Middle East respiratory syndrome (MERS)

The right clinical information, right where it's needed
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Definition

Middle East respiratory syndrome (MERS) is an acute viral respiratory tract infection caused by the novel betacoronavirus Middle East respiratory syndrome coronavirus (MERS-CoV). It was first identified in Saudi Arabia in 2012. Cases have been limited to the Arabian Peninsula and its surrounding countries, and to travellers from the Middle East or their contacts. The clinical spectrum of infection varies from no symptoms or mild respiratory symptoms to severe, rapidly progressive pneumonia, acute respiratory distress syndrome, septic shock, or multi-organ failure resulting in death.

[World Health Organization (WHO): Middle East respiratory syndrome coronavirus (MERS-CoV)]
[Centers for Disease Control and Prevention (CDC): Middle East respiratory syndrome (MERS)]

Epidemiology

The first case of MERS was reported in a 60-year-old man in Jeddah, Saudi Arabia in 2012.[14] The patient died from severe pneumonia and multi-organ failure. Since then, many cases and clusters have been reported with the majority of infections acquired in the Arabian Peninsula and its surrounding countries, most commonly Saudi Arabia, the United Arab Emirates (UAE), Oman, Qatar, and Jordan.

Cases associated with travel from these countries have been limited to small clusters of a few individuals,[15][16][17][18] except for one large outbreak of 186 reported cases in the Republic of Korea (South Korea) in 2015,[19][20][21] and one superspreader event in Riyadh (Saudi Arabia) in 2017 where 44 cases were linked to one patient who presented with acute renal failure.[11] Two cases were reported in the US in 2014, both in travellers from Saudi Arabia.[22] There have been no cases reported in the US since. Five laboratory-confirmed cases have been reported in the UK since 2012, with the latest reported in August 2018.[23] Other countries with travel-associated cases include France, Italy, Greece, Turkey, Lebanon, Germany, Austria, Netherlands, China, Malaysia, Thailand, Philippines, and Egypt. A case was reported in the Republic of Korea in September 2018 in a Korean national who visited Kuwait and returned to Korea via Dubai. Twenty-one contacts are currently under active surveillance.[24]

As of the end of August 2018, 2248 laboratory-confirmed cases, including 798 deaths (35.5% case fatality rate), were reported globally since 2012 across 27 countries. The majority of these cases were reported from Saudi Arabia (1871 cases). The 50-59 years age group is at highest risk for acquiring primary infection.[25][26]

[World Health Organization (WHO): disease outbreak news]

Ninety-eight percent of cases have been reported in adults (defined as age >14 years).[8] Although infection has been reported in different age groups within the adult population, the median age of patients ranges from 50 to 67 years of age.[4][9][26] Age ≥50 years is associated with a higher risk of mortality.[5][27] In one cohort study, mortality increased with increasing age to reach 75% in patients >60 years of age.[8] The majority of cases occur in males.[25] Infection in children is rare, although the reason for this is unknown.[12][13]

The majority of cases are a result of human-to-human transmission rather than camel-to-human transmission, with peaks of confirmed cases occurring during nosocomial outbreaks.[6][7][28] Transmission has been well documented in family clusters.[18][29][30] However, it has been reported more commonly in nosocomial outbreaks (e.g., haemodialysis units, intensive care units, medical wards).[6][7][30][31][32][33][34]
Aetiology

Virology

• Infection is caused by the novel betacoronavirus Middle East respiratory syndrome coronavirus (MERS-CoV), an enveloped, positive-sense, single-stranded RNA virus with a genomic size of approximately 30,000 nucleotides.[35]
• The virus is a member of the Coronaviridae family (order: Nidovirales; subfamily: Coronavirinae; genus Betacoronavirus) and is part of the lineage C group.[14] [36] It is phylogenetically distinct from all previously known betacoronavirus species, which include human coronaviruses HKU1 and OC43, severe acute respiratory syndrome (SARS) coronavirus, and bat coronaviruses HKU4, HKU5, and HKU9.[37]
• MERS-CoV genomes are classified into 2 clades: clade A (the earliest clusters of infection, i.e., EMC/2012 and Jordan N3/2012) and clade B (new clusters which are genetically distinct from clade A).[38]

Animal hosts

• It is thought that dromedary camels are the primary animal host for MERS-CoV.[39]
• Antibodies to the virus have been found in the serum of these camels in the Arabian Peninsula and its surrounding countries in multiple studies, some dating back to the 1990s.[40] [41] [42] [43] [44] [45] [46] [47] [48] [49] [50] [51] [52] [53] [47] [54] [55] [56] The camels may show no sign of infection, but still excrete the virus in their nasal fluids, faeces, milk, or urine.
• Experimental MERS-CoV infection in camels resulted in mild upper respiratory infection and mild fever.[57]
• Bats are also thought to be an earlier reservoir of MERS-CoV; however, this is yet to be proven.[58]

Animal-to-human transmission

• The exact mode of transmission is unknown, but it is thought to occur from direct or indirect contact with dromedary camels (e.g., camel milking, contact with camel nasal secretions, urine, or faeces) or camel products (e.g., unpasteurised camel milk, raw or undercooked camel meat).
• Near-identical strains of the virus were isolated from epidemiologically linked dromedary camels and human cases in Saudi Arabia, Qatar, and the United Arab Emirates.[32] [59] [60] The strongest evidence for camel-to-human transmission comes from a study in Saudi Arabia where the virus was isolated from a patient and one of his camels and the genome was found to be almost identical.[61] [62] However, there are inconsistencies when it comes to camel-to-human transmission, and more data are required to gain a better understanding of how transmission occurs.[63]
• A case-control study identified contact with camels to be a risk factor for MERS-CoV infection.[64]

Human-to-human transmission

• The majority of cases are a result of human-to-human transmission (rather than camel-to-human transmission) with peaks of confirmed cases occurring during nosocomial outbreaks.[6] [7] [28] Despite this, human-to-human transmission is generally considered to be inefficient.
• Transmission is via respiratory droplets (e.g., coughing, sneezing) from an infected patient, or close contact with an infected patient. However, airborne or fomite transmission cannot be ruled out.[65]
incubation period is 2 to 14 days and transmission is thought to occur during either the symptomatic or incubation stages.[8] [66]

- Transmission has been well documented in family clusters.[18] [29] [30] However, it has been reported more commonly in nosocomial outbreaks (e.g., haemodialysis units, intensive care units, medical wards).[6] [7] [30] [31] [32] [33] This is likely to be due to factors which include late recognition of the infection, overcrowding of patients in hospitals, and inadequate infection control precautions.[6] [27] [29] [31] [67] Outbreaks are facilitated by extensive environmental contamination of the patients’ surroundings and the ability of the virus to survive for long periods on plastic and steel surfaces.[68] [69]
- With an effective reproductive number of less than one, the epidemic potential of the infection is considered low at present unless the virus mutates.[70] [71] [72] Outbreaks are more restricted compared with SARS. Super-spreader events have not been reported; however, future adaptations of the virus may potentially increase human-to-human transmission or virus virulence.

Pathophysiology

The pathogenesis is not completely understood. The virus is transmitted primarily via respiratory droplets from an infected person which enter the human body via the respiratory tract mucosa.[73] The virus binds to the functional receptor dipeptidyl peptidase-4 (DPP4; also called CD26) on the surface of host cells (e.g., type I and II alveolar cells, ciliated and non-ciliated bronchial epithelium, endothelium, alveolar macrophages, leukocytes). Binding is mediated by a receptor binding domain on the S1 subunit of the virus’ surface spike (S) proteins.[74] [75] Membrane fusion and cell entry is facilitated by the S2 unit through the actions of 2 heptad repeat domains (HR1 and HR2) and a fusion protein.[76] [77] The virus can also bind to DPP4 receptors in several species (e.g., camels, rabbits, sheep, goats, non-human primates).

DPP4 is expressed on the epithelial and endothelial cells of most human organs (e.g., kidney, liver, intestines). This may explain the multisystem clinical spectrum of the infection which includes severe (and sometimes fatal) pneumonia, acute respiratory distress syndrome, and multi-organ failure.[78]

Classification

Virus taxonomy

MERS-CoV is a member of the Coronaviridae family (order: Nidovirales; subfamily: Coronavirinae; genus Betacoronavirus) and is part of the lineage C group.[1] [2] It is phylogenetically distinct from all previously known betacoronavirus species, which include human coronaviruses HKU1 and OC43, severe acute respiratory syndrome (SARS) coronavirus, and bat coronaviruses HKU4, HKU5, and HKU9.[3]
Primary prevention

There is currently no vaccine available for the prevention of MERS in humans or camels, although there are three vaccines in development (one to prevent transmission from camels to people, and two for use in humans during outbreaks and longer-term protection of people at high risk).[83] [84] Therefore, primary prevention is focused on preventing transmission from infected people and dromedary camels.

General prevention measures include:

• Wash hands with soap and water (or alcohol-based hand sanitiser)
• Use appropriate respiratory hygiene measures (e.g., cover mouth and nose when coughing or sneezing)
• Avoid touching nose, eyes, or mouth if hands have not been washed
• Clean and disinfect surfaces and objects
• Avoid close personal contact with people who are unwell.

Prevention of human-to-human transmission:[85] [86]

• Human-to-human transmission occurs most commonly in healthcare settings, and community spread is rare
• Infection prevention and control measures should be instituted in all suspected or confirmed cases of MERS. Standard precautions and droplet precautions are recommended, as well as airborne precautions when performing aerosol-generating procedures
• Patients with probable or confirmed infection should be placed in an adequately ventilated single room, clearly segregated from other patient care areas if possible. The number of healthcare workers and visitors should be kept to a minimum
• In addition to standard precautions, all healthcare workers and visitors when in close contact (i.e., approximately 1 metre) with a probable or confirmed case, should always use:
  • A medical mask
  • Eye protection
  • A clean, non-sterile, long-sleeved gown
  • Gloves
  • Hand hygiene should always be performed before and after contact with the patient and their surroundings, and immediately after the removal of personal protective equipment
  • Movement of the patient outside of the barrier nursing room or area should be avoided unless medically necessary.

These precautions should be implemented for the duration of the symptomatic illness and continued for 24 hours after the resolution of symptoms. Detailed infection prevention and control recommendations are available from the Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO):

[Centers for Disease Control and Prevention (CDC): interim infection prevention and control recommendations for hospitalized patients with MERS-CoV]

[World Health Organization (WHO): infection prevention and control during health care for probable or confirmed cases of MERS-CoV infection]

Prevention of camel-to-human transmission:[60] [87]
• In countries where Middle East respiratory syndrome coronavirus (MERS-CoV) infection is prevalent in dromedary camels (i.e., the Arabian Peninsula and its surrounding countries), the following interventions should be considered to prevent camel-to-human transmission:

• Individuals who are at risk of developing severe infection (i.e., age ≥50 years, diabetes mellitus, heart disease, chronic renal failure, immunocompromised) should avoid direct contact with camels (including nasal and eye discharge, urine, and faeces) and camel products (e.g., milk, meat)
• Frequent hand washing and use of personal protective equipment while handling dromedary camels, including farmers, veterinarians, market workers, and slaughterhouse workers
• Educational campaigns that target camel owners and the general public to inform them of the risks of consuming unpasteurised camel products (e.g., milk) and undercooked meat
• Camels with detectable MERS-CoV RNA should be quarantined and tested at regular intervals
• Strict regulation of camel movement, including a requirement for MERS-CoV infection clearance prior to importation and transport of camels between farms or to slaughterhouses.

Screening

Contact screening

Contact screening identified secondary infection in only 4% of 280 close family contacts and 2% of 5065 healthcare facility contacts.[115] [116]

People who may have been exposed to the virus are advised to monitor their health for 14 days from the last day of possible contact and seek medical attention if they develop symptoms, especially fever, cough, or dyspnoea. Isolation or quarantine is not currently warranted.

With an effective reproductive number of less than one, the epidemic potential of the infection is considered low at present unless the virus mutates. Although there has been considerable concern over the potential global spread of infection during the annual Hajj pilgrimage to Mecca, where millions of pilgrims from many countries travel to Saudi Arabia, surveillance studies have not identified infection in pilgrims while in Saudi Arabia or after returning home.[117] [118] [119] [120] [121] [122]

Asymptomatic patients who test positive

Patients may be asymptomatic but test positive for infection on real-time reverse transcription polymerase chain reaction (RT-PCR) as part of active case monitoring or contact investigations. These patients may go on to develop symptoms during the course of the infection. The potential for transmission from these patients is unknown, and until more is known, patients should be isolated (hospital or home), followed up daily to see whether symptoms have developed, and tested at least weekly. The choice of isolation location depends on numerous factors including hospital bed capacity, the hospital's ability to monitor patients at home, conditions of the household and its occupants, and patient risk factors for developing severe infection. Isolation should continue until 2 consecutive upper respiratory tract specimens taken at least 24 hours apart test negative on RT-PCR. Further specific guidance for managing the patient in each location is available from the World Health Organization (WHO).[123]

Surveillance

The aims of surveillance are to detect early, sustained human-to-human transmission and determine the geographic risk area for infection. The WHO has produced detailed guidance on surveillance for human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) infection:
Secondary prevention

MERS is a notifiable disease and all suspected and confirmed cases should be reported to the appropriate authority.

Transmission of the virus can be readily interrupted with the effective implementation of infection control precautions. The essential elements for effective secondary prevention include:[89] [85]

- Effective environmental cleaning and adequate spatial separation of patients with suspected or confirmed infection from other patients
- Appropriate clinical triage protocols to identify patients presenting with acute respiratory illness who have history of travel within the past 14 days to the Middle East
- Visitors and healthcare personnel caring for patients with suspected infection should perform appropriate hand hygiene and use personal protective equipment to ensure contact and droplet precautions (e.g., gloves, gowns, face masks)
- Airborne precautions should also be applied during any aerosol-generating procedures such as endotracheal intubation. Such procedures should only be performed in negative-pressure rooms with adequate ventilation
- Infection control precautions should be continued up to 24 hours after resolution of all clinical symptoms and at least one negative real-time reverse transcription polymerase chain reaction (RT-PCR)
- All healthcare contacts and close contacts of patients should be identified and screened for symptoms of infection. Only those who are symptomatic should be tested. Asymptomatic contacts should be followed up daily for 14 days and tested if they develop any symptoms suggestive of infection.
Case history

Case history #1

A 50-year-old man presents with a 4-day history of fever, progressive dyspnoea, and dry cough, and a 2-day history of nausea and diarrhoea. His history is significant for smoking and type 2 diabetes mellitus. He reports arriving in the UK from the Arabian Peninsula, where he lives, 10 days ago for the purpose of a vacation. He reports recent contact with his brother, a camel herder, who is currently in hospital being investigated for an acute viral respiratory infection. Examination reveals a temperature of 38.2°C (100.8°F), a respiratory rate of 22 breaths per minute, and oxygen saturation of 88%. Chest examination is normal. Laboratory work-up reveals leukopenia, lymphopenia, thrombocytopenia, elevated ALT, and elevated creatinine.

Other presentations

The majority of patients present with fever and respiratory symptoms (e.g., cough, dyspnoea); however, some patients may present with gastrointestinal symptoms only (e.g., nausea, vomiting, diarrhoea, abdominal pain). Other symptoms include myalgia, arthralgia, headache, chills/rigors, sore throat, and rhinorrhoea.[4] [5] [6] [7] [8] [9] Fever may be absent in older patients, immunocompromised patients, pregnant women, and patients with end-stage renal disease, diabetes mellitus, or haemochromatosis.[5] Some patients, particularly young, healthy patients, may be asymptomatic or present with mild respiratory symptoms and a normal chest x-ray.[10] However, others, particularly older patients or those with comorbidities, may present with severe, rapidly progressive pneumonia, acute respiratory distress syndrome, septic shock, or multi-organ failure resulting in death. A patient who presented with acute renal failure caused a superspreader event in Riyadh (Saudi Arabia) in 2017, highlighting the difficulties in diagnosing pneumonia in patients with renal and cardiac failure.[11] Infection in children is rare.[12] [13]

Step-by-step diagnostic approach

Although MERS has not yet reached pandemic potential, it is a potentially severe infection with a high case fatality rate. Therefore, quick diagnosis is essential to prevent transmission and to provide supportive care in a timely manner. Physicians should have a high index of suspicion for all patients who present with fever and/or respiratory symptoms in the correct epidemiological context (i.e., travel from the Middle East), and these patients should be promptly evaluated. There are no pathognomonic features; therefore, molecular and serological testing is required to confirm the diagnosis. Co-infection with other respiratory viruses has been reported.

MERS is a notifiable disease and all suspected and confirmed cases should be reported to the appropriate authority.

Infection prevention and control measures

Isolation procedures should be initiated in all suspected or confirmed cases of MERS. An increased level of infection control precautions is recommended. Specifically, the World Health Organization (WHO) recommends standard, droplet, and contact precautions, as well as airborne precautions when performing aerosol-generating procedures.[85]
Detailed infection prevention and control recommendations are available from the Centers for Disease Control and Prevention (CDC) and WHO:

- [Centers for Disease Control and Prevention (CDC): interim infection prevention and control recommendations for hospitalized patients with MERS-CoV]
- [World Health Organization (WHO): infection prevention and control during health care for probable or confirmed cases of MERS-CoV infection]

Diagnostic laboratory work on clinical specimens from patients who are suspected or confirmed to be infected should be conducted under Biosafety Level (BSL-2) practices and procedures.

**History**

A detailed history helps to clarify the level of risk for MERS and assess the possibility of other causes. Obtaining an epidemiological history is crucial for timely diagnosis and preventing potential outbreaks.[19][21] All confirmed cases have either travelled to, resided in, or been in contact with someone who has travelled to the Middle East in the 14 days prior to the onset of symptoms.[17][19][79][80] This includes the Arabian Peninsula (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen) and its surrounding countries (Iraq; Iran; Israel, the West Bank, and Gaza; Jordan; Lebanon; Syria). Failure to recognise this risk resulted in a large outbreak in the Republic of Korea (South Korea) in 2015.[19][20][21] Contact with infected dromedary camels is also a risk factor.[64]

Ninety-eight percent of cases have been reported in adults (defined as age >14 years).[8] Although infection has been reported in different age groups within the adult population, the median age of patients ranges from 50 to 67 years of age.[4][9][26] Infection in children is rare, although the reason for this is unknown.[12][13]

Comorbid conditions, specifically diabetes mellitus, chronic renal impairment, heart disease, and obesity, are all risk factors for infection, as is smoking.[64] Approximately 75% of patients with MERS have at least one comorbid illness.[4]

The WHO has developed a questionnaire designed to gather initial information about the potential exposures of a suspected or confirmed case in the 14 days before symptom onset:

- [World Health Organization (WHO): MERS-CoV - initial interview questionnaire of cases]

**Clinical presentation**

MERS may present in a similar way to the common cold. The majority of patients present with fever and respiratory symptoms (e.g., cough, dyspnoea).

- Fever (temperature >38°C [100.4°F]): common symptom reported in 40% to 98% of cases.[7][8][9] Fever may be absent in older patients, immunocompromised patients, pregnant women, and patients with end-stage renal disease, diabetes mellitus, or haemochromatosis;[5] therefore, absence of fever should not preclude work-up for MERS.[88]
- Cough: common symptom reported in 54% to 86% of cases. It is usually dry; however, has been reported to be productive in 23% to 36% of patients.[8][9][27]
- Dyspnoea: common symptom reported in 60% to 72% of cases.[8][9][27]
- Haemoptysis: less common symptom reported in 7% to 17% of cases.[8][9][27]

Patients may also present with gastrointestinal symptoms:
• Diarrhoea: reported in 7% to 26% of cases[5] [8] [9]
• Abdominal pain: reported in 17% to 24% of cases[8] [27]
• Nausea/vomiting: reported in 7% to 21% of cases.[5] [8] [9]

Patients may present with gastrointestinal symptoms only, going on to develop respiratory symptoms or pneumonia later in the course of infection. Other symptoms include myalgia, arthralgia, headache, chills/rigors, sore throat, and rhinorrhea.[4] [5] [6] [7] [8] [9] Some patients, particularly young, healthy patients, may be asymptomatic or present with mild respiratory symptoms and a normal chest x-ray.[10] However, others, particularly older patients or those with comorbidities, may present with severe, rapidly progressive pneumonia, acute respiratory distress syndrome, septic shock, or multi-organ failure resulting in death.

Pneumonia is a common finding, but not always present. Rapid progression to pneumonia can occur in less than a week. Crackles/rales and bronchial breath sounds may be noted on auscultation. Chest pain, dyspnoea, tachypnoea, tachycardia, and cyanosis may be present.

Case definitions

Case definitions have been published by the CDC, WHO, and the Ministry of Health (Saudi Arabia).[89] [90] [91] Since MERS is considered an emerging disease, definitions are constantly evolving and not all clinical presentations will fit the case definitions. Physicians should be vigilant for identifying suspected cases regardless of whether they fit the case definitions or not. For example, the absence of fever has been reported in cases of confirmed infection, despite most case definitions including fever as a prerequisite for diagnosis.

Current case definitions:

• [Centers for Disease Control and Prevention (CDC): interim patient under investigation (PUI) guidance and case definitions]
• [World Health Organization (WHO): case definition for reporting to WHO]
• [Ministry of Health (Saudi Arabia): case definition]

Initial laboratory investigations

Laboratory testing is recommended in any patient who presents with symptoms such as fever, respiratory symptoms, gastrointestinal symptoms, and/or myalgia in the correct epidemiological context.

FBC commonly reveals leukopenia, lymphopenia, and thrombocytopenia.[8] [26] [81] Patients may have leukocytosis, particularly in the setting of a secondary bacterial infection. Specific diagnostic testing for MERS should be pursued even in the absence of a typical FBC result.

A comprehensive metabolic panel should also be ordered, and may show elevated creatinine, LFTs, and lactate dehydrogenase.[8] [26] [81]

Blood cultures should be collected to test for potential bacterial pathogens that can also cause pneumonia or sepsis.[92] They should be collected before empirical antimicrobial therapy is started, if possible.

The CDC and WHO have produced detailed guidance on laboratory testing:

• [Centers for Disease Control and Prevention (CDC): interim guidelines for collecting, handling, and testing clinical specimens from patients under investigation for MERS-CoV]
Molecular testing

All patients with suspected MERS should undergo molecular testing. Confirmation of infection is based on the detection of unique sequences of viral RNA by real-time reverse transcription polymerase chain reaction (RT-PCR), with confirmation by nucleic acid sequencing if necessary.

Lower respiratory tract specimens (e.g., sputum, tracheal aspirates, bronchoalveolar lavage fluid) are the preferred specimen for RT-PCR as sputum and tracheal aspirates contain the highest viral loads, and hence have the highest yield.[5] [93] However, bronchoscopy may generate aerosols and is generally not recommended. Upper respiratory tract specimens (e.g., nasopharyngeal and oropharyngeal swabs, nasopharyngeal aspirate/wash) and serum collection for virus detection are recommended, especially if lower respiratory specimens are not available and it is 7 days or less since symptom onset. Both upper and lower respiratory tract specimens should be collected whenever possible.[89] [94] [95] Urine and stool specimens may also be used; however, these specimens contain lower levels of the virus compared with respiratory tract specimens. Healthcare workers should wear appropriate personal protective equipment (e.g., mask, eye protection, gloves, gown) when collecting specimens.[94]

There are 3 RT-PCR assays currently recommended for the diagnosis of Middle East respiratory syndrome coronavirus (MERS-CoV) infection:[94]

- MERS-CoV RT-PCR (upE): highly sensitive screening assay targeting regions upstream of the E protein gene (upE)
- MERS-CoV RT-PCR (ORF 1b): confirmatory assay targeting the open reading frame 1b (ORF 1b).
  It is less sensitive than the upE assay, but is more specific as it does not exhibit cross-reactivity with the 4 main coronaviruses known to infect humans (i.e., OC43, NL63, 229E, SARS)
- MERS-CoV RT-PCR (ORF 1a): confirmatory assay targeting the open reading frame 1a (ORF 1a).
  It is highly specific and more sensitive than the ORF 1b assay, but has similar sensitivity to the upE assay.

Assays targeting sequencing amplicons on the viral genome are also available and can aid confirmation of the diagnosis. An assay targeting the RdRp gene (RdRpSeq) broadly detects betacoronavirus clade C sequences; however, it is not specific and will detect other coronavirus strains including human coronaviruses HKU1 and OC43.[96] Another assay targets N gene sequencing (NSeq). This region was chosen as it comprised a 2 amino acid deletion in the corresponding sequence published from a patient treated in the UK. It is highly sensitive and specific for detection of human coronavirus Erasmus Medical Center/2012 (hCoV-EMC), the strain isolated from the first person infected with MERS.[96] Both of these assays are sensitive enough to detect the virus at very low concentrations, but if used should be coupled with a subsequent confirmatory assay.

The WHO recommends a screening assay to be performed first and, if positive, a confirmatory assay should be performed. If the confirmatory assay is positive, infection is confirmed. If the confirmatory assay is negative, consider repeating the tests (if epidemiological evidence is suggestive of infection) or perform sequencing assays. If sequencing indicates the presence of MERS-CoV, infection is confirmed.[94]
The WHO defines a confirmed case as a person with laboratory confirmation of infection. Presence of nucleic acid can be confirmed by either a positive RT-PCR result on at least 2 specific genomic targets or a single positive target with sequencing of a second target.[90]

The CDC requires a positive PCR on at least 2 specific genomic targets or a single positive target with sequencing on a second for confirmation of the diagnosis.[91] The CDC has developed RT-PCR assays targeting the viral nucleocapside (N) protein gene which can be used to complement the upE and ORF 1a assays for screening and confirmation.

False-negative results can occur due to poor specimen quality, incorrect handling of the specimen, or the time of collection; therefore, in patients who test negative where there is a high index of suspicion for infection, additional specimens should be collected (preferably lower respiratory tract specimens) and tested.

**Serological testing**

Serological testing is generally not used for diagnosis, but for epidemiological surveillance or investigational purposes (e.g., retrospective diagnosis). It may be used to confirm the diagnosis; however, a single specimen would only identify a probable case. Paired sampling taken at least 14 to 21 days apart is required to confirm the diagnosis.

Several serological tests have been developed for detecting MERS-CoV antibodies including an indirect fluorescent antibody (IFA) test, an enzyme-linked immunosorbent assay (ELISA), and a serum neutralisation test.
Middle East respiratory syndrome (MERS)

Diagnosis

The WHO defines a confirmed case to be a patient with evidence of seroconversion in at least one screening assay (e.g., IFA, ELISA) and confirmation by a neutralisation assay in samples taken at least 14 days apart. They define a probable case as a symptomatic patient without a positive RT-PCR test who has a positive result for at least one screening assay (e.g., IFA, ELISA) plus a positive result for a neutralisation assay in a single specimen.[94]

The CDC has developed a two-stage approach to serological testing which uses an ELISA test for screening, followed by a microneutralisation test to confirm diagnosis.[95] False-positive results can occur due to cross-reactivity with other betacoronaviruses.

Imaging

A chest x-ray should be ordered in all patients with suspected pneumonia. Diffuse bilateral infiltrates have been reported in 22% to 67% of cases. Lobar infiltrates or the absence of infiltrates have also been reported, particularly in healthy, young patients.[5] [8]

A CT scan of the chest may be helpful in patients with suspected pneumonia who have a normal chest x-ray. CT may reveal bilateral subpleural and basal airspace opacities, with more extensive ground-glass opacities than consolidation.[97] Recognition of these patterns can aid early diagnosis of MERS; however, routine use of this test is not recommended.

Useful links

- [Centers for Disease Control and Prevention (CDC): Middle East respiratory syndrome (MERS)]
- [World Health Organization (WHO): Middle East respiratory syndrome coronavirus (MERS-CoV)]
- [Ministry of Health (Saudi Arabia): coronavirus (MERS-CoV)]

Risk factors

Strong residence in, or travel to, the Middle East (or country where there is an active outbreak) in previous 14 days

- All confirmed cases have either resided in, or travelled to, the Middle East in the 14 days prior to the onset of symptoms.[17] [19] [79] [80] This includes the Arabian Peninsula (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen) and its surrounding countries (Iraq; Iran; Israel, the West Bank, and Gaza; Jordan; Lebanon; Syria).

Close contact with infected individuals

- Majority of cases are a result of human-to-human transmission (rather than camel-to-human transmission) with peaks of confirmed cases occurring during nosocomial outbreaks.[6] [7] [28] Transmission has been well documented in family clusters.[18] [29] [30] However, it has been reported more commonly in nosocomial outbreaks (e.g., haemodialysis units, intensive care units, medical wards).[6] [7] [30] [31] [32] [33]Transmission is via respiratory droplets (e.g., coughing, sneezing) from an infected patient, or close contact with an infected patient. However, airborne or fomite transmission cannot be ruled out.[65] The incubation period is 2 to 14 days and transmission is thought to occur during either the symptomatic or incubation stages.[8] [66]
• All patients diagnosed outside of the Middle East have been in contact with someone who has travelled from the Middle East in the preceding 14 days.[17] [19] [79] [80]

exposure to infected dromedary camels
• Dromedary camels are thought to be the primary animal host.[39]
• Exact mode of transmission is unknown, but it is thought to occur from direct or indirect contact with dromedary camels (e.g., camel milking, contact with camel nasal secretions, urine, or faeces) or camel products (e.g., unpasteurised camel milk, raw or undercooked camel meat).
• Strongest evidence for camel-to-human transmission comes from a study in Saudi Arabia where the virus was isolated from a patient and one of his camels and the genome was found to be almost identical.[61] [62]
• A case-control study identified contact with camels to be a risk factor.[64]

age ≥50 years
• Although infection has been reported in different age groups within the adult population, the median age of patients ranges from 50 to 67 years of age.[4] [9] [26]
• Age ≥50 years is associated with more severe presentation, worse outcomes, and a higher risk of mortality.[5] [27] In one cohort study, mortality increased with increasing age to reach 75% in patients >60 years of age.[8]

diabetes mellitus
• Reported in 65% to 87% of confirmed cases and has been associated with severe infection.[5] [8] [9] [26]
• Most common comorbid condition in one cohort of 12 critically ill patients admitted to the intensive care unit.[81]
• Identified as a risk factor in a case-control study.[64]

chronic renal impairment
• Reported in 33% of confirmed cases (compared with 7% of patients who were initially suspected of being infected but who later tested negative).[9]
• Patients with end-stage renal disease were reported to develop severe infection and had worse clinical outcomes.[81] In one case series, a mortality rate of 100% was reported in patients with chronic renal impairment, including 8 patients who were undergoing haemodialysis.[5]
• May be related to the immune dysregulation that occurs in patients with end-stage renal disease on haemodialysis.[82]

heart disease
• Identified as a risk factor in a case-control study.[64]

obesity
• Patients with confirmed infection had a median BMI of 32 compared with 27.8 in controls in one case-control study.[9]
• Reported to be associated with severe infection and worse clinical outcomes in several case series.[8] [81]

tobacco smoking
• Identified as a risk factor in a case-control study.[64]
# Middle East respiratory syndrome (MERS)

## Diagnosis

### History & examination factors

#### Key diagnostic factors

**residence in, or travel to, the Middle East (or country where there is an active outbreak) in previous 14 days (common)**

- All confirmed cases have either resided in, or travelled to, the Middle East in the 14 days prior to the onset of symptoms.\[98\] \[99\] \[100\] \[101\] This includes the Arabian Peninsula (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates, Yemen) and its surrounding countries (Iraq; Iran; Israel, the West Bank, and Gaza; Jordan; Lebanon; Syria).

**age >14 years (common)**

- Ninety-eight percent of cases have been reported in adults (defined as age >14 years).\[102\]
- Infection in children is rare, although the reason for this is unknown.\[103\] \[104\]

**fever (common)**

- Reported in 40% to 98% of cases.\[105\] \[102\] \[106\]
- Fever may be absent in older patients, immunocompromised patients, pregnant women, and patients with end-stage renal disease, diabetes mellitus, or haemochromatosis;\[107\] therefore, absence of fever should not preclude work-up for MERS.\[108\]

**cough (common)**

- Reported in 54% to 86% of cases. It is usually dry; however, has been reported to be productive in 23% to 36% of patients.\[102\] \[106\] \[109\]

**dyspnoea (common)**

- Reported in 60% to 72% of cases.\[102\] \[106\] \[109\]

#### Other diagnostic factors

**haemoptysis (common)**

- Reported in 7% to 17% of cases.\[102\] \[106\] \[109\]

**diarrhoea (common)**

- Reported in 7% to 26% of cases.\[107\] \[102\] \[106\]

**abdominal pain (common)**

- Reported in 17% to 24% of cases.\[102\] \[109\]

**nausea/vomiting (common)**

- Reported in 7% to 21% of cases.\[107\] \[102\] \[106\]

**chills/rigors (common)**

- Usually associated with fever.

**myalgia (common)**

- Non-specific symptom reported in some cases.\[110\] \[107\] \[111\] \[105\] \[102\] \[106\]
arthralgia (common)
  • Non-specific symptom reported in some cases.\[110\] [107] [111] [105] [102] [106]

malaise (common)
  • Non-specific symptom reported in some cases.\[110\] [107] [111] [105] [102] [106]

headache (common)
  • Non-specific symptom reported in some cases.\[110\] [107] [111] [105] [102] [106]

sore throat (common)
  • Non-specific symptom reported in some cases.\[110\] [107] [111] [105] [102] [106]

rhinorrhoea (common)
  • Non-specific symptom reported in some cases.\[110\] [107] [111] [105] [102] [106]

tachypnoea (common)
  • Present in some cases, including patients with acute respiratory distress.

tachycardia (common)
  • Present in some cases, including patients with acute respiratory distress.

cyanosis (common)
  • Present in some cases, including patients with acute respiratory distress.

chest pain (common)
  • May indicate pneumonia.

crackles/rales on auscultation (common)
  • May indicate pneumonia.
  • Bronchial breath sounds may also be heard.
# Diagnostic tests

## 1st test to order

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FBC</strong></td>
<td><strong>leukopenia; lymphopenia; thrombocytopenia</strong></td>
</tr>
<tr>
<td>• Recommended in all patients with suspected MERS. Commonly reveals leukopenia, lymphopenia, and thrombocytopenia. Patients may have leukocytosis, particularly in the setting of a secondary bacterial infection.</td>
<td><strong>elevated creatinine; elevated LFTs; elevated lactate dehydrogenase</strong></td>
</tr>
<tr>
<td>• Other diagnostic testing for MERS should be pursued even in the absence of a typical FBC result.</td>
<td></td>
</tr>
<tr>
<td><strong>comprehensive metabolic panel</strong></td>
<td></td>
</tr>
<tr>
<td>• Recommended in all patients with suspected MERS. May reveal elevated creatinine, AST, ALT, and lactate dehydrogenase.</td>
<td><strong>low oxygen saturation (SpO2 &lt;90%)</strong></td>
</tr>
<tr>
<td><strong>pulse oximetry</strong></td>
<td></td>
</tr>
<tr>
<td>• Indicated in patients with respiratory distress and cyanosis.</td>
<td><strong>negative</strong></td>
</tr>
<tr>
<td><strong>blood cultures</strong></td>
<td></td>
</tr>
<tr>
<td>• Blood cultures should be collected to test for potential bacterial pathogens that can also cause pneumonia or sepsis. Should be collected before empirical antimicrobial therapy is started, if possible.</td>
<td><strong>positive for MERS-CoV RNA</strong></td>
</tr>
<tr>
<td><strong>real-time reverse transcription polymerase chain reaction (RT-PCR)</strong></td>
<td></td>
</tr>
<tr>
<td>• Confirms Middle East respiratory syndrome coronavirus (MERS-CoV) infection.</td>
<td></td>
</tr>
<tr>
<td>• Lower respiratory tract specimens (e.g., sputum, tracheal aspirates, bronchoalveolar lavage fluid) are the preferred specimen for RT-PCR as sputum and tracheal aspirates contain the highest viral loads, and hence have the highest yield. However, bronchoscopy may generate aerosols and is generally not recommended. Upper respiratory tract specimens (e.g., nasopharyngeal and oropharyngeal swabs, nasopharyngeal aspirate/wash) and serum collection for virus detection are recommended, especially if lower respiratory specimens are not available and it is 7 days or less since symptom onset. Urine and stool specimens may also be used; however, these specimens contain lower levels of the virus compared with respiratory tract specimens. Healthcare workers should wear appropriate personal protective equipment (e.g., mask, eye protection, gloves, gown) when collecting specimens.</td>
<td></td>
</tr>
<tr>
<td>• MERS-CoV RT-PCR (upE): highly sensitive screening assay targeting regions upstream of the E protein gene (upE).</td>
<td></td>
</tr>
<tr>
<td>• MERS-CoV RT-PCR (ORF 1b): confirmatory assay targeting open reading frame 1b (ORF 1b). Less sensitive than the upE assay, but more specific.</td>
<td></td>
</tr>
<tr>
<td>• MERS-CoV RT-PCR (ORF 1a): confirmatory assay targeting ORF 1a. Highly specific and more sensitive than ORF 1b assay, but similar sensitivity to upE assay.</td>
<td></td>
</tr>
<tr>
<td>• The World Health Organization (WHO) recommends a screening assay first and, if positive, a confirmatory assay performed. If confirmatory assay is positive, infection is confirmed. If the confirmatory assay is negative, consider repeating the tests if</td>
<td></td>
</tr>
</tbody>
</table>
### Diagnosis

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>epidemiological evidence is suggestive, or perform sequencing assays.[94]</td>
<td></td>
</tr>
<tr>
<td>• Diagnosis requires a positive PCR on at least 2 specific genomic targets or a single positive target with sequencing on a second target.[90] [91]</td>
<td></td>
</tr>
<tr>
<td>RT-PCR sequencing assay</td>
<td>detects MERS-CoV nucleotide sequences</td>
</tr>
<tr>
<td>• An assay targeting the RdRp gene (RdRpSeq) broadly detects betacoronavirus clade C sequences; however, it is not specific and will detect other coronavirus strains including human coronaviruses HKU1 and OC43.[96]</td>
<td></td>
</tr>
<tr>
<td>• N gene sequencing (NSeq) can also be used. This region was chosen as it comprised a 2 amino acid deletion in the corresponding sequence published from a patient treated in the UK. Highly sensitive and specific for detection of human coronavirus Erasmus Medical Center/2012 (hCoV-EMC), the strain isolated from the first person infected with MERS.[96]</td>
<td></td>
</tr>
<tr>
<td>• Both assays are sensitive enough to detect virus at very low concentrations, but if used should be coupled with a subsequent confirmatory assay.</td>
<td></td>
</tr>
<tr>
<td>chest x-ray</td>
<td>diffuse bilateral infiltrates; possibly lobar infiltrates or absence of infiltrates</td>
</tr>
<tr>
<td>• Recommended in all patients with suspected pneumonia. Diffuse bilateral infiltrates have been reported in 22% to 67% of cases. Lobar infiltrates or the absence of infiltrates have also been reported, particularly in healthy, young patients.[5] [8]</td>
<td></td>
</tr>
</tbody>
</table>
### Other tests to consider

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>serology</strong></td>
<td></td>
</tr>
<tr>
<td>• Generally used for epidemiological surveillance or investigational purposes (e.g., retrospective diagnosis). May also be used to confirm diagnosis; however, a single specimen would only identify a probable case. Paired sampling taken at least 14 to 21 days apart is required to confirm diagnosis.</td>
<td>positive for MERS-CoV antibodies</td>
</tr>
<tr>
<td>• Includes indirect fluorescent antibody (IFA), enzyme-linked immunosorbent assay (ELISA), and serum neutralisation.</td>
<td></td>
</tr>
<tr>
<td>• The WHO defines a confirmed case as a patient with evidence of seroconversion in at least one screening assay (e.g., IFA, ELISA) and confirmation by a neutralisation assay in samples taken at least 14 days apart. They define a probable case as a symptomatic patient without a positive RT-PCR test who has a positive result for at least one screening assay (e.g., IFA, ELISA) plus a positive result for a neutralisation assay in a single specimen.[94]</td>
<td></td>
</tr>
<tr>
<td>• The CDC has developed a two-stage approach to serological testing which uses an ELISA test for screening, followed by a microneutralisation test to confirm diagnosis.[91]</td>
<td></td>
</tr>
<tr>
<td>• False-positive results can occur due to cross-reactivity with other betacoronaviruses.</td>
<td></td>
</tr>
<tr>
<td><strong>CT chest</strong></td>
<td></td>
</tr>
<tr>
<td>• May be helpful in patients with suspected pneumonia who have a normal chest x-ray. May reveal bilateral subpleural and basal airspace opacities, with more extensive ground-glass opacities than consolidation.[97]Recognition of these patterns can aid early diagnosis of MERS; however, routine use of this test is not recommended.</td>
<td>bilateral subpleural and basal airspace opacities, with more extensive ground-glass opacities than consolidation</td>
</tr>
</tbody>
</table>
## Differential diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| Coronavirus disease 2019 (COVID-19)      | • Residence in/travel to a country/area or territory with local transmission, or close contact with a confirmed or probable case of COVID-19, in the 14 days prior to symptom onset.  
  • Signs and symptoms are similar so it may be difficult to differentiate between the conditions clinically.  
  • The situation is evolving rapidly; see our COVID-19 topic for further information.   | • Real-time reverse transcription polymerase chain reaction (RT-PCR): positive for SARS-CoV-2 RNA.  
  • It is not possible to differentiate COVID-19 from other causes of pneumonia on chest imaging.                                                                                                                 |
| Severe acute respiratory syndrome (SARS) | • Lack of travel history to or from the Middle East (or country where there is an ongoing outbreak) in the preceding 14 days.  
  • No close contact with a symptomatic traveller from the Middle East or a suspected or confirmed case of MERS in the preceding 14 days.  
  • Patients have lower incidence of comorbidities compared with MERS.  
  • Clinical features are similar; however, patients are less likely to present with haemoptysis (1% of patients with SARS) or dyspnoea (42% of patients with SARS).[8]  
  • Usually less aggressive than MERS as reflected by the lower mortality rate.[113]                                                                                     | • RT-PCR: positive for SARS-CoV RNA.[96] [114]                                                                                                                                                                           |
| Common cold                              | • Lack of travel history to or from the Middle East (or country where there is an ongoing outbreak) in the preceding 14 days.  
  • No close contact with a symptomatic traveller from the Middle East or a suspected or confirmed case of MERS in the preceding 14 days.                                                                 | • RT-PCR: negative for MERS coronavirus (MERS-CoV) RNA.                                                                                                                                   |
<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
| **Influenza infection**                 | • Lack of travel history to or from the Middle East (or country where there is an ongoing outbreak) in the preceding 14 days.  
• No close contact with a symptomatic traveller from the Middle East or a suspected or confirmed case of MERS in the preceding 14 days.  
• Seasonal outbreak during winter.  
• Differentiating MERS from community-acquired respiratory tract infections is not possible from signs and symptoms. | • RT-PCR: positive for influenza A or B viral RNA. |
| **Avian influenza A (H5N1) virus infection** | • Lack of travel history to or from the Middle East (or country where there is an ongoing outbreak) in the preceding 14 days.  
• No close contact with a symptomatic traveller from the Middle East or a suspected or confirmed case of MERS in the preceding 14 days.  
• Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas) or living in an area where avian influenza is endemic.  
• Differentiating MERS from community-acquired respiratory tract infections is not possible from signs and symptoms. | • RT-PCR: positive for H5N1 viral RNA. |
| **Avian influenza A (H7N9) virus infection** | • Lack of travel history to or from the Middle East (or country where there is an ongoing outbreak) in the preceding 14 days. | • RT-PCR: positive for H7-specific viral RNA. |
### Diagnosis

<table>
<thead>
<tr>
<th>Condition</th>
<th>Differentiating signs / symptoms</th>
<th>Differentiating tests</th>
</tr>
</thead>
</table>
|                                   | - No close contact with a symptomatic traveller from the Middle East or a suspected or confirmed case of MERS in the preceding 14 days.  
- Close contact with infected birds (e.g., farmer or visitor to a live market in endemic areas) or living in an area where avian influenza is endemic. Up until now, the epidemic has been geographically focused in China.  
- Differentiating MERS from community-acquired respiratory tract infections is not possible from signs and symptoms.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Respiratory syncytial virus (RSV) infection | - Lack of travel history to or from the Middle East (or country where there is an ongoing outbreak) in the preceding 14 days.  
- No close contact with a symptomatic traveller from the Middle East or a suspected or confirmed case of MERS in the preceding 14 days.  
- Common cause of lower respiratory tract infection in children <1 year of age.  
- Seasonal outbreak during winter.  
- Differentiating MERS from community-acquired respiratory tract infections is not possible from signs and symptoms.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | - RT-PCR: positive for RSV RNA.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| Community-acquired pneumonia | - Lack of travel history to or from the Middle East (or country where there is an ongoing outbreak) in the preceding 14 days.  
- No close contact with a symptomatic traveller from the Middle East or a suspected or confirmed case of MERS in the preceding 14 days.  
- Differentiating MERS from community-acquired respiratory tract infections is not possible from signs and symptoms.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       | - Blood or sputum culture, or multiplex RT-PCR testing: positive for causative organism (e.g., *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Moraxella catarrhalis*).                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
### Diagnostic criteria

**Case definitions**

Case definitions have been published by the Centers for Disease Control and Prevention (CDC), World Health Organization (WHO), and Ministry of Health (Saudi Arabia).[89] [90] [91] Since MERS is considered an emerging disease, definitions are constantly evolving and not all clinical presentations will fit the case definitions. Physicians should be vigilant for identifying suspected cases, regardless of whether they fit the case definitions or not. For example, the absence of fever has been reported in cases of confirmed infection, despite some definitions including fever as a prerequisite for diagnosis.

**CDC: interim patient under investigation (PUI) guidance and case definitions[91]**

Patient under investigation (PUI):

- A person with both clinical features and an epidemiological risk
- Severe illness:
  - fever (may be absent in specific patient groups) and pneumonia or acute respiratory distress syndrome (based on clinical or radiological evidence) PLUS a history of travel from countries in or near the Arabian Peninsula within 14 days before symptom onset, or close contact with a symptomatic traveller who developed fever and acute respiratory illness (not necessarily pneumonia) within 14 days after travelling from countries in or near the Arabian Peninsula, or...
Middle East respiratory syndrome (MERS)

Diagnosis

a member of a cluster of patients with severe acute respiratory illness of unknown aetiology in which MERS is being evaluated.

• Milder illness:

• fever (may be absent in specific patient groups) and symptoms of respiratory illness (e.g., cough, dyspnoea) PLUS a history of being in a healthcare facility (as a patient, worker, or visitor) within 14 days before symptom onset in a country or territory near the Arabian Peninsula in which recent healthcare-associated cases of MERS have been identified
• fever (may be absent in specific patient groups) or symptoms of respiratory illness (e.g., cough, dyspnoea) PLUS close contact (i.e., within approximately 2 metres or the room/care area of a case for a prolonged period of time [such as caring for, living with, visiting, or sharing a healthcare waiting area or room with a confirmed MERS case] without recommended personal protective equipment, or direct contact with infectious secretions of a confirmed MERS case while not wearing recommended personal protective equipment).

Probable case:

• PUI with absent or inconclusive laboratory results for infection who is a close contact of a laboratory-confirmed case.

Confirmed case:

• Person with laboratory confirmation of infection (i.e., a positive real-time reverse transcription polymerase chain reaction [RT-PCR] on at least 2 specific genomic targets, or a single positive target with sequencing on a second).

Note: fever may be absent in the very young, elderly, immunocompromised, or patients receiving certain medications.

[Centers for Disease Control and Prevention (CDC): interim patient under investigation (PUI) guidance and case definitions]

WHO: case definition for reporting to WHO[90]

Probable case:

• A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g., pneumonia or acute respiratory distress syndrome) PLUS a direct epidemiological link with a confirmed case PLUS testing is unavailable, negative on a single inadequate specimen, or inconclusive
• A febrile acute respiratory illness with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g., pneumonia or acute respiratory distress syndrome) PLUS the person resides in, or travelled to, the Middle East or in countries where the virus is known to be circulating in dromedary camels or where infections have recently occurred PLUS testing is inconclusive
• An acute febrile respiratory illness of any severity PLUS a direct epidemiological link with a confirmed case PLUS testing is inconclusive.

Confirmed case:
• Person with laboratory confirmation (i.e., detection of viral nucleic acid or serology) of infection irrespective of clinical signs and symptoms. Presence of nucleic acid can be confirmed by either a positive RT-PCR result on at least 2 specific genomic targets or a single positive target with sequencing of a second target. Cases confirmed by serology require demonstration of seroconversion in 2 samples, ideally taken 14 days apart, by ELISA or immunofluorescence antibody assay and a neutralisation assay.

[World Health Organization (WHO): case definition for reporting to WHO]

Ministry of Health (Saudi Arabia): case definition[89]

Suspected case:

• I. Severe pneumonia (severity score ≥3 points on CURB 65) or acute respiratory distress syndrome (based on clinical or radiological evidence)

[VIDEO: CURB-65 pneumonia severity score]

• II. Unexplained deterioration of a chronic condition in patients with congestive heart failure or chronic kidney disease who are on haemodialysis

• III. Acute febrile illness with or without respiratory symptoms PLUS an epidemiologic link

• IV. Gastrointestinal symptoms and leukopenia or thrombocytopenia PLUS an epidemiologic link.

Confirmed case:

• A suspected case with laboratory confirmation of infection.

An epidemiologic link is defined as one of the following within 14 days before symptom onset:

• Exposure (contact within 1.5 metres) to a confirmed case of MERS-CoV infection

• Visit to a healthcare facility where an infected patient has recently (within 2 weeks) been identified or treated

• Contact with dromedary camels or consumption of camel products.

[Ministry of Health (Saudi Arabia): case definition]
Step-by-step treatment approach

No specific treatment exists for MERS; however, many drugs show promise and may prove to be valuable therapies in the future. Therefore, treatment is supportive and should focus on relieving symptoms and preventing or treating complications. Specific management depends on the clinical presentation, and patient factors such as age and the presence or absence of comorbidities.

Infection prevention and control measures

Isolation procedures should be initiated in all suspected or confirmed cases of MERS. An increased level of infection control precautions is recommended. Specifically, the World Health Organization (WHO) recommends standard, droplet, and contact precautions, as well as airborne precautions when performing aerosol-generating procedures.[85]

Patients with probable or confirmed infection should be placed in an adequately ventilated single room, clearly segregated from other patient care areas if possible. The number of healthcare workers and visitors should be kept to a minimum. In addition to standard precautions, all healthcare workers and visitors, when in close contact (i.e., approximately 1 metre) with a probable or confirmed case, should always use:

- A medical mask
- Eye protection
- A clean, non-sterile, long-sleeved gown
- Gloves.

Hand hygiene should always be performed before and after contact with the patient and their surroundings, and immediately after the removal of personal protective equipment. Movement of the patient outside of the barrier nursing room or area should be avoided unless medically necessary.

These precautions should be used for the duration of the symptomatic illness and continued for at least 24 hours after the resolution of symptoms.[85] Patients should be monitored for the clearance of infection using the recommended real-time reverse transcription polymerase chain reaction (RT-PCR) assays until there are 2 negative results on specimens taken at least 24 hours apart.[89] [92] Infection control measures can be discontinued in non-ventilated patients (e.g., those in home isolation) when the patient is asymptomatic and a single RT-PCR is negative.[89]

Detailed infection prevention and control recommendations are available from the Centers for Disease Control and Prevention (CDC) and WHO:

- [Centers for Disease Control and Prevention (CDC): interim infection prevention and control recommendations for hospitalized patients with MERS-CoV]
- [World Health Organization (WHO): infection prevention and control during health care for probable or confirmed cases of MERS-CoV infection]

Specimen collection

The following specimens should be collected in all patients for diagnostic testing:[92]

- Blood cultures: for potential bacterial pathogens that can also cause pneumonia or sepsis
Middle East respiratory syndrome (MERS)

### Treatment

- Lower respiratory tract specimens (e.g., sputum, tracheal aspirates, bronchoalveolar lavage): for bacterial and viral testing
- Upper respiratory tract specimens (e.g., nasopharyngeal and throat swabs): for molecular viral testing
- Serum: for molecular and serological testing.

Specimens should be collected according to the appropriate infection control measures. Blood cultures should be collected before antimicrobial therapy is started, if possible. Lower respiratory tract specimens are preferable to upper respiratory tract specimens, but both should be collected if possible. Upper respiratory tract specimens (e.g., nasopharyngeal swab) are sufficient in patients isolated at home.

Frequency of specimen collection depends on local circumstances. The WHO recommends that respiratory tract specimens for RT-PCR should be collected at least every 2 to 4 days in the initial 2 weeks, and continue until there are 2 negative test results to confirm clearance of the virus.[92] The Ministry of Health (Saudi Arabia) recommends repeat testing one week after diagnosis, and then every 3 days.[89]

### Management of patients with pneumonia or comorbidities

Patients with pneumonia or respiratory distress should be promptly admitted to an appropriate healthcare facility and infection prevention and control measures instituted.

Any patient with the following signs should be admitted to hospital:

- Respiratory rate >30 breaths/minute
- Hypoxaemia (SpO2 <90% on room air)
- Severe respiratory distress
- Clinical and/or radiological evidence of pneumonia.

These patients may rapidly progress to severe pneumonia or respiratory failure; therefore, it is important to pay attention to these clinical signs.[81]

Presence of comorbidities (e.g., diabetes mellitus, heart disease, chronic renal failure, obesity), smoking, and age ≥50 years increases the risk of developing severe infection, and these patients should also be admitted.

Supportive therapies should be started promptly:[92] [89]

- Oxygen: patients with signs of severe respiratory distress, shock, or hypoxaemia should be started on oxygen therapy immediately. Initiate at 5 L/minute and titrate so that SpO2 ≥90%
- Fluids: cautious fluid management is recommended in patients if necessary, provided that there is no evidence of shock (more aggressive resuscitation may be required in patients with shock)
- Antimicrobials: empirical antimicrobial therapy (including antibiotics and antivirals) should be started in inpatients with suspected MERS pneumonia (within one hour if sepsis is suspected) to cover all likely community-acquired or hospital-acquired (if patient has been admitted for >48 hours) pathogens. Antimicrobial selection should be based on local epidemiology, susceptibility data, and guidelines until diagnosis is confirmed, and empirical therapy adjusted based on results
- Antipyretics/analgesics: recommended for the control of fever and pain.

Patients with impending or established respiratory failure should be admitted to the ICU. Intubation and mechanical ventilation are recommended if the patient is deteriorating and cannot maintain a SpO2 ≥90% with oxygen therapy. Noninvasive mechanical ventilation, mechanical ventilation, or extracorporeal support might be used.
membrane oxygenation (ECMO) have been used in patients with MERS.[81] [124] However, noninvasive ventilation should be avoided due to the high risk of generating aerosols, and because it lacks evidence of efficacy compared to endotracheal intubation and mechanical ventilation.[89] A small observational study found that ECMO was associated with lower mortality in MERS patients with refractory hypoxaemia.[125]

Corticosteroids are generally not recommended; however, stress doses may be given if needed (e.g., patient with adrenal suppression). High doses should not be used for prolonged periods of time due to a high risk of adverse effects, the risk of developing opportunistic infections, and a lack of proven efficacy in treating MERS.[92] [126]

Patients should be monitored closely for signs of deterioration and the development of complications including respiratory failure, acute respiratory distress syndrome, acute renal failure, septic shock, and multi-organ failure. Supportive therapy (e.g., haemodialysis, vasopressor therapy, fluid resuscitation, antimicrobials) should be initiated immediately if required.[5] [8] [26] [81] [124]

Data on pregnant women are limited. Pregnant women can be treated with the supportive therapies detailed above (except ibuprofen, which is not recommended in pregnant women especially in the third trimester), taking into account the physiological changes that occur with pregnancy.

**Management of patients without pneumonia or comorbidities**

Patients who are young and healthy with no comorbidities are at a lower risk of developing complications, and can be considered for home isolation, if appropriate.[89] [86] [127] These patients generally have mild, non-specific symptoms such as fever, headache, malaise, cough, sore throat, or possibly gastrointestinal symptoms. Chest x-ray is normal.[10]

The CDC recommend that this is appropriate only once a healthcare professional, in consultation with their local or state health department, deems that the residential setting is suitable and that the patient is capable of adhering to recommended infection control precautions.[128] The WHO recommend that confirmed symptomatic cases should be isolated and monitored in a hospital setting whenever possible; however, home isolation may be considered in certain patients with mild symptoms and no underlying conditions (e.g., heart disease, renal failure) or immunocompromising conditions if inpatient care is not available or is unsafe. The decision requires careful clinical judgement and should be informed by assessing the safety of the patient’s home environment.[127]

Infection control measures are still recommended for these patients and include using a single room, single bathroom (if possible), minimising contact with other household members, and wearing a surgical mask if contact is necessary.[89] [86]

Supportive therapies are recommended including antipyretic and analgesics (e.g., paracetamol, ibuprofen) for the relief of pain and fever. Patients should keep hydrated, but should not take in too much fluid as this can worsen oxygenation.[92]

Detailed guidelines for home isolation are available from the WHO and CDC:

- [World Health Organization (WHO): home care for patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection presenting with mild symptoms and management of contacts]
- [Centers for Disease Control and Prevention (CDC): implementing home care and isolation or quarantine of people not requiring hospitalization for MERS-CoV]
Experimental therapies

There is no conclusive evidence at this time to recommend any virus-specific treatments for patients with suspected or confirmed infection. However, a number of treatments (e.g., interferon beta, interferon alfa, lopinavir, ribavirin, mycophenolate, and ciclosporin) have been studied for the treatment of MERS based on encouraging in vitro and animal studies.[129] [130] So far, none of these treatments have proven to be effective. This is partly due to a lack of randomised controlled trials and the limited number of patients that are included in retrospective studies.

Some countries, such as Republic of Korea (South Korea), have issued guidance that permits physicians to cautiously use some of the studied therapies.[131]

These therapies are generally only used in unstable patients with extensive pneumonia. If investigational agents are used, the WHO recommends that these drugs only be used under standard research treatment protocols and occur in the context of research trials.[92] Further studies are needed to evaluate the safety and efficacy of these agents in people with MERS.

See Emerging Therapies for more detailed information about specific experimental drugs.

Useful links

- [Centers for Disease Control and Prevention (CDC): Middle East respiratory syndrome (MERS)]
- [World Health Organization (WHO): Middle East respiratory syndrome coronavirus (MERS-CoV)]
- [Ministry of Health (Saudi Arabia): coronavirus (MERS-CoV)]

Treatment details overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

<table>
<thead>
<tr>
<th>Initial</th>
<th>( summary )</th>
</tr>
</thead>
<tbody>
<tr>
<td>suspected MERS</td>
<td>1st isolation procedures</td>
</tr>
<tr>
<td></td>
<td>plus supportive care + monitoring</td>
</tr>
<tr>
<td></td>
<td>plus empirical antimicrobial therapy</td>
</tr>
</tbody>
</table>
## Acute

Confirmed MERS: post initial stabilisation and isolation measures

<table>
<thead>
<tr>
<th></th>
<th>1st</th>
<th>Supportive Care + Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>With pneumonia or comorbidities</strong></td>
<td>admit to hospital + isolation procedures</td>
<td>plus mechanical ventilation</td>
</tr>
<tr>
<td><strong>Adjunct</strong></td>
<td></td>
<td>adjunct experimental therapies</td>
</tr>
<tr>
<td><strong>Without pneumonia or comorbidities</strong></td>
<td>consider home isolation</td>
<td>plus supportive care + monitoring</td>
</tr>
</tbody>
</table>
Treatment options

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer.
Initial suspected MERS

1st isolation procedures

» Isolation procedures should be initiated in all suspected cases of MERS.

» Patients with comorbidities (e.g., diabetes mellitus, heart disease, chronic renal impairment), age ≥50 years, or with the following signs should be admitted to hospital: respiratory rate >30 breaths/minute; hypoxaemia (SpO2 <90% on room air); severe respiratory distress; or clinical and/or radiological evidence of pneumonia.

» Patients should be placed in an adequately ventilated single room, clearly segregated from other patient care areas if possible. The number of healthcare workers and visitors should be kept to a minimum.

» The World Health Organization (WHO) recommends standard, droplet, and contact precautions, as well as airborne precautions when performing aerosol-generating procedures.[85]

» All healthcare workers and visitors, when in close contact (i.e., approximately 1 metre) with a probable or confirmed case, should always use: a medical mask; eye protection; a clean, non-sterile, long-sleeved gown; and gloves.

» Hand hygiene should always be performed before and after contact with the patient and their surroundings, and immediately after the removal of personal protective equipment.

» Movement of the patient outside of the barrier nursing room or area should be avoided unless medically necessary.

» Patients who do not require hospitalisation for medical reasons can be isolated at home. Infection control measures are still recommended and include using a single room, single bathroom (if possible), minimising contact with other household members, and wearing a surgical mask if contact is necessary.[86] [89] [127]

» [Centers for Disease Control and Prevention (CDC): interim infection prevention and control recommendations for hospitalized patients with MERS-CoV]
Middle East respiratory syndrome (MERS)

Treatment

Initial

» [World Health Organization (WHO): infection prevention and control during health care for probable or confirmed cases of MERS-CoV infection]

» [Centers for Disease Control and Prevention (CDC): implementing home care and isolation or quarantine of people not requiring hospitalization for MERS-CoV]

» [World Health Organization (WHO): home care for patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection presenting with mild symptoms and management of contacts]

plus supportive care + monitoring

Treatment recommended for ALL patients in selected patient group

Primary options

» paracetamol: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

OR

» ibuprofen: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

» Supportive therapies (e.g., oxygen, fluids, antipyretics/analgesics) should be started promptly depending on the clinical presentation.

» Patients with signs of severe respiratory distress, shock, or hypoxaemia should be started on oxygen therapy immediately. Initiate at 5 L/minute and titrate so that SpO2 ≥90%.[92]

Patients with impending or established respiratory failure should be admitted to the ICU. Intubation and mechanical ventilation are recommended if the patient is deteriorating and cannot maintain a SpO2 ≥90% with oxygen therapy.[81] [124]

» Cautious fluid management is recommended in patients if necessary, provided that there is no evidence of shock (more aggressive resuscitation may be required in patients with shock).[92]

» Data on pregnant women are limited. Pregnant women can be treated with the supportive therapies detailed above (except ibuprofen, which is not recommended in pregnant women especially in the third trimester), taking into account the physiological changes that occur with pregnancy.
**Initial**

» Specimens (e.g., blood cultures, serum, lower/upper respiratory tract specimens) should be collected according to the appropriate infection control measures. Blood cultures should be collected before antimicrobial therapy is started, if possible. Lower respiratory tract specimens are preferable to upper respiratory tract specimens, but both should be collected if possible.[92] Upper respiratory tract specimens (e.g., nasopharyngeal swab) are sufficient in patients isolated at home.

» Patients should be monitored closely for signs of deterioration and the development of complications including respiratory failure, acute respiratory distress syndrome, acute renal failure, septic shock, and multi-organ failure. Supportive therapy (e.g., haemodialysis, vasopressor therapy, fluid resuscitation, antimicrobials) should be initiated immediately if required.[5] [8] [26] [81] [124]

### plus empirical antimicrobial therapy

Treatment recommended for ALL patients in selected patient group

» Empirical antimicrobial therapy (including antibiotics and antivirals) should be started in inpatients with suspected MERS pneumonia (within one hour if sepsis is suspected) to cover all likely community-acquired or hospital-acquired (if patient has been admitted for >48 hours) pathogens.[92]

» Antimicrobial selection should be based on local epidemiology, susceptibility data, and guidelines until diagnosis is confirmed, and empirical therapy adjusted based on results.

» Treatment can be discontinued once a diagnosis of MERS is confirmed.
**Acute**

**confirmed MERS: post initial stabilisation and isolation measures**

1. **with pneumonia or comorbidities**

   - **1st admit to hospital + isolation procedures**

     - Patients with comorbidities (e.g., diabetes mellitus, heart disease, chronic renal impairment), age ≥50 years, smoking history, or with the following signs should be admitted to hospital: respiratory rate >30 breaths/minute; hypoxaemia (SpO2 <90% on room air); severe respiratory distress; or clinical and/or radiological evidence of pneumonia.

     - Isolation procedures should be initiated in all confirmed cases of MERS. Patients should be placed in an adequately ventilated single room, clearly segregated from other patient care areas. The number of healthcare workers and visitors should be kept to a minimum.

     - The WHO recommends standard, droplet, and contact precautions, as well as airborne precautions when performing aerosol-generating procedures.[85] All healthcare workers and visitors, when in close contact (i.e., approximately 1 metre) with a probable or confirmed case, should always use: a medical mask; eye protection; a clean, non-sterile, long-sleeved gown; and gloves.

     - Hand hygiene should always be performed before and after contact with the patient and their surroundings, and immediately after the removal of personal protective equipment.

     - Movement of the patient outside of the barrier nursing room or area should be avoided unless medically necessary.

     - These precautions should be used for the duration of the symptomatic illness and continued for at least 24 hours after the resolution of symptoms. Patients should be monitored for the clearance of infection using the recommended real-time reverse transcription polymerase chain reaction (RT-PCR) assays until there are 2 negative results on specimens taken at least 24 hours apart.[92] [89]

       - [Centers for Disease Control and Prevention (CDC): interim infection prevention and control recommendations for hospitalized patients with MERS-CoV]

       - [World Health Organization (WHO): infection prevention and control during health care for
### Treatment

**Acute** probable or confirmed cases of MERS-CoV infection  

**plus** supportive care + monitoring

Treatment recommended for ALL patients in selected patient group

**Primary options**

- **paracetamol**: 500-1000 mg orally every 4-6 hours when required, maximum 4000 mg/day

  **OR**

  - **ibuprofen**: 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day

  - Supportive therapies (e.g., oxygen, fluids, antipyretics/analgesics) should be started promptly depending on the clinical presentation.

  - Patients with signs of severe respiratory distress, shock, or hypoxaemia should be started on oxygen therapy immediately. Initiate at 5 L/minute and titrate so that SpO₂ ≥90%.[92]

  - Cautious fluid management is recommended in patients if necessary, provided that there is no evidence of shock (more aggressive resuscitation may be required in patients with shock).[92]

  - Data on pregnant women are limited. Pregnant women can be treated with the supportive therapies detailed above (except ibuprofen, which is not recommended in pregnant women especially in the third trimester), taking into account the physiological changes that occur with pregnancy.

  - Specimens (e.g., blood cultures, serum, lower/upper respiratory tract specimens) should be collected according to the appropriate infection control measures. Blood cultures should be collected before antimicrobial therapy is started, if possible. Lower respiratory tract specimens are preferable to upper respiratory tract specimens, but both should be collected if possible.[92] Frequency of specimen collection depends on local circumstances. The WHO recommends that respiratory tract specimens for RT-PCR should be collected at least every 2 to 4 days in the initial 2 weeks, and continue until there are 2 negative test results to confirm clearance of the virus.[92] The Ministry of Health (Saudi Arabia) recommends repeat testing one week after diagnosis, and then every 3 days.[89]
### Treatment

<table>
<thead>
<tr>
<th>Acute</th>
<th></th>
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<tbody>
<tr>
<td>» Patients should be monitored closely for signs of deterioration and the development of complications including respiratory failure, acute respiratory distress syndrome, acute renal failure, septic shock, and multi-organ failure. Supportive therapy (e.g., haemodialysis, vasopressor therapy, fluid resuscitation, antimicrobials) should be initiated immediately if required.[5] [8] [26] [81] [124]</td>
<td></td>
</tr>
</tbody>
</table>

### Adjunct mechanical ventilation

Treatment recommended for SOME patients in selected patient group

» Patients with impending or established respiratory failure should be admitted to the ICU.

» Intubation and mechanical ventilation are recommended if the patient is deteriorating and cannot maintain a SpO2 ≥90% with oxygen therapy.

» Noninvasive mechanical ventilation, mechanical ventilation, or extracorporeal membrane oxygenation (ECMO) have been used in patients with MERS.\[81\] \[124\] However, noninvasive ventilation should be avoided due to the high risk of generating aerosols, and because it lacks evidence of efficacy compared to endotracheal intubation and mechanical ventilation.\[89\] A small observational study found that ECMO was associated with lower mortality in MERS patients with refractory hypoxaemia.\[125\]

### Adjunct consider experimental therapies

Treatment recommended for SOME patients in selected patient group

» These therapies are generally only used in unstable patients with extensive pneumonia.

» There is no conclusive evidence at this time to recommend any virus-specific treatments; however, a number of treatments (e.g., interferon beta, interferon alfa, lopinavir, ribavirin, mycophenolate, and ciclosporin) have been studied for the treatment of MERS based on encouraging in vitro and animal studies.\[129\] \[130\]

» The WHO recommends that these drugs only be used under standard research treatment protocols and occur in the context of research trials.\[92\]

| without pneumonia or comorbidities | 1st consider home isolation |  |
TREATMENT

Acute

» Young, healthy patients with no comorbidities are at a lower risk of developing complications, and can be considered for home isolation if they do not require hospitalisation for medical reasons.\[86\] [89] [127] These patients generally have mild, non-specific symptoms such as fever, headache, malaise, cough, sore throat, or possibly gastrointestinal symptoms.\[10\]

» The CDC recommend that this is appropriate only once a healthcare professional, in consultation with their local or state health department, deems that the residential setting is suitable and that the patient is capable of adhering to recommended infection control precautions.\[128\]

» The WHO recommend that confirmed symptomatic cases should be isolated and monitored in a hospital setting whenever possible; however, home isolation may be considered in certain patients with mild symptoms and no underlying conditions (e.g., heart disease, renal failure) or immunocompromising conditions, if inpatient care is not available or is unsafe. The decision requires careful clinical judgement and should be informed by assessing the safety of the patient's home environment.\[127\]

» Infection control measures are still recommended and include using a single room, single bathroom (if possible), minimising contact with other household members, and wearing a surgical mask if contact is necessary.\[86\] [89]

» [Centers for Disease Control and Prevention (CDC): implementing home care and isolation or quarantine of people not requiring hospitalization for MERS-CoV]

» [World Health Organization (WHO): home care for patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection presenting with mild symptoms and management of contacts]

**plus** supportive care + monitoring

Treatment recommended for ALL patients in selected patient group

**Primary options**

» paracetamol: 500–1000 mg orally every 4-6 hours when required, maximum 4000 mg/day OR
### Acute

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>» ibuprofen:</strong> 200-400 mg orally every 4-6 hours when required, maximum 2400 mg/day</td>
</tr>
</tbody>
</table>

» Supportive therapies are recommended including antipyretics/analgesics (e.g., paracetamol, ibuprofen) for the relief of pain and fever. Patients should keep hydrated, but should not take in too much fluid as this can worsen oxygenation.[92]

» Data on pregnant women are limited. Pregnant women can be treated with the supportive therapies detailed above (except ibuprofen, which is not recommended in pregnant women especially in the third trimester), taking into account the physiological changes that occur with pregnancy.

» Patients should be monitored for the clearance of infection using the recommended RT-PCR assays every 2 to 4 days until there are 2 negative results.[92] [89] Infection control measures can be discontinued in these patients when the patient is asymptomatic and a single RT-PCR is negative.[89] Upper respiratory tract specimens (e.g., nasopharyngeal swab) are sufficient in these patients.
Emerging Experimental therapies

There is no conclusive evidence at this time to recommend any virus-specific treatments for patients with suspected or confirmed infection. If investigational agents are used, the World Health Organization (WHO) recommends that these drugs only be used under standard research treatment protocols and occur in the context of research trials.[92] Further studies are needed to evaluate the safety and efficacy of these agents in people with MERS.

Interferon alfa

Middle East respiratory syndrome coronavirus (MERS-CoV) has been found to be 50 to 100 times more sensitive to pegylated interferon alfa compared with severe acute respiratory syndrome (SARS) coronavirus.[130] The combination of interferon alfa-1b plus ribavirin has shown activity against MERS-CoV in vitro.[132] Infected rhesus macaques treated with this combination had lower viral loads, and a decreased incidence of respiratory distress and bilateral infiltrates on chest x-ray compared with infected controls.[133] However, the combination did not prove to be effective in a cohort of 5 confirmed human cases.[134] Pegylated interferon alfa-2a plus ribavirin was studied in a retrospective study in humans and compared with standard supportive treatment. This combination demonstrated significantly improved survival at 14 days; however, it did not reach statistical significance by 28 days.[26] Studies of this same combination in patients with various underlying conditions, including renal transplant, produced variable results.[88] [135] [136]

Interferon beta

Interferon beta has been shown to have superior activity in vitro against MERS-CoV compared with interferon alfa-2b and alfa-2a.[129] The combination of interferon beta plus ribavirin was compared with pegylated interferon alfa-2a plus ribavirin in a retrospective study of 24 patients. The study found no significant difference in 28-day survival between the 2 patient groups.[5]

Lopinavir

A protease inhibitor that has previously shown efficacy in treating SARS when used in combination with ribavirin.[137] It has been tested against MERS-CoV in in vitro studies; however, it has demonstrated suboptimal efficacy so far.[130] Superior clinical outcome and survival advantage have been reported compared with mycophenolate when tested in animal studies.[138] A case report has documented resolution of viraemia when used in combination with interferon and ribavirin.[139] A placebo-controlled trial of lopinavir/ritonavir with interferon-beta is in progress in Saudi Arabia.[140]

Ciclosporin

An immunosuppressant with known antiviral activity. Has demonstrated activity against MERS-CoV in vitro; however, the peak plasma levels needed for activity against the virus are not achievable with current approved doses.[141] Case reports of 2 patients, who were already receiving ciclosporin for other medical reasons and subsequently died of MERS, have been published.[17] [136] Based on the limited evidence available, use of ciclosporin is questionable.

Mycophenolate

An immunosuppressant with known antiviral activity. A number of in vitro studies have demonstrated activity against MERS-CoV.[129] [130] [142] [143] It has not been used in animal studies. There is a case report of a renal transplant patient, who was already on mycophenolate plus prednisolone, surviving MERS. There is also a case report of a patient receiving mycophenolate plus ciclosporin and prednisolone who did not survive.[136] [144]

Monoclonal antibodies
Monoclonal antibodies which target different epitopes in the receptor binding domain on the S1 subunit of the MERS-CoV spike (S) protein have been developed (e.g., Mersmab).[145] [146] [147] These antibodies have a higher affinity (i.e., 10 to 450 times higher) for the receptor binding domain compared with the functional receptor dipeptidyl peptidase-4 (DPP4; also called CD26) on the surface of host cells.[146] [148] [149] [150]

**Synthetic peptides**

A synthetic peptide (HR2P) has been developed to block the HR1 domain on the S2 subunit of the MERS-CoV virus, and has demonstrated a potent antiviral effect in vitro.[37] [76] [151] An intranasal formulation of this drug (HR2P-M2) has been developed. One study showed that it was effective in mice and was enhanced by using in combination with interferon beta.[152] Enfuvirtide, a HIV fusion inhibitor, is a HR2 peptide and is therefore another potential option for treatment.[153]

**Convalescent plasma**

Safety and efficacy of convalescent plasma for the treatment of MERS-CoV infection is being investigated; however, there are no data as yet and availability is extremely limited. The WHO has published a position paper on this matter and does not recommend its use outside of a clinical trial. [World Health Organization (WHO): position paper on collection and use of convalescent plasma or serum as an element in MERS-CoV response]

**Other drugs**

A cell-based enzyme-linked immunosorbent assay (ELISA) assay was used to screen a number of compounds for activity against MERS-CoV and found that 60 agents demonstrated activity, including chlorpromazine, tamoxifen, and chloroquine.[37]
Recommendations

Monitoring

Patients with confirmed infection should have their vital signs (i.e., respiratory rate, heart rate, blood pressure, oxygen saturation) monitored regularly. Renal function, liver function, and coagulation profile should also be monitored.

Frequency of specimen collection depends on local circumstances. The World Health Organization (WHO) recommends that respiratory tract specimens for real-time reverse transcription polymerase chain reaction (RT-PCR) should be collected at least every 2 to 4 days in the initial 2 weeks, and continue until there are 2 negative test results to confirm clearance of the virus. The Ministry of Health (Saudi Arabia) recommends repeat testing one week after diagnosis, and then every 3 days.

Patient instructions

Patients in home isolation should be advised to:

- Stay home
- Separate themselves from other people in the home
- Call ahead before visiting their doctor
- Wear a facemask when in the same room as other people
- Practise respiratory hygiene (i.e., cover mouth and nose when coughing and sneezing)
- Wash hands often using soap and water (or alcohol-based hand sanitiser)
- Avoid sharing household items
- Monitor their symptoms and seek prompt medical attention if illness is getting worse (e.g., difficulty breathing).

Detailed guidance for home isolation patients is available from the Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO):

- Centers for Disease Control and Prevention (CDC): preventing MERS-CoV from spreading to others in homes and communities
- World Health Organization (WHO): home care for patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection presenting with mild symptoms and management of contacts

Education:

- A fact sheet is available from the CDC: Centers for Disease Control and Prevention (CDC): information about MERS - fact sheet
- A fact sheet is also available from the WHO: World Health Organization (WHO): Middle East respiratory syndrome coronavirus (MERS-CoV) fact sheet

Travel:

- The CDC currently recommends practicing enhanced precautions (level 2 alert) when travelling to the Arabian Peninsula: Centers for Disease Control and Prevention (CDC): travelers' health - MERS in the Arabian Peninsula
- The WHO has produced detailed travel guidance for people participating in pilgrimages and mass gatherings: World Health Organization (WHO): technical guidance on travel and mass gatherings
- The CDC offers the following recommendations for travellers: wash hands often with soap and water (or alcohol-based sanitiser); avoid contact with people who are sick; wash hands before and after touching animals; avoid sick animals; avoid contact with camels or camel products if at a higher risk of infection (e.g., patients who are immunocompromised, or have diabetes mellitus,
Middle East respiratory syndrome (MERS)

kidney failure, or chronic lung disease); avoid consumption of raw or undercooked meat; practise respiratory hygiene if sick (e.g., cover mouth when coughing or sneezing).

Complications

<table>
<thead>
<tr>
<th>Complications</th>
<th>Timeframe</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>acute respiratory failure</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Reported in 25% to 95% of confirmed cases that required hospitalisation.[8] [26] [33]</td>
<td></td>
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<tr>
<td>Median time to invasive mechanical ventilation was 7 days in a cohort of 47 patients.[8]</td>
<td></td>
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<tr>
<td>Extracorporeal membrane oxygenation has been used in some cases; however, efficacy has not been confirmed.[26] [81]</td>
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<td></td>
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<tr>
<td>Risk factors include age ≥50 years, diabetes mellitus, end-stage renal disease, and obesity.[5] [8] [9] [26]</td>
<td></td>
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<tr>
<td>acute respiratory distress syndrome</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>New or worsening respiratory symptoms within one week of presentation. Chest x-ray shows bilateral opacities.[92]</td>
<td></td>
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<tr>
<td>High-flow oxygen (up to 50 mL/minute) is recommended in some patients, although mechanical ventilation and intubation is usually required.[92]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>acute renal failure</td>
<td>short term</td>
<td>medium</td>
</tr>
<tr>
<td>Initially reported in a few case reports.[14] [30] [82] Has since been reported in 58% of critically ill patients in one study, and 26% of patients in one cohort.[81] [156]</td>
<td></td>
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<tr>
<td>Possibly due to the presence of dipeptidyl peptidase-4 (DPP4) receptors in renal epithelial cells.[157]</td>
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<tr>
<td>Detection of the virus in urine samples has been previously documented.[155]</td>
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<td></td>
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<tr>
<td>multi-organ failure</td>
<td>short term</td>
<td>low</td>
</tr>
<tr>
<td>Occurs in a minority of patients late in the course of illness.</td>
<td></td>
<td></td>
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<tr>
<td>Underlying mechanism of action is unknown.</td>
<td></td>
<td></td>
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<tr>
<td>Usually presents with thrombocytopenia, prolonged coagulation profile, and circulatory collapse.[26] [33] [81]</td>
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<tr>
<td>Patients may require vasopressor and inotrope support.</td>
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</table>

Prognosis

The case fatality rate is approximately 35%.[154] This fatality rate is lower than previously reported rates in the literature as cohort studies generally include only patients who are sick enough to require hospitalisation.[5] [8] [9] [26]
Age ≥50 years has been associated with more severe presentation, worse outcomes, and a higher risk of mortality.\[5\] [27] In one cohort study, mortality increased with increasing age to reach 75% in patients >60 years of age.\[8\]

Presence of comorbidities (e.g., diabetes mellitus, chronic renal impairment, heart disease, obesity) increases the risk of acute respiratory failure and worse outcomes.\[5\] [8] [9] [26] [81]

**Natural course of infection**

As the clinical presentation is highly variable and ranges from no symptoms to rapidly progressive pneumonia, the natural course is also variable.

The median time from symptom onset to death ranges from 16.5 to 20.5 days in cohort studies.\[8\] [27] Median time to viral clearance, documented by negative real-time reverse transcription polymerase chain reaction (RT-PCR) on respiratory specimens, is 11 days (range 6 to 35 days).\[5\] [155] In patients who survived, median time from symptom onset to discharge from hospital was 27 days (range 20 to 31.5 days).\[27\]

Recurrence of infection in patients who have recovered has not been reported. There are currently no data on whether previous infection offers protection against future infection.
Diagnostic guidelines

International

Laboratory testing for Middle East respiratory syndrome coronavirus: interim guidance

Published by: World Health Organization (WHO)  Last published: 2018

North America

CDC laboratory testing for Middle East respiratory syndrome coronavirus (MERS-CoV)

Published by: Centers for Disease Control and Prevention (CDC)  Last published: 2018

CDC health information for international travel (Yellow Book): Middle East respiratory syndrome (MERS)

Published by: Centers for Disease Control and Prevention  Last published: 2017

Treatment guidelines

Europe

Middle East respiratory syndrome coronavirus (MERS-CoV): clinical management and guidance

Published by: Public Health England  Last published: 2018

MERS-CoV: clinical decision making support for treatment

Published by: Public Health England  Last published: 2017
### International

<table>
<thead>
<tr>
<th>Title</th>
<th>Published by</th>
<th>Last published</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home care for patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection presenting with mild symptoms and management of contacts - interim guidance</td>
<td>World Health Organization</td>
<td>2018</td>
</tr>
<tr>
<td>Surveillance for human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) - interim guidance</td>
<td>World Health Organization</td>
<td>2018</td>
</tr>
<tr>
<td>Considerations for mass gathering events and Middle East respiratory syndrome coronavirus (MERS-CoV) - interim guidance</td>
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<td>Management of asymptomatic persons who are RTPCR positive for Middle East respiratory syndrome coronavirus (MERS-CoV) - interim guidance</td>
<td>World Health Organization</td>
<td>2018</td>
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<td>Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected</td>
<td>World Health Organization (WHO)</td>
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### North America

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<tr>
<th>Title</th>
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<tr>
<td>Middle East respiratory syndrome (MERS): interim guidance for healthcare professionals</td>
<td>Centers for Disease Control and Prevention</td>
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<tr>
<td>Interim US guidance for monitoring and movement of persons with potential Middle East respiratory syndrome coronavirus (MERS-CoV) exposure</td>
<td>Centers for Disease Control and Prevention</td>
<td>2017</td>
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<td>Interim infection prevention and control recommendations for hospitalized patients with Middle East respiratory syndrome coronavirus (MERS-CoV)</td>
<td>Centers for Disease Control and Prevention</td>
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<td>CDC health information for international travel (Yellow Book): Middle East respiratory syndrome (MERS)</td>
<td>Centers for Disease Control and Prevention</td>
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<td>Asia</td>
<td>Middle East respiratory syndrome coronavirus: guidelines for healthcare professionals</td>
<td>Ministry of Health (Saudi Arabia)</td>
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<td>Antiviral treatment guidelines for Middle East Respiratory Syndrome</td>
<td>Korean Society of Infectious Diseases; Korean Society for Chemotherapy</td>
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<tr>
<td>Oceania</td>
<td>Middle East Respiratory Syndrome (MERS): information for health professionals</td>
<td>Australian Government Department of Health</td>
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Online resources

1. World Health Organization (WHO): Middle East respiratory syndrome coronavirus (MERS-CoV) (external link)
2. Centers for Disease Control and Prevention (CDC): Middle East respiratory syndrome (MERS) (external link)
3. World Health Organization (WHO): disease outbreak news (external link)
4. Centers for Disease Control and Prevention (CDC): interim infection prevention and control recommendations for hospitalized patients with MERS-CoV (external link)
5. World Health Organization (WHO): infection prevention and control during health care for probable or confirmed cases of MERS-CoV infection (external link)
6. World Health Organization (WHO): MERS-CoV - initial interview questionnaire of cases (external link)
7. Centers for Disease Control and Prevention (CDC): interim patient under investigation (PUI) guidance and case definitions (external link)
8. World Health Organization (WHO): case definition for reporting to WHO (external link)
9. Ministry of Health (Saudi Arabia): case definition (external link)
10. Centers for Disease Control and Prevention (CDC): interim guidelines for collecting, handling, and testing clinical specimens from patients under investigation for MERS-CoV (external link)
11. World Health Organization (WHO): laboratory testing for Middle East respiratory syndrome coronavirus (MERS-CoV) (external link)
12. Ministry of Health (Saudi Arabia): coronavirus (MERS-CoV) (external link)
13. World Health Organization (WHO): surveillance for human infection with Middle East respiratory syndrome coronavirus (MERS-CoV) (external link)
14. Centers for Disease Control and Prevention (CDC): implementing home care and isolation or quarantine of people not requiring hospitalization for MERS-CoV (external link)
15. World Health Organization (WHO): position paper on collection and use of convalescent plasma or serum as an element in MERS-CoV response (external link)
16. Centers for Disease Control and Prevention (CDC): preventing MERS-CoV from spreading to others in homes and communities (external link)
17. Centers for Disease Control and Prevention (CDC): information about MERS - fact sheet (external link)
18. World Health Organization (WHO): Middle East respiratory syndrome coronavirus (MERS-CoV) fact sheet (external link)

19. Centers for Disease Control and Prevention (CDC): travelers' health - MERS in the Arabian Peninsula (external link)

20. World Health Organization (WHO): technical guidance on travel and mass gatherings (external link)
Key articles


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22. Centers for Disease Control and Prevention. MERS in the US. September 2017 [internet publication]. Full text


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<th>Reference</th>
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<th>Journal</th>
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66. Centers for Disease Control and Prevention. MERS clinical features. September 2017 [internet publication]. Full text


Abstract

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85. World Health Organization. Infection prevention and control during health care for probable or confirmed cases of Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Interim guidance. June 2015 [internet publication].  Full text

86. Centers for Disease Control and Prevention. Preventing MERS-CoV from spreading to others in homes and communities. September 2017 [internet publication].  Full text


89. Ministry of Health (Saudi Arabia). Middle East respiratory syndrome coronavirus; guidelines for healthcare professionals, version 5.1. May 2018 [internet publication].  Full text

90. World Health Organization (WHO). Middle East respiratory syndrome coronavirus: case definition for reporting to WHO. July 2017 [internet publication].  Full text

91. Centers for Disease Control and Prevention. Interim patient under investigation (PUI) guidance and case definitions. September 2017 [internet publication].  Full text


95. Centers for Disease Control and Prevention. CDC laboratory testing for Middle East respiratory syndrome coronavirus (MERS-CoV). June 2018 [internet publication]. Full text


128. Centers for Disease Control and Prevention. Implementing home care and isolation or quarantine of people not requiring hospitalization for MERS-CoV. September 2017 [internet publication].  Full text


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Figure 1: Electron micrograph of a thin section of Middle East respiratory syndrome coronavirus (MERS-CoV) showing the spherical particles within the cytoplasm of an infected cell

Centers for Disease Control and Prevention (CDC)
Figure 2: Negative stain electron microscopy showing Middle East respiratory syndrome coronavirus (MERS-CoV) particles with characteristic club-like projections from the viral membrane

Centers for Disease Control and Prevention (CDC)
Figure 3: Algorithm for testing cases under investigation by reverse transcription polymerase chain reaction (RT-PCR)

Produced by the BMJ Evidence Centre (adapted from WHO laboratory testing for Middle East respiratory syndrome coronavirus - interim guidance (revised) WHO/MERS/LAB/15.1/Rev1/2018)
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