Middle East respiratory syndrome novel corona (MERS-CoV) infection

Epidemiology and outcome update

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ABSTRACT

متلازمة الشرق الأوسط التنفسي التاجي (MERS-COV) هو فيروس الجهاز التنفسي الناشئ حديثاً مع ارتفاع معدل إماتة الحالات. ويعتقد أن الفيروس يتسبب في مرض شديد في المرضى الذين يعانون من أمراض أخرى متزامنة. أن تحديد المرضى الذين يعانون من أعراض خفيفة بين أفراد الأسرة والعاملين في الرعاية الصحية تشير إلى الطيف الأوسع للمظاهر السريرية للمرض. غالبية المرضى يعانون من حمى (98%)، والحمى مع السعال (83%)، وضيق في التنفس (72%). مجموعة مظاهر التصوير الشعاعي أبرزت إصابة فص رئوى واحد (43%)، علامات زيادة الشعبة الهوائية والأوعية الدموية (17%)، والنمط الشبكي العقيدي (4%). أن فهمنا لعلم الأوبئة والسريرية لهذا المرض آخذ في الإزدياد مع الوقت. لا يزال لايعرف ماهو مصدر الفيروس وما ينبغي أن يكون أفضل طريقة العلاج لهذا المرض.

Middle East respiratory syndrome coronavirus (MERS-CoV) is a newly emerging respiratory virus with a high case fatality rate among identified cases. The virus is thought to cause a severe disease in patients with underlying comorbidities. The identification of asymptomatic patients and mild cases among family and healthcare worker contacts of confirmed cases indicates a wider spectrum of clinical manifestation of the disease. The majority of patients presented with fever (98%), fever with cough (83%), and shortness of breath (72%). Radiographic manifestations range from unilateral infiltrate (43%), to increased bronchovascular markings (17%), and diffuse reticulonodular pattern (4%). Our understanding of the epidemiology and clinical presentation of the disease is increasing overtime. It is still not known what the source of the virus is and what the best treatment modality should be.

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Since mid-2012, a novel coronavirus was found to cause severe disease in humans. The virus was recently named Middle East Respiratory Syndrome coronavirus (MERS-CoV).[1] This virus was initially identified in September 2012 from samples obtained from a Saudi Arabian patient who developed a severe acute respiratory infection and later had acute renal failure and he died.[2] The virus was subsequently reported as a cause of pneumonia in additional cases from Saudi Arabia,[2-6] Qatar,[7] Jordan,[8,9] United Kingdom,[10,11] Germany,[12] France,[13] Tunisia,[14] United Arab Emirates,[15] and Italy.[16,17] In this article, we review the current situation and updates regarding the epidemiology and clinical situation based on literature review.

Current situation and review of cases. The initial cases from Saudi Arabia occurred before the recent Al-Hasa outbreak in April-May 2013. In April to May 2013, there were 27 cases and the majority of those cases were linked to different healthcare facilities in Al-Hasa, the eastern province of the Kingdom of Saudi Arabia (KSA).[3] The majority of these cases occurred in patients with underlying comorbidities. As of September 19, 2013, globally, the World Health Organization (WHO) recorded 132 laboratory-confirmed cases of infection with MERS-CoV, including 58 deaths.[18] Although the disease was thought to be restricted to adults, a total of 7 pediatric cases have been reported globally thus far.

Clinical presentation and laboratory data. Two recent publications shed light on the overall clinical presentations.[3,4] The majority of patients presented with fever (98%), fever with chills/rigors (87%), cough (83%), shortness of breath (72%), and dry cough (56%). The frequency of these and other symptoms

are shown in **Table 1**, of note that 21% of patients had diarrhea and 21% had vomiting. Radiographic manifestations range from unilateral infiltrate (43%), to increased bronchovascular markings (17%), bilateral infiltrate (22%), and diffuse reticulonodular pattern (4%).[3] Middle East Respiratory Syndrome coronavirus infection is associated with a high case fatality rate with more than 50% death among diagnosed patients. Case-fatality rates seem to be higher with increasing age, 39% in patients <50 years, to 75% in cases >60 years (**Table 2**).[4] However, this difference did not reach statistical difference. More recently asymptomatic and mild cases have been documented among family and healthcare worker contacts of confirmed cases.[19] These cases demonstrate that a wider spectrum of clinical manifestations may be observed with MERS-CoV infection and may affect the currently observed mortality rate favorably.

Table 1 - Symptoms of Middle East respiratory syndrome in Saudi cases at presentation (N=47).

Symptoms	n	(%)
Fever	46	(98.0)
Fever with chills/rigors	41	(87.0)
Respiratory symptoms		
Cough	39	(83.0)
Dry	22	(56.0)
Productive (sputum)	17	(44.0)
Hemoptysis	8	(17.0)
Shortness of breath	34	(72.0)
Chest pain	7	(15.0)
Sore throat	10	(21.0)
Runny nose	2	(4.0)
Gastro-intestinal symptoms		
Abdominal pain	8	(17.0)
Nausea	10	(21.0)
Vomiting	10	(21.0)
Diarrhea	12	(26.0)
Other symptoms		
Myalgia	15	(32.0)
Headache	6	(13.0)

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Discussion. Middle East Respiratory Syndrome coronavirus infection is characterized by a spectrum of illness ranging from mild to an acute and fulminant disease.[7-12] The current case-fatality rate is 58%. The median age of affected individuals is 56 years (range: 2-94 years), with a male-to-female ratio of 2.6-1. The best specimen for testing is a lower respiratory tract specimen as nasopharyngeal swabs were negative in a few instances.[20]

It is strongly advised that lower respiratory specimens such as sputum, endotracheal aspirate, or bronchoalveolar lavage should be used when possible until more information is available. If patients do not have signs or symptoms of lower respiratory tract infection and lower tract specimens are not possible or clinically indicated, both nasopharyngeal and oropharyngeal specimens should be collected.[21] The 2 can be combined in a single collection container and tested together. If initial testing of a nasopharyngeal swab is negative in a patient who is strongly suspected to have MERS-CoV infection, patients should be retested using a lower respiratory specimen or a repeat nasopharyngeal specimen with additional oropharyngeal specimen if lower respiratory specimens are not possible.[21] For patients in whom adequate lower respiratory samples are not possible, clinicians may also want to consider other types of auxiliary testing such as nasopharyngeal wash. Virus has also been demonstrated in other body fluids such as blood, urine, and stool but the usefulness of

Table 2 - Mortality rates of 47 Middle East respiratory syndrome coronavirus infection cases by age and gender.

Age range (years)	Female		Male		Total	
	Total	Dead	Total	Dead	Total	Dead
	1	1	1	0		
10-19					**2**	**0**
20-29	0	1	0	1	**1**	**1**
30-39	0	5	3	2	**5**	**2**
40-49	1	9	5	4	**10**	**4**
50-59	2	7	2	5	**9**	**6**
60-69	5	6	2	4	**11**	**8**
70-79	1	4	0	4	**5**	**4**
80-89	1	2	1	1	**3**	**2**
90-99	0	1	0	1	**1**	**1**
Total	11*	36*	14	22	**47**	**28**
Percentage	45%	55%	39%	61%	**40%**	**60%**

*Male to female ratio 3.3:1

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those body fluids in diagnosing MERS-CoV infection is uncertain. The best clinical specimen for the diagnosis of MERS-CoV using real time reverse-transcriptase PCR is a lower respiratory specimen (sputum, endotracheal aspirate, or bronchoalveolar lavage), in the absence of lower respiratory tract infection.

Recently, a group of scientists identified dipeptidyl peptidase 4 (DPP4) as a functional receptor for MERS-CoV. This receptor is mainly found on non-ciliated bronchial cells in the lower respiratory tract.[22] Lower respiratory tract specimens may be better for the diagnosis of MERS-CoV infection.

From the available data and as was announced by a joint mission of KSA and the WHO, there are 3 main epidemiological patterns.[23] The first pattern is the occurrence of sporadic cases in communities. The source or how these people became infected is not known at the present time. In the second pattern is intra-familial infection. This is likely related to person-to-person transmission limited to close contacts with a sick family member. The third pattern contains clusters of healthcare transmission. Such events were reported in France, Jordan, and KSA. The transmission of SARS to healthcare workers was a predominant feature of the infection. The first indication that MERS-CoV could be transmitted in health care setting was observed in Jordan in April 2012.[24] Subsequently, on 15 May 2013, the Ministry of Health in Saudi Arabia announced that 2 patients are health care workers who were exposed to patients with confirmed MERS-CoV.[24]

Although the exact mode of transmission is not known, the occurrence of 8 clusters in France, Italy, Jordan, Saudi Arabia, Tunisia, and the UK pointed out the occurrence of human-to-human transmission among healthcare workers,[25] patient-to-patient nosocomial transmission in France,[20] and in family clusters.[19,26] A clear evidence of person-to-person transmission was supported by epidemiological and phylogenetic analysis.[3] This transmission could be through respiratory droplets, direct or indirect contact.[3] Health care workers are advised to follow the recommended infection control measures. These measures include: standard precaution and additional precautions of droplet isolation should be observed when caring for patients with suspected or confirmed MERS-CoV. Health care workers and visitors should wear a medical mask when in close contact (namely, within approximately 1 m) and upon entering the room or cubicle of the patient.[27] For aerosol generating procedures such as intubation additional airborne infection isolation procedures should be followed. Moreover, because 22% of patients had diarrhea and 17% had vomiting,[3] the addition of contact precautions is highly recommended.[4] The virus is found in low concentrations in stool, despite diarrheal/GI symptoms.

The CDC recommends that patients under investigation and probable and confirmed cases be managed in health-care facilities using standard, contact, and airborne precautions.[28] Currently, the best option for therapy of MERS-CoV is not well established. A recent review shed light on the possible therapeutic options for MERS-CoV.[29] Convalescent plasma, ribavirin and interferon are possible interventions with various level of evidence.[29] The suggested Ribavirin oral dosage is 2000 mg loading dose then 1200mg q8h for 4 days, then 600mg po q8h for 4-6 days with pegelated interferon 1.5mcg/kg once per week.[30] More recently, antibodies to MERS-CoV or a related virus were identified in dromedary camels in countries where the disease had not been identified in humans yet.[30] It is important to isolate the MERS-CoV virus from animals and show that the virus is similar to the human virus.

In conclusion, MERS-CoV is a newly emerging virus with an international interest. The epidemiology and clinical features of the disease are being elucidated. It remains to identify the source of infection and the intermediate hosts.

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