CHAPTER

4

THE MIDDLE EAST RESPIRATORY SYNDROME CORONAVIRUS RESPIRATORY INFECTION: AN EMERGING INFECTION FROM THE ARABIAN PENINSULA

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1 INTRODUCTION

Coronaviruses (CoV) are a group of viruses known to cause mild to severe diseases in humans. Known human coronaviruses causing disease belong to the genera alpha-coronavirus and beta-coronavirus. These viruses usually cause mild upper respiratory tract disease in humans. The Middle East Respiratory Syndrome Coronavirus (MERS-CoV) belongs to the beta-coronaviruses and was first identified in the Kingdom of Saudi Arabia in 2012.[1] The virus was isolated from the sputum of a 60-year-old man who presented with community acquired pneumonia and subsequently developed a fatal disease associated with acute renal failure and respiratory failure.[1] Since Apr. 2012 to date, the virus has caused a total of 1611 cases including 575 deaths that were reported by the World Health Organization in 26 countries.[2] The majority of these cases occurred in the Arabian Peninsula and the other cases were linked to this geographic area, usually through travel. The disease has a wide range of clinical presentation and epidemiology.[3–7] The clinical spectrum ranges from mild disease to a rapidly fatal disease. The presence of asymptomatic cases was also described. Three main factors contribute to the transmission of MERS-CoV, these are the virus, the host, and the environment. Cases occurred as sporadic patients, limited intrafamilial transmission, and clusters of healthcare associated transmissions. The sporadic cases may result from camel to human transmission with subsequent cases being secondary cases among human contacts. The virus seems to have a peculiar tendency to cause healthcare-associated transmissions as exemplified by multiple hospital outbreaks, as will be discussed later. The emergence of MERS-CoV caused great attention to the emergent respiratory pathogens and the potential for global spread of the disease with the current spread of globalization. Understanding the pathogen, the mode of

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transmission, and the spectrum of the diseases allows the development of preventive measures and the application of effective infection control practices. The prospect for the development of a novel therapy or the use of previous therapy for the treatment of MERS-CoV would further enhance our abilities to combat the disease. Here, we review the epidemiology of the disease, clinical presentations, and the outcome.

2 THE ORGANISM

Coronaviruses are parts of the Nidovirales order. The name stems from the presence of crown-like spikes on their surfaces. Coronaviruses were first identified as human pathogens in the mid-1960s. Coronaviruses are enveloped RNA viruses and there are four virus clusters within the Coronavirinae subfamily: alpha, beta, gamma, and delta coronaviruses. Pathogenic human coronaviruses are classified into the genera alpha-coronavirus (HCoV-229E and HCoV-NL63) and beta-coronavirus (HCoV-OC43, HCoV-HKU1, and SARS-CoV).[1] MERS-CoV emerged as a significant pathogen after the initial identification in 2012 from a patient with rapidly fatal community acquired pneumonia and is the first human coronavirus in lineage C of the beta-coronavirus genus.[1,8] The MERS-CoV virus is known to have multiple clades circulating in humans. In one study, four different phylogenetic MERS-CoV clades were circulating in Saudi Arabia in Sep. 2012 to May 2013.[9] Only one clade persisted at the end of the observation period.[9] The length of each clade was different: Al-Hasa clade from Apr. 21, 2013 to Jun. 22, 2013 (62 days), Riyadh_3 clade from Feb. 5, 2013 to Jul. 2, 2013 (147 days), Buraidah_1 clade from May 3, 2013 to Aug. 5, 2013 (84 days), and Hafr-Al-Batin_1 clade from Jun. 4, 2013 to Oct. 1, 2013 (119 days).[9] Most of the cases in the 2014 Jeddah outbreak belong to a single clade indicating human-to-human transmission.[10] The imported case into South Korea showed that the MERS-CoV is a recombinant of groups 3 and 5 elements and that the recombination event occurred in the second half of 2014.[11]

3 MERS-COV EPIDEMIOLOGY

Since Apr. 2012 to Oct. 2015, a total of 1611 cases including 575 deaths have been reported by the World Health Organization in 26 countries.[2] Most of these cases were reported from Saudi Arabia (Table 4.1). Multiple healthcare associated infections occurred within Saudi Arabia and contributed to the significant increase in the number of the cases. The most studied outbreaks occurred in Al-Hasa,[7] Jeddah,[12–16] and Riyadh.[12–16] The Al-Hasa outbreak occurred in Apr. 2013 and involved 23 confirmed cases and 11 probable cases of MERS-CoV in 4 hospitals.[7] In Mar.–Apr. 2014, a large number of cases were reported in Saudi Arabia and the United Arab Emirates.[12–16] During the 2014 Jeddah outbreak, a total of 14 hospitals were involved and they had a total of 128 cases.[10,13] The largest outbreak outside the Arabian Peninsula occurred in the Republic of Korea and was initiated by an index patient after returning from a trip to multiple countries in the Middle East (Bahrain/Saudi Arabia/UAE/Qatar).[16] In about 2 weeks, the outbreak involved 5 health care facilities and there were 63 cases.[17] Subsequently, the outbreak in the Republic of Korea involved 72 health care facilities and 6 health care facilities had nosocomial transmission.[18] The total number of cases as of Jun. 26, 2015 were 182 cases with 31 deaths.[19,20]

Table 4.1 Number of Cases and Deaths of MERS-CoV Among Most Frequent Countries

Country	Number of Cases	Number of Deaths (% Case Fatality Rate)
Saudi Arabia	1255	539 (43)
South Korea	185	36 (19.5)
United Arab Emirates	81	11 (13.6)
Jordan	35	14 (40)
Qatar	13	5 (38.5)
All countries	1611	275 (35.7)

4 CLINICAL PRESENTATIONS

The clinical presentation of MERS-CoV varies from asymptomatic or mildly symptomatic cases to severe and often fatal disease. A large number of the patients had underlying medical comorbidities.[3–7] These comorbidities include: diabetes mellitus (44%), cardiac disease (21%), renal failure (26%), hemodialysis (6.2%), and hypertension (24%) (Table 4.2).[6,7,21–25]

According to the Saudi Ministry of Health, 38% of the cases were primary, 45% were healthcare-associated infection, and 14% were household infections.[26] These numbers summarize three epidemiological pattern of the disease: sporadic cases occurring in the communities, probably from an animal contact, and human to human transmission as a result of healthcare-associated infection and intrafamilial transmission of MERS-CoV.[3,5,7,27–29]

Most of the affected patients were adults with a mean age of 56 years (range: 14–94) years[4,21] and a number of pediatric cases were described.[30–32] A study of 1898 combined nasal and throat swabs yielded no MERS-CoV by PCR in children <2 years of age in Jordan.[33] The relative low number of MERS-CoV in children is not readily explained.

Although, initially MERS-CoV cases were severe requiring intensive care unit services, subsequent cases included less severe disease.[34] The proportion of asymptomatic cases varied from 0% to 30%.[34] The initial phase of the clinical illness is nonspecific and includes fever and mild nonproductive cough lasting several days.[4,7] Progressive pneumonia then follows with multiorgan failure and this may result in death with a case fatality rate of 30% to 60%.[4,21] Most of the patients present with fever (87%), cough (87%), and shortness of breath (48%) (Table 4.2).[4,7] About 35% of patients may have gastrointestinal symptoms such as: diarrhea (22%) and vomiting (17%). Of the total cases, 50% had 2 medical comorbidities, diabetes, and chronic renal disease.[4] Acute renal failure developed in a proportion of patients, and three patients developed neurological signs: altered level of consciousness, confusion or coma, ataxia, and focal motor deficit.[22]

Many nonspecific laboratory abnormalities exist in patients with MERS-CoV and include: leucopenia (14%), lymphopenia (34%), thrombocytopenia (36%), increased lactate dehydrogenase (LDH) (49%), and increased hepatic transaminases (11–15%).[4,7,21,22–25,35] Chest radiographic abnormalities include: increased bronchovascular markings (17%), unilateral infiltrate (43%), bilateral infiltrates (22%), and diffuse reticulonodular pattern (4%).[7] Other studies showed ground-glass opacity in 66% and consolidation in 18%.[36–37] In one study utilizing CT-scan imaging, the lower lobes were more commonly

Table 4.2 Most Common Underlying Comorbidities, Clinical Signs and Symptoms, and Laboratory Findings in Patients With MERS-CoV From Various Studies

	%
Comorbidities	
Diabetes Mellitus	44
Cardiac disease	20.7
Renal failure	25.9
Hemodialysis	6.2
Malignancy	1.6
Hypertension	23.8
Clinical signs and symptoms	
Fever	75.6
Dyspnea	61.7
Chest pain	15
Cough	62.2
Hemoptysis	8.3
Sore throat	6.7
Headache	9.8
Myalgia	15.5
Vomiting	20.7
Diarrhea	22.8
Weakness	18.7
Abdominal pain	14
Rhinorrhea	4.7
Lymphopenia	31.6
Thrombocytopenia	11.9

involved than the upper and middle lobes combined.[37] In fatal cases, the mean number of lung segments involved was 12.3 segments compared to 3.4 segments in those who survived.[37]

Laboratory diagnosis relies on respiratory tract samples for the detection of MERS-CoV using real-time reverse transcriptase polymerase-chain-reaction (RT-PCR). The virus may be detected in the lower and upper respiratory tract samples. Lower respiratory tract samples yielded better diagnostic results,[38] and had higher viral loads.[39] Lower respiratory tract samples had the highest viral loads (mean 5.01×10^6 copies/mL), compared with upper respiratory tract samples (2×10^4 copies/mL), urine (1.26×10^2 copies/mL), stool (1.58×10^4 copies/mL), and serum (2.51×10^3 copies/mL).[39] Serologic tests had been used for the diagnosis of MERS-CoV.[40,41] Data on the sensitivity and specificity of antibody tests for MERS-CoV are limited. In one study, the use of plaque reduction neutralization tests

(PRNT), microneutralisation (MN), MERS-spike pseudoparticle neutralization (ppNT) and MERS S1-enzyme-linked immunosorbent assay (ELISA) were found to be sensitive and specific.[41]

5 TREATMENT OF MERS-COV

The main therapeutic options for MERS-CoV infection are not known. In vitro, MERS-CoV is sensitive to alpha interferon (IFN-α).[42] No randomized controlled trials exists to establish the efficacy and side effects of any therapeutic modalities. Learning from the SARS experience, interferon and ribavirin was suggested as a therapy for MERS-CoV.[43] The combination of interferon-α2b and ribavirin prevented pneumonia in animals.[44] The first report of the use of ribavirin and interferon showed no survival advantage[45] because the combination was started late in the course of the disease.[45] A 14-day survival advantage was documented with this combination but there was no survival advantage at 28 days.[24] There was no difference in therapy between interferon-α2a with ribavirin and interferon-β1a with ribavirin in treating MERS-CoV.[25] In a case report from Greece, pegylated interferon, ribavirin, and lopinavir/ritonavir was initiated on day 13 of illness.[46] MERS-CoV was detectable in the respiratory tract secretions of the patient for 4 weeks after onset illness and viraemia lasted 2 days after initiation of therapy.[46]

6 PREVENTIVE AND CONTROL OF MERS-COV

The prospect for the control and prevention of MERS-CoV relies on the identification of the definite host, the interruption of the animal to human transmission, and the application of the proper infection control measures in the healthcare settings. The available data links dromedary camels with human cases of MERS-CoV.[47] A high prevalence of MERS-CoV antibodies was detected in dromedary camels from across the Arabian Peninsula, North Africa, and Eastern Africa.[48–54] In addition, viral MERS-CoV was detected in samples from dromedary camels in multiple locations in the Arabian Peninsula using RT-PCR.[52,54–61] The main infection control measures in healthcare settings include: contact isolation, droplet isolation, and airborne infection isolation precautions especially when during aerosol generating procedures.[62] The centers for disease control and preventions (CDC) recommends placing patients with suspected or confirmed MERS-CoV infection in an airborne infection isolation rooms (AIIR).[63]

7 SUMMARY

MERS-CoV infection is an emerging infectious disease with a high mortality rate. The exact incidence and prevalence of the disease was evaluated in a large population based survey using serology in the Kingdom of Saudi Arabia. The study showed that anti-MERS-CoV antibodies were present in 0·15% of 10,009 people.[40] The mean age of seropositive individuals was significantly younger than that of patients with reported, laboratory-confirmed, primary MERS (43·5 years vs 53·8 years), and that men had a higher antibody prevalence than did women [11 (0·25%) of 4341 vs two (0·05%) of 4378] and antibody prevalence was significantly higher in central versus coastal provinces [14 (0·26%) of 5479 vs one (0·02%) of 4529].[40] The diagnosis of MERS-CoV infection relies on detection of the virus using real-time RT-PCR. Currently, the best therapeutic options for MERS-CoV are not known and there are no available vaccines.

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