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# Middle East respiratory syndrome (MERS)

## A new zoonotic viral pneumonia

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Coronaviruses have traditionally been associated with mild upper respiratory tract infections throughout the world. In the fall of 2002, a new coronavirus emerged in Asia causing severe viral pneumonia, i.e., severe acute respiratory syndrome (SARS). Nearly a decade following the SARS epidemic, a new coronavirus causing severe viral pneumonia has emerged, i.e., middle east respiratory syndrome (MERS). Since the initial case of MERS-CoV occurred in June of 2012 in Saudi Arabia there have been 688 confirmed cases and 282 deaths in 20 countries.

Although both SARS and MERS are caused by coronaviruses, SARS was characterized by efficient human transmission and relatively low mortality rate. In contrast, MERS is relatively inefficiently transmitted to humans but has a high mortality rate. Given the potential overlap in presentation and manifestation, it is important to understand the clinical and epidemiologic differences between MERS, SARS and influenza.

### Background

Coronaviruses have worldwide distribution and previously were associated with mild upper respiratory tract infections, e.g., the common cold is caused by coronavirus types 229E and OC 43.<sup>1</sup> From Guangdong Province in southern China in the fall of 2002, a new coronavirus emerged causing severe viral pneumonia, i.e., severe acute respiratory syndrome (SARS). This new coronavirus variant was termed SARS-CoV. The intermediate host of SARS-CoV was the masked palm civet cat.<sup>2</sup> From China this new zoonotic viral pneumonia rapidly spread worldwide to 30 countries. In one year, 8273 SARS cases occurred with 774 deaths. In addition, the financial impact from limiting travel, tourism, disruption of trade and commerce, shifting of hospital services, quarantine of exposed patients and health care workers, and lost wages suffered from victims of SARS, isolation of patients suspected of carrying the contagious virus was enormous. Mutation of SARS-CoV surface spike proteins found in the coronavirus that usually circulates in the animal reservoir permitted binding to human ACE 2 receptors with a sudden switch in susceptible vertebrate hosts facilitating transmission to

humans.<sup>1,2</sup> As mysteriously as SARS appeared in 2002, it disappeared in the summer of 2003.

Nearly a decade following the SARS epidemic, a new coronavirus causing severe viral pneumonia in the Arabian peninsula has emerged, i.e., middle east respiratory syndrome (MERS). In June 2012, the index case of MERS-CoV occurred in Saudi Arabia.<sup>3,4</sup> Since that time, according to the World Health Organization, there have been 688 confirmed cases and 282 deaths in 20 countries. Most cases have occurred in the Arabian peninsula, i.e., Saudi Arabia, United Arab Emirates, Qatar, Oman, Jordan, Kuwait and Lebanon. In addition, travel-related MERS cases have been reported from Europe (United Kingdom, Italy, Greece, Netherlands, France, and Germany) as well as Tunisia, Malaysia, Philippines, Egypt, and most recently Iran and the United States. The zoonotic vector and possible reservoir of MERS has been found to be dromedary camels, with bats as another possible vector for transmission to humans.<sup>5</sup> Although both SARS and MERS are caused by coronaviruses, SARS was characterized by efficient human transmission and relatively low mortality rate while MERS is relatively inefficiently transmitted to humans but has a high mortality rate, i.e., 35–50%.<sup>6</sup> In terms of virulence, MERS most closely resembles pandemic influenza (H<sub>1</sub>N<sub>1</sub>) and avian influenza (H<sub>7</sub>N<sub>9</sub>) not SARS, but MERS potential for widespread transmissibility is less than avian influenza (H<sub>7</sub>N<sub>9</sub>).

### Virology

Coronaviruses are enveloped single stranded RNA viruses. The glycoprotein spikes (S) surrounding the spherical virion gives the virus its characteristic “halo appearance”, i.e., a corona on electron microscopy. Six coronavirus subgroups are known human pathogens, the  $\alpha$  coronavirus subgroup includes 229E and NL229E, and the  $\beta$  coronavirus subgroup includes OC43, HKU1, SARS-CoV, and MERS-CoV. Coronaviruses have relatively large genome (26–32 kb) and all six human coronavirus subgroups have been cultured in vitro except for the  $\beta$  coronavirus subtype HKU1.<sup>1,2</sup> MERS-CoV is the first C lineage  $\beta$  coronavirus known to infect humans. Although MERS-CoV is genetically closely related to other  $\beta$  coronaviruses isolated from bats in Europe, Mexico, Africa, and Hong Kong, dromedary camels are the likely reservoir for MERS-CoV in the Arabian Peninsula.<sup>5</sup> In tissue culture, MERS-CoV shows cytopathic effects (CPEs) in LLC-MK2 or Vero cell lines. Distinctive from

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the SARS-CoV receptor, the MERS-CoV cell receptor has been identified as DDP4 (dipeptidyl peptidase 4) which interacts with the MERS-CoV surface protein. MERS-CoV is present in ciliated bronchial epithelium, in terminal bronchial epithelium, and alveolar macrophages.<sup>5</sup>

Aside from tissue culture, MERS-CoV may be diagnosed by ELISA, IFA, or microneutralization assay (MNT). The CDC has developed a real-time reverse transcriptase (RT) PCR assay that is available worldwide to diagnose MERS. MERS-CoV is present in serum, feces, and urine but highest concentrations are in lower respiratory secretions. Previous exposure to SARS, i.e., anti-SARS-CoV antibodies appears to confer some protective immunity to MERS-CoV, i.e., less severe infections.<sup>6-8</sup>

## Epidemiology

In June 2012 a novel  $\beta$  coronavirus (MERS-CoV) was first isolated from the respiratory tract of a fatal case of viral pneumonia in a Saudi businessman. Since that time, MERS has been reported in 20 countries. The spectrum of MERS ranges from a mild viral respiratory illness to a rapidly fatal viral pneumonia complicated by acute respiratory distress syndrome (ARDS) and acute renal failure (ARF). There have been MERS outbreaks in health facilities and clusters within families and person-to-person transmission has been demonstrated. Household and nosocomial transmission may occur as well.<sup>9,10</sup>

At the present time, the pandemic potential for MERS appears low. While having a high case fatality rate, the transmissibility of MERS appears to be modest. In contrast, SARS had low case fatality rate but was highly transmissible.<sup>11-13</sup> Pandemic influenza is feared because the viral strains causing pandemic influenza (e.g., the 1918 H1N1 strain) can possess both the ability to rapidly transmit the influenza among humans and has a high fatality rate, particularly in young healthy adults.<sup>14,15</sup> Among the zoonotic viral pneumonias, avian influenza ( $H_7N_9$ ) has a comparable high fatality rate, and a high pandemic potential since the zoonotic vectors are migratory birds.<sup>16</sup>

Outside of the Arabian Peninsula, MERS cases have been travel-related and traceable to the Arabian Peninsula. According to the CDC, the first United States case occurred on May 2, 2014 in Indiana. This first US case was a traveler from Saudi Arabia to Indiana via London and Chicago. The patient was a healthcare worker and lived and worked in Saudi Arabia. The second case of MERS occurred in Florida on May 11, 2014 and was also imported from a traveler from Saudi Arabia. This patient was also a healthcare worker who traveled to Florida from Saudi Arabia via London, Boston, and Atlanta. The third US case had casual contact with the initial Indiana case, raising questions about person-to-person spread. The probable third US case was diagnosed on the basis of positive ELISA and IFA with a negative MNT. According to the WHO another MERS case was reported in Jordan on May 25, 2014 in a 69-y-old male. He was initially hospitalized for a surgical procedure and subsequently discharged. After 5 d he developed fever and was readmitted to

the same hospital 3 d later. After 2 d in hospital, he developed a cough and chest radiograph showed pneumonia. MERS was suspected but MERS testing was negative. He remains critically ill in the ICU 10 d after the initial MERS testing. A second specimen was taken that was positive for MERS.

This case illustrates many of the clinical and infection control aspects of MERS. There are several unanswered questions in this case. Was MERS contracted at home or during his first hospitalization? Were the first and second MERS specimens obtained from the same anatomical location, i.e., lower respiratory tract? Why was the first specimen negative and the second positive for MERS ten days later? As with non-pandemic influenza, the mortality of MERS is highest in those with comorbidities.<sup>5,14</sup> Most MERS cases occur in healthy adults (median age 50 y), but MERS can effect hosts of any age.

As of June 1, 2014, WHO has reported an additional case of MERS. The case is a 26-y-old male health-care worker (HCW) who developed pneumonia and gastrointestinal symptoms and was admitted to the hospital on May 30, 2014. He is currently in a stable condition. He has no known comorbidities, but does have a history of contact with a laboratory confirmed MERS-CoV HCW case. He has no travel history and no history of animal contact.

## Clinical Features

The median incubation period for human-to-human transmission is approximately 5 d (range 1.9–14.7 d). The median time from onset of MERS to hospitalization is approximately 4 d. The median time from onset of illness to ICU admission is approximately 5 d. The median onset to death is approximately 12 d. The median duration of mechanical ventilation is 16 d and the median duration of an ICU stay is 30 d. The mortality for MERS patients in the ICU for 90 d is 58%.<sup>5,17,18</sup>

Patients with MERS present as an influenza-like illness (ILI). SARS and MERS have some features in common, i.e., fever with chills, headache, and dry cough, but SARS was a biphasic illness, and not an ILI.<sup>5</sup> Some patients are asymptomatic or present with mild respiratory symptoms without fever or diarrhea before developing MERS.<sup>19</sup> Typically, MERS rapidly progresses to viral pneumonia about a week after the onset of the infection. As with influenza, some patients report a sore throat. The chest radiograph is abnormal in patients ill enough to be hospitalized. A unilateral basilar infiltrate is common initially resembling a lobar/segmental bacterial pneumonia. More commonly, MERS presents with bilateral interstitial infiltrates which may be somewhat ovoid or nodular in appearance.<sup>5</sup> Small pleural effusions are not uncommon. Consolidation may occur but cavitation is not a feature of MERS pneumonia.<sup>17</sup> Bacterial co-infection does not occur with MERS.<sup>15</sup> Patients rapidly progress to ARDS (small lung volumes without cardiomegaly) with severe hypoxemia and bilateral interstitial infiltrates as with severe pandemic influenza ( $H_1N_1$ ) or severe avian influenza ( $H_7N_9$ ). Death is from hypoxemia from acute respiratory failure and or ARDS. As with any

patient intubated with respiratory failure on prolonged ventilatory support, nosocomial pneumonia (not co-infection) may complicate MERS.<sup>5</sup>

Non-specific laboratory tests with MERS include leukopenia, relative lymphopenia, and thrombocytopenia. Thrombocytopenia occurs less frequently than in influenza pneumonia where it is a near universal finding in hospitalized adults. Serum transaminases are often mildly to moderately elevated in hospitalized patients with MERS. MERS-CoV is present in blood, urine, and feces, but the diagnosis is made by demonstrating the SARS-CoV in lower respiratory secretions by RT PCR. In hospitalized patients with severe viral pneumonia, the likelihood of recovery of MERS is highest in lower respiratory tract specimen secretions rather than nasal swabs.<sup>5,17,18</sup> Without a travel history linking the patient to the Arabian peninsula or a known MERS case, the clinical presentation may be indistinguishable from other severe viral pneumonias.<sup>17</sup> The clinical feature which distinguishes MERS from influenza is the relatively high frequency of renal involvement, i.e., renal failure with MERS.<sup>5,14-16</sup> (Table 1).

Interferon- $\alpha$  2b and ribavirin reduce coronavirus replication and moderates the host's immune response in experimental studies in monkeys, but there is no definitive treatment for MERS in humans.<sup>21,22</sup> Therapy is supportive and may require mechanical ventilation or extra-corporal membrane oxygenation (ECMO).

## Infection Control Aspects

Infection control aspects of MERS have to do with preventing MERS exposures and minimizing person-to-person spread. Patients particularly from countries near the Arabian Peninsula who have an influenza-like illness should avoid travel until they are well. The following are based on CDC recommendations. If any patient has been exposed to a potential or known MERS case travel should be avoided. Household or family members exposed to potential or actual MERS cases should use masks. Such household and family members, while ill, if a family household member develops an ILI they should avoid public transportation, school, and work while ill. The individuals who are at increased risk for MERS include recent travelers from the Arabian Peninsula, particularly if such travelers develop fever and an ILI, including cough and shortness of breath, within 14 d after traveling from countries in or near the Arabian Peninsula. Those that have had close contact with someone that has recently traveled with respiratory symptoms and fever from countries in or near the Arabian Peninsula should be observed for 14 d starting from the day the patient was last exposed to the person.<sup>20</sup> Those with increased risk for MERS also include those with close contact with a probable or confirmed case of MERS. Care should be taken with the exposed individual to monitor fever, cough, shortness of breath,

and other symptoms, i.e., chills, myalgias, sore throat, nausea, vomiting, or diarrhea for 14 d counting from the last day of exposure to the ill contact. Healthcare personnel not utilizing proper infection control precautions are at increased risk for MERS.<sup>23,24</sup> Close contact may be defined as any person that provides care for a patient, including healthcare workers, family members, or someone who had similarly close physical contact or any person who stayed at the same place, lived with, or visited the patient when the patient was ill.<sup>21-23</sup> Infection control contact, and airborne precautions should be used while in close contact with symptomatic individuals or patients with MERS in the differential diagnosis.<sup>25</sup> Infection control precautions should be observed when obtaining or conducting respiratory specimen testing for MERS. To prevent transmission to household members, masks should be worn in the house. Since person-to-person transmission has been demonstrated with MERS the use of masks and handwashing are important interventions to reduce transmission.

It has been shown that healthcare workers in contact with or taking care of MERS patients are at particularly high risk for developing MERS.<sup>23,26,27</sup> Contact and airborne precautions should be used with appropriate personal protective devices to minimize the exposure of healthcare workers to suspected or known hospitalized MERS cases.<sup>26</sup> Since it is not known how long MERS-CoV is present in respiratory secretions, it seems prudent that MERS patients remain on contact and airborne precautions until discharged.

## Prognosis

MERS is a viral pneumonia with rapidly progressive respiratory failure leading to ARDS. As with severe pandemic influenza (H<sub>1</sub>N<sub>1</sub>), and severe avian influenza (H<sub>5</sub>N<sub>9</sub>) death is due to hypoxemia from acute respiratory failure.<sup>14-16</sup> Like SARS and avian influenza (H<sub>7</sub>N<sub>9</sub>), MERS has not been complicated by bacterial co-infections.<sup>5,28-30</sup> Pandemic influenza, in contrast, which may be complicated by simultaneous bacterial co-infection, with *S. aureus* (MSSA or MRSA), or sequential co-infection in patients who improve ~1 wk who then may develop a secondary bacterial pneumonia due to *Haemophilus influenzae* or *S. pneumoniae*.<sup>14,15</sup> Since any patient, including MERS or influenza patients, that receive prolonged mechanical ventilation may develop late nosocomial bacterial pneumonia.<sup>5</sup> These are not co-infections, per se, but rather are nosocomial complications of mechanical ventilation. Like pandemic influenza, MERS mortality can be high in normal young adults, but mortality is highest in those with comorbidities.<sup>5</sup>

### Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

**Table 1.** Clinical features of selected zoonotic viral pneumonias

Clinical and epidemiologic aspects	MERS-CoV	SARS-CoV	Pandemic influenza (H <sub>1</sub> N <sub>1</sub> )	Avian influenza (H <sub>7</sub> N <sub>9</sub> )
Year first recognized	2012	2002	2009	2013
Zoonotic vector	Camels	Civets	Pigs	Migratory birds or poultry
Nosocomial transmission	+	+	+	–
Predominant age group affected	Median: 50 y (1–94 y)	Median: 40 y (1–91 y)	Young adults	Young adults
Comorbidities affect mortality	+++	–	–	–
Influenza-like illness	+++	–	+++	+++
Biphasic illness	–	+	–	–
Bacterial co-infection	–	–	± <sup>c,d</sup>	–
Median incubation period	5.2 d (1.9–14.7 d)	4.6 d (3.8–5.8 d)	2 d (1–7 d)	5 d (2–8 d)
<b>Symptoms</b>				
Headache	+	++	+++	++
Fever and chills	+++	++	+++	+++
Prominent fatigue	+	–	+++	+
Myalgias	++	+++	+++	+++
Dry cough	+++	++	+++	++
Shortness of breath	+++	++	+++	+++
Sore throat	+	+	±	+
Nausea/vomiting	+	+	±	–
Diarrhea	±	±	±	±
Abdominal pain	±	–	–	–
Hemoptysis	±	–	±	±
<b>Signs</b>				
Tachycardia	+	+	+ <sup>a</sup>	+
Conjunctival suffusion	+	–	–	–
Diminished breath sounds	+	+	+	+
Acute renal failure (ARF)	±	–	–	–
<b>Laboratory tests</b>				
Normal WBC count	–	+	+ <sup>b</sup>	–
Leukopenia	+	++	–	+
Relative lymphopenia	+++	+++	+++	+++
Thrombocytopenia	++	±	+++	++
Elevated serum transaminases	+	++	±	+
Elevated Idh	+	++	–	+
Elevated cpk	++	–	+++	++
<b>Chest film</b>				
Normal/minimal basilar infiltrates (early)	–	+	+	+
Unilateral infiltrates (early)	+	–	– <sup>c</sup>	–
Bilateral infiltrates (late)	+++	++ <sup>e</sup>	+++	+++
Pleural effusion	+	–	±	±
Cavitation	–	–	– <sup>d</sup>	–
ARDS (severe cases)	+++	+	+++	+++

Notes: <sup>a</sup>particularly with myocarditis; <sup>b</sup>usually leukocytosis; <sup>c</sup>unless sequential coinfection a week after improvement with *S. pneumoniae* or *H. influenzae*; <sup>d</sup>unless simultaneous coinfection with MSSA or MRSA; <sup>e</sup>predominately peripheral infiltrates; WBC, white blood count; LDH, lactate dehydrogenase test; CPK, creatine phosphokinase test. Adapted from references 6, 15, 16, and 17.



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