MERS (MIDDLE EAST RESPIRATORY SYNDROME) - AN EMERGING LIFE-THREATENING HEALTH PROBLEM (CURRENT STATUS OF RESEARCHES AND FUTURE PRIORITIES – A REVIEW)

Sharma Chakrapany
Professor & HoD, Deptt of Dravyaguna Vigyan, Dr. S R Rajasthan Ayurveda University Jodhpur-India
Email: chakrapany2006@gmail.com

ABSTRACT
Middle East Respiratory Syndrome (MERS) is viral respiratory illness first reported in Saudi Arabia in 2012. It is caused by a coronavirus called MERS-CoV. Most people who have been confirmed to have MERS-CoV infection developed severe acute respiratory illness. They had fever, cough, and shortness of breath. More than 30% of these people died. On May 2, 2014, the first U.S. case of MERS was confirmed in a traveler from Saudi Arabia to the U.S. On May 11, 2014, a second U.S. imported case of MERS was confirmed in a traveler who also came to the U.S. from Saudi Arabia. MERS-CoV can cause severe acute respiratory disease, particularly in people with underlying conditions, and this group has comprised the majority of primary cases since the beginning of the outbreak. Mild flu-like illnesses and asymptomatic cases are common in secondary cases. WHO is now warning that the MERS-CoV virus is a "threat to entire world." The IHR Emergency Committee on MERS-CoV convened by the WHO Director General is chaired by Australia’s Chief Medical Officer. The committee has met four times, most recently on 4 December 2013, and has determined that as of that date, the conditions were not met for the outbreak of MERS-CoV to be declared a public health emergency of international concern. The WHO recommends people at high risk of severe disease due to MERS-CoV, including those with diabetes, chronic lung disease, pre-existing renal failure, or those who are immunocompromised. There are no specific treatments recommended for illnesses caused by MERS-CoV. Medical care is supportive and to help relieve symptoms. Some of studies are on progress in different part of world to come over on this issue by finding anti-viral compound or vaccine but so far exercise is going on. Some of studies are facing controversies in Saudi Arabia. It has been observed that the Saudi officials had not given permission to Dr. Zaki to send a sample of the virus to Fouchier and they were angered when Fouchier claimed the patent on the full genetic sequence of the Middle East respiratory syndrome coronavirus. Present review is an attempt to explore the current status of researches and future priorities for finding an effective treatment of Middle East Respiratory Syndrome (MERS).

Keywords: MERS; MERS-CoV; ACE2; SARS-CoV; HCoV.

INTRODUCTION
The Middle East respiratory syndrome coronavirus (MERS-CoV), also termed EMC/2012 (HCoV-EMC/2012), is positive-sense, single-stranded RNA novel species of the genus Betacoronavirus. First called Novel coronavirus 2012 or simply novel coronavirus, it was first reported in 2012 after genome sequencing of a virus isolated from sputum samples from patients who fell ill in a 2012 outbreak of a new flu. As of 2 May 2014, MERS-CoV syndrome cases have been reported in several countries, including Saudi Arabia, Malaysia, Jordan, Qatar, Egypt, the United Arab Emirates, Tunisia, the Philippines, Indonesia, and the United States. The earliest cases of MERS were of clade A clusters (EMC/2012 and Jordan-N3/2012), and new cases are genetically distinct (clade B). Coronaviruses are species in the genera of virus belonging to one of two subfamilies Coronavirinae and Torovirinae in the family Coronaviridae, in the order Nidovirales. (a,b) 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. The virus MERS-CoV is a new member of the beta group of coronavirus, Betacoronavirus, lineage C. MERS-CoV genomes are phylogenetically classified into two clades, clad A and B.

MERS-CoV is distinct from SARS and distinct from the common-cold coronavirus and known endemic human betacoronaviruses HCoV-OC43 and HCoV-HKU1. Until 23 May 2013, MERS-CoV had frequently been referred to as a SARS-like virus,[4] or simply the novel coronavirus, and early it was referred to colloquially on messageboards as the "Saudi SARS".

On 13 February 2013, the World Health Organization stated "the risk of sustained person-to-person transmission appears to be very low."[5] The cells MERS-CoV infects in the lungs only account for 20% of respiratory epithelial cells, so a large number of virions are likely needed to be inhaled to cause infection.[6] As of 29 May 2013, the WHO is now warning that the MERS-CoV virus is a "threat to entire world."[7] However, Dr. Anthony S. Fauci of the National Institutes of Health in Bethesda, Maryland, stated that as of now MERS-CoV "does not spread in a sustained person to person way at all." Dr. Fauci stated that there is potential danger in that it is possible for the virus to mutate into a strain that does transmit from person to person.[8] The infection of healthcare workers (HCW) leads to concerns of human to human transmission.[9] Clusters of cases in several countries are being investigated.[10]

**Tropism & Transmission**

A tropism is a biological phenomenon, indicating growth or turning movement of a biological organism, usually a plant, in response to an environmental stimulus. In tropisms, this response is dependent on the direction of the stimulus (as opposed to nastic movements which are non-directional responses).

Viruses and other pathogens also affect what is called "host tropism" or "cell tropism" in which case tropism refers to the way in which different viruses/pathogens have evolved to preferentially target specific host species, or specific cell types within those species. In humans, the MERS-CoV virus has a strong tropism for nonciliated bronchial epithelial cells, and it has been shown to effectively evade the innate immune responses and antagonize interferon (IFN) production in these cells.

This tropism is unique in that most respiratory viruses target ciliated cells.[11] (a,b) Due to the clinical similarity between MERS-CoV and SARS-CoV, it was proposed that they may use the same cellular receptor; the exopeptidase, angiotensin converting enzyme 2 (ACE2).[12] However, it was later discovered that neutralization of ACE2 by recombinant antibodies does not prevent MERS-CoV infection.[13]

Further research identified dipeptidyl peptidase 4 (DPP4; also known as CD26) as a functional cellular receptor for MERS-CoV.[14] Unlike other known coronavirus receptors, the enzymatic activity of DPP4 is not required for infection. As would be expected, the amino acid sequence of DPP4 is highly conserved across species and is expressed in the human bronchial epithelium and
kidneys. Bat DPP4 genes appear to have been subject to a high degree of adaptive evolution as a response to coronavirus infections, so the lineage leading to MERS-CoV may have circulated in bat populations for a long period of time before being transmitted to people.

**Symptoms of MERS**

Most people who got infected with MERS-CoV developed severe acute respiratory illness with symptoms of fever, cough, and shortness of breath. 30% of them died. Some people were reported as having a mild respiratory illness. The other main symptoms of MERS are: difficulty in breathing, diarrhea, high fever (over 38°C or 100.4°F) As the virus aggressively invades the body’s cells, the immune response is destroyed causing systemic breakdown. Death eventually results from multiple organ collapse in MERS-CoV victims in approximately 10 days for those not responding to conventional treatments.

**Diagnosis**

For the diagnose MERS, a physical examination is must at first along with the check for fever and swollen glands. So, lungs examination is required. Buildup of fluid in the lungs can be seen with a chest X-ray, CT scan, or magnetic resonance imaging (MRI) scan. The sample of sputum (phlegm) may be examined in laboratory to confirm the diagnosis by identifying the exact strain of virus that may be causing symptoms.

**Treatment & Preventive Measures**

There are no specific treatments recommended for illnesses caused by MERS-CoV. Medical care is supportive and to help relieve symptoms. Pneumonia develops after several days along with other symptoms of Acute Respiratory Distress Syndrome and the patient may be treated with “convalescent plasma,” recommended by WHO. This is the clear fluid part of the blood containing antibodies taken from MERS-CoV survivors.

**Researches**

Between April 2012 and June 2013, 72 patients were infected with MERS-CoV and 38 patients died. The first cases were reported in Saudi Arabia and Qatar and cases have since been reported in six additional countries (France, Italy, Jordan, Qatar, Tunisia and the United Arab Emirates). Dr. Fauci identified the following MERS-CoV research needs: Basic research on MERS-CoV biology, pathogenesis, immune response, surveillance, and “omics” animal models. Therapeutics Vaccines. 

Short- and medium-term basic research priorities for MERS-CoV and PEDV (Porcine epidemic diarrhea virus) could include:

- Identifying basic research priorities in replication and pathogenesis
- Understanding CoV biodiversity
- Studying mechanisms that regulate potential for cross-species transmission
- Constructing panels of representative heterologous viruses to design, develop, and test broad-based vaccines and therapeutics
- Improving translational outcomes of vaccines, therapeutics, and diagnostics
Development of Antiviral Compounds against MERS-CoV

Windows of opportunity for treatment and potential treatments are:

- Pre-exposure: antivirals with no or minimal side effects
- Acute illness: antivirals (possibly interferon and/or ribavirin)
- Late disease: antivirals (possibly interferon and/or ribavirin) or immune antagonists (if symptoms are due more to immune response than viral replication at this stage)

Findings and Facts

Studies from the SARS outbreak found that SARS-CoV titer in respiratory secretions peaks 10 days after the onset of fever. If the MERS-CoV titer follows a similar timeline, antiviral treatment initiated early in the course of the disease would reduce the viral titer and potentially reduce mortality. CoV replication dramatically modifies the entire cell environment. Six hours after infection of the mouse with CoVs, double-membrane and convoluted vesicles develop. These modified membranes are the “factories” that drive viral RNA synthesis. Sequence analysis revealed that SARS-CoV and MERS-CoV replicase is 50 percent identical at the amino acid level, but the protease domains and enzyme functions are conserved and the overall pattern of proteolytic processing is likely to be the same. Therefore, we should be able to apply the information gained from studies of protease inhibitors directed against SARS-CoV to develop protease inhibitors against MERS-CoV.

A Chinese study reveals that researchers of a team used a purified, intact receptor-binding domain of the MERS virus to attract antibodies from "single-chain variable region fragments" (scFv) of a nonimmune human antibody library. The collection of antibodies was displayed on the surface of Saccharomyces cerevisiae yeast, provided by Pacific Northwest National Laboratory. They found two monoclonal antibodies (mAbs), labeled MERS-4 and MERS-27, that had strong neutralizing activity against MERS-CoV. The virus sample they used was provided by Erasmus University Medical Center in the Netherlands. The authors found a synergistic effect when they were used together against pseudo-typed MERS-CoV, suggesting that they could be combined for use in future animal and clinical tests. The study refers that “The combined effect of the two mAbs would be expected to provide stronger and broader neutralizing activity against wild-type or mutant. MERS-CoVs should mutations occur during viral infection and transmission.”

Controversies

It has been reported that the Saudi officials had not given permission to Dr. Zaki to send a sample of the virus to Fouchier and they were angered when Fouchier claimed the patent on the full genetic sequence of the Middle East respiratory syndrome coronavirus. At their annual meeting of the World Health Assembly in May 2013, WHO chief Margaret Chan declared that intellectual property, or patents on strains of new virus, should not impede nations from protecting their citizens by limiting scientific investigations. Deputy Health Minister Ziad Memish raised concerns that scientists who held the patent for the MERS-CoV virus would not allow other scientists to use patented material and...
were therefore delaying the development of diagnostic tests.\textsuperscript{23}

Erasmus MC responded that the patent application did not restrict public health research into MERS coronavirus,\textsuperscript{24} and that the virus and diagnostic tests were shipped—free of charge—to all that requested such reagents.

**Vaccination and Role of Ayurveda Herbal Treatment**

Though vaccines prepared from the “convalescent plasma” taken from the blood of MERS-CoV survivors are used to treat the disease, they do not yield much result. In fact vaccines are not only ineffective in almost every kind of disease, but they also increase the chances of dying. According to Gaia Health vaccines are responsible for increasing the child mortality rate by at least 50 percent, which is quite alarming at present. In the last 20 years a large number of children have fallen prey to multiple vaccine doses, resulting in almost 103,500 extra deaths.\textsuperscript{25} The only way to fight viruses like MERS-CoV is to add more strength to the immunity of the human body. Various Ayurveda herbs possess the immunity enhancer properties. Though, the Ayurveda does not follow the microbial theory as a cause of disease. But it advocates improving immune system using with such herbs which contains the anti-microbial activity along with the immunomodulation property.

Some of herbs are as followed:-

1. Rason (\textit{Allium lapa})
2. Shunthi (\textit{Zinziber officinalae})
3. Pippali (\textit{Piper longum})
4. Kulinjan (\textit{Alpina galanga})
5. Guduchi (\textit{Tinospora cordifolia})

**CONCLUSION**

It can be concluded that the Middle East respiratory syndrome coronavirus (MERS-CoV), (also termed EMC/2012 (HCoV-EMC/2012), is an emerging life threatening health problem and spreading all over word speedily. As it has been found that the cause of this syndrome is MERS-CoV virus, that is a coronaviruses viruses with a positive-sense RNA genome and with a nucleocapsid of helical symmetry. There is no any effective, safe and specific treatment is available of this disease, so far. Some of studies and researches are reported to come over on this issue and some of are facing controversies. Development of Antiviral Compounds against MERS-CoV is a current need to secure and save the human life. Future prospective for finding the treatment is a tedious job but a holistic approach from the different field of science – Virology, Microbiology, Pharmacology, and Immunology may open new path of hope. Author is of opine that herbal remedies should be valuated and validated for finding anti-viral agent and Immunomodulator agent.

**REFERENCES**


(b) International Committee on Taxonomy of Viruses (24 August 2010). "ICTV Master Species List 2009 – v10" (xls).


10. Centers for Disease Control and Prevention FAQ on MERS


13. Müller, MA.; Raj, VS.; Muth, D.; Meyer, B.; Kallies, S.; Smits, SL; Wollny, R.; Bestebroer, TM.; Specht, S. (11 December 2012). "Human coronavirus EMC does not require the SARS-


20. Middle East Respiratory Syndrome Coronavirus (MERS-CoV Research, Current Status and Future Priorities, Meeting Summary, National Institute of Allergy and Infectious Diseases www.niaid.nih.gov, Natcher Conference


22. Pandemic preparedness: Coming, ready or not". The Economist. 20 April 2014.

23. WHO urges information sharing over novel coronavirus”. BBC News, 23 May 2013
