tracheotomy (n = 1 case-control; 4.2 [1.5, 11.5])

Manual ventilation before intubation (n = 1 cohort; 2.8 [1.3, 6.4]).

Data from Tran K, Cimon K, Severn M, et al. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PLoS One 2012;7:e35797.

Box 3
World Health Organization case definitions of the Middle East respiratory syndrome

Confirmed case

A person with laboratory confirmation of MERS-CoV infection,[1] irrespective of clinical signs and symptoms.

Probable case

- A febrile acute respiratory illness with clinical, radiologic, or histopathologic evidence of pulmonary parenchymal disease (eg, pneumonia or ARDS)
  AND
  Direct epidemiologic link[2] with a confirmed MERS-CoV case
  AND
  Testing for MERS-CoV is unavailable, negative on a single inadequate specimen[3] or inconclusive[4]

- A febrile acute respiratory illness with clinical, radiologic, or histopathologic evidence of pulmonary parenchymal disease (eg, pneumonia or ARDS)
  AND
  The person resides or traveled in the Middle East or in countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred
  AND
  Testing for MERS-CoV is inconclusive[4]

- An acute febrile respiratory illness of any severity
  AND
  Direct epidemiologic link[2] with a confirmed MERS-CoV case
  AND
  Testing for MERS-CoV is inconclusive[4]

Notes

1 A case may be laboratory confirmed by detection of viral nucleic acid or serology. The presence of viral nucleic acid can be confirmed by either a positive RT-PCR result on at least 2 specific genomic targets or a single positive target with sequencing of a second target. A case confirmed by serology requires demonstration of seroconversion in 2 samples ideally taken at least 14 days apart, by a screening (ELISA or immunofluorescence assay) *and* a neutralization assay.
The interim recommendations for laboratory testing for MERS-CoV should be consulted, however, for the most recent standard for laboratory confirmation (http://www.who.int/csr/disease/coronavirus_infections/en/).

2 A direct epidemiologic link with a confirmed MERS-CoV patient may include

- Health care–associated exposure, including providing direct care for MERS-CoV patients, working with HCWs infected with MERS-CoV, visiting patients, or staying in the same close environment of individuals infected with MERS-CoV

- Working together in close proximity or sharing the same classroom environment with individuals infected with MERS-CoV

- Traveling together with individuals infected with MERS-CoV in any kind of conveyance

- Living in the same household as individuals infected with MERS-CoV

- The epidemiologic link may have occurred within a 14-day period before or after the onset of illness in the case under consideration

3 An inadequate specimen would include a nasopharyngeal swab without an accompanying lower respiratory specimen or a specimen that has had improper handling, is judged to be of poor quality by the testing laboratory, or was taken too late in the course of illness.

4 Inconclusive tests may include

- A positive screening test on a single rRT-PCR target without further confirmation

- Evidence of seroreactivity by a single convalescent serum sample ideally taken at least 14 days after exposure by a screening assay (ELISA or immunofluorescence assay) and a neutralization assay, in the absence of molecular confirmation from respiratory specimens.

From WHO. Middle east respiratory syndrome coronavirus case definition for reporting to WHO interim case definition 14 July 2015. Available at: http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/. Accessed July 2, 2016.

MERS-CoV and seem to be the major source of zoonotic human infection. The virus has been isolated from dromedary camels in the Arabian Peninsula and across North Africa, East Africa, West Africa, and Central Africa but is not found in dromedary camels in Kazakhstan[79] or in Bactrian camels in Mongolia[80] or other countries.[81,82] Only a minority of reported MERS human cases, however, have reported direct camel exposure.[83]

Epidemiology

Although MERS-CoV was first described in September 2012,[74] retrospective analysis of a cluster of hospital cases dated back to April 2012 in Jordan confirmed MERS-CoV by RT-PCR and serology as the etiology of the outbreak, which involved at least 10 HCWs.[84] The epidemiology of MERS-CoV is characterized by sporadic zoonotic transmission events, sometimes followed by nosocomial outbreaks within health care settings due to failure in infection control and prevention measures. Saudi Arabia has the largest MERS-CoV caseload, followed by South Korea as the country with the highest caseload outside the Arabic Peninsula.[75]

The risk factors for primary MERS-CoV infection were addressed in a case-control study, consisting of 30 primary MERS-CoV cases reported from March 2014 to November 2014 in Saudi Arabia, with 2 to 4 controls matched by age, gender, and neighborhood for each case patient.[85] Using multivariable analysis, the investigators demonstrated that direct dromedary exposure in the 2 weeks before illness onset was strongly associated with MERS-CoV illness (adjusted OR 7.45; 95% CI, 1.57–35.28), along with having diabetes mellitus (adjusted OR 6.99; 95% CI, 1.89–25.86) or heart disease (adjusted OR 6.87; 95% CI, 1.81–25.99) and current tobacco smoking (adjusted OR 6.84; 95% CI, 1.68–27.94).[85] The risk for secondary transmission from patients to household contacts was estimated at approximately 4%.[86] Risk factors for household transmission included sleeping in an index patient's room and touching respiratory secretions from an index patient whereas casual contact and simple proximity were not associated with transmission.[87]

In a cross-sectional serosurveillance study of 10,009 healthy individuals in Saudi Arabia, 0.15% had evidence of positive MERS-CoV serology, suggesting that the number of mild or asymptomatic infections far exceeds those that are recognized.[88] Seropositivity was more common in men than in women, in central than in coastal provinces, and in camel shepherds (2.3%) and slaughterhouse workers (3.6%) than the general population.[88]

Nosocomial transmission is a hallmark of MERS-CoV infection. Superspreading events of MERS-CoV infection have been reported in Jordan,[84] Al Hasa,[89] Jeddah,[90] and Abu Dhabi,[91] whereas the major outbreak in South Korea in 2015 is characterized by several superspreading events in the hospital settings.[92] Failure in infection control and prevention in health care facilities (HCFs) has resulted in large numbers of secondary cases of MERS-CoV infection involving HCWs, existing patients, and visitors in Saudi Arabia[89,90] and several other countries over the past few years.[84,91,92] Common predisposing factors include exposure to contaminated and overcrowded HCFs, poor compliance with appropriate personal protection equipment (PPE) when assessing patients with febrile respiratory illness, application of potentially aerosol-generating procedures (resuscitation, continuous positive airway pressure, and nebulized medications), and lack of proper isolation room facilities.[84,89–93] The customs of patients seeking care at different HCFs (doctor shopping) and having friends and family members stay with patients as caregivers at already overcrowded HCFs are unique factors in South Korea.[94]

In contrast to SARS, approximately 75% of patients with MERS had at least 1 comorbid illness whereas fatal cases were more likely to have an underlying condition (86% among fatal cases vs 42% among recovered or asymptomatic cases; P<.001). Index/sporadic cases were older (median age 59 years vs 43 years; P<.001) and more likely to suffer from severe disease requiring hospitalization (94% vs 59%; P<.001) in comparison to the secondary cases. Cases specifically reported as "mild disease" or "asymptomatic" occurred only among secondary cases.[89,90] Most (90%) index/sporadic cases had severe disease whereas a higher proportion of patients with renal failure was noted among secondary cases in Saudi Arabia, due to the nosocomial outbreak involving the hemodialysis units in hospitals in Al Hasa.[89] Good infection control measures in reported clusters involving HCS probably limited onward transmission to HCW and hospitalized patients.[89]

Clinical Features

The clinical presentation of MERS-CoV infection ranges from asymptomatic to very severe pneumonia with ARDS, septic shock, and multiorgan failure resulting in death. In contrast to SARS, the clinical course of MERS is more severe in immunocompromised patients and generally mild in individuals without comorbid illness.[95] Few cases have been reported in children less than 5 years

of age. Typically, MERS-CoV infection begins with fever, cough, chills, sore throat, myalgia, and arthralgia, followed by dyspnea and rapid progression to pneumonia within the first week (in contrast to SARS), often requiring ventilatory and other organ support.[84,89,96,97] Most patients present with respiratory illness although immunocompromised patients may present with fever, chills, and diarrhea before developing pneumonia due to MERS-CoV.[98] At least one-third of patients also had gastrointestinal symptoms, such as vomiting and diarrhea.[84,89,96–99]

Neurologic complications, such as intracerebral hemorrhage (due to thrombocytopenia, disseminated intravascular coagulation, and platelet dysfunction) and critical illness polyneuropathy, complicating a long ICU stay, have been reported.[100] Pregnant women infected with MERS may develop severe disease and a fatal outcome, including stillbirth.[101–104] Concomitant infections and low albumin were found predictors of severe infection, whereas age greater than or equal to 65 years was the only predictor of increased mortality.[83]

Based on data related to human-to-human transmission in several clusters, the incubation period has been estimated to be more than 5 days but could be as long as 2 weeks (median 5.2 days [95% CI, 1.9–14.7]).[89] The median times from symptom onset of MERS to hospitalization, admission to an ICU, or death were 4.0 (range 0–16, n = 62), 5.0 (1–15, n = 35), and 11.5 days (4–298, n = 40), respectively.[96]

Laboratory Features

Similar to SARS and other severe viral illness, common laboratory findings of MERS include leukopenia, in particular lymphopenia.[74,84,97,99] Reports from several cases found viral RNA in blood, urine, and stool but at much lower viral loads than in the respiratory tract.[98,105] The viral load in upper respiratory tract specimens is generally lower than in the lower respiratory specimens.[106]

Radiologic Features

Radiographic findings of MERS are consistent with viral pneumonitis and ARDS, with bilateral hilar infiltration, unilateral or bilateral patchy densities or infiltrates, segmented or lobar opacities, ground-glass opacities, and small pleural effusions in some cases. Lower lobes are affected more than upper lobes early in the course of illness with more rapid radiographic progression than SARS. The most common CT finding in hospitalized patients with MERS-CoV infection is that of bilateral predominantly subpleural and basilar airspace changes, with more extensive ground-glass opacities than consolidation. The subpleural and peribronchovascular predilection of the abnormalities is suggestive of an organizing pneumonia pattern.[107]

Pathogenesis

The dipeptidyl peptidase 4 (DPP4), also known as CD26, has been identified as the functional cellular receptor for MERS-CoV.[108,109] DPP4 homologues permitting MERS-CoV infection are present in a variety of cell lines.[110,111] Cell-based studies have revealed that MERS-CoV evades innate immune response and this may explain the large number of severe cases.[112–114] Widespread MERS-CoV Ag expression has been observed in type I and type II alveolar cells, ciliated bronchial epithelium, and unciliated cuboid cells of terminal bronchioles. Virus Ag was also found in endothelial cells of pulmonary vessels and rarely in alveolar macrophages[115]

In contrast to a patient who survived nosocomial MERS-CoV infection in France, the index patient with a fatal outcome did not promote type I IFN, especially IFN-α, in response to MERS-CoV. Levels of both mediators IL-12 and IFN-γ that promote viral clearance were much lower in the fatal case than the patient who survived.[116] Lower respiratory tract (LRT) excretion of MERS-CoV could be observed for more than 1 month. The most severely ill patient presented an expression of the virus in blood and urine, consistent with impairment of a type I IFN–mediated immunologic response in the index patient, but such response was developed by the patient who survived.[117]

In a study of 37 adult patients infected with MERS-CoV in Saudi Arabia, viral loads were much higher in the LRT specimens than in the upper respiratory tract; 33% of all 108 serum samples tested yielded viral RNA whereas only 14.6% of stool and 2.4% of urine samples yielded viral RNA. All seroconversions occurred during the first 2 weeks after diagnosis, corresponding to the second and third weeks after symptom onset. All surviving patients, but only slightly more than half of all fatal cases, produced IgG and neutralizing antibodies. The levels of IgG and neutralizing antibodies were weakly and inversely correlated with LRT viral loads. Presence of antibodies did not lead to the elimination of virus from LRT.[106] In most patients in South Korea, robust antibody responses developed by the third week of illness whereas delayed antibody responses with the neutralization test were associated with more severe disease.[118] MERS-CoV antibodies, including neutralizing antibodies, were detectable in 6 (86%) of 7 persons

serologically positive or indeterminate for at least 34 months after the nosocomial outbreak in Jordan in 2012.[119]

Autopsy of a 45 year-old man who died of MERS-CoV infection in Abu Dhabi in 2014 revealed DAD. Pneumocytes and epithelial syncytial cells were important targets of MERS-CoV Ag, because DPP4 receptors were found in scattered pneumocytes and syncytial cells but no evidence of extrapulmonary MERS-CoV Ags were detected, including the kidneys.[120] In a renal biopsy, which was performed 8 weeks after the onset of symptoms in a patient infected with MERS-CoV infection in South Korea, acute tubular necrosis was the main finding, whereas proteinaceous cast formation and acute tubule-interstitial nephritis were found. There were no electron dense deposits observed with electron microscopy. The investigators could not verify the virus itself by in situ hybridization and confocal microscopy (MERS-CoV costained with DPP4).[121]

Treatment

MERS-CoV causes cytokine and chemokine dysregulation by inducing significantly higher expression levels of cytokines (IL-12 and IFN-γ) and chemokines (IP-10/C-X-C motif chemokine ligand 10 (CXCL-10), MCP-1/C-C motif chemokine ligand 2 (CCL-2), major intrinsic protein (MIP)-1α/CCL-3, RANTES/CCL-5, and IL-8) than SARS-CoV in human monocyte–derived macrophages.[122] The host innate IFN response is crucial for the control of viral replication after infection because the absence of IFN-α impairs the development of a robust antiviral adaptive T$_H$1 immune response, mediated by IL-12 and IFN-γ that promote viral clearance and bring substantial arguments for the indication of early IFN-α treatment during MERS-CoV infection.[116]

Many compounds have been found to have in vitro inhibitory activity against MERS-CoV infection. Notable are the type I IFNs, with IFN-β showing the strongest inhibitory activity[112,114,123,124] whereas IFN-α2b and ribavirin in combination was superior to individual components in reducing MERS-CoV viral load on Vero cells.[113] In rhesus macaques infected with MERS-CoV, combination therapy with high doses of IFN-α2b with ribavirin modestly reduced viral titers and measures of lung injury[125] but observational studies of clinical use have reported inconsistent findings. A small case series showed 100% mortality in 5 patients who received IFN-α2b plus ribavirin administered at a median of 19 days (range 10–20 days from admission).[126] A study of 32 patients compared outcomes in 13 patients treated with IFN-α2a (180 μg

subcutaneously once weekly) combined with ribavirin (loading dose of 2 g orally followed by 600 mg orally every 12 h) versus 11 patients treated with IFN-β1a (44 μg subcutaneously 3 times weekly) combined with ribavirin and found high mortality in both groups and no significant difference between them, 85% versus 64% ($P = .24$).[127] Although an earlier study of 20 patients treated with IFN-α2a combined with ribavirin found an improved survival rate at 14 days, these favorable findings were no longer significant by day 28 (70% mortality vs 83% in a comparator group of untreated patients with confirmed MERS-CoV infection; $P = .54$). The investigators attributed the lack of effectiveness to older age, presence of comorbid conditions, and delay in treatment initiation.[128] One case study described the use of lopinavir as part of triple-therapy regimen (in combination with IFN and ribavirin) in a MERS-CoV infected patient who subsequently died in Greece despite initial resolution of viraemia.[129]

Nitazoxanide is another potent type I IFN inducer that has been used in humans for parasitic infections. It is a synthetic nitrothiazolyl-salicylamide derivative that exhibits broad-spectrum antiviral activities against both RNA and DNA viruses, including canine CoV, influenza viruses, hepatitis B virus, hepatitis C virus, HIV, rotavirus, norovirus, and flaviviruses.[130] The combinational use of these IFN inducers (eg, nitazoxanide and chloroquine) and innate immunomodulators with effective antiviral agents may be synergistic and should be evaluated in animal models.

Systemic corticosteroids have been used empirically in some patients with MERS-CoV infection to dampen immunopathologic host responses, but no survival benefit has been reported.[126,131] A comprehensive review has shown that the use of systemic corticosteroids in patients with severe influenza A(H1N1)pdm09 infection was associated with increased risks of nosocomial pneumonia, higher 90-day mortality, and longer length of stay.[132] Systemic corticosteroids should be used cautiously because their use was associated with worsened outcomes in patients infected with SARS-CoV during the 2003 epidemic,[65] including fatal aspergillosis[66] and osteonecrosis.[67]

The nucleosides/nucleotides are building blocks of viral nucleic acids. Drugs that target nucleosides/nucleotides and/or viral nucleic acids generally have broad-spectrum activities against a wide range of CoVs and other viruses. Mycophenolate mofetil is an antirejection drug that inhibits inosine monophosphate dehydrogenase and guanine monophosphate synthesis. The active compound, mycophenolic acid, exhibits antiviral activity in vitro against various viruses that include hepatitis B virus, hepatitis C virus,

and arboviruses. Mycophenolic acid was identified as a potential anti–MERS-CoV drug using high-throughput screening and exhibits potent anti–MERS-CoV activity in vitro.[133] In vitro activity, however, does not necessarily translate to in vivo effectiveness. A follow-up study by the same group of investigators has shown that MERS-CoV–infected common marmosets treated with mycophenolate mofetil had worsened outcome with more severe disease and higher viral loads in necropsied lung and extrapulmonary tissues compared with untreated animals.[134] Renal transplant recipients who were on maintenance mycophenolate mofetil therapy also developed severe or fatal MERS-CoV infection.[116,135] Thus, usual dosages of mycophenolate mofetil monotherapy are unlikely to be useful for either prophylaxis or treatment of CoV infections.

A systematic review and exploratory meta-analysis of patients with SARS-CoV and influenza virus treated with convalescent plasma showed a reduction in mortality[71] and thus should be considered a potential treatment of MER-CoV infection. Convalescent plasma from patients who have fully recovered from MERS-CoV infection with well-defined levels of MERS-CoV neutralizing antibodies, however, is not readily available. There are limiting factors, such as the appropriate window period for plasma retrieval from suitable donors and timely administration to other ill patients with MERS-CoV infection, in addition to the concern that the treatment dose may result in undesired volume expansion in patients with ARDS who require fluid restriction.

Various monoclonal and polyclonal antibody preparations with neutralizing activity inhibiting MERS-CoV are now in preclinical models.[136–140] There are no published human data, however, to date on the use of these preparations or of convalescent plasma for treatment of patients with MERS-CoV infection.

Although there is some concern that challenge of marmosets with MERS-CoV may not consistently lead to severe disease in the marmoset model,[141] more data are needed from suitable animal studies and carefully conducted clinical and virologic studies of priority treatments, such as convalescent plasma and IFNs (ideally in randomized clinical trials if sufficient numbers of patients are available). At present, clinical management of patients with severe disease largely relies on meticulous ICU support and prevention of complications.[142] The more feasible clinical trial options at present include monotherapy or combination therapy with lopinavir/ritonavir, IFN-β1b, passive immunotherapy with convalescent plasma, and human monoclonal or polyclonal antibody. More clinical trial data are needed to assess the role of IFN and ribavirin in

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Box 4
Treatment modalities for Middle East respiratory syndrome–coronavirus infection

1. Treatment benefits likely to exceed risks

   Convalescent plasma, IFN, lopinavir, and monoclonal and polyclonal neutralizing antibody

2. Treatment data inadequate for assessment

   Interferon and ribavirin combination, nitazoxanide, and chloroquine

3. Risks likely to exceed benefits

   Systemic corticosteroids, ribavirin monotherapy, intravenous gammaglobulin, and mycophenolic acid

Adapted from Treatment of MERS-CoV: information for clinicians. Clinical decision-making support for treatment of MERS-CoV patients. 2015. Version 3.0. Public Health England and ISARIC. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/459835/merscov_for_clinicians_sept2015.pdf. Accessed September 5, 2015.

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combination, nitazoxanide, and chloroquine whereas systemic corticosteroids, ribavirin monotherapy, intravenous gammaglobulin, and mycophenolic acid would pose more harm than benefits (**Box 4**).[143]

SUMMARY

Bats seem the common natural source of both SARS-CoV and MERS-CoV. The clinical features are similar but MERS progresses to respiratory failure much more rapidly than SARS. Although the estimated pandemic potential of MERS-CoV is lower than that of SARS-CoV,[144] the case fatality rate of MERS is much higher and likely related to older age and comorbid illness of the sporadic cases. Lots of knowledge gaps remain since the first discovery of MERS-CoV in 2012.[145] More studies are needed to understand the pathogenesis, viral kinetics, mode of disease transmission, and intermediary source of MERS-CoV to guide public health infection control measures and treatment. It is also important to watch for any emergence and mutation of other SARS-like clusters of circulating CoVs in the bat populations that may threaten human health.[146]

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