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Chapter 14

Middle East Respiratory Syndrome-Coronavirus (MERS-CoV) Infection

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CASE PRESENTATION

A 45-year-old male had a history of heavy smoking, type 2 diabetes mellitus, a history of atrophied right kidney, and ischemic heart disease. He presented with a 3-day complaint of fever of 38°C and a cough that had become productive. A chest film was unremarkable, and he was discharged home. The following day, he visited the hospital's emergency room with the same complaints. The oxygen saturation on room air and chest film was normal, and he was discharged home on oral cefuroxime. Two days later, he returned to the emergency room with worsening dyspnea and required continuous positive airway pressure (CPAP) to maintain oxygenation. Chest film revealed patchy infiltrates in his right lower lobe. Treatment with parenteral ceftriaxone, azithromycin, and oral oseltamivir were commenced after specimens were collected for diagnostic testing. He became progressively more hypoxic over the next 24 hours. Chest film revealed patchy infiltrates in his right lower lobe. Routine bacteriology, acid-fast bacillus smears, and screening influenza exams were negative. He further deteriorated and required intubation and mechanical ventilation.

Antibiotics were changed to piperacillin-tazobactam plus linezolid; treatment with corticosteroids was initiated. Immunofluorescent staining of respiratory epithelial cells for influenza A, B, respiratory syncytial virus (RSV), parainfluenza 1-3, and adenovirus were negative, and he was confirmed to be seronegative for human immunodeficiency virus (HIV), *Mycoplasma pneumoniae*, Q fever, and *Brucella*. Upper tract swabs in viral transport media were forwarded to the Saudi Ministry of Health regional

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laboratory for Middle East respiratory syndrome-coronavirus (MERS-CoV) upE reverse transcriptase polymerase chain reaction (RT-PCR). A second set of specimens including tracheal aspirate was collected. Respiratory specimens were positive for MERS-CoV.

In the intensive care unit, renal function deteriorated, and he was started on continuous renal replacement for 2 days then three hemodialysis sessions. Subsequently, oxygen requirements were moderated and he gradually defervesced, although chest radiographs continued to show infiltrates. He was then weaned off mechanical ventilation and was extubated. He was subsequently discharged home.

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1. WHAT IS THE CAUSATIVE AGENT?

Middle East respiratory syndrome-coronavirus (MERS-CoV) is a new human disease that was first reported from Saudi Arabia in September 2012, after identification of a novel coronavirus (CoV) from a male Saudi Arabian patient who died from severe pneumonia.[2,3] MERS-CoV had caused a significant mortality of about 50% since that time.[4]

The MERS-CoV is a novel coronavirus that was initially designated HCoV-EMC.[3] The virus was later designated after global consensus as MERS-CoV.[5] Coronaviruses are common viruses that usually cause mild to moderate upper-respiratory tract illnesses in humans. The viruses have crown-like spikes on their surfaces and hence the name coronavirus. Human coronaviruses, enveloped RNA viruses, are not new and were first identified in the mid-1960s. There are four virus clusters within the *Coronavirinae* subfamily. These are alphacoronavirus, betacoronavirus, and gammacoronavirus. The fourth cluster is a provisionally assigned new group called delta coronaviruses. All known human coronaviruses belong to the genera *Alphacoronavirus* (HCoV-229E and HCoV-NL63) and *Betacoronavirus* (HCoV-OC43, HCoV-HKU1, and SARSCoV).[3] MERS-CoV, formerly HCoV-EMC, is the first human coronavirus in lineage C of the *Betacoronavirus* genus.[3]

2. WHAT IS THE FREQUENCY OF THE DISEASE? PREVALENCE, INCIDENCE, BURDEN, AND IMPACT OF THE DISEASE

Between April 2012 and February 7, 2014 there were 182 documented cases of MERS-CoV infection worldwide.[5a] The majority of these occurred in the Kingdom of Saudi Arabia where 148 cases were reported. MERS-CoV appears to have a predilection for individuals with underlying medical comorbidities.[1,4,6−8]

3. WHAT ARE THE TRANSMISSION ROUTES?

The main modes of transmission are contact transmission, droplet transmission, and person-to-person transmission as supported by epidemiologic and phylogenetic analyses.[4] Currently, the MERS-CoV seems to have three epidemiological patterns of the disease. There are sporadic cases occurring in the communities of different Middle East countries, mainly the Kingdom of Saudi Arabia, Qatar, United Arab Emirates, and Jordan. The second pattern is nosocomial transmission within healthcare facilities to healthcare workers and other patients.[4] Intrafamilial transmission of MERS-CoV was also described.[1,4,7,9–11]

4. WHICH FACTORS ARE INVOLVED IN DISEASE PATHOGENESIS? WHAT ARE THE PATHOGENIC MECHANISMS?

The pathogenesis of the disease has been elucidated in recent studies. MERS-CoV has spike glycoprotein (S) that targets the cellular receptor, dipeptidyl peptidase 4 (DPP4).[12,13] This viral spike has a putative receptor-binding domain (RBD).[13] MERS-CoV RBD has a core and a receptor-binding subdomain, which interacts with DPP4 β-propeller MERS-CoV RBD.[13]

The MERS-CoV spike protein interacts with CD26 (also known as DPP4) and causes viral attachment to host cells and virus-cell fusion.[14] This is thought to be the first step in viral infection. The MERS-CoV infection results in profound apoptosis of infected respiratory cells within 24 hr.[15]

5. WHAT ARE THE CLINICAL MANIFESTATIONS?

MERS-CoV causes respiratory tract infection that ranges in severity from mild to fulminant respiratory infection. Mild respiratory illness was described in patients from Tunisia[16] and from the United Kingdom.[11]

The clinical presentation of MERS-CoV is similar to SARS3. The initial phase is non-specific fever and mild, non-productive cough lasting several days, followed by progressive pneumonia.[4,6] In MERS-CoV infections, most patients present with serious respiratory disease, resulting in a high mortality rate of 60%.[6] The mean age of affected patients was 56 years with a range of 14–94 years.[6] A recent case of a 2-year-old patient was described.[17] The most common symptoms are fever (87%), cough (87%), and shortness of breath (48%).[4,6] About 35% of patients had accompanying gastrointestinal symptoms, including diarrhea (22%) and vomiting (17%). Of the total cases, 50% had two medical co-morbidities, diabetes and chronic renal disease.[6]

Important laboratory abnormalities in patients with MERS-CoV include: leucopenia (14%), lymphopenia (34%), thrombocytopenia 36%, increased lactate dehydrogenase (LDH) (49%), increased alanine aminotransferase

(ALT) (11%), and increased aspartate aminotransferase (AST) (15%).[6] Chest radiographic abnormalities include: increased bronchovascular markings (17%), unilateral infiltrate (43%), bilateral infiltrates (22%), and diffuse reticulonodular pattern (4%).[4]

6. HOW DO YOU DIAGNOSE?

Laboratory testing for MERS-CoV is a challenge. Currently, there are no validated serologic assays. The main testing method relies on identification of MERS-CoV using real-time reverse transcriptase-polymerase chain reaction (RT-PCR) from respiratory tract secretions. It is not clear at this point of time whether sputum or nasopharyngeal samples are superior to throat swabs.[4]

7. HOW DO YOU DIFFERENTIATE THIS DISEASE FROM SIMILAR ENTITIES?

To date, there are no specific laboratory abnormalities or clinical data that differentiate pneumonia due to MERS-CoV from pneumonia caused by other viruses or other bacterial pathogens. The primary diagnosis of MERS-CoV infection relies on the identification of the virus in respiratory secretions using real-time RT-PCR.

8. WHAT IS THE THERAPEUTIC APPROACH?

The main therapeutic options for MERS-CoV infection are not known. There is no specific therapy for MERS-CoV infection. Recently, *in vitro* studies showed that MERS-CoV is 50−100 times more sensitive to alpha interferon (IFN-α) treatment than SARS-CoV.[18] In a recent decision support document, convalescent plasma was given an order of recommendation of 1, followed by interferon, protease inhibitors (order of recommendations of 2), and intravenous globulin (order of recommendations of 3).[19] Further randomized controlled trials of these agents are needed to establish the efficacy and side effects.

9. WHAT ARE THE PREVENTIVE AND INFECTION CONTROL MEASURES

The main infection control measures to prevent the transmission of MERS-CoV include contact isolation, standard precautions, droplet isolation, and airborne infection isolation precautions especially when healthcare workers perform aerosol generating procedures.[20] Droplet precautions include wearing a medical mask when in close contact (within 1 meter) and upon entering the room or cubicle of the patient. The Centers for Disease Control

and Prevention (CDC) recommends placing patients with suspected or confirmed MERS-CoV infection in an airborne infection isolation room (AIIR).[21] If an AIIR is not available, the patient should be transferred as soon as is feasible to a facility where an AIIR is available. Pending transfer, place a facemask on the patient and isolate him/her in a single-patient room with the door closed.[21] Performing hand hygiene in accordance with the World Health Organization's (WHO) 5 moments of hand hygiene is of paramount importance and could not be stressed more. Additional measures include wearing a particulate respirator when performing aerosol-generating procedures in addition to other precautions. In a recent MERS-CoV outbreak in a healthcare setting, there was evidence of person-to-person transmission and the outbreak was aborted by the implementation of infection control measures.[4]

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