Middle East Respiratory Syndrome Coronavirus (MERS-CoV): Global alert and response

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ABSTRACT

Middle East Respiratory Syndrome Coronavirus (MERS-CoV) is a newly emerging respiratory virus with a high case fatality rate among identified cases. The virus is thought to cause a severe disease in patients with underlying co- morbidities. The identification of asymptomatic patients and mild cases among family and healthcare workers contacts of confirmed cases indicates a wider spectrum of clinical manifestation of the disease. The majority of patients presented with fever (98%), fever with cough (83%), and shortness of breath (72%). The understanding of the epidemiology and clinical presentation of the disease is increasing overtime.

Key words: MERS-CoV, Human Coronavirus-EMC, Dipeptidyl peptidase 4 (DPP4)

INTRODUCTION

Coronaviruses are RNA viruses which usually cause mild upper respiratory illnesses. The emergence of SARS (Severe Acute Respiratory Syndrome) MERS (Middle East Respiratory Syndrome) has focused global attention on the clinical significance of coronaviruses. Since mid-2012, a novel coronavirus was found to cause severe disease in humans. The virus was recently named Middle East Respiratory Syndrome Coronavirus (MERS-CoV) 1. Other terms that have been used to describe this virus include novel Coronavirus (nCoV) and human Coronavirus-EMC (for Erasmus Medical Center).

This virus was initially identified in September 2012 from samples obtained from a Saudi Arabian patient who developed a severe acute respiratory infection and later had acute renal failure and ultimately died2. The virus was subsequently reported as a cause of pneumonia in additional cases from Saudi Arabia, Qatar and United Arab Emirates 3, 4. The initial cases from Saudi Arabia occurred before the Al-Hasa outbreak in April-May 2013. The majority of these cases occurred in patients with underlying comorbidities. As of September 19, 2013, globally, the World Health Organization (WHO) recorded 132 laboratory-confirmed cases of infection with MERS-CoV, including 58 deaths 5. A major resurgence of MERS-CoV cases during April 2014 expanded the geographic distribution of confirmed MERS-CoV cases to include countries in Asia (Malaysia, Bangladesh) and North America and several additional countries the Middle East (Yemen, Egypt) and Europe (Greece) 6. Moreover, as of June 16, 2014, 249 of 701 patients (36%) with laboratory-confirmed MERS-CoV infection reported to the WHO have died 7.

In addition to humans, MERS-CoV has been found in camels in Qatar, Oman, Egypt and Saudi Arabia, and a bat in Saudi Arabia. Camels in several other countries have also tested positive for antibodies to MERS-CoV, indicating that the camels were previously infected with MERS-CoV or a closely related virus. It may be that people became infected after contact with camels, although more information is needed to figure out the possible role that camels, bats, and other animals may play in the transmission of MERS-CoV 8. . It is likely that camels serve as the source of infection to human for MERS-CoV . Researchers investigated a case of human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) after exposure to infected camels 9. Analysis of the whole human-derived virus and 15% of the camel-derived virus sequence yielded nucleotide polymorphism signatures suggestive of cross-species transmission. Camels may act as a direct source of human MERS-CoV infection.

The first-ever case of MERS infection was detected in Bangladesh 15th June, 2014. The Institute of the Epidemiology, Disease Control and Research (IEDCR) diagnosed a Bangladeshi expatriate living in the US with MERS corona virus after examining samples. The 53-year-old Bangladeshi returned home from New York via Abdu Dhabi airport. He was admitted to the hospital with syndromes of fever, cough and respiratory problems. The National Rapid Response Team of the IEDCR kept those who came in close contact with the patient under observation, said a Directorate General of Health Services release (UNB).

The most urgent needs include detailed outbreak investigations, understanding how humans become infected from animal or environmental source(s) through case-control studies, identifying risk factors for infection in health care settings, and enhancing community studies and surveillance for community-acquired pneumonia10.

VIROLOGY

MERS-CoV is a betacoronavirus, different from the other human betacoronaviruses (severe acute respiratory syndrome coronavirus, OC43, and HKU1) but closely related to several bat coronaviruses 11. Dipeptidyl peptidase 4 (DPP4), which is present on the surfaces of human nonciliated bronchial epithelial cells, is a functional receptor for MERS-CoV. Expression of human and bat DPP4 in nonsusceptible cells enables infection by MERS-CoV. The DPP4 protein displays high amino acid sequence conservation across different species, including the sequence that was obtained from bat cells. In a cell line susceptibility study, MERS-CoV infected several human cell lines, including lower respiratory, kidney, intestinal, and liver cells, as well as histiocytes.

The range of tissue tropism in vitro was broader than that for any other known human coronavirus. MERS-CoV can also infect nonhuman primate, porcine, bat, civet, and rabbit cell lines12.
Genetic analysis

In an analysis of the full or partial genomes of MERS-CoV obtained from 21 patients with MERS-CoV infection in Saudi Arabia between June 2012 and June 2013, there was sufficient heterogeneity to support multiple separate animal-to-human transfers 13. Moreover, even within a hospital outbreak in Al-Hasa, Saudi Arabia, there was evidence of more than one virus introduction. By estimating the evolutionary rate of the virus, the authors concluded that MERS-CoV emerged around July 2011.

SEROLOGY

The Top of form Serologic studies have shown low prevalence of MERS-CoV antibodies in humans in Saudi Arabia. In 130 blood donors sampled during 2012 in Jeddah, Saudi Arabia, and 226 slaughterhouse workers sampled in October 2012 in Jeddah and Makkah, Saudi Arabia, eight reactive sera were observed using a screening immunofluorescence assay, but on further testing, the antibodies were found to be specific for other established human coronaviruses, not MERS-CoV 14. Two further serologic studies were conducted in the Eastern Province of Saudi Arabia: one was of 158 pediatric sera obtained before the MERS-CoV outbreak was recognized, and the second was of 110 plasma samples from adult male blood donors in December 2012. No MERS-CoV antibody-positive samples were found 15.

TRANSMISSION

Bats

Coronaviruses are recognised causes of mild respiratory tract infections in humans, first identified in the 1960s 16. These large RNA viruses affect a wide range of animals including domestic and companion animals and bats 17. Limited surveillance data show that bats host the greatest diversity of coronaviruses, varying by region and species18, suggesting that they may be the natural reservoir. Studies performed in Europe, Africa, and Asia, including the Middle East, have shown that coronavirus RNA sequences are found frequently in bat fecal samples and that some of these sequences are closely related to MERS-CoV sequences. In a study from Saudi Arabia, 823 fecal and rectal swab samples were collected from bats, and using a PCR assay, many coronavirus sequences were found 19. Most were unrelated to MERS-CoV, but notably, one 190 nucleotide sequence in the RNA-dependent RNA polymerase (RdRp) gene was amplified that had 100 percent identity with a MERS-CoV isolate cloned from the index patient with MERS-CoV infection; the sequence was detected from a fecal pellet of a Taphozous perforatus bat captured from a site near the home of the patient. MERS-CoV grows readily in several bat-derived cell lines20. Although bats might be a reservoir of MERS-CoV, it is unlikely that they are the immediate source for most human cases because human contact with bats is uncommon.
Camels

The strongest evidence of camel-to-human transmission of MERS-CoV comes from a study in Saudi Arabia in which MERS-CoV was isolated from a man with fatal infection and from one of his camels; full-genome sequencing demonstrated that the viruses isolated from the man and his camel were identical 21. There are also substantial data add to recent findings showing high similarity of MERS-CoVs carried by humans and camels 22, supporting the hypothesis that human MERS-CoV infection may be acquired directly from camels. Given the synchronized parturition pattern of dromedary camels, with birthing in the winter months, an increase of epizootic activity might be expected after some latency during the first half of each year23.

Human-to-human transmission

The case clusters in the United Kingdom, Tunisia, Italy, and in healthcare facilities in Saudi Arabia and France strongly suggest that human-to-human transmission occurs 24. The number of contacts infected by individuals with confirmed infections, however, appears to be limited. Secondary cases have tended to be milder than primary cases, and many secondary cases have been reported to be asymptomatic. The majority of cases in the spring of 2014 in Saudi Arabia were acquired through human-to-human transmission in healthcare settings, likely due at least in part to systemic weaknesses in infection control. Possible modes of transmission may include droplet and contact transmission 25.

CLINICAL MANIFESTATIONS

In an outbreak of MERS-CoV in Saudi Arabia that resulted in laboratory-confirmed MERS-CoV in 23 individuals, the median incubation period was found as 5.2 days. In one secondary case that occurred in a patient in France who shared a room with an infected patient, the incubation period was estimated at 9 to 12 days 26. The WHO and the United States Centers for Disease Control and Prevention (CDC) recommend that an evaluation for MERS-CoV be considered in individuals with a syndrome of MERS who returned from travel to the Arabian peninsula or neighboring countries within the past 14 days 27. Most patients with MERS-CoV infection have been severely ill with pneumonia and acute respiratory distress syndrome, and some have had acute kidney injury. Other clinical manifestations that have been reported are gastrointestinal symptoms (anorexia, nausea, vomiting, abdominal pain, and diarrhea), pericarditis, and disseminated intravascular coagulation 28. As of late September 2013, 27 of 130 patients (21%) have had mild or no symptoms. A few reports have described individuals with a mild respiratory illness not requiring hospitalization 29. Several individuals with

asymptomatic infection have been identified among contacts of patients with symptomatic infection.

It remains unclear whether persons with specific conditions are disproportionately infected with MERS-CoV or have more severe disease. In a study of 47 patients with MERS-CoV infection in Saudi Arabia, 45 (96%) had underlying comorbidities, including diabetes mellitus (68%), hypertension (34%), chronic cardiac disease (28%), and chronic kidney disease (49%). One patient was receiving long-term immunosuppressive therapy with glucocorticoids 30.

DIAGNOSIS

The United States Centers for Disease Control and Prevention (CDC) recommends that lower respiratory tract specimens should be the first priority for collection and real-time reverse-transcriptase polymerase chain reaction (rRT-PCR) testing, since rRT-PCR testing of lower respiratory specimens appears to be more sensitive for detection of MERS-CoV than testing of upper respiratory tract specimens 31. Given the potential severity of MERS-CoV infections, the risk for human-to-human transmission, and the limited data about the sensitivity of each diagnostic test, researchers suggest that multiple specimens should be collected from different sites and at different times to increase the likelihood of detecting MERS-CoV 13. Several serological assays have been developed for the detection of MERS-CoV antibodies, including immunofluorescence and a protein microarray assay 32. The CDC has developed a two-stage approach, which uses an enzyme-linked immunosorbent assay (ELISA) for screening followed by an indirect immunofluorescence test or microneutralization test for confirmation. Any positive test by a single serological assay should be confirmed with a neutralization assay.

TREATMENT

As with other coronaviruses, no antiviral agents are recommended for the treatment of MERS-CoV infection. In cell culture and animal experiments, combination therapy with interferon (IFN)-alpha-2b and ribavirin appears promising 33. In a study in which MERS-CoV was grown in two different cell lines, high concentrations of interferon-alpha-2b or ribavirin were required to inhibit viral replication. However, when used in combination at lower concentrations, IFN-alpha-2b and ribavirin resulted in a comparable reduction in viral replication as high concentrations of either agent alone. Other experimental therapies being investigated include convalescent plasma, monoclonal antibodies, and inhibition of the main viral protease 34.

PREVENTION

Infection control

The World Health Organization (WHO) and the United States Centers for Disease Control and Prevention (CDC) have issued recommendations for the prevention and control of MERS-CoV infections in healthcare settings 35. The WHO recommends that standard and droplet precautions be used when caring for patients with acute respiratory tract infections. Contact precautions and eye protection should be added when caring for probable or confirmed cases of MERS-CoV infection. Airborne precautions should be used when performing aerosol-generating procedures. The CDC recommends the use of standard, contact, and airborne precautions for the management of hospitalized patients with known or suspected MERS-CoV infection 36.

Avoiding camels

The individuals at high risk of severe disease, such as immunocompromised hosts and those with diabetes, chronic lung disease, or preexisting renal failure, take precautions when visiting farms, camel pens, or market environments where camels are present 37. These measures include avoiding contact with camels, practicing good hand hygiene, avoiding drinking raw camel milk, avoiding eating meat that has not been cooked thoroughly, and avoiding eating food that may be contaminated with animal secretions or products unless they are properly washed, peeled, or cooked. Unless protected, people should avoid contact with any animal that has been confirmed positive for MERS-CoV until subsequent tests have confirmed that the animal is free of the virus.

Travel recommendations

The WHO recommends that countries outside the affected region maintain a high level of vigilance, especially countries with large numbers of travelers or guest workers returning from the Middle East 38. In May 2014, the United States Centers for Disease Control and Prevention's (CDC's) travel notice was upgraded to a Level 2 Alert, which includes enhanced precautions for travelers to countries in or near the Arabian Peninsula who plan to work in healthcare settings. Such individuals should review the CDC's recommendations for infection control for confirmed or suspected MERS patients before they depart, practice these precautions while in the area, and monitor their health closely during and after their travel.

Vaccine

There is no licensed vaccine for MERS-CoV, although one manufacturer has developed an experimental candidate MERS-CoV vaccine based on the major surface spike protein using recombinant nanoparticle technology. Other candidate vaccines that are being studied include a full-length infectious cDNA clone of the MERS-CoV genome in a bacterial artificial chromosome and a recombinant Modified Vaccine Ankara (MVA) vaccine expressing full-length MERS-CoV spike protein39.

CONCLUSION

MERS-CoV is closely related to coronaviruses found in bats, suggesting that bats might be a reservoir of MERS-CoV. Camels are likely serve as intermediate hosts for MERS-CoV. The presence of case clusters strongly suggests that human-to-human transmission occurs. There is currently no treatment recommended for coronavirus infections except for supportive care as needed. The emergence of a novel coronavirus with a global threat requires a thorough assessment which is currently being coordinated at international level.

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