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HOW TREATMENT AND PREVENTION OF MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS (MERS-CoV)

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ABSTRACT

A severe viral illness caused by a newly discovered coronavirus was first reported in the Middle East in 2012. The virus has since been named the Middle East respiratory syndrome coronavirus (MERS-CoV). The source of the virus remains unclear, but camels are a possible source. Most MERS patients developed severe acute respiratory illness with symptoms of fever, cough and shortness of breath. MERS-CoV is a newly described viral disease that causes severe respiratory illness and is associated with high mortality. Since April 2012 and as of 20 February 2015, 1042 cases (including 419 deaths) of MERS-CoV have been reported by local health authorities worldwide. The majority of MERS-CoV cases are still being reported from the Arabian Peninsula, specifically from Saudi Arabia. MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person. Laboratory confirmation of MERS-CoV infections to date has largely been by real-time reverse transcription polymerase chain reaction (rRT-PCR) of lower respiratory tract specimens. CDC routinely advises that people help protect themselves from respiratory illnesses by taking everyday preventive actions. Neither a vaccine nor effective therapy against the virus is available. There is no specific antiviral treatment recommended for MERS-CoV infection. In the case of MERS-CoV infections, interferon-alpha 3b and ribavirin may work primarily by reducing damaging inflammation of the lung and promoting healing by altering the host response, rather than directly targeting the virus.

KEYWORDS: MERS-CoV; SARS-CoV; rRT-PCR; ribavirin and interferon.

INTRODUCTION

Middle East respiratory syndrome (MERS) is a newly betacoronavirus of the Coronaviridae family that causes severe respiratory illness and is allied with high mortality than that of SARS-CoV.[1-2] The identification of closely related viruses in animal hosts is a condition for establishing the ecology of viral emergence along with reconstruction of evolutionary pathways. [3] MERS-CoV is a beta-coronavirus, in the same family as SARS-CoV.[4] Middle East Respiratory Syndrome (MERS) is an illness caused by a virus (COV) called Middle East Respiratory Syndrome Coronavirus (MERS-CoV). A novel corona-virus causing severe respiratory infection was first described in Sept. 2012.[5] MERS-CoV was first reported in June 2012, a novel human coronavirus was identified in a Saudi Arabian businessman who died of an acute respiratory illness and renal failure.[6] MERS affects the respiratory system. Most MERS patient presentation symptoms of fever, shortness of breath and cough.[7] MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person.[8] In May 2014, CDC confirmed two unlinked imported cases of MERS in the United States.[9] As of 28 July 2013 MERS-CoV has caused 91 laboratory confirmed cases and 46 deaths, representing a high case fatality rate.[10] In 2014, a large outbreak originated in the Kingdom of Saudi Arabia concentrated in healthcare facilities in Riyadh and Jeddah resulting in over 300 infections and approximately 40 deaths.[11] The Coronavirus Study Group After careful consideration has decided to call the new coronavirus Middle East respiratory syndrome coronavirus, by the WHO and Saudi Ministry of Health.[12] Primary infections, to which all cases were linked directly or indirectly, occurred in Middle Eastern countries including Saudi Arabia, Jordan, Oman, Qatar and United Arab Emirates and subsequently spread to UK, Tunisia, France, Italy and Germany with Egypt and the US recently reporting their first laboratory confirmed cases.[13] Whole genome sequencing showed that human and camel viruses from Saudi Arabia are indistinguishable.[14] The stability of the virus for prolonged periods in camel milk suggests the potential of excretion of the virus into camel milk and spread through consuming raw milk.[15] MERS-CoV-induced disease is particularly severe in aged patients and those with pre-existing co-morbidities. MERS-CoV does not appear to be highly pathogenic or virulent in camels.[16] New data suggest A 43 year old previously healthy Saudi man at Jeddah who died of laboratory confirmed MERS-CoV infection after close contact with camels.[17] The number of reported cases of Middle East Respiratory Syndrome coronavirus (MERS-CoV) increased sharply in April and May 2014. All cases have been linked with travel to or residence in the Middle Eastern countries of Saudi Arabia, the United Arab Emirates (UAE), Qatar, Oman, Jordan,

Kuwait, Lebanon and Yemen, or with contact with travellers retuning from these areas.[18] MERS-CoV is still ongoing after two years, and as of June 2014 has apparently infected only 688 people and killed 282.[19] Since April 2012 and as of 20 February 2015, 1042 cases (including 419 deaths) of Middle East respiratory syndrome coronavirus (MERS-CoV) have been reported by local health authorities worldwide. The incidence of Middle East respiratory syndrome coronavirus cases has been on an increase in Saudi Arabia.[20]

VIROLOGY

Coronaviruses (CoV) are found in a wide variety of animals in which they can cause respiratory, enteric, hepatic, and neurological diseases of varying severity. As a result of the unique mechanism of viral replication, CoV have a high frequency of recombination.[21] Coronaviruses are enveloped single-stranded positive-sense RNA viruses (Figure: 1) with genomes of about 30 kb[22], a genus within the *Coronaviridae* family and *Coronavirinae* subfamily.[23] The novel virus is a representative of a new species in lineage C of the genus *Betacoronavirus*, which currently includes the species *Tylonycteris bat coronavirus* HKU4 and *Pipistrellus bat coronavirus* HKU5.[12] At present, six CoVs have been identified that infect humans. Human CoVs HKU1, NL63, 229E and OC43 predominantly cause a mild respiratory tract infection, characterized by upper respiratory tract disease that includes coryza, cough and sore throat.[24]

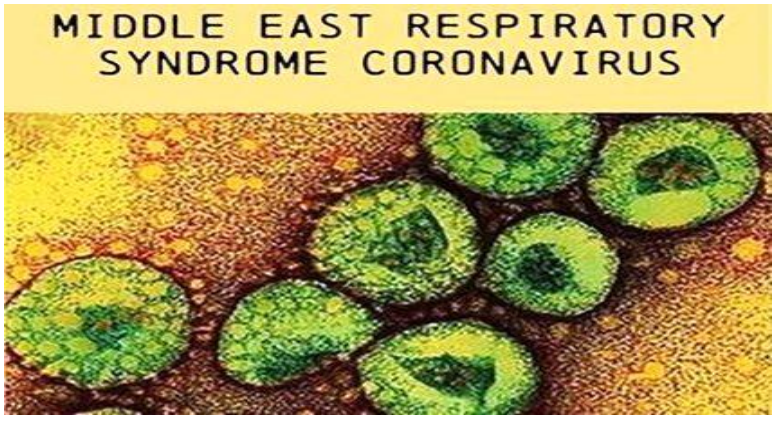

Figure: 1. Novel Coronaviruses (CoVs)

PATHOGENESIS AND TRANSMISSION

MERS-CoV has spread from ill people to others through close contact, such as caring for or living with an infected person.[25] The source of MERS-CoV infection and the mode of transmission have still not been confirmed. The transmission pattern observed in early 2014, which showed increased transmission from a primary animal source, most likely camels or

camel products, amplified by nosocomial transmission (Figue:3). The importation of a case in the Philippines demonstrates the possibility of importation of cases from abroad, especially in relation with healthcare workers infected while caring for patients in Saudi Arabia.[20]

Figure: 2.Transmission of MERS-CoV Virus

The latest importation of a case to Germany from the United Arab Emirates demonstrates the continued risk of case importation to Europe after exposure in the Middle East.[26] All reported cases have been linked to countries in and near the Arabian Peninsula. Most infected people either lived in the Arabian Peninsula or recently traveled from the Arabian Peninsula before they became ill. A few people became infected with MERS-CoV after having close contact with an infected person who had recently traveled from the Arabian Peninsula.[27] Currently, human-to-human transmission of MERS-CoV appears limited, particularly outside a hospital setting.[28-29]

CLINICAL FEATURES

Most people confirmed to have MERS-CoV infection have had severe acute respiratory illness with symptoms of fever, cough and shortness of breath. Some people also had gastrointestinal symptoms including diarrhea and nausea/vomiting.[5-7, 30] For many people with MERS, more severe complications followed, such as pneumonia and kidney failure. Most of the people who died had an underlying medical condition. Some infected people had mild symptoms (such as cold-like symptoms) or no symptoms at all; they recovered.[8, 31] The most common presenting Symptoms include fever cough, Shortness of breath in and gastrointestinal symptoms.[32-33] Patients with hypertension, diabetes, cardiomyopathy, chronic renal failure, malignancy, and decreased immunity appear to be at a higher risk of developing severe disease.[34]

DIAGNOSIS

Mostly Two Real-time RT-PCR (upE and ORF1a sets) assays are currently available for novel human coronavirus (CoV) detection with high specificity and sensitivity.[35-36] The upE assay used in combination with the 1a assay has been reported to provide a rigorously validated and highly sensitive result.[37] Performed RT-PCR assays on RNA that was extracted from upper respiratory tract swabs, with screening for the MERS-CoV genomic region upstream of the envelope gene (upE) and within open reading frame (ORF) 1a [38],Confirmation of upE results by ORF1a detection involved the re extraction of RNA from the original samples.[39] Laboratory confirmation of MERS-CoV infections to date has largely been by real-time reverse transcription polymerase chain reaction (rRT-PCR) of lower respiratory tract specimens[4], which can be positive from nasopharyngeal aspirate, sputum, tracheal aspirate, and urine specimens.[40] A simplified and biologically safe protocol for the detection of antibody response by immunofluorescence microscopy has been developed using convalescent patient serum. Immunofluorescence assays were performed with slides carrying Vero cells infected with full MERS-CoV.[41] Routine confirmation of cases of MERS-CoV infection is based on detection of unique sequences of viral RNA by real-time reverse-transcription polymerase chain reaction (r-RT-PCR) with confirmation by nucleic acid sequencing.[42-43]

PREVENTION

Currently, there is no vaccine to prevent MERS-CoV infection. The U.S. National Institutes of Health is exploring the possibility of developing one. CDC routinely advises that people help protect themselves from respiratory illnesses by taking everyday preventive actions: Hands Wash with soap and water for 20 seconds, Cover nose and mouth with a tissue when you cough or sneeze, Avoid touching eyes, nose and mouth with unwashed hands and Avoid personal contact, such as kissing, or sharing cups or eating utensils, with sick people.[44] WHO recommends that probable and confirmed cases should be admitted to adequately ventilate single rooms. Healthcare workers caring for probable or confirmed cases of MERS-CoV infection should use contact and droplet precautions (medical mask, eye protection – i.e. goggles or face shield -gown and gloves in addition to standard precautions. Airborne precautions should be applied when performing aerosol-generating procedures.[18,45-47] 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.[48] CDC continues to recommend that U.S. travelers to countries in or near the Arabian Peninsula protect themselves from respiratory diseases, including MERS, by washing their hands often and avoiding contact with persons who are ill. If travelers to the region have onset of fever and symptoms of respiratory illness during their trip or within 14 days of returning to the United States, they should seek medical care.[49-50]

TREATMENT

There is no specific antiviral treatment recommended for MERS-CoV infection. Individuals with MERS can seek medical care to help relieve symptoms. For severe cases, current treatment includes care to support vital organ functions.[44] Treatment for MERS requires the development of specific antiviral agents based on novel insights into the viral genome and structural biology of MERS-CoV. The successful control of the expanding MERS epidemic will depend on the development of an effective camel vaccine to stop ongoing camel-to-human transmissions, compliance with infection control measures, and timely contact tracing to prevent secondary health care-associated outbreaks.[51] The outbreak of MERS-CoV poses a serious threat to global public health and highlights an urgent need for the development of effective therapeutic and prophylactic agents to treat and prevent MERS-CoV infection.[2] Therapeutic modalities based on monoclonal antibodies (mAbs) have shown clinical success in the treatment of many diseases.[52] Treatment consists of limited to supportive care, including mechanical ventilation for respiratory failure and/or hemodialysis in the setting of renal failure. Widely disparate agents including chloroquine, chlorpromazine, loperamide, lopinavir, cyclosporine, and mycophenolic acid have in vitro activity against MERS-CoV.[53-54] The clinical experience from SARS suggests that a number of interventions including ribavirin with and without corticosteroids, interferon alfa with corticosteroids, ribavirin with lopinavir and ritonavir, and convalescent plasma may improve the outcome in patients but the data are not conclusive.[10, 55] In the case of MERS-CoV infections, interferon-alpha 3b and ribavirin may work primarily by reducing damaging inflammation of the lung and promoting healing by altering the host response, rather than directly targeting the virus [4]. Treatment with ribavirin and IFN-α2b may be effective in patients infected with MERS CoV.[56-57] Early ribavirin and interferon (IFN) reduced severity of respiratory symptoms, radiology, inflammatory markers and viral load in rhesus macaque monkeys but was in

effective in humans with MERS and ARDS.[58] MERS-CoV is more sensitive to IFN treatment than are other coronaviruses like SARS-CoV.[59-60] The treatment of MERS-CoV-infected human airway epithelium cultures with IFN of type I or III has been found to efficiently reduce viral replication. This finding supports the recommendation of IFN as a promising treatment for Middle East Respiratory Syndrome Coronavirus. IFN-β1b with mycophenolic acid was also found to be a successful combination that possessed antiviral activity against MERS-CoV.[53]

CONCLUSION

There is no doubt that MERS-CoV remains a serious threat and has exhibited a significant public health impact in the affected countries. Currently, health care associated transmission plays a pivotal role in the evolution of the MERS-CoV epidemic in countries in the Arabian Peninsula. Recent advances in epidemiological and molecular surveillance techniques have made some improvements in our ability to manage the public health response to such viruses, but many aspects remain unknown. The identification of closely related viruses in animal hosts is a prerequisite for establishing the ecology of viral emergence along with reconstruction of evolutionary pathways; however, complex ecosystems make this difficult. The successful control of the expanding MERS epidemic will depend on the development of an effective camel vaccine to stop ongoing camel-to-human transmissions, compliance with infection control measures, and timely contact tracing to prevent secondary health care-associated outbreaks.

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