Clinical management of severe acute respiratory infection when Middle East respiratory syndrome coronavirus (MERS-CoV) infection is suspected

Interim guidance

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Introduction

The first edition of this document was published in 2013 and was revised in 2015. The current version is aligned with other WHO documents on case definitions and laboratory testing for MERS and incorporates changes to recommendations in supportive care of patients with critical illness based on evidence published since the last update.

This document is intended for clinicians taking care of hospitalised adult and paediatric patients with severe acute respiratory infection (SARI) when MERS-CoV infection is suspected. It is not meant to replace clinical judgment or specialist consultation but rather to strengthen clinical management of these patients and provide references to up-to-date guidance.

This document is organized into the following sections:

1. Early recognition of patients with SARI
2. Immediate implementation of appropriate infection prevention and control (IPC) measures
3. Early supportive therapy and monitoring
4. Collection of specimens for laboratory diagnosis
5. Management of hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS)
6. Management of septic shock
7. Prevention of complications
8. Specific anti-MERS-CoV treatments
9. Special considerations for pregnant patients

These symbols are used to flag interventions:

Do: the intervention is beneficial (strong recommendation) **OR** the intervention is a best practice statement

Don't: the intervention is known to be harmful.

Consider: the intervention may be beneficial in selected patients (weak recommendation) **OR** be careful when considering this intervention.

The emergence of a novel coronavirus in 2012, later named the Middle East respiratory syndrome coronavirus (MERS-CoV), has presented challenges for clinical management. As of December 2018, there have been 2266 laboratory-confirmed cases of human infection reported to WHO and 804 deaths, for a case-fatality rate of 35.5%. Twenty-seven countries have reported cases, including those in the Middle East, Africa, Europe, North America and Asia. For epidemiologic updates, see the WHO MERS-CoV website at http://www.who.int/emergencies/mers-cov/en/.

MERS-CoV is a zoonotic virus with dromedary camels as the source of human infection. Approximately half of the reported MERS-CoV infections have resulted from human-to-human transmission in health care settings; contact with respiratory droplets, body fluids, and contaminated environmental surfaces, and aerosol-generating procedures have contributed to spread.[1,2] MERS-CoV does not appear to transmit easily from person to person unless there is close contact, such as providing clinical care to an infected patient while not applying appropriate IPC measures, although super-spreading events have been reported in some health care facilities.[3,4] Secondary cases among household contacts have been reported less often.[5] Sustained human-to-human transmission of MERS-CoV has not been observed. Seroepidemiologic studies of high-risk workers and results from comprehensive contact tracing and testing have identified asymptomatic infections.[6]

The clinical manifestations of MERS-CoV infections range from asymptomatic infection to severe pneumonia, often complicated by ARDS, septic shock, and multi-organ failure leading to death. Patients with clinical illness (MERS) present after an incubation period of 2 to 14 days with signs and symptoms of fever, chills, myalgias, cough, and dyspnoea.[7] Some patients have gastrointestinal symptoms such as nausea, vomiting and diarrhoea. Fever may be absent in up to 15% of hospitalized cases.[8] Rapid progression to ARDS occurs, with a median of 2 days from hospitalization to intensive care unit (ICU) admission. Laboratory abnormalities include cytopenias and elevated transaminases. Co-infections with other respiratory viruses and bacterial pathogens have been reported.[9]

The majority of patients with severe disease have been >50 years old and with at least one comorbid condition (e.g. diabetes, hypertension, cardiac disease, obesity, chronic lung disease, end-stage renal disease, cancer, or receiving immunosuppressive

therapy). Mild illness or asymptomatic infections have occurred predominantly among younger healthy persons, including health care workers. Infections among children are uncommon. Predictors of mortality include older age and chronic lung disease. A more detailed description of clinical and laboratory features of MERS-CoV infection can be found in a recent review.[9]

This document aims to provide clinicians with updated interim guidance on timely, effective, and safe supportive management of patients with MERS-CoV and SARI, particularly those with critical illness.

The recommendations in this document are derived from WHO publications.[10-13] Where WHO guidance is not available, we refer to evidence-based guidelines and data from published randomized clinical trials (RCTs) and observational studies. Members of a WHO global network of clinicians, MERS experts and clinicians who have treated MERS patients have reviewed the recommendations (see Acknowledgements). For queries, please email outbreak@who.int with 'MERS-CoV clinical question' in the subject line.

Related WHO documents include those focussed on home care for patients with mild infections and management of contacts,[14] management of asymptomatic individuals who are positive for MERS-CoV by reverse transcriptase-polymerase chain reaction (RT-PCR),[15] and IPC.[16]

1. Early recognition of patients with SARI

Recognize all patients with suspected MERS-CoV infection, including those with SARI.

Remarks: Life-threatening manifestations of MERS-CoV infection include severe pneumonia, ARDS, sepsis and septic shock. Early recognition of these clinical syndromes allows for timely initiation of IPC and treatment of patients.

Table 1. Definitions of MERS-CoV confirmed and probable cases and related clinical syndromes

Confirmed MERS-CoV case	A person with laboratory confirmation of MERS-CoV infection (viral nucleic acid detection or serology), irrespective of clinical signs and symptoms.
Probable MERS-CoV case (either [1], [2], or [3])[17]	1. A febrile ARI with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or ARDS), AND Direct epidemiologic link with a laboratory-confirmed MERS-CoV case, AND Testing for MERS-CoV is unavailable, negative on a single inadequate specimen, or inconclusive (as defined in [17]) 2. A febrile ARI with clinical, radiological, or histopathological evidence of pulmonary parenchymal disease (e.g. pneumonia or ARDS) not explained fully by any other etiology, AND The person resides or travelled in the Middle East, or in countries where MERS-CoV is known to be circulating in dromedary camels or where human infections have recently occurred, AND Testing for MERS-CoV is inconclusive 3. An acute febrile respiratory illness of any severity, AND Direct epidemiologic link with a confirmed MERS-CoV case, AND Testing for MERS-CoV is inconclusive
Severe acute respiratory infection (SARI)	An ARI with history of fever or measured temperature ≥38 C° and cough; onset within the last ~10 days; and requiring hospitalization.[18] However, the absence of fever does NOT exclude MERS-CoV infection.[8] Thus, even in the absence of fever, a patient with a history of cough or other respiratory symptoms should still be evaluated for MERS-CoV exposure.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of respiratory rate >30 breaths/min, severe respiratory distress, or SpO_2 <90% on room air (adapted from [10]). Child with cough or difficulty in breathing, plus at least one of the following: central cyanosis or SpO_2 <90%; severe respiratory distress (e.g. grunting, very severe chest indrawing); signs of pneumonia with a general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions. Other signs of pneumonia may be present: chest indrawing, tachypnoea (in breaths/min): <2 months, ≥60; 2–11 months, ≥50; 1–5 years, ≥40.[11] The diagnosis is clinical; chest imaging can exclude complications.
Acute Respiratory Distress Syndrome[19-21]	**Onset:** new or worsening respiratory symptoms within one week of known clinical insult. **Chest imaging (radiograph, CT scan, or lung ultrasound):** bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules. **Origin of oedema:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present. **Oxygenation (adults):** • Mild ARDS: 200 mmHg < PaO_2/FiO_2 ≤ 300 mmHg (with PEEP or CPAP ≥5 cmH_2O,[19] or non-ventilated[20]) • Moderate ARDS: 100 mmHg < PaO_2/FiO_2 ≤200 mmHg with PEEP ≥5 cmH_2O,[19] or non-ventilated[20]) • Severe ARDS: PaO_2/FiO_2 ≤ 100 mmHg with PEEP ≥5 cmH_2O,[19] or non-ventilated[20]) • When PaO_2 is not available, SpO_2/FiO_2 ≤315 suggests ARDS (including in non-ventilated patients) **Oxygenation (children; note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2):** • Bilevel NIV or CPAP ≥5 cmH_2O via full face mask: PaO_2/FiO_2 ≤ 300 mmHg or SpO_2/FiO_2 ≤264 • Mild ARDS (invasively ventilated): 4 ≤ OI < 8 or 5 ≤ OSI < 7.5 • Moderate ARDS (invasively ventilated): 8 ≤ OI < 16 or 7.5 ≤ OSI < 12.3 • Severe ARDS (invasively ventilated): OI ≥ 16 or OSI ≥ 12.3
Sepsis[22,23]	Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction defined by an increase in the Sequential [Sepsis-related] Organ Failure Assessment (SOFA) score[24] of ≥2 points. Assume the baseline score is zero if data are not available. The SOFA score ranges from 0 to 24 and includes points related to 6

	organ systems: respiratory (hypoxemia defined by low PaO_2/FiO_2), coagulation (low platelets), liver (high bilirubin), cardiovascular (hypotension), central nervous system (low level of consciousness defined by Glasgow Coma Scale), and renal (low urine output or high creatinine). Children: suspected or proven infection and ≥2 SIRS criteria, of which one must be abnormal temperature or white blood cell count.
Septic shock[22,25]	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥65 mmHg and serum lactate level >2 mmol/L. Children (based on [25]): any hypotension (SBP <5th centile or >2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR <90 bpm or >160 bpm in infants and HR <70 bpm or >150 bpm in children); prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

Abbreviations: ARI, acute respiratory infection; BP, blood pressure; bpm, beats/minute; CPAP, continuous positive airway pressure; FiO_2, fraction of inspired oxygen; MAP, mean arterial pressure; NIV, noninvasive ventilation; OI, Oxygenation Index; OSI, Oxygenation Index using SpO_2; PaO_2, partial pressure of oxygen; PEEP, positive end-expiratory pressure; SBP, systolic blood pressure; SD, standard deviation; SIRS, systemic inflammatory response syndrome; SpO_2, oxygen saturation. *If altitude is higher than 1000m, then correction factor should be calculated as follows: PaO_2/FiO_2 x Barometric pressure/760. ♦Small studies have found that in patients with MERS-CoV infection, the most common radiographic finding is peripherally predominant ground glass opacities. However, consolidation, mixed ground glass and consolidation and pleural effusion have also been described.[26]

2. Immediate implementation of appropriate IPC measures

IPC is a critical and integral part of clinical management of patients and should be initiated at the point of entry of the patient to hospital (typically the Emergency Department). WHO IPC guidance related to MERS-CoV is available.[16]

Table 2. How to implement infection prevention and control measures[16,27]

When caring for ALL patients	Apply routinely in all health-care settings for all patients. Standard precautions include hand hygiene; use of PPE to avoid direct contact with patients' blood, body fluids, secretions (including respiratory secretions) and non-intact skin. Standard precautions also include prevention of needle-stick or sharps injury; safe waste management; cleaning and disinfection of equipment; and cleaning of the environment.
When caring for patients with cough or other respiratory symptoms (ARI)	Droplet precautions prevent large droplet transmission of respiratory viruses. Use a medical mask if working within 1 metre of the patient. Place patients in single rooms, or group together those with the same etiological diagnosis. If an etiological diagnosis is not possible, group patients with similar clinical diagnosis and based on epidemiological risk factors, with a spatial separation of at least 1 metre. When providing care in close contact with a patient with respiratory symptoms (e.g. coughing or sneezing), use eye protection (face-mask or goggles), because sprays of secretions may occur. Limit patient movement within the institution and ensure that patients wear medical masks when outside their rooms.
When caring for patients with suspected MERS	Droplet and contact precautions prevent direct or indirect transmission from contact with contaminated surfaces or equipment (i.e. contact with contaminated oxygen tubing/interfaces). Use PPE (medical mask, eye protection, gloves and gown) when entering room and remove PPE when leaving. If possible, use either disposable or dedicated equipment (e.g. stethoscopes, blood pressure cuffs and thermometers). If equipment needs to be shared among patients, clean and disinfect between each patient use. Ensure that health care workers refrain from touching their eyes, nose, and mouth with potentially contaminated gloved or ungloved hands. Avoid contaminating environmental surfaces that are not directly related to patient care (e.g. door handles and light switches). Ensure adequate room ventilation. Avoid movement of patients or transport. Perform hand hygiene.
When performing an aerosol-generating procedure in patient with ARI	Ensure that healthcare workers performing aerosol-generating procedures **(i.e. open suctioning of respiratory tract, high-flow nasal oxygen, non-invasive ventilation, intubation, bronchoscopy, cardiopulmonary resuscitation)** use PPE, including gloves, long-sleeved gowns, eye protection, and fit-tested particulate respirators (N95 or equivalent, or higher level of protection). (The scheduled fit test should not be confused with user seal check before each use.) Whenever possible, use adequately ventilated single rooms when performing aerosol-generating procedures, meaning negative pressure rooms with minimum of 12 air changes per hour or at least 160 litres/second/patient in facilities with natural ventilation. Avoid the presence of unnecessary individuals in the room. Care for the patient in the same type of room after mechanical ventilation commences.

Abbreviations: ARI, acute respiratory infection; PPE, personal protective equipment

3. Early supportive therapy and monitoring

Give supplemental oxygen therapy immediately to patients with SARI and respiratory distress, hypoxaemia, or shock.

Remarks: Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO_2 ≥90% in non-pregnant adults and SpO_2 ≥92-95 % in pregnant patients.[10,11] Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive oxygen therapy during resuscitation to target SpO_2 ≥94%; otherwise, the target SpO_2 is ≥90%.[13] All areas where patients with SARI are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask, and mask with reservoir bag). Use contact precautions when handling contaminated oxygen interfaces of patients with MERS-CoV infection.

Use conservative fluid management in patients with SARI when there is no evidence of shock.

Remarks: Patients with SARI should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation.[28]

Give empiric antimicrobials to treat all likely pathogens causing SARI. Give antimicrobials within one hour of initial patient assessment for patients with sepsis.

Remarks: Although the patient may be suspected to have MERS, administer appropriate empiric antimicrobials within **ONE hour** of identification of sepsis.[29] Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia [if infection was acquired in healthcare setting], or sepsis), local epidemiology and

susceptibility data, and treatment guidelines. Empiric therapy includes a neuraminidase inhibitor for treatment of influenza when there is local circulation or other risk factors, including travel history or exposure to animal influenza viruses.[30] Empiric therapy should be de-escalated on the basis of microbiology results and clinical judgment.

Do not routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason.

Remarks: A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance).[31] A systematic review of observational studies in influenza found a higher risk of mortality and secondary infections with corticosteroids; the evidence was judged as very low to low quality due to confounding by indication.[32] A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality.[33] Finally, a recent study of patients receiving corticosteroids for MERS used a similar statistical approach and found no effect of corticosteroids on mortality but delayed lower respiratory tract (LRT) clearance of MERS-CoV.[34] Given lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. See section 6 for the use of corticosteroids in sepsis.

Closely monitor patients with SARI for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and apply supportive care interventions immediately.

Remarks: Application of timely, effective, and safe supportive therapies is the cornerstone of therapy for patients that develop severe manifestations of MERS.

Understand the patient's co-morbid condition(s) to tailor the management of critical illness and appreciate the prognosis. Communicate early with patient and family.

Remarks: During intensive care management of SARI, determine which chronic therapies should be continued and which therapies should be stopped temporarily. Communicate proactively with patients and families and provide support and prognostic information. Understand the patient's values and preferences regarding life-sustaining interventions.

4. Collection of specimens for laboratory diagnosis

WHO guidance on specimen collection, processing, and laboratory testing, including related biosafety procedures, is available.[35]

Collect blood cultures for bacteria that cause pneumonia and sepsis, ideally before antimicrobial therapy. DO NOT delay antimicrobial therapy to collect blood cultures.

When possible, collect specimens from BOTH the upper respiratory tract (URT; nasopharyngeal and oropharyngeal) AND lower respiratory tract (LRT; sputum, endotracheal aspirate, or bronchoalveolar lavage) for MERS-CoV testing by RT-PCR. Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients).

Serology for diagnostic purposes is recommended only when RT-PCR is not available.[35]

Remarks: Use appropriate PPE for specimen collection (droplet and contact precautions for URT specimens; airborne precautions for LRT specimens). When collecting URT samples, use viral swabs (sterile Dacron or rayon, not cotton) and viral transport media. Do not sample the nostrils or tonsils. In a patient with suspected MERS, especially with pneumonia or severe illness, a single URT sample does not exclude the diagnosis, and additional URT and LRT samples are recommended.[35] LRT (vs. URT) samples are more likely to be positive and for a longer period.[35] Clinicians may elect to collect only LRT samples when these are readily available (for example, in mechanically ventilated patients).

If there is diagnostic uncertainty, both URT and LRT specimens can tested for other respiratory viruses, such as influenza A and B (including zoonotic influenza A), respiratory syncytial virus, parainfluenza viruses, rhinoviruses, adenoviruses, enteroviruses (e.g. EVD68), human metapneumovirus, and endemic human coronaviruses (i.e. HKU1, OC43, NL63, and 229E). LRT specimens can also be tested for bacterial pathogens, including *Legionella pneumophila*.

Although routine blood collection for MERS-CoV testing using RT-PCR is not recommended, a positive RT-PCR result is associated with a more severe clinical course and higher mortality.[36]

Serology for diagnostic purposes is recommended only when RT-PCR is not available, and is not useful for early diagnosis of MERS-CoV infection because 3 weeks are often required for the detection of seroconversion. Paired samples can be collected for retrospective diagnosis. Ideally, these should be collected 14–21 days apart, with the first being taken during the first week of illness. If only one sample can be collected, do so at least 14 days after the onset of symptoms.[35]

In hospitalized patients with confirmed MERS-CoV infection, repeat URT and LRT samples should be collected to demonstrate viral clearance. The frequency of specimen collection will depend on local circumstances but should be at least every 2 to 4 days until there are two consecutive negative results (both URT and LRT samples if both are collected) in a clinically recovered patient at least 24 hours apart. If local infection control practice requires two negative results before removal of droplet precautions, specimens may be collected as often as daily.

Remarks: Prolonged viral shedding (>1 month) has been detected in respiratory tract of patients, particularly in LRT samples,[37] those with severe illness or if treated with corticosteroids,[34] and can occur even when patients have clinically recovered.[38,39]

5. Management of hypoxemic respiratory failure and ARDS

Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy.

Remarks: Patients may continue to have increased work of breathing or hypoxemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10-15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO_2 0.60-0.95). Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation.

High-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) should only be used in selected patients with hypoxemic respiratory failure. The risk of treatment failure is high in patients with MERS treated with NIV, and patients treated with either HFNO or NIV should be closely monitored for clinical deterioration.

Remarks:

1. HFNO systems can deliver 60 L/min of gas flow and FiO_2 up to 1.0; paediatric circuits generally only handle up to 15 L/min, and many children will require an adult circuit to deliver adequate flow. Compared to standard oxygen therapy, HFNO reduces the need for intubation.[40] Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), hemodynamic instability, multi-organ failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia.[41] Patients receiving HFNO should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hr). Evidence-based guidelines on HFNO do not exist, and reports on HFNO in MERS patients are limited.[42]

2. NIV guidelines make no recommendation on use in hypoxemic respiratory failure (apart from cardiogenic pulmonary oedema and post-operative respiratory failure) or pandemic viral illness (referring to studies of SARS and pandemic influenza).[43] Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate when MERS patients receive NIV.[44] Patients receiving a trial of NIV should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hr). Patients with hemodynamic instability, multiorgan failure, or abnormal mental status should not receive NIV.

3. Because of the potential for aerosol generation, use airborne precautions when MERS patients receive HFNO or NIV.

Endotracheal intubation should be performed by a trained and experienced provider.

Remarks: Patients with ARDS, especially young children or those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenate with 100% FiO_2 for 5 minutes, via a face mask with reservoir bag, bag-valve mask, HFNO, or NIV. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation. Use airborne precautions.

The following recommendations in this section pertain to mechanically ventilated patients with ARDS.[29,45] *These focus on adults; consensus-based recommendations for children are available.*[46]

Implement mechanical ventilation using lower tidal volumes (4–8 ml/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure <30 cmH_2O).

Remarks: This is a strong recommendation from a clinical guideline for patients with ARDS,[45] and is suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria.[29] The initial tidal volume is 6 ml/kg PBW; tidal volume up to 8 ml/kg PBW is allowed if undesirable side effects occur (e.g. dyssynchrony, pH <7.15). Hypercapnia is permitted if meeting the pH goal of 7.30-7.45. Ventilator protocols are available.[47] The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets. Although high driving pressure (plateau pressure−PEEP) may more accurately predict increased mortality in ARDS compared to high tidal volume or plateau pressure,[48] RCTs of ventilation strategies that target driving pressure are not currently available.

In patients with moderate or severe ARDS, higher PEEP instead of lower PEEP is suggested.

Remarks: PEEP titration requires consideration of benefits (reducing atelectrauma and improving alveolar recruitment) vs. risks (end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance). Tables are available to guide PEEP titration based on the FiO_2 required to maintain SpO_2.[47] A related intervention of recruitment manoeuvres (RMs) is delivered as episodic periods of high continuous positive airway pressure [30–40 cm H_2O], progressive incremental increases in PEEP with constant driving pressure, or high driving pressure; considerations of benefits vs. risks are similar. Higher PEEP and RMs were both conditionally recommended in a clinical practice guideline.[45] For PEEP, the guideline considered an individual patient data meta-analysis[49] of 3 RCTs. However, a subsequent RCT of high PEEP and prolonged high-pressure RMs showed harm; suggesting that the protocol in this RCT should be avoided.[50] Monitoring of patients to identify those who respond to the initial application of higher PEEP or a different RM protocol, and stopping these interventions in non-responders, is suggested.[51]

Avoid disconnecting the patient from the ventilator, which results in loss of PEEP and atelectasis. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator).

In patients with severe ARDS, prone ventilation for >12 hours per day is recommended.

Remarks: Application of prone ventilation is strongly recommended for adult and paediatric patients with severe ARDS[45] but requires sufficient human resources and expertise to be performed safely.[52,53]

In patients with moderate-severe ARDS (PaO_2/FiO_2 <150), consider neuromuscular blockade by continuous infusion for the initial 48 hours.

Remarks: One trial found that this strategy improved survival in patients with severe ARDS (PaO_2/FiO_2 <150) without causing significant weakness,[54] but results of a larger trial are pending (NCT02509078).

In high-resource settings, consider referral of patients with refractory hypoxemia to a centre with expertise in extracorporeal life support (ECLS).

Remarks: A recent guideline made no recommendation about ECLS in patients with ARDS.[45] Since then, an RCT of ECLS for patients with ARDS was stopped early and found no statistically significant difference in 60-day mortality between ECLS and standard medical management (including prone positioning and neuromuscular blockade).[55] However, ECLS was associated with a reduced risk of the composite outcome of mortality and crossover to ECLS,[55] and a *post hoc* Bayesian analysis of this RCT showed that ECLS is very likely to reduce mortality across a range of prior levels of enthusiasm or scepticism.[56] In patients with MERS-CoV infection, ECLS vs. conventional treatment was associated with reduced mortality in a cohort study.[57] ECLS should only be offered in expert centres with a sufficient case volume to maintain expertise.[58]

Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.

Remarks: This is a strong guideline recommendation;[29] the main effect is to shorten the duration of ventilation. See reference [59] for details of a sample protocol.

6. Management of septic shock

Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) ≥65 mmHg AND lactate is ≥2 mmol/L, in absence of hypovolemia.
Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] <5th centile or >2 SD below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR <90 bpm or >160 bpm in infants and HR <70 bpm or >150 bpm in children); prolonged capillary refill (>2 sec) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

Remarks: In the absence of a lactate measurement, use MAP and clinical signs of perfusion to define shock. Standard care includes early recognition and the following treatments within 1 hour of recognition: antimicrobial therapy and fluid loading and vasopressors for hypotension.[60] The use of central venous and arterial catheters should be based on resource availability and individual patient needs. Detailed guidelines are available for the management of septic shock in adults[29] and children.[11,12,25]

In resuscitation from septic shock in adults, give at least 30 ml/kg of isotonic crystalloid in adults in the first 3 hours. In resuscitation from septic shock in children, give 20 ml/kg as a rapid bolus and up to 40-60 ml/kg in the first 1 hr.

Do not use hypotonic crystalloids, starches, or gelatins for resuscitation.

Fluid resuscitation may lead to volume overload, including respiratory failure. If there is no response to fluid loading and signs of volume overload appear (for example, jugular venous distension, crackles on lung auscultation, pulmonary oedema on imaging, or hepatomegaly in children), then reduce or discontinue fluid administration. This step is particularly important where mechanical ventilation is not available.

Remarks: Crystalloids include normal saline and Ringer's lactate. Determine need for additional fluid boluses (250-1000 ml in adults or 10-20 ml/kg in children) based on clinical response and improvement of perfusion targets. Perfusion targets include MAP (>65 mmHg or age-appropriate targets in children), urine output (>0.5 ml/kg/hr in adults, 1 ml/kg/hr in children), and improvement of skin mottling, capillary refill, level of consciousness, and lactate. Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local resources and experience.[29] These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation.

Starches are associated with an increased risk of death and acute kidney injury vs. crystalloids. The effects of gelatins are less clear, but they are more expensive than cyrstalloids.[61,62] Hypotonic (vs. isotonic) solutions are less effective at increasing intravascular volume. Surviving Sepsis also suggests albumin for resuscitation when patients require substantial amounts of crystalloids, but this weak recommendation is based on low-quality evidence.[29]

Administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥65 mmHg in adults and age-appropriate targets in children.

If central venous catheters are not available, vasopressors can be given through a peripheral IV, but use a large vein and closely monitor for signs of extravasation and local tissue necrosis. If extravasation occurs, stop infusion. Vasopressors can also be administered through intraosseous needles.

If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider an inotrope such as dobutamine.

Remarks: Vasopressors (i.e. norepinephrine, epinephrine, vasopressin, and dopamine) are most safely given through a central venous catheter at a strictly controlled rate, but it is also possible to safely administer them via peripheral vein[63] and intraosseous needle. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose necessary to maintain perfusion and prevent side effects. Norepinephrine is considered first-line in adult patients; epinephrine or vasopressin can be added to achieve the MAP target. Because of the risk of tachyarrhythmia, reserve dopamine for selected patients with low risk of tachyarrhythmia or those with bradycardia. In children with cold shock (more common), epinephrine is considered first-line, while norepinephrine is used in patients with warm shock (less common).

No RCTs have compared dobutamine to placebo for clinical outcomes.[29]

In patients with sepsis, consider intravenous hydrocortisone (up to 200 mg/day, 1 mg/kg every 6 hours for children) or prednisolone (up to 50 mg/day).

Remarks: A recent guideline that incorporates the findings of 2 recent large RCTs makes a weak recommendation for corticosteroids for all patients with sepsis (including septic shock).[64] Surviving Sepsis guidelines, written before these RCTs were reported, recommend corticosteroids only for patients in whom adequate fluids and vasopressor therapy do not restore hemodynamic stability.[29] Clinicians considering corticosteroids for a patient with MERS-CoV and with sepsis must balance the potential small reduction in mortality with the downside of prolonged shedding of MERS-CoV in the respiratory tract.[34,37,65] If corticosteroids are prescribed, monitor and treat hyperglycaemia, hypernatraemia, and hypokalaemia. Monitor for recurrence of inflammation and signs of adrenal insufficiency after stopping corticosteroids, which may have to be tapered.

7. Prevention of complications

Implement the following interventions (Table 3) to prevent complications associated with critical illness. These interventions are based on Surviving Sepsis[29] or other guidelines,[66-69] and are generally limited to feasible recommendations based on high quality evidence.

Table 3. Prevention of complications

Anticipated Outcome	Interventions
Reduce days of invasive mechanical ventilation	• Use weaning protocols that include daily assessment for readiness to breathe spontaneously • Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions
Reduce incidence of ventilator-associated pneumonia	• Oral intubation is preferable to nasal intubation in adolescents and adults • Keep patient in semi-recumbent position (head of bed elevation 30-45º) • Use a closed suctioning system; periodically drain and discard condensate in tubing • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged but not routinely • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days
Reduce incidence of venous thromboembolism	• Use pharmacological prophylaxis (low molecular-weight heparin [preferred if available] or heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).
Reduce incidence of catheter-related bloodstream infection	• Use a checklist with completion verified by a real-time observer as reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed
Reduce incidence of pressure ulcers	• Turn patient every two hours
Reduce incidence of stress ulcers and gastrointestinal bleeding	• Give early enteral nutrition (within 24–48 hours of admission) • Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for gastrointestinal bleeding include mechanical ventilation for ≥48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score
Reduce incidence of ICU-related weakness	• Actively mobilize the patient early in the course of illness when safe to do so

8. Specific anti-MERS-CoV treatments

There is no current evidence from RCTs to recommend any specific anti-MERS-CoV treatment for patients with suspected or confirmed MERS.

Unlicenced treatments should be administered only in the context of peer-reviewed research studies with local ethics committee approval.

Open access SARI data collection protocols and case record forms are available at https://isaric.tghn.org/protocols/severe-acute-respiratory-infection-data-tools/

Remarks: Various treatments have been postulated to have anti-MERS-CoV efficacy, based on *in vitro*, animal, or clinical studies with SARS-CoV or MERS-CoV. These agents include interferons, ribavirin, lopinavir/ritonavir, polyclonal anti-MERS-CoV human antibodies and immunoglobulin, humanized murine anti-S monoclonal antibodies, nucleoside viral RNA polymerase inhibitors (e.g. remdesivir), peptidic inhibitors (e.g. HR2P-M2), and mycophenolate mofetil (MMF) (details in [9]).

Observational studies in patients with MERS-CoV of interferons, ribavirin, and lopinavir/ritonavir with IFN-β1b have not shown consistent effects.[9] Of note, while MMF is inhibitory in cell culture,[70] it was harmful and associated with increased MERS-CoV replication in a non-human primate study.[71] Ribavirin does not inhibit viral replication *in vitro* at a concentration that could be achieved reliably with current human dosing regimens.[70] One RCT of lopinavir/ritonavir and recombinant IFN-β1b vs. standard care is currently enrolling patients.[72] A trial protocol for convalescent plasma from recovered patients is registered,[73] but feasibility may be limited by the low prevalence of MERS survivors with high antibody titres.[74,75] A phase 1 study of a fully human polyclonal IgG antibody (SAB-301) produced from the hyperimmune plasma of transchromosomic cattle immunized with a MERS-CoV vaccine showed no safety concerns at single doses up to 50 mg/kg.[76] Other studies on MERS can be found on the WHO International Clinical Trials Registry Platform (http://apps.who.int/trialsearch/).

RCTs are needed to evaluate these agents, ideally with standardized approaches to supportive care and pre-planned individual patient data meta-analyses to combine studies performed in different outbreaks. WHO through the WHO R&D Blueprint is working with academic, medical and public health partners to identify suitable therapies for clinical trials and is in the process of developing clinical protocols for the study of specific anti-MERS-CoV agents.[77] A list of potential therapies have also been previously been compiled by Public Health England and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC).[78]

9. Special considerations for pregnant patients

- **Pregnant women with MERS should be treated with supportive therapies as described above, taking into account the physiologic adaptations of pregnancy.**

- **The use of investigational therapeutic agents outside of a research study should be guided by individual risk-benefit analysis based on potential benefit for mother and safety to fetus, with consultation from an obstetric specialist and ethics committee.**

Remarks: Ribavirin has been shown to be genotoxic in vitro and teratogenic in animal models. Other potential specific anti-MERS-CoV treatments have not been tested for safety in pregnancy and therefore their use should be considered only when potential benefits outweigh the risks.

- **Emergency delivery and pregnancy termination decisions are challenging and based on many factors: gestational age, maternal condition, and fetal stability. Consultations with obstetric, neonatal, and intensive care specialists (depending on the condition of the mother) are essential.**

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Non-WHO experts: Mohammed Al-Hajri, Ministry for Health, Qatar; Farida Al-Hosani, Abu Dhabi; Majid Alshamrani, King Abdulaziz Medical Center, Saudi Arabia; Yaseen Arabi, King Saud Bin Abdulaziz University for Health Sciences, Saudi Arabia; Abdullah Assiri, Ministry of Health, Saudi Arabia; Hail Al Abdely, Ministry of Health, Saudi Arabia; Kenneth Baillie, University of Edinburgh, UK; Adeel Butt, Hamad Medical Corporation and Weill Cornell Medical College, Qatar; Antonio Di Caro, National Institute for Infectious Diseases, Italy; Jake Dunning, Imperial College London, UK; William Fischer II, University of North Carolina, USA; Rob Fowler, University of Toronto, Canada; Zhancheng Gao, Peking University People's Hospital, China; Susan Gerber, Centers for Disease Control and Prevention, USA; Benoit Guery, University of Lille Nord de France, France; Frederick Hayden, University of Virginia, USA; David Hui, Chinese University of Hong Kong, Hong Kong SAR; Youngmee Jee, Korea Centers for Disease Control and Prevention, Korea; Yae-Jean Kim, Sungkyunkwan University, Samsung Medical Center,