Middle East respiratory syndrome coronavirus (MERS-CoV) infection

Middle East respiratory syndrome coronavirus was first described in 2012. More than 1800 cases have been reported so far, the majority from countries in the Middle East region. This article outlines current understanding of the epidemiological and clinical features of Middle East respiratory syndrome coronavirus infection.

Middle East respiratory syndrome coronavirus (MERS-CoV) was first isolated from a patient who died with severe pneumonia and multi-organ failure in Saudi Arabia in June 2012 (Zaki et al, 2012). Additional cases were retrospectively identified from a nosocomial outbreak that had taken place in Jordan in April the same year (Hijawi et al, 2013). Up to 2 December 2016, a total of 1841 cases of laboratory-confirmed MERS-CoV infection were reported to the World Health Organization, with an overall case fatality rate of 35% (World Health Organization, 2016). This article summarizes the current status of knowledge around MERS-CoV, including its epidemiology, role of animal reservoirs, clinical features and outcomes, and control.

The virus

MERS Co-V is a novel coronavirus which belongs to lineage C of the genus betacoronaviruses. It expresses ten open reading frames that encode the production of non-structural proteins as well as structural proteins such as spike (S), envelope (E), nucleocapsid (N) and membrane (M) protein (Chan et al, 2015). To gain access to the host cells, MERS-CoV attaches to its functional receptor, human dipeptidyl-peptidase 4 (hDDP4). The receptor is expressed widely in endothelial and subendothelial tissues of multiple organs including the lungs, gastrointestinal tract and kidneys, an observation that may explain the multi-system nature of the associated clinical illness (Chan et al, 2015). Following attachment to hDDP4 receptors, protein S is cleaved by host proteases resulting in cell fusion and release of RNA into the cytoplasm. N protein then transports viral RNA to the endoplasmic reticulum and Golgi apparatus where viral assembly takes place (Zumla et al, 2015).

Dr Reem S Almaghrabi, Associate Consultant Infectious Diseases Physician, Section of Infectious Diseases, Department of Medicine, King Faisal Specialist Hospital and Research Centre, Riyadh, Saudi Arabia

Dr Ali S Omrani, Consultant Infectious Diseases Physician, Section of Infectious Diseases, Department of Medicine, King Faisal Specialist Hospital and Research Centre, PO Box 3354, MBC 46, Riyadh 11211, Saudi Arabia

Correspondence to: Dr AS Omrani (asomrani@kfshrc.edu.sa)

Animal origin of MERS-CoV

Current evidence suggests that MERS-CoV originated in bats before its transmission to intermediate hosts, mainly dromedary camels and onwards to humans (Omrani et al, 2015). Several closely related coronaviruses have been isolated from bats from different parts of the world. An amplified 816-nucleotide fragment of the RNA-dependent RNA polymerase from a novel coronavirus that was isolated from a vesper bat from South Africa differed from that of MERS-CoV by only one amino acid (Ithete et al, 2013). Furthermore, a 190-nucleotide RNA-dependent RNA polymerase fragment isolated from a faecal pellet obtained from a bat in Saudi Arabia showed 100% match to MERS-CoV (Memish et al, 2013). These findings support the presence of MERS-CoV ancestors in bats.

MERS-CoV antibodies and RNA are highly prevalent in dromedary camels in the Middle East and Africa (Omrani et al, 2015). Dromedary camels experimentally exposed to MERS-CoV develop fever and mild respiratory symptoms, in addition to viable virus excretion, rising antibody titres and histological changes in their respiratory tracts (Adney et al, 2014). Furthermore, near-identical MERS-CoV strains have been isolated from epidemiologically linked dromedaries and human cases (Haagmans et al, 2014). Additionally, recent contact with camels is an independent risk factor for MERS-CoV infection (odds ratio 7.67, 95% confidence interval 2.10–36.08, P=0.001) (Alraddadi et al, 2016). Multiple serological studies failed to identify MERS-CoV antibodies in pets or farming animals (Omrani et al, 2015). It is therefore reasonable to conclude that dromedary camels are the primary source of human MERS-CoV infections.

Epidemiology and clinical features

The median age of reported patients with MERS-CoV infection is 52 years (interquartile range 36–65 years) and nearly two thirds of patients are males (World Health Organization, 2016). For poorly understood reasons, MERS-CoV infection is rare in children (Thabet et al, 2015). To date, no primary MERS-CoV infection has been reported outside the Middle East. MERS-CoV infections reported from countries outside the Middle East have involved individuals who travelled to seek medical care, expatriates returning from countries in the Middle East or short-term visitors to the region (Omrani and Shalhoub, 2015; World Health Organization, 2016).

The typical incubation period is 2–14 days (World Health Organization, 2016). The clinical spectrum of MERS-CoV infection ranges from asymptomatic virus detection or mild respiratory symptoms to severe disease with multi-organ failure and death (Saad et al, 2014). Myalgia, headache, confusion, nausea, vomiting and diarrhoea are also common (Saad et al, 2014). Older individuals and those with significant comorbidities are more likely to develop complicated disease, require admission to an intensive care unit and to die (Saad et al, 2014). Common laboratory abnormalities include leucopaenia, lymphopaenia, anaemia and renal impairment (Saad et al, 2014). When present, radiological findings may include lobar infiltrates, interstitial infiltrates and pleural effusions (Das et al, 2015).

Human-to-human transmission

Human MERS-CoV infections occur sporadically, often with documented camel contact, or in clusters (Omrani and Shalhoub, 2015). Occasional outbreaks in extended families or communities have been documented, but transmission within households remains very limited (Arwady et al, 2016). For example, only 12 probable MERS-CoV infections were identified among 280 close household contacts of 26 documented MERS-CoV cases (4%, 95% confidence interval 2–7%) (Drosten et al, 2014). On the other hand, nosocomial transmission, including large hospital outbreaks, continues to contribute the majority of reported cases (Omrani and Memish, 2015). The largest hospital outbreak outside the Middle East occurred in South Korea (Oh et al, 2015). The index patient was a 68-year-old South Korean man who developed symptoms shortly after returning from a visit to Bahrain, the United Arab Emirates and Saudi Arabia. He visited emergency departments in three different hospitals in Seoul before the diagnosis of MERS-CoV was made. The resulting outbreak involved 186 confirmed cases, including 25 health-care workers, across 16 hospitals and resulted in 36 deaths (19.4%) (Oh et al, 2015).

Hospital outbreaks have consistently been driven by a combination of late recognition, over-crowding and inadequate infection control procedures (Oh et al, 2015; Hastings et al, 2016). Underlining the importance of adequate cleaning processes and appropriate implementation of infection control precautions is the extensive environmental contamination that has been documented in association with MERS-CoV outbreaks, including a single report of isolation of viable MERS-CoV from air samples from patients' rooms and adjoining hospital corridors (Kim et al, 2016). Such contamination is of great concern as, under certain conditions, MERS-CoV can survive for up to 48 hours (van Doremalen et al, 2013).

Severe MERS-CoV infections are associated with high respiratory tract viral loads and prolonged viral shedding (Oh et al, 2016). However, extended viral shedding has also been documented in mild or asymptomatic cases, suggesting a possible role for such individuals in human-to-human MERS-CoV transmission (Al-Gethamy et al, 2015).

With a basic reproduction number (R_0) of less than one, the epidemic potential of MERS-CoV is considered low. Appropriate implementation of infection control procedures usually results in prompt control of nosocomial outbreaks (World Health Organization, 2016).

Laboratory diagnosis

MERS-CoV infection is usually confirmed by real-time polymerase chain reaction assays targeting upstream of the E protein gene (upE), open reading frame 1A and open reading frame 1B (World Health Organization, 2015b). Real-time polymerase chain reaction is more sensitive when samples from the lower respiratory tract rather than the upper respiratory tract are tested (Oh et al, 2016). In patients with a negative initial sample despite clinically suspected MERS-CoV infection, a second respiratory sample should be tested by real-time polymerase chain reaction before the diagnosis is excluded (World Health Organization, 2015b). The virus can also be detected in blood, faeces and urine, but such samples are seldom tested in clinical practice (Drosten et al, 2013).

Serological assays, including immunofluorescence and neutralisation assays, can be used in the context of contact screening or seroprevalence studies (World Health Organization, 2015b). However, after 18 months of follow up, MERS-CoV antibodies were undetectable in the majority of patients with mild or asymptomatic infections, questioning the reliability of serology as a tool for historic assessment of MERS-CoV burden (Alshukairi et al, 2016).

Clinical management

Management of patients with MERS-CoV infection is largely supportive. To date, no specific therapy has consistently been shown to be effective for MERS-CoV infection (Omrani and Memish, 2015). In-vitro screening of large libraries of approved agents demonstrated useful antiviral activity with compounds such as interferon, ribavirin, mycophenolate mofetil, lopinavir-ritonavir and ciclosporin (Omrani and Memish, 2015). The combination of interferon alfa and ribavirin is synergistic against MERS-CoV in vitro and was associated with improved outcomes in experimentally infected rhesus monkeys (Omrani and Memish, 2015). A retrospective study from Saudi Arabia included 44 patients with severe MERS-CoV infection requiring mechanical ventilation. A survival benefit was seen at 14 days in 20 patients who received a combination of interferon alfa and ribavirin within a median of 3 days compared with 24 patients who did not receive this combination (70% *vs* 29%, P=0.004). However, there was no statistically significant difference in survival at 28 days (30% *vs* 17%, P=0.054) (Omrani et al, 2014).

Various monoclonal antibodies have been shown to have potent anti-MERS-CoV activity in vitro and some clinical benefit in small animal studies (Omrani and Memish, 2015). However, it is not yet clear if such therapeutic options are safe or effective in human MERS-CoV infections.

Infection prevention and control

The most important element in MERS-CoV control is early recognition and implementation of appropriate isolation and infection control precautions (Omrani and Shalhoub, 2015). In endemic countries, robust triage processes in emergency departments and heightened awareness are essential. Outside the Middle East, travel history should be obtained from patients presenting with symptoms consistent with MERS-CoV infection.

Current World Health Organization guidelines recommend droplet and contact precautions when dealing with patients with suspected or proven MERS-CoV infection. Those should include good hand hygiene, wearing gloves, surgical masks and gowns (World Health Organization, 2015a). Airborne precautions should be used during aerosol-generating procedures such as airway suctioning or intubation (World Health Organization, 2015a). For hospitalized patients, isolation procedures should be continued until at least one respiratory sample is negative by real-time polymerase chain reaction for MERS-CoV (Saudi Arabia Ministry of Health, 2014).

Conclusions

More than 1800 MERS-CoV infections have been reported so far, with an overall mortality of 35%. The majority of cases are epidemiologically linked to the Middle East. Dromedary camels are the main reservoir for human infection. Although human-to-human MERS-CoV transmission is generally inefficient, nosocomial outbreaks continue to be of major concern. Early recognition is essential to allow early implementation of control measures and prevention of in-hospital transmission. Clinical management is mainly supportive. **BJHM**

Conflict of interest: none.

KEY POINTS

- Middle East respiratory syndrome coronavirus (MERS-CoV) is a novel respiratory virus that was first described in 2012.
- To date, all reported MERS-CoV infections have been epidemiologically linked to the Middle East.
- MERS-CoV infection is associated with a clinical illness that ranges from mild or asymptomatic infection to severe multi-organ failure and death.
- Older individuals and those with significant comorbidities are at an increased risk of severe disease and death.
- Dromedary camels are the main reservoir for human MERS-CoV infections.
- Human-to-human MERS-CoV transmission is generally inefficient.
- Hospital outbreaks of MERS-CoV infection are associated with late recognition, overcrowding and inadequate infection control procedures.
- There is no specific therapy for MERS-CoV infection; management is largely supportive.

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