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Clinical spectrum of the Middle East respiratory syndrome coronavirus (MERS-CoV)

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Introduction

Middle East respiratory syndrome coronavirus (MERS-CoV) was first recognized as a cause of severe acute respiratory infection in the Kingdom of Saudi Arabia in 2012. As of February 2, 2016, 1638 laboratory-confirmed cases have been reported to the World Health Organization, including at least 587 deaths [1]. While MERS-CoV has affected 26 countries, the majority of cases have been reported in the Middle East [2]. Transmission has most commonly been associated with nosocomial outbreaks [3—7] and is occasionally due to animal-to-human (most commonly camel-to-human) transmission and sporadic human-to-human transmission in the community [3,8—12]. Although the number of symptomatic cases resulting from secondary and tertiary transmission in human populations appears to be limited, little is known about potential human-to-human spread among asymptomatic or minimally symptomatic individuals [3,6,11,13].

Epidemiology of patients

The majority of MERS-CoV infections have been observed in adults (98%), with a slight male predominance (65%) [14]. Older adults and those with comorbidities, such as diabetes, renal disease, respiratory disease, and immunosuppression, have been more commonly represented among those with severe illness [13,14]. Younger and previously healthy individuals appear more likely

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to exhibit mild symptoms or be asymptomatic [5,6,11,13,15,16]. The true incidence of symptomatic and asymptomatic MERS-CoV cases remains unclear. Mild and asymptomatic cases may be misdiagnosed, which can lead to underreporting and misclassification of the disease and may also result in a possible detection bias depending on the type of health facility/unit that the patients seek treatment from. Health care workers appear to be at an increased risk of being infected with MERS-CoV, and this is likely mediated by inadequate infection prevention and control (IPC) measures and the amplification of cases amidst nosocomial outbreaks.

Clinical characteristics

After an incubation period ranging from 2 to 14 days, the majority (>70%) of symptomatic patients present with fever, chills, cough, and dyspnea. Approximately, one-third have myalgia, malaise, and gastrointestinal symptoms [6,17]. Among those with severe illness, the most prominent clinical manifestations have been acute, rapidly progressive viral pneumonia and pneumonitis, leading to hypoxic lung injury and acute respiratory distress syndrome [3,4,13,17—21]. For those who become severely ill, the median time from the onset of symptoms to intensive care unit (ICU) admission is only 5 days [14].

Approximately, half of the known adult symptomatic patients have been admitted to an ICU, with 40—70% requiring mechanical ventilation [3—5,12,13,17—28] and 4—17% needing 'rescue' oxygenation or ventilation therapy [3,17,20,29], such as extracorporeal membrane oxygenation and high frequency oscillatory or prone ventilation [13,21,29]. Renal replacement therapy was required in as many as 70% of critically ill patients [3,17,18,21]. However, the incidence of renal failure may be over-estimated due to nosocomial outbreaks involving patients with pre-existing renal disease [3]. In another hospital outbreak that was not epidemiologically related, renal dysfunction was reported in only 22% of cases [4]. Circulatory shock requiring intravenous vasoactive medication has been described in as many as 92% of critically ill patients [4,21,28].

Although not commonly observed, severe neurological syndrome characterized by varying degrees of consciousness, ataxia, focal motor deficit, and bilateral hyperintense lesions has been described in 3 patients [30]. MERS-CoV has not been isolated from the cerebrospinal fluid or the brain tissue of any of these patients infected with the virus, but radiological evidence suggests that MERS-CoV associated vasculopathy may be an underlying cause [30].

Both community- and nosocomial-acquired bacterial and viral co-infections have been reported in patients with severe illness and have been associated with increased mortality [20,24,25,31—33]. This underscores the importance of preventive measures and the need to consider a broad range of pathogens when treating patients with either suspected or confirmed MERS-CoV.

Liver inflammation, evidenced by elevated aspartate aminotransferase and alanine aminotransferase levels, is common, especially among those who are critically ill [3,17—21]. Other laboratory findings include lymphopenia and leukopenia, as well as renal injury and coagulopathy in patients with severe illness and multi-system organ dysfunction [4,20,21].

Chest computed tomography has typically revealed unilateral or bilateral infiltrates, ground-glass opacities, occasional pleural effusions, and intralobular thickening consistent with acute respiratory distress syndrome and viral pneumonitis [13,21—23].

Among all patients, the median time from symptom onset to death was 11.5 days (ranging from 4 to 298 days) [6,14]. The median length of stay in the hospital was 41 days (ranging from 8 to 96 days) [21]. Higher viral load determination in the upper respiratory tract has been associated with increased severity of the disease, admission to the ICU and increased mortality [34].

Treatment

Since there are no specific treatments that have proven to be effective for MERS-CoV, case management has largely relied on organ-supportive therapy and prevention of complications. While co-infections can be treated with specific antimicrobial and antiviral medications, potential agents to treat MERS-CoV infection have been derived from experience with non-influenza respiratory viral infections, including severe acute respiratory syndrome (SARS). Case studies have reported on the outcomes of patients treated with oral ribavirin and interferon a2b. However, such studies are at a high risk of selection bias and confounding by indication because the inclusion of patients has largely depended on the severity of the illness. Such non-randomized allocations cannot separate the influence of many other potentially confounding conditions and co-interventions. Previous studies may also have been affected by the immortal time bias, as the patients needed to remain alive long

enough to receive a particular therapy. All of these forms of bias and confounding variables preclude any valid estimation of the true treatment effect.

Currently, a phase II, open-label, single group assignment, safety/efficacy study of convalescent plasma therapy (plasma derived from survivors of MERS-CoV infection) is underway at the King Abdullah International Medical Research Center in Saudi Arabia, and it is expected to be completed by June 2017 [36]. A recombinant modified vaccinia virus Ankara vaccine expressing the full-length MERS-CoV spike glycoprotein has been developed for preventative purposes, and it has been endorsed by the German Center for Infection Research (DIFZ) for phase I clinical trials in humans. However, there is not yet any human data regarding the potential effectiveness of the vaccine [37,38].

Little is known about the long-term outcomes of patients with MERS-CoV. However, according to the largest cohort of confirmed MERS-CoV patients ($n = 14$) who were intubated and received invasive mechanical ventilation, those ($n = 5$) who recovered from the acute infection and its complications have survived to the one year follow-up period [39].

Conclusion

In the short time since MERS-CoV has been discovered, significant progress has been made in understanding the epidemiology, pathophysiology, clinical manifestations, and potential treatment options. However, many important questions remain. Although exposure to camels has been implicated in human MERS-CoV cases, all potential animal reservoirs have not yet been identified. Effective treatments and vaccines have also yet to be developed. Because of the sporadic nature of MERS-CoV outbreaks, a collaborative research effort across the most affected countries will be necessary to better assess the potential animal reservoirs, epidemiology, risk factors, and transmission of MERS-CoV to develop controlled and ideally blinded treatment evaluations. Research protocols and data collection tools should be prepared, vetted, approved, and pre-positioned across the Middle East and elsewhere to facilitate the timely implementation of research activities and close many of the remaining knowledge gaps.

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Competing interests

None declared.

Ethical approval

Not required.

Disclaimer

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