Middle East Respiratory Syndrome: Knowledge to Date*

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Objective: To provide a conceptual and clinical review of Middle East respiratory syndrome.

Data Sources: Peer-reviewed articles were identified through searches of PubMed using the terms "Middle East respiratory syndrome," "coronavirus respiratory illness in Saudi Arabia," and "novel (beta) coronavirus and human coronavirus Erasmus Medical Center". In addition, articles were searched on the websites of the World Health Organization and the U.S. Centers for Disease Control and Prevention using the terms "Middle East respiratory syndrome" and "novel coronavirus in Middle East." The reference lists of these articles and relevant review articles were also reviewed.

Study Selection and Data Extraction: Final references were selected for inclusion in the review on the basis of their relevance.

Data Synthesis: The emerging Middle East respiratory syndrome coronavirus causes severe pulmonary disease with multiorgan involvement and a high fatality rate. Within months after its emergence, Middle East respiratory syndrome coronavirus was reported in several countries worldwide in people who had traveled from the Middle East. Middle East respiratory syndrome coronavirus is considered a zoonotic virus that has crossed the species barrier to humans, but the pathogenesis and the routes of transmission are not completely understood. There is currently no recommended treatment for Middle East respiratory syndrome coronavirus, although supportive treatment has played an important role.

Conclusions: This syndrome has raised global public health concerns about the dissemination of an emerging infectious disease and highlights the need for a coordinated global response to contain such a disease threat. (*Crit Care Med* 2015; 43:1283–1290)

Key Words: communicable diseases; coronavirus; pneumonia; Saudi Arabia; severe acute respiratory syndrome; viral RNA

***See also p. 1344.**

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An outbreak of a respiratory illness in ICUs was reported in Jordan on April 19, 2012. Eight healthcare workers were among the 11 people affected. The cause was unknown at that time (1). Then, on June 13, 2012, a patient in Saudi Arabia presented with pneumonia that progressed to acute respiratory distress syndrome and renal failure that led to death. A novel coronavirus (human coronavirus EMC, hCoV-EMC) was isolated from the patient and identified as the possible causative agent (2). In September 2012, a case was reported concerning a patient who was transferred to the United Kingdom from Qatar. He had a history of traveling to Saudi Arabia and was infected with hCoV-EMC. The disease was renamed Middle East respiratory syndrome (MERS) by international consensus (3). The disease spread to more than 20 countries in Europe, Asia, North Africa, and North America, and most patients were reported to have links to the Arabian Peninsula.

The objective of this article is to summarize the literature that has described the etiology, epidemiology, pathophysiology, clinical presentation, diagnostic evaluation, and treatments related to this disease and to provide clinicians with updated knowledge about MERS.

METHODS

References to published articles for this review were identified through searches of PubMed by using the terms "Middle East Respiratory Syndrome (MERS)," "coronavirus respiratory illness in Saudi Arabia," and "novel (beta) coronavirus (nCoV) and human coronavirus EMC (HCoV-EMC)." Relevant published articles were identified through searches on the websites of the World Health Organization (WHO; http://www.who.org) and the U.S. Centers for Disease Control and Prevention (CDC; http://www.cdc.gov) for documents containing the terms "Middle East Respiratory Syndrome (MERS)" or "novel coronavirus in Middle East." In addition, the reference lists of these articles were also reviewed, as were relevant review articles.

Etiology

Coronaviruses are a family of large, enveloped, positive-sense, single-stranded RNA viruses with high mutation rates. They are associated with respiratory, enteric, and neurological diseases in humans and animals. Their clinical severities vary on the basis of genotypic characteristics. One human coronavirus

with a high fatality rate is severe acute respiratory syndrome (SARS) coronavirus, which causes SARS (4).

Four other human coronaviruses are HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. These agents are associated with mild, self-limiting upper respiratory tract infections and only occasionally cause lower respiratory tract infections, particularly in elderly and immunocompromised persons (5, 6). A case definition was established for MERS, the newly identified coronaviral disease (3, 7). The complete genetic sequence of the MERS coronavirus (MERS-CoV) genome has been determined, and the virus is categorized as a betacoronavirus, placing it in the same genus as the coronavirus that causes SARS (8).

The presence of MERS-CoV has been confirmed by reverse-transcriptase polymerase chain reaction (RT-PCR). The virus has primarily been detected by using respiratory secretion samples, and the highest viral loads have been found in samples from the lower respiratory tract (9). In addition, the virus has been isolated at low concentrations from fecal, urine, and blood samples, indicating that the infection may not be limited to the respiratory tract (10).

Pathogenesis

While the pathogenesis of MERS-CoV is not completely understood because of a lack of autopsies of MERS-CoV patients, animal models have shown that MERS-CoV can cause pathological changes in the lungs, suggesting a capacity to produce a pneumonia that is similar to MERS in humans (11).

In ex vivo models, MERS-CoV can infect and replicate in type I and II alveolar cells (12). Virus entry occurs via dipeptidyl peptidase 4, which is expressed in human lungs and in many cell types (12). Histological changes include the detachment of MERS-CoV-infected type II cells from the alveolar base membrane; the disruption of the alveolar tight junctions leads to alveolar damage, and the chromatin condensation, nuclear fragmentation, and membrane blebbing of infected type II cells (nuclear and cytoplasmic border changes) are evidence of apoptosis (12).

The mixture of high viral replication and immune-mediated pathology is another important factor in the pathogenesis of MERS. In addition, the lymphopenia that develops along with MERS is attributed to immune cell recruitment and sequestration in the lower respiratory tract, which can cause severe inflammation and tissue damage (13). Systemic virus dissemination in MERS may explain why the virus affects multiple systems in addition to the respiratory tract epithelium (9, 13). This dissemination hypothesis is supported by the fact that MERS-CoV has been grown in an in vitro renal cell culture model (14).

Epidemiology

The seroepidemiological data suggest that MERS originally appeared in animals; it was circulating in dromedaries in the Arabian Peninsula as early as 1993 (15). Thus, MERS-CoV is considered a zoonotic virus that crossed the species barrier to humans. This conclusion is supported by the report of a fatal case of a human MERS-CoV infection that was transmitted through close contact with an infected camel (16). Other animals, such as goats, cows, sheep, water buffalo, swine, and wild birds, were tested negative for antibodies to MERS-CoV. The virus was, however, detected in fecal samples from the *Taphozous perforatus* bat, notably showing 100% nucleotide identity with a MERS-CoV isolate from the index patient (17, 18). The virus was also detected in the South African *Neoromicia capensis* bat; 85% of the coronavirus (NeoCoV) genome from this species was identical to MERS-CoV at the nucleotide level (19).

The presence of cluster cases and secondary transmission from human to human has also been confirmed in both healthcare and household settings. This finding strongly suggests that human-to-human transmission occurs, a hypothesis that was further supported by the full-genome deep sequencing of 21 MERS cases (20). Most children with MERS-CoV infections have been asymptomatic secondary cases, but severe disease can occur in children with underlying conditions (21). The basic reproduction number (R_0) was estimated to be 0.69 (95% CI, 0.50–0.92). Other reported estimated R_0 values were 0.74 (95% CI, 0.53–1.03) before June 1, 2013, and 0.32 (95% CI, 0.14–0.65) after that date (22, 23).These changes can be explained by the faster detection of cases and the introduction of control measures. The finding of an R_0 less than 1 suggests that MERS-CoV does not yet have pandemic potential and can be contained once control measures are in place.

The estimated incubation period for MERS-CoV is 5.2 days; however, periods from 9 to 12 days have also been reported, and the maximum reported incubation period is 14 days (10, 24). The WHO and the CDC recommend a MERS evaluation if a patient has visited the Arabian Peninsula within the previous 14 days. It has been reported that the virus can be detected with RT-PCR several weeks after the onset of illness, but such detection may not necessarily mean the virus is contagious (25, 26). The secondary attack rate and intrafamilial rate of transmission were reported to be 1.3% and 3.6%, respectively (27).

The routes of direct and indirect transmission from camels to humans or from humans to humans have not yet been determined. The presence of high viral loads in the nasal passages of infected camels suggests the probability of transmission via a nasal route to humans through close contact. Additionally, MERS-CoV RNA fragments detected in an air sample from an infected camel barn indicate the possibility of droplet or aerosol transmission between an infected camel and a human (28, 29). Other routes of transmission, such as foodborne transmission, are unknown but may be important; one report noted that MERS-CoV RNA was detected in the milk of infected camels that were actively shedding the virus (30, 31).

The presence of high viral loads in samples from the lower respiratory tracts of infected patients indicates that MERS-CoV is predominantly shed during coughing and via exudates from the lower respiratory tract (9, 32). Fecal-oral transmission is unknown, although diarrhea is a common feature of the disease, and MERS-CoV is shed in the stool in low concentrations (10). To date, there have been no reports of vertical or perinatal MERS-CoV transmission. The role of seasonality in

the transmission of MERS is unknown, but it is notable that the number of cases peaked in March, April, and May. This prevalence may correspond to a seasonal factor related to the population's exposure to camels. A high viral load has been reported among young camels, and it is noteworthy that the peak months for MERS cases correspond to the end of the camel calving season in Saudi Arabia (33, 34).

In addition, studies have shown that MERS-CoV is stable in aerosol form at 20°C and 40% relative humidity; thus, MERS-CoV can remain viable in an airborne state, but viability rapidly decreases at high temperatures and in high humidity (31, 35). These findings support the hypothesis that MERS-CoV is transmitted via aerosol transmission and that direct contact transmission, rather than fomite transmission, is the most likely route for zoonotic and human-to-human transmission in outdoor settings (31, 35).

Clinical Presentation

MERS can affect people of all ages. Its clinical presentation ranges from asymptomatic infection to rapidly progressive multiple organ failure and death. Of the 146 patients with clinical descriptions of MERS reported in the literature, 71% had a fever, 68% had cough, 66% had dyspnea, and 32% had gastrointestinal symptoms (**Table 1**) (24, 25, 36–38). Other reported clinical manifestations included CNS symptoms, such as headache, confusion, and weakness (25, 38). It appears that the patients at highest risk for critical complications are men; are over 60 years; have comorbidities such as diabetes mellitus, hypertension, asthma, ischemic heart disease, compromised immune systems, or end-stage kidney disease; and require hemodialysis (36, 37). A presentation with fever and diarrhea but without respiratory symptoms has also been reported in an immunocompromised patient (39).

Lymphocytopenia and thrombocytopenia are commonly associated with MERS, with concomitant increases in the levels of alanine transaminase, aspartate transaminase, and lactate dehydrogenase enzymes (25, 37). However, these blood abnormalities are nonspecific.

Initial chest radiographs were abnormal in 86–100% of infected patients; the main characteristics were airspace diseases ranging from unilateral infiltrate to bilateral infiltrate, consistent with acute respiratory distress syndrome patterns (24, 37). In addition, in a cohort study of seven MERS cases, the CT findings showed that bilateral airspace opacity changes were more common than interstitial changes and appeared predominantly in the subpleural and basilar lung regions. No mediastinal lymph node enlargement or cavitations were noted (40).

Diagnosis

The case definition developed by the WHO (**Table 2**) has been refined over time, and the diagnosis of MERS has relied on a combination of clinical and epidemiological factors and the detection of the virus in upper respiratory and lower respiratory samples by using real-time RT-PCR assay (41). This detection is performed by targeting regions upstream of the E gene (upE) or within open reading frame (ORF)1b, using upE for screening and ORF1b for confirmation (42). Another real-time RT-PCR assay targeting the MERS-CoV nucleocapsid protein gene was developed and can be used for screening and confirmation (43). When there are discordant results between two real-time RT-PCR assays, the sequencing of an amplicon generated from an appropriate RT-PCR assay should be performed to confirm the test results (44). Lower respiratory tract specimens have been found to be more sensitive than upper respiratory tract specimens for the detection of MERS-CoV (32). In addition, the development of a rapid diagnostic kit is important for the timely diagnosis of suspected MERS-CoV cases (45). Serological testing for MERS-CoV has been developed to detect antibodies, and it can be used to screen the contacts of infected patients and to retrospectively confirm MERS-CoV infections (46). Finally, the WHO and the CDC have compiled additional information about diagnostic testing that is available online.

Prognosis

As of January 12, 2015, a total of 950 patients with laboratory-confirmed MERS-CoV infections had been reported to the WHO, with an average case-fatality ratio of 35% (41). In one epidemiological analysis, the case-fatality ratio for primary cases was 74% (95% CI, 49–91), whereas for secondary cases, it was 20% (95% CI, 7–42) (22). In fact, the high case-fatality ratio is overestimated and biased upward because of detection bias. Age and comorbidities, such as diabetes mellitus, hypertension, asthma, ischemic heart disease, immunocompromised systems, and end-stage kidney disease with hemodialysis use, were associated with a poor prognosis (36, 37). Among the patients whose illness progressed, the median time from the onset of symptoms to ICU admission was 5 days (range, 1–10), the median time before requiring mechanical ventilation was 7 days (range, 3–11), the median ICU stay was 30 days (range, 7–104 d), and the median time to death was 11 days (range, 5–27) (25, 37).

Management

There is currently no recommended treatment for MERS-CoV, although supportive treatment has played an important role. However, a number of pharmacological agents that were used during the SARS epidemic of 2003 might prove helpful. Ribavirin, lopinavir, interferon (INF), mycophenolic acid, and convalescent plasma may be considered for the treatment of MERS-CoV patients.

Convalescent plasma is a type of passive immunotherapy. It is considered the immunotherapy method most likely to be beneficial in the treatment of MERS (47). Several case reports have described the survival benefits of convalescent plasma therapy during the SARS and H1N1 epidemics (48). Plasma is typically obtained from patients who recovered from MERS and is used to produce high antibody titers against MERS-CoV. A clinical trial to study the efficacy of convalescent plasma in patients with MERS-CoV is in progress (49).

Ribavirin is a broad-spectrum antiviral that works as a purine nucleoside analog to inhibit guanosine triphosphate synthesis and viral RNA polymerase activity. In SARS, ribavirin treatment resulted in symptom improvement in 71.4–80% of

TABLE 1. The Demographic, Comorbidity, and Clinical Characteristics of Patients With Confirmed Middle East Respiratory Syndrome Coronavirus Infection

Variable	Saad et al (38)	Al-Tawfiq et al (65)	Arabi et al (25)	Assiri et al (37)
No. of cases	70	17	12	47
Period	October 1, 2012, to May 31, 2014	April 1, 2013, to June 3, 2013	May 26, 2013, to October 31, 2013	September 1, 2012, to June 15, 2013
Demographics				
Male sex, *n* (%)	46 (65.7)	11 (65)	8 (67)	36 (77)
Age, yr, median (range)	62 (1–90)	62 (14–87)	59 (36–83)	56 (14–94)
Body mass index, mean (SD)	Not reported	32.02 (6.78)	31.8 (21.6–46.1)[a]	Not reported
Comorbidities				
Diabetes, *n* (%)	Not reported	13 (76)	8 (67)	32 (68)
Cardiac disease (any), *n* (%)	Not reported	11 (65)	7 (58)	13 (28)
Pulmonary disease (any), *n* (%)	Not reported	10 (59)	1 (8)	12 (26)
Renal insufficiency, *n* (%)	Not reported	Not reported	5 (42)	23 (49)
End-stage renal disease (on dialysis), *n* (%)	Not reported	5 (29)	1 (8)	Not reported
Malignant disease, *n* (%)	Not reported	1 (6)	1 (8)	1 (2)
Hypertension, *n* (%)	Not reported	Not reported	6 (50)	16 (34)
Presenting symptoms				
Onset to admission, d, median (range)	5.0 (3.0–8.5)	3 (0–45)	1 (0–33)	Not reported
Fever, *n* (%)	43 (61.4)	6 (35)	8 (67)	46 (98)
Dyspnea, *n* (%)	42 (60)	10 (59)	11 (92)	34 (72)
Chest pain, *n* (%)	Not reported	1 (6)	Not reported	7 (15)
Cough, *n* (%)	38 (54.3)	12 (71)	10 (83)	39 (83)
Hemoptysis, *n* (%)	6 (8.6)	1 (6)	1 (8)	8 (17)
Sore throat, *n* (%)	Not reported	1 (6)	1 (8)	10 (21)
Headache, *n* (%)	9 (12.9)	1 (6)	2 (17)	6 (13)
Myalgia, *n* (%)	14 (20)	1 (6)	3 (25)	15 (23)
Vomiting, *n* (%)	21 (30)[b]	1 (6)	Not reported	10 (21)
Diarrhea, *n* (%)	21 (30)[b]	1 (6)	2 (17)	12 (26)
Weakness, *n* (%)	Not reported	Not reported	2 (17)	Not reported
Abdominal pain, *n* (%)	17 (24.3)	Not reported	Not reported	8 (17)
Rhinorrhea, *n* (%)	Not reported	Not reported	1 (8)	2 (4)
Laboratory findings				
Leukopenia ($< 4.0 \times 10^9$ cells/L), *n* (%)	Not reported	Not reported	Not reported	7 (14)
Neutropenia (absolute neutrophil count $< 0.5 \times 10^9$ cells/L), *n* (%)	27 (36)	Not reported	Not reported	Not reported
Lymphopenia ($< 1.5 \times 10^9$ cells/L), *n* (%)	36 (51)	6 (35)	9 (75)	16 (34)
Thrombocytopenia ($< 140 \times 10^9$ cells/L), *n* (%)	Not reported	Not reported	2 (17)	17 (36)
Elevated alanine aminotransferase, *n* (%)	5 (7)	3 (18)	2 (17)	5 (11)
Elevated aspartate aminotransferase, *n* (%)	Not reported	9 (53)	6 (50)	7 (15)
Elevated lactate dehydrogenase, *n* (%)	Not reported	8 (47)	Not reported	23 (49)

[a]Reported as range.
[b]Reported as vomiting or diarrhea.

TABLE 2. World Health Organization and Centers for Disease Control and Prevention Case Definitions for Middle East Respiratory Syndrome Coronavirus

World Health Organization Case Definition as of July 3, 2013	Centers for Disease Control and Prevention Case Definition
Probable case Three combinations of clinical, epidemiological, and laboratory criteria can define a probable case: A. A person with a febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease AND Testing for MERS-CoV is unavailable or negative for a single inadequate specimen AND The patient has a direct epidemiologic link with a confirmed MERS-CoV case B. A person with a febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease AND An inconclusive MERS-CoV laboratory test (i.e., a positive screening test without confirmation) AND A resident of or traveler to Middle Eastern countries where MERS-CoV virus is believed to be circulating in the 14 d before the onset of the illness C. A person with an acute febrile respiratory illness of any severity AND An inconclusive MERS-CoV laboratory test (i.e., a positive screening test without confirmation) AND The patient has a direct epidemiologic link with a confirmed MERS-CoV case	Patient under investigation A person with the following characteristics should be considered a patient under investigation: A. Fever AND pneumonia or acute respiratory distress syndrome (based on clinical or radiological evidence) AND EITHER: A history of travel from countries in or near the Arabian Peninsula within 14 d before symptom onset, OR Close contact with a symptomatic traveler who developed fever and acute respiratory illness (not necessarily pneumonia) within 14 d after traveling from countries in or near the Arabian Peninsula, OR A member of a cluster of patients with severe acute respiratory illness of unknown etiology in which MERS-CoV is being evaluated, in consultation with state and local health departments OR B. Fever AND symptoms of respiratory illness (not necessarily pneumonia; e.g., cough, shortness of breath) AND having been in a healthcare facility within 14 d before symptom onset in a country or territory in or near the Arabian Peninsula in which recent health care-associated cases of MERS have been identified Probable case A probable case is a patient under investigation with absent or inconclusive laboratory results for MERS-CoV infection who is a close contact of a laboratory-confirmed MERS-CoV case Confirmed case A confirmed case is a person with laboratory confirmation of MERS-CoV infection. Confirmatory laboratory testing requires a positive polymerase chain reaction for at least two specific genomic targets or a single positive target with sequencing on a second
Confirmed case A person with laboratory confirmation of MERS-CoV infection	

MERS-CoV = Middle East respiratory syndrome coronavirus.

patients, but its mortality benefits were inconsistent, with rates of between 5% and 42.8%. Ribavirin treatment also resulted in a significant prevalence of adverse events, especially hemolysis, which was reported in 68.5% of patients (50). In vitro, ribavirin showed a reduction in MERS-CoV replication, but the concentrations required to achieve beneficial effects were higher than what is achievable in humans. Therefore, the risk is likely to exceed the possible benefit when ribavirin is used as a monotherapy (51).

INFs are pleiotropic cytokines with antiviral activity that interferes with viral replication. A variety of INF products are used as antiviral agents in the clinical setting. In vitro, INF-α and INF-β have been shown to have an inhibitory effect on MERS-CoV replication, with INF-β showing greater biological activity against MERS-CoV infection compared with INF-α (51, 52).

In addition, rhesus macaque models showed that a combination of INF-α2b and ribavirin improved clinical outcomes and reduced the severity of the illness. This combination showed the greatest benefit when it was used as an early intervention therapy (53). A retrospective cohort study of 20 patients who received ribavirin and INF found a significant 14-day survival benefit in this group compared with a standard treatment group of 24 patients who did not receive these agents,

TABLE 3. Summary of Ribavirin and Interferon Therapy in the Treatment of Patients With Middle East Respiratory Syndrome

Type of Study and No. of Patients	Medication	Dosage Regimen	Adverse Events Reported	Outcome
Al-Tawfiq et al (55) Observational study Five patients received ribavirin and interferon α-2a	Ribavirin	Loading dose: 2 g via enteral route Followed by 400 mg enteral route every 8 hr for 5 d	Increase lipase: two cases Thrombocytopenia: one case	Inconclusive Died: five cases
	Interferon α-2b	100–144 μg/wk, subcutaneous injection for 1–2 wk	Hemolysis: one case	
Omrani et al (2014) (54) Retrospective cohort study 20 patients received ribavirin and interferon α-2a 24 patients in comparator group	Ribavirin	Creatinine clearance > 0.833 mL/s/m^2 Loading dose: 2,000 mg via enteral route Followed by 1,200 mg every 8 hr for 4 d, then 600 mg every 8 hr for 4–6 d Creatinine clearance: 0.333–0.833 mL/s/m^2 Loading dose: 2,000 mg via enteral route Followed by 600 mg every 8 hr for 4 d, then 200 mg every 6 hr for 4–6 d Creatinine clearance < 0.333 mL/s/m^2 or on dialysis Loading dose: 2,000 mg via enteral route Followed by 200 mg every 12 hr for 4 d, then 200 mg every 12 hr for 4–6 d	Hemolysis: significant drop in hemoglobin in the treatment group	14-d survival 14 of 20 patients (70%) in the treatment Seven of 24 patients (29%) in the comparator group ($p = 0.004$) 28-d survival Six of 20 patients (30%) in the treatment Four of 24 patients (17%) in the comparator group ($p = 0.054$)
	Interferon α-2a	180 μg/wk, subcutaneous injection for 2 wk		

but there was no survival benefit at 28 days (54) (**Table 3**). In another report, a clinical observation study of five critically ill MERS-CoV patients who received combination therapy with INF-α2b and ribavirin late in their course of treatment showed that it had no effect on mortality (55).

Mycophenolic acid has broad antiviral activity, but its mechanism of action is not clearly understood. It may have both direct and indirect antiviral activity through the modulation of INF response activities, and it has been shown to have a solitary or synergistic effect with INF on MERS-CoV replication in vitro (52).

Newly identified human monoclonal antibodies targeting the receptor-binding domain of MERS-CoV are promising discoveries for the development of a vaccine and for the treatment of MERS-CoV infections in humans (56). In addition, other potential therapies, such as chloroquine, chlorpromazine, loperamide, and lopinavir, have had an inhibitory effect on MERS-CoV replication in vitro, but there are no controlled studies documenting the efficacy of these therapies in humans (57, 58).

Infection Control

In the absence of a vaccine or of specific treatments, preventing the transmission of the virus is an important component of dealing with MERS-CoV. Thus, management entails early case detection, the isolation of MERS patients, and the application of infection control measures. In addition to standard precautions, three infection control transmission precautions are used: contact precautions, droplet precautions, and airborne precautions. Contact precautions are required when patients are known or suspected to have illnesses that are easily transmitted by direct patient contact or by contact with items in the patient's environment; thus, the stability of MERS-CoV in aerosol form and the presence of diarrhea in infected patients mandate the requirement of contact precaution measures (35, 38, 59). Droplet precautions are required when patients are known or suspected to have illnesses transmitted by large-particle droplets (droplet particle > 5 μm in diameter), and airborne precautions are required when patients are known or suspected to have illnesses transmitted by airborne droplet particles (droplet particle < 5 μm in diameter) (59). In fact, there is no consensus on the precaution

recommendations for MERS-CoV. The CDC recommends contact precautions and airborne precautions for hospitalized patients with confirmed or suspected MERS-CoV infection for all patient care activities (60). This recommendation stems from the high fatality rate among infected patients (61). The WHO, on the other hand, advocates the use of droplet precautions and contact precautions when caring for confirmed or suspected MERS-CoV infection and the use of airborne precautions when aerosol-generating procedures are required. These recommendations arise from the fact that MERS is transmitted by large respiratory droplets (≥ 10 μm in diameter) (62). Although no information is available on the duration of infection control precautions, it is recommended that they be maintained for at least 48 hours after symptoms have resolved; nonetheless, the applicability of such an approach is difficult in the ICU setting (63). Further information on prevention and preparedness measures in hospital and home care settings is available on the WHO and the CDC websites. Finally, public education about the risks of infection is vital to maintain the correct balance between public awareness and panic (64).

CONCLUSIONS

More than 2 years following the detection of the first MERS-CoV infection in humans, MERS continues to be a major international concern because of its high fatality rate and the gaps in our knowledge about the disease. Despite extensive work toward understanding its pathogenesis, host susceptibility factors, viral virulence, viral kinetics, periods of infectiousness, underlying mechanisms of protective immunity, and optimal treatments, many unanswered questions remain. The reason for the long persistence of the virus in human populations despite its low reproduction number (R_0) remains unknown. However, sustained human-to-human transmission appears to have not yet occurred.

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