



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

Middle East Respiratory Syndrome- A Review Study

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ABSTRACT

Middle East Respiratory Syndrome (MERS) is a viral respiratory illness which caused by a beta corona virus. The initial occurrence of MERS-CoV was thought to have particular predominance for male patients and those with comorbid diseases. Median incubation period of a MERS-CoV infection is 5 days. Potential risk factors are obesity, diabetes mellitus, end-stage renal disease, cardiac disease, hypertension, lung disease, including asthma and cystic fibrosis, and any immunosuppressive condition. Clinical symptoms include gastro-intestinal, respiratory, chest pain, malaise, myalgia, fever etc. Complications are ventricular tachycardia, cardiac arrest, pericarditis and multi-organ failure. Treatment for MERS CoV is not clear. The control of MERS-CoV infection relies on prompt identification of cases within health care facilities, with institutions applying appropriate infection control measures. In addition, determining the exact route of transmission from camels to humans would further add to the control measures of MERS-CoV infection.

Keywords: middle East respiratory syndrome, Coronavirus, Complications, Dromedary camels.

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Received 30 November 2017, Accepted 29 December 2017

Please cite this article as: Kumar V *et al.*, Middle East Respiratory Syndrome- A Review Study. American Journal of PharmTech Research 2018.

INTRODUCTION

Corona Virus⁽¹⁾

Coronaviruses are species in the genera of virus belonging to the subfamily Coronavirinae in the family Coronaviridae. Coronaviruses are enveloped viruses with a positive-sense RNA genome and with a nucleocapsid of helical symmetry. The genomic size of coronaviruses ranges from approximately 26 to 32 kilobases, extraordinarily large for an RNA virus. With its characteristic surface, the virions appear as a crown like image under the electron microscope and so the viruses are named after the Latin word corona, meaning 'crown' or 'halo'. In people, coronaviruses can cause illnesses ranging in severity from the common cold to Severe Acute Respiratory Syndrome (SARS). . In people, coronaviruses can cause illnesses ranging in severity from the common cold to Severe Acute Respiratory Syndrome (SARS). First Human CoVs isolated in the 2060s. The human coronaviruses mainly infect the upper respiratory and gastrointestinal tract. They often result in upper respiratory tract infections (simple colds) in humans, causing mild illnesses usually of short lasting nature with a rhinitis, cough, sore throat, as well as fever.

Six human CoVs (HCoVs) have been identified to date:

1. HCoV-220E
2. HCoV-OC43
3. HCoV-NL63
4. HCoV-HKU1
5. SARS-CoV
6. Middle East Respiratory Syndrome Coronavirus (MERS-CoV)

DIFFERENT TYPES OF CORONA VIRUS⁽¹⁾

Alpha Co-V: Human examples: HCoV-220E, HCoV-NL63 – Pig, dog, and cat CoVs.

Beta Co-V: HCoV-OC43, HCoV-HKU1, HCoV-SARS – MHV, rat, pig and cow CoVs – MERS-CoV.

Gamma Co-V: Chicken and turkey CoVs.

Delta Co-V: Bird CoVs.

History and Origin Of Middle East Respiratory Syndrome Coronavirus (MERS-COV)^(1,2)

Dr. Zaki isolated and identified a previously unknown coronavirus from the lungs of a 60-year-old Saudi Arabian man with pneumonia and acute renal failure. He used a broad-spectrum "pan-coronavirus" RT-PCR method and got a positive result. The UK Health Protection Agency (HPA) confirmed the diagnosis of severe respiratory illness associated with a new type of coronavirus in a

second patient, a 49-year-old Qatari man who had recently been flown into the UK. He died from an acute, serious respiratory illness in a London hospital. On 25 September 2012, the World Health Organization (WHO) announced that it is "engaged in further characterizing the novel coronavirus" and that it has "immediately alerted all its Member States about the virus and has been leading the coordination and providing guidance to health authorities and technical health agencies." In May 2013, the Coronavirus Study Group of the International Committee on Taxonomy of Viruses adopted the official designation, the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which was adopted by the World Health Organization to "provide uniformity and facilitate communication about the disease.". Fouchier and his team of researchers successfully sequenced the whole genome of the new coronavirus naming the viral strain Human Coronavirus- Erasmus Medical Center (hCoV-EMC) after their research center. They published its genomic sequence in the GenBank (accession code: JX869059) in the fall of 2012. Middle East Respiratory Syndrome (MERS) is a viral respiratory illness. MERS is caused by a corona virus called —Middle East Respiratory Syndrome Corona virus (MERS-CoV). MERS-CoV is a beta corona virus.

It is believed that MERS-CoV, like many other coronaviruses, originated in bats. This is based on the isolation of other lineage C beta-coronaviruses that are very closely related to MERS-CoV on phylogenetic analysis.^(3,4) A large screening study for beta-coronaviruses from 5030 bats fecal specimens was conducted between 2009 and 2011. In that study 4758 bats of ten different species from Ghana, and 272 Pipistrellus bats from four European countries were included.

Reverse Transcription Polymerase Chain Reaction (RT-PCR) was used to detect coronavirus RNA. Of the ten bat species tested in Ghana, only *Nycteris gambiensis* was found to carry 2c betacoronavirus. A round one fourth of the 185 *Nycteris* bats tested positive; this accounted for 1 % of whole tested bat's population from Ghana. Of the *Pipistrellus* bat species tested in Europe, 40 out of 272 (14.7 %) carried 2c beta coronavirus. Both 2c beta-coronaviruses isolated are genetically very closely related to MERS-CoV. This relatedness indicates that MERS-CoV likely originated from bats.⁽⁵⁾ Though the study had a good sample size and screened different geographical areas, none of those areas is known for MERS-CoV infection in humans or domestic animals. A report from South Africa identified a bat derived coronavirus that has a very close phylogenetic relationship to MERS-CoV.⁽⁶⁾

Epidemiology ⁽⁷⁾

The initial occurrence of MERS-CoV was thought to have particular predominance for male patients and those with comorbid diseases. The male-to-female ratio was between 2.8:1 to 3.3:1.

This male predominance might have been related to the nature of the outbreak. Initial cases were reported among elderly patients with a median age of 56 years.

Structural Features of MERS-COV⁽¹⁾

Here the virus of MERS-CoV contains mainly spike like structures mainly consists of glycoproyein for mainly receptor binding and antigenic activity. It also contains nucleocapsid phosphoprotein for RNA-binding, Membrane glycoprotein for triple membrane spanning, and positive strand RNA (+) ss RNA. The glycoprotein spike serves as the shape of crown for the virus so called as corona virus.

Transmission⁽⁷⁾

A stronger evidence of the connection comes from the detection of MERS-CoV by polymerase chain reaction from camels from Jeddah, KSA and in Qatar. The presence of a few genomic variants of MERS-CoV in dromedary camels suggests the transmission of MERS-CoV from camels to humans. The route of transmission of MERS-CoV from camels to humans remains to be identified. Camels' milk may play a role as MERS-CoV was detected in 41.7% of 12 tested camel milk samples which were collected according to the custom of the people in the region. People working with camels such as farm workers, slaughterhouse workers, and veterinarians may be at higher risk of MERS-CoV infection than other people. Goats, cows, sheep, water buffalo, and birds were negative for antibodies to MERS-CoV. Thus, so far no other animal link has been identified apart from camels and bats.

Evidence for Bats as Natural Reservoirs of MERS-COV

Bats have been implicated as the main reservoir of members of the genera Alphacoronavirus and Betacoronavirus^(8, 9) and play pivotal roles in interspecies transmission of CoVs. This is best exemplified by SARS-CoV, which was shown to originate from Chinese horseshoe bats and was probably transmitted directly to humans⁽¹⁰⁾ or through an intermediate host, such as the palm civet.

Evidence Supporting Camels as Direct Sources of MERS-COV

The close phylogenetic relationship of human MERS-CoV isolates with those obtained from bats initially suggested that MERS-CoV might have originated from bats. However, bats were unlikely to be the direct source of the MERS outbreak, since MERS cases were rarely found to have a history of contact with bats. Therefore, other animals were searched as direct sources of zoonotic transmission of MERS-CoV.

Anecdotal reports mentioned contact of MERS cases with camels and goats, suggesting that livestock might be an intermediate reservoir for MERS-CoV.⁽¹¹⁾ A research team found that 100 % (50/50) of retired racing camels from Oman and 14 % (15/105) of camels from Spain had

antibodies against MERS in their serum. ⁽¹²⁾ The high seroprevalence of MERS-CoV in camels indicated that camels may play a major role in the spread of MERSCoV among Middle Eastern countries.

Serological and molecular findings also indicated that camels were direct sources of human infection. Several groups reported a high seroprevalence of MERS-CoV or a closely related virus in camels across the Arabian Peninsula and parts of eastern and northern Africa, while MERSCoV antibodies were not found in other species of livestock/leisure animals, including cattle, goats, sheep, horses and chickens. ^(13, 14)

Modes of Camel-to-Human Transmission of MERS-COV ⁽¹⁵⁾

MERS-CoV sequences have been detected more commonly in nasal swabs than in rectal specimens of camels. Infection of camels in the laboratory also confirmed susceptibility, with a large quantity of virus shedding from the upper respiratory tract. Therefore, droplet transmission or direct contact with infected camels may be the most likely mode of camel-to-human transmission of MERS-CoV. Direct contact with camels can only explain some of the primary cases, since some MERS cases did not report any direct contact with camels. Other possible routes for camel-to-human transmission include food-borne transmission through consumption of unpasteurized camel milk/raw meat and the medicinal use of camel urine. Camels are an important source of milk in some Middle East countries and parts of Africa, and more than half of the camel milk is sold as unpasteurized fresh or fermented milk to local and urban consumers in Saudi Arabia. A survey found the presence of MERS-CoV RNA in the milk of camels actively shedding the virus. Whether MERS-CoV in milk is secreted by infected camels or is introduced as a contaminant during the milking process needs further investigation. An experimental study of the stability of MERSCoV in milk showed that viable viruses could still be recovered after 48 h regardless of reduction in virus titre, indicating that infection could happen by consumption of unpasteurized fresh raw milk. Consumption of undercooked meat from infected camels and handling of infected raw camel meat without proper protective equipment may also pose risks for getting MERS-CoV from camels. Camel urine is part of the traditional pharmacopoeia, and is used as a natural remedy for a variety of ailments in Middle Eastern countries. These practices may represent risk factors for infection, and further studies are needed to prove their camel-to-human transmission potential.

An oral–faecal transmission mode was also suspected. Using protein intrinsic disorder prediction, MERS-CoV was placed into disorder group C and was likely to persist in the environment for a rather long period of time, and showed high oral–faecal transmission chances.

Incubation Period ⁽¹⁶⁾

The median incubation period of a MERS-CoV infection is 5 days. Current data indicate that, overall, more men than women have become infected, with a median age of 47 years (range 9 months–94 years), and most fatalities are observed in patients over 60 years.

Clinical Aspects of Mers-Cov Infection in Humans

Clinical symptoms observed include fever, cough, sore throat, shortness of breath, myalgia, chest pain, malaise and gastro-intestinal symptoms, such as diarrhea, vomiting and abdominal pain. Less common symptoms include chills, wheezing, palpitations and confusion.⁽¹⁷⁾ Respiratory symptoms are mainly related to lower respiratory tract disease (dyspnoea, cough and fever), while upper respiratory tract disease is reported infrequently. A large proportion of the severely ill patients required mechanical ventilation.⁽¹⁸⁾

Radiology of MERS patients revealed mild to severe pulmonary consolidation. Chest radiographs of a large percentage of the patients admitted to hospital showed airspace and interstitial opacities, with subtle to extensive, unilateral to bilateral, and focal to diffuse distribution. Air space opacities are variable in their distribution, described as reticular or reticulonodular, and demonstrate thickening of bronchovascular areas. Computed tomography (CT) examination of hospitalized patients with MERS revealed bilateral, mostly sub pleural and basilar, airspace involvement, with ground-glass opacities and limited consolidation. The fact that most lesions were found in the subpleural and peribronchovascular region is suggestive of organizing pneumonia.⁽¹⁹⁾

During the course of the infection, MERS-CoV is mainly detected in the lower respiratory tract, while earlier in the infection virus is detected in the upper, as opposed to the lower respiratory tract. Although virus is detected in urine and blood of some MERS patients, this is not a consistent finding, but indicates that systemic infection can occur.⁽²⁰⁾

Potential risk factors for the development of severe disease are obesity, diabetes mellitus, end-stage renal disease, cardiac disease, hypertension, lung disease, including asthma and cystic fibrosis, and any immunosuppressive condition.⁽²¹⁾

Complications described in fatal cases are hyperkalaemia with associated ventricular tachycardia, disseminated intravascular coagulation leading to cardiac arrest, pericarditis and multi-organ failure.⁽²²⁾

Laboratory analyses of blood from MERS patients have revealed mild to severe abnormalities. Haematological abnormalities included elevated leukocyte counts and lymphopenia, while a few cases showed lymphocytosis, thrombocytopenia and coagulopathy. Other laboratory findings included elevated creatinine, lactate dehydrogenase, alanine aminotransferase and aspartate aminotransferase levels, suggestive of renal and liver disease or failure. Most importantly, chest

radiographs and imaging results of patients with MERS showed opacities and distribution of lesions that resemble the findings of organizing pneumonia seen in patients with pandemic influenza virus A (H₁N₁).⁽¹⁹⁾

Pathogenesis of MERS-COV

Although MERS and SARS resemble each other clinically, *in vitro* studies have highlighted remarkable differences between these viruses with respect to their growth characteristics, receptor usage and host responses, suggesting that their pathogenesis may be quite different. One way to predict the changes in the lungs after MERS-CoV infection is to use human tissue that has been infected *ex vivo*.⁽²³⁾ Widespread MERS-CoV antigen expression in type I and II alveolar cells, ciliated bronchial epithelium and unciliated cuboid cells of terminal bronchioles, using spectral confocal microscopy. Virus antigen was also found in endothelial cells of pulmonary vessels and rarely in alveolar macrophages. Electron microscopy revealed alveolar epithelial damage, consisting of detachment of type II alveolar epithelial cells and associated disruption of tight junctions, chromatin condensation, nuclear fragmentation and membrane blabbing, the latter suggesting apoptosis.⁽²⁴⁾ Although this *ex vivo* model does not fully mimic the situation *in vivo*, these changes are in line with observations in cell lines infected with MERS-CoV. Severe cytopathic effects were observed in human hepatoma cells infected with MERS-CoV; these were more severe than those due to SARS-CoV infection, although the *in vivo* relevance of this observation remains unclear.⁽²⁵⁾

DPP4 (also named CD26) has been identified as the receptor for MERS-CoV. All HCoV receptors identified to date are exopeptidases, although their proteolytic activity is not necessary for the virus to bind to the receptors, nor for them to enter the host cell. A comparative analysis of HCoV receptor expression across the respiratory tract of humans may provide clues regarding differences in pathobiology between HCoVs. In cell lines and *ex vivo* lung cultures, DPP4 is expressed in type I and II alveolar cells, ciliated and non-ciliated bronchial epithelium, bronchial submucosal glands, endothelium, alveolar macrophages and leukocytes. This largely corresponds with viral tropism in *ex vivo* human lung cultures, which show infection of non-ciliated cells in bronchi, bronchioles, endothelial cells and type I and II pneumocytes, but rarely in alveolar macrophages.⁽²⁶⁾ Remarkably, the binding site of DPP4 is different in different species, explaining why not all animals can be infected with MERS-CoV.⁽²⁷⁾

Pathology of MERS-COV Infection in Humans⁽²⁸⁾

So far, no reports describing autopsies of fatal MERSCoV cases have been published. From the clinical data and X-rays of the severe cases of MERS that have been described in humans, a severe

and progressive pneumonia may be suspected, as described for SARS, with diffuse alveolar damage (DAD) in the acute phase and more proliferative change in the later phase of the disease. Pulmonary fibrosis was seen frequently in SARS, including in patients who survived the infection. In the absence of accurate follow-up of MERS patients, there is limited information on the exact course of the disease in the long term. Comparison of the epidemiology, clinical manifestations and host cell response in MERS-CoV infection to infection with SARS-CoV may provide further insight into the pathogenesis and pathological potential of MERS-CoV.

MERS-COV Antigen Detection ⁽³⁰⁾

The detection of MERS-CoV antigen has not been common to date but the combination of short turn-around time from test to result, high throughput and identification of viral proteins makes this an attractive option. Detection of viral proteins rather than viral RNA indicates the likely presence of infectious virus. The first rapid immunochromatographic tool described could detect recombinant MERS-CoV nucleocapsid protein from DC nasal swabs with 94 % sensitivity and 100 % specificity compared to RT-rtPCR. ⁽²⁹⁾ A different approach used a monoclonal antibody-based capture ELISA targeting the MERS-CoV nucleocapsid protein with a sensitivity of 103 TCID₅₀ and 100 % specificity.

Infection Control Measures ^(31, 1)

Specimens Collection:

Exercise standard, contact, droplet and airborne precautions for patients under isolation.

Transport of patients:

Patient should wear a surgical mask and attendants should practice standard, contact, droplet and airborne precautions.

Linen and Laundry:

Pack on site and avoid shaking and Send to laundry as soon as possible.

Waste Management:

All wastes arising from the patient care should be considered as clinical waste using the red bags. Staff removing wastes should wear appropriate PPEs.

Administration Support:

Management should ensure adequate resources, issue formal instructions for visitors and patients, and post appropriate signage.

A SPECIAL PREVENTION FOR PERSONS WHO TRAVELS IN ARABIAN AND NEIGHBOURING COUNTRY

CDC does not recommend that travelers change their plans because of MERS. However, the Saudi Arabia Ministry of Health has made special recommendations for travelers to Hajj and Umrah. Because of the risk of MERS, Saudi Arabia recommends that the following groups should postpone their plans for Hajj and Umrah this year:

- People over 65 years old
- Children under 12 years old
- Pregnant women
- People with chronic diseases (such as heart disease, kidney disease, diabetes, or respiratory disease)
- People with weakened immune systems

People with cancer or terminal illnesses CDC encourages people traveling to Saudi Arabia to perform Hajj or Umrah to consider this advice. People who are concerned about MERS should discuss their travel plans with their doctor.

PREVENTION FOR INDIVIDUAL ^(31, 1)

There are specific precautions which are acquired for the prevention and protection of the Disease.

- Avoid to going into the hospital where the chances of getting infection is very high.
- Wash your hands often with soap and water for 20 seconds, and help young children do the same. If soap and water are not available, use an alcohol-based hand sanitizer.
- Cover your nose and mouth with a tissue when you cough or sneeze then throw the tissue in the trash.
- Avoid touching your eyes, nose, and mouth with unwashed hands.
- Avoid close contact, such as kissing, sharing cups, or sharing eating utensils, with sick people.
- Clean and disinfect frequently touched surfaces, such as toys and doorknobs. Wash your hands before and after visiting someone in a care home (many hospitals provide antibacterial gel in wards).

Prevention for Hospital Staff

- Hospital staff that comes into contact with patients should maintain very high standards of hygiene and take extra care when treating patients with pneumonia and MERS-CoV.
- Staff should thoroughly wash and dry their hands before and after caring for a patient, before and after touching any potentially contaminated patients.
- Patients with a known or suspected MERS-CoV infection should be isolated.

- The hospital environment, including floors, toilets and beds, should be kept as clean and dry as possible.

Prevention for Visitor to the Patients

- ✓ Visitors can reduce the chance of spreading MRSA to other people by not sitting on the patient's bed and by cleaning their hands before and after entering the ward.
- ✓ They should use hand wipes or hand gel before touching the person they are visiting.

Patients WHO Travels to the Arabian Countries

Taking these everyday actions can help prevent the spread of germs and protect against colds, flu, and other illnesses:

- Wash your hands often with soap and water. If soap and water are not available, use an alcohol-based hand sanitizer
- Avoid touching your eyes, nose, and mouth. Germs spread this way.
- Avoid close contact with sick people.
- Be sure you are up-to-date with all of your shots, and if possible, see your healthcare provider at least 4–6 weeks before travel to get any additional shots.
- If you are sick:
 - 1) Cover your mouth with a tissue when you cough or sneeze, and throw the tissue in the trash.
 - 2) Avoid contact with other people to keep from infecting them.

Treatment In Clinical Trial Study At Dammam University Saudi Arabia⁽³²⁾

Use of antiviral medications like ribavirin or other anti-viral medications, steroid medications, interferons like immunoglobulin, vasopressor medications like norepinephrine or vasopressin, neuromuscular blockades, inotropic medications like dobutamine, epinephrine, milirinone, levosimendan should be administered for the time of 2 months after admission to hospital.

Need for renal replacement therapy, Changes in blood cell count, white and red blood cells and platelets counts, renal function tests, serum creatinine and blood urea nitrogen levels, arterial blood gases levels, variables should be monitored for the time of 2 months after admission to hospital.

CONCLUSION

MERS-CoV infection is a serious disease that affects multiple organs and causes pulmonary, renal, hematological and gastrointestinal complications. MERS-CoV spread moderately ineffective from human-to-human. In spite of ongoing and possibly seasonal introduction of virus to the human population via infected dromedary camels and conceivably other animals yet to be identified, the

greater part of MERS-CoV transmission has occurred from infected to uninfected humans in close and prolonged contact through circumstances created by poor infection control. Strengthening the infection control measures in the health care setting is of great importance.

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