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 emergence of a novel coronavirus in 2012, named the Middle East respiratory syndrome coronavirus (MERS-CoV) has presented challenges for clinical management. As of 2 July 2015, there have been 1361 laboratory confirmed cases of human infection and at least 477 deaths. The case fatality in those hospitalized with serious illness has been approximately 40%. Twenty-six countries have reported cases, including those in the Middle East, Africa, Europe, North America and Asia. Since May 2015, three new countries have been affected: Republic of Korea, China and Thailand. For latest updates and map, see the WHO MERS-CoV website at http://www.who.int/emergencies/mers-cov/en/.

MERS-CoV causes zoonotic infections in humans by direct or indirect contact with infected dromedary camels or camel-related products, but such primary infections account for a minority of all cases. The majority of cases are secondary and have resulted from human-to-human transmission in health care settings, related to breaches in infection prevention and control (IPC) practices[1,2] and less often in households. The virus 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 strict hygiene measures. To date, sustained community wide MERS-CoV transmission has not been observed.

The clinical manifestations of MERS-CoV infections range from asymptomatic infection to severe pneumonia, often complicated by acute respiratory distress syndrome (ARDS), septic shock and multi-organ failure leading to death[1]. The most common early signs and symptoms in more severe infections are fever (98%), chills (87%), cough (83%), and dyspnoea (72%); however, nearly 25% of cases also report gastrointestinal symptoms such as vomiting and diarrhoea[3]. Fever may be absent in up to 15 % of hospitalized cases[4]. Rapid progression to severe pneumonia and respiratory failure usually happens within the first week (median 7 days from symptom onset to initiation of mechanical ventilation)[3]. Reported laboratory abnormalities include leukopenia, lymphopenia, thrombocytopenia, consumptive coagulopathy, and elevated serum creatinine, lactate dehydrogenase and liver enzymes[3,5]. Co-infections with other respiratory viruses and bacterial pathogens have also been reported[3].

The majority of cases have been reported in adults (98%) and males (66%, n=1329), with a median age of 50 years (range, 9 months-99 years, n=1335)[3]. There are very few reports on children with MERS-CoV infection[6]. The presence of at least one co-morbid condition (e.g, immuno-compromised state, malignancies, obesity, diabetes, cardiac disease, renal disease and lung disease) has been reported in 76% of cases, and is associated with a higher risk of death[3,5-8]. In a case series of 70 patients, concomitant infections and low serum albumin levels were found to be predictors of severe infection, while age ≥ 65 years was the only independent predictor of increased mortality (OR 4.39, CI 2.13–9.05; $p < 0.001$)[9].

Although our knowledge of the clinical features of MERS-CoV infection has grown over the past three years, the pathogenesis of disease is incompletely understood, and there is no proven MERS-CoV-specific treatment or vaccine. This updated interim guidance document aims to help clinicians provide timely, high quality and safe supportive management of patients who have acute respiratory failure and/or septic shock. Protocols for experimental MERS-CoV-specific treatments that are candidates for clinical investigation will also be discussed in this guideline.

This document is intended for clinicians taking care of critically ill patients (adults and children) with severe acute respiratory infection (SARI). It is not meant to replace clinical training or specialist consultation but rather to strengthen current clinical management of SARI and provide links to the most up-to-date guidance. Because the critical care of children is conceptually similar to that of adult patients, the recommendations are generalized to both populations; with certain distinctions emphasized.

This document is organized into the following sections:

1. Early recognition of patients with SARI
2. Implementation of IPC measures
3. Collection of specimens for laboratory diagnosis and antimicrobial therapy
4. Early supportive therapy and monitoring
5. Management of severe respiratory distress, hypoxemia and ARDS
6. Management of septic shock
7. Prevention of complications
8. Experimental virus-specific therapeutics
9. Special considerations for pregnant patients

Three symbols are used throughout the text with regard to interventions:

- Do: the intervention is known to be beneficial.
- Don't: the intervention is known to be harmful.
- Be careful when considering this intervention.

The recommendations in this document are derived mainly from evidence-based guidelines published by WHO,

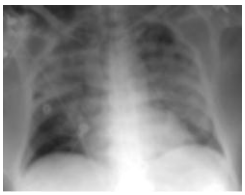
including the *WHO Integrated Management of Adolescent and Adult Illness (IMAI) District Clinician Manual*[10]. Where WHO guidance is not available, we have used widely accepted global consensus statements, such as guidelines of the 2012 Surviving Sepsis Campaign[11], and the results of recently published randomized controlled trials, as well as observational studies of MERS-CoV and SARS-CoV infections. The recommendations have also been reviewed by a WHO global network of clinicians (see Acknowledgements for names and affiliations).Links are given to additional sources and evidence. For queries, please email outbreak@who.int with 'MERS-CoV clinical question' in the subject line.

1. Early recognition of patients with SARI

Recognize suspect cases with severe manifestations of acute respiratory infection (ARI)

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 as well as therapeutics.

Table 1. Case Definitions

Severe acute respiratory infection (SARI)	An acute respiratory infection (**ARI**) with history of fever or measured fever of ≥ 38 C° and cough; with onset within the last 10 days; and requires hospitalization[12]. However, an absence of fever does NOT exclude MERS-COV infection[4]. Thus, even in the absence of fever, a patient with a history of cough or other respiratory symptoms should still be evaluated for risk of MERS-CoV exposure.
"Probable Case" of MERS-CoV	A person with an **ARI**, which may include history of fever or measured fever (≥ 38˚C, 100.4˚F) and cough; **AND** suspicion of pulmonary parenchymal disease (e.g. pneumonia or ARDS), based on clinical (dyspnea, hypoxemia, crackles on chest auscultation) or radiological evidence of infiltrates: **AND** direct epidemiologic risk: • health care associated exposure (caring for infected patients or working with infected health care workers), • **OR** working, studying, traveling or living with individuals infected with MERS-CoV; • **OR** 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. See updates of the case definition at: http://www.who.int/csr/disease/coronavirus_infections/case_definition/en/
Severe pneumonia	Adolescent or adult patient with fever or suspected respiratory infection, cough, respiratory rate > 30 breaths/min, severe respiratory distress, oxygen saturation (SpO2) < 90% on room air[10]. Child with chest indrawing, signs of distress (nasal flaring, grunting), central cyanosis, not able to drink, lethargy, SpO_2 < 90%, or tachypnoea (< 2 months, ≥ 60 breaths; 2–11 months, ≥ 50 breaths; 1–5 years, ≥ 40 breath or (13). Chest radiograph is recommended to establish diagnosis◆.
Acute Respiratory Distress Syndrome 	**Onset:** new or worsening respiratory symptoms within one week of known clinical insult[14]. **Chest imaging (X-ray or CT scan):** bilateral opacities, not fully explained by effusions, lobar/lung collapse or nodules[14]. **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[14]. **Oxygenation*:** • Mild ARDS: 200 mm Hg < PaO_2/FiO_2 ≤ 300 mm Hg with PEEP or CPAP ≥ 5 cm H_2O • Moderate ARDS: 100 mm Hg < PaO_2/FiO_2 ≤ 200 mm Hg with PEEP ≥ 5 cm H_2O • Severe ARDS: PaO_2/FiO_2 ≤ 100 mm Hg with PEEP ≥ 5 cm H_2O • When PaO_2 is not available, the SpO_2/FiO_2 ratio ≤ 315 suggests ARDS[15]
Sepsis¶	Documented or suspected infection associated with any organ dysfunction such as oliguria, acute kidney injury, hypoxemia (PaO_2/FiO_2 ≤ 300), transaminase elevations, coagulopathy, thrombocytopenia, altered mental status, ileus, hyperbilirubinemia; **OR** signs of hypoperfusion such as lactic acidosis, decreased capillary refill or skin mottling; **OR** hypotension.
Septic shock	Sepsis-induced hypotension despite adequate fluid resuscitation (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg or less than two standard deviations below normal for age in children); or signs of hypoperfusion (lactate > 4 mmol/L)[11].

Abbreviations: SpO_2, oxygen saturation; PaO_2, partial pressure of oxygen; FiO_2, fraction of inspired oxygen; CPAP, continuous positive airway pressure; PEEP, positive end-expiratory pressure; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; MAP, mean arterial blood pressure; sd, standard deviation.

* 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 are peripherally predominant ground glass opacities. However, consolidation, mixed ground glass and consolidation and pleural effusion have also been described[16].

¶ Sepsis definitions are currently being re-defined by the European Society of Intensive Care Medicine and the Society of Critical Care Medicine based on recent publication that found the presence ≥ 2 SIRS criteria failed to identify all patients at increased risk of death. Information presented here is from an electronic communication with working group member[17,18]

2. Implementation of IPC measures

Administrative, engineering, environmental and hospital infection control teams should work in harmony to promote safety from the patient's first point of contact with the health care system, through hospital admission and until discharge.

- **Apply STANDARD precautions routinely to ALL patients in ALL health care settings[19].**
- **At triage, recognize patient with ARI, give the patient a medical mask and place the patient in separate area. When feasible, using medical masks by ARI patients will contribute to source control and diminish potential for environmental contamination[19].**
- **Organize the space and process to permit spatial separation[19]. Keep at least 1-2 meter between each patient with ARI and other individuals not wearing PPE.**
- **Ensure that triage and waiting areas are adequately ventilated[19].**
- **Encourage respiratory hygiene (i.e. covering the mouth and nose during coughing or sneezing with a tissue, sleeve or flexed elbow), followed by hand hygiene and disposing tissue immediately[19].**
- **When caring for patient with ARI also apply DROPLET precautions. If patient is suspected to have MERS-CoV, additionally apply CONTACT precautions. See TABLE 2 for details .**
- **For patients with suspected MERS-CoV infection that require hospitalization, place patient in an adequately ventilated single room away from other patient care areas.**
- **Do not place suspect patients in the same area or room as those who are confirmed MERS-CoV cases.**

If single rooms are insufficient for the number of individuals, then apply cohorting (placement of patients with the same etiological diagnosis in the same designated unit or ward) to reduce transmission to other patients or health care workers. Limit the number of people entering the assigned area to the minimum number required for patient care.

- **When performing an aerosol generating procedure (i.e. aspiration or open suctioning of respiratory tract, intubation, bronchoscopy, cardiopulmonary resuscitation) also apply AIRBORNE precautions[19].**

Tracheal intubation has been consistently associated with an increased risk of pathogen transmission during SARS-CoV outbreaks (20). Increased risk of SARS-CoV transmission was also reported when performing non-invasive ventilation, tracheotomy and manual ventilation before intubation; however, these findings were identified from a limited number of very low-quality studies[20].

- **Though definitive evidence is lacking, non-invasive ventilation, high-flow nasal cannula, aerosolized nebulizer treatments, chest physiotherapy also have the potential to generate aerosols and facilitate transmission of respiratory viruses. When performing these treatments, also implement AIRBORNE precautions.**
- **Advise visitors and family members about risk of transmission. Instruct them on personal protection equipment (PPE) use and hand hygiene. Evaluate for symptoms of ARI before visit. Limit visitors to those essential for support. Advise that anyone who is at increased risk of severe disease does not care for the ill person**.

For WHO IPC guidance related to MERS-CoV, please see http://www.who.int/csr/disease/coronavirus_infections/technical-guidance-infection/en/.

Table 2. How to implement infection control measures

When caring for ALL patients	Apply routinely in all health-care settings for all patients. Standard precautions include: hand hygiene; use of personal protective equipment (PPE) to avoid direct contact with patients' blood, body fluids, secretions (including respiratory secretions) and non-intact skin. Standard precautions also includes: prevention of needle-stick or sharps injury; safe waste management; cleaning and disinfection of equipment; and cleaning of the environment[19].
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 1-2 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[19].
When caring for patients with suspected MERS-CoV	Contact precautions prevent direct or indirect transmission from contact with contaminated surfaces or equipment (i.e. contact with contaminated oxygen tubing/interfaces). Use PPE (a medical mask, eye protection, gloves and gown) when entering room and remove it 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 it between each patient use. Ensure that health care workers refrain from touching their eyes, nose or 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[19].
When performing an aerosol-generating procedure in patient with ARI	Ensure that healthcare workers performing aerosol-generating procedures **(i.e. aspiration or open suctioning of respiratory tract specimens, intubation, cardiopulmonary resuscitation, bronchoscopy)** use PPE, including gloves, long-sleeved gowns, eye protection, and particulate respirators (N95 or equivalent, or higher level of protection). Whenever possible, use adequately ventilated single rooms when performing aerosol-generating procedures. This means negative pressure rooms with minimum of 6 to 12 air changes per hour or at least 60 liters/second/patient in facilities with natural ventilation. Avoid unnecessary individuals in the room[19].

3. Collection of specimens for laboratory diagnosis and antimicrobial therapy

- **Collect blood cultures for potential bacterial pathogens that can also cause pneumonia and sepsis, ideally before antimicrobial therapy. This must NOT significantly delay the start of antimicrobial therapy[11].**
- **Collect upper respiratory tract specimens, preferably both nasopharyngeal and throat swabs, for viral testing.**

When collecting upper respiratory tract (URT) samples ensure to use sterile dacron or rayon swabs (not cotton), to take sample from nasopharynx (preferably flocked swabs) not just the nostrils or tonsils, and to transport samples in viral transport medium. Single negative samples from the URT are common. Thus, collect multiple URT samples along with lower respiratory tract (LRT) samples when suspicion of MERS-CoV infection remains high[21].

- **Collect lower respiratory tract specimens, i.e., sputum (not saliva), endotracheal aspirate, bronchoalveolar lavage, for both bacterial and viral testing[21].**

In those with serious illness and/or pneumonia, the most appropriate specimens for MERS-CoV testing are LRT specimens. LRT samples are more likely to be positive than URT specimens and virus can be detected in LRT specimens for longer periods than in URT specimens[21,22].

- **Collect serial respiratory specimens to examine early MERS-CoV replication kinetics and to confirm viral clearance. The frequency of specimen collection will depend on local circumstances, but in the initial two weeks, collect specimen at least every 2 to 4 days. Continue to collect until there are two consecutive negative results to confirm clearance of the virus[21].**

Viral testing should be done by reverse-transcriptase polymerase chain reaction (RT-PCR) assay if possible. Initially, include testing for other respiratory viruses, such as influenza A and B including zoonotic influenza A viruses (eg. avian H5 or H7); RSV, parainfluenza viruses, rhinoviruses, adenoviruses, enterovirus (EVD68) human metapneumovirus, and non-SARS coronaviruses.

For antibody detection, paired serum samples should ideally be collected 14 –21 days apart, with the first being taken during the first week of illness. If only a single sample can be collected, this should be done at least 14 days after the onset of symptoms[21]. Consider serology also when virology testing by RT-PCR is limited or the infection is considered late in the course of the illness (> 14 days)[23].

For research and perhaps prognostic purposes, consider collecting specimens from other sites (blood, urine, stool) for viral testing; also conjunctival swabs if conjunctivitis is clinically present and cerebrospinal fluid (if lumbar puncture is performed for clinical reasons). This can provide additional information about MERS-CoV replication and detection patterns. Of note, in one case series of 19 patients tested with both respiratory tract and serum samples for virus by RT-PCR, a positive serum RT-PCR was associated with increased mortality[4].

Contact WHO or relevant national public health body for information about laboratories that can test for the presence of MERS-CoV.

- **Give empiric, effective antimicrobials to treat all likely pathogens, including community-acquired pneumonia or health care-associated pneumonia (if infection was acquired in health care setting) and sepsis. Give within one hour.**

Although the patient may be suspected to have MERS-CoV infection, administer appropriate empiric antimicrobials as soon as possible-within **ONE hour** if sepsis (11). Antibiotic treatment should be selected based on local epidemiology, susceptibility data and guidance until the diagnosis is confirmed. Empiric therapy can then be adjusted on the basis of laboratory results. This recommendation includes antiviral therapy with neuraminidase inhibitor for treatment of influenza, when there is local circulation or possible risk factors for exposure to animal influenza viruses (e.g., avian H5)[24].

4. Early supportive therapy and monitoring

- **Give supplemental oxygen therapy to patients with SARI with signs of respiratory distress, hypoxaemia (SpO_2 < 90%) or shock immediately.**

Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target $SpO_2 \geq 90\%$ in non-pregnant adults and children and $SpO_2 \geq$ 92-95 % in pregnant patients[10,13,24]. 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)[24]. 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.**

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[24].

- **Do not give high-dose systemic corticosteroids or other adjunctive therapies for viral pneumonitis or ARDS outside the context of clinical trials unless they are indicated for another reason.**

Prolonged use of systemic high-dose corticosteroids can result in serious adverse events in patients with SARI caused by respiratory viruses[24,27-33]. A meta-analysis of therapies administered to patients with SARS-CoV reported no survival benefit and possible harms of corticosteroid treatment like avascular necrosis, psychosis, diabetes, and prolonged viral replication[33]. Furthermore, use of high-dose methylprednisolone can promote immunosuppression and promote bacterial or fungal suprainfection[30-32]. Therefore, corticosteroids should be avoided unless they are indicated for another reason[3,24].

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

Application of timely, high quality and safe intensive care supportive therapies is the cornerstone of therapy for patients that develop severe manifestations of MERS-CoV infection.

Understand the patient's co-morbid condition(s) as this will impact the management of their critical illness and their prognosis. Communicate early with patient and family.

During intensive care management of acute respiratory illnesses, determine which chronic therapies should be continued and which therapies should be stopped temporarily. Communicate proactively with patients and families and provide support because more deaths have been reported in older patients with co-morbid diseases. Get to know the patient's values and preferences in regards to intensive care treatments, especially in patients with a known terminal illness.

5. Management of severe respiratory distress, hypoxemia and ARDS

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

Patients may continue to have increased work of breathing or hypoxemia even when standard oxygen therapy is delivered via a face mask with reservoir bag (flow rates of 10 -15 L/min delivers oxygen concentration, FiO_2, between 0.60 and 0.95). Hypoxemic respiratory failure in ARDS is commonly caused by a high intrapulmonary shunt fraction. Therapy usually requires mechanical ventilation.

Wherever available, and with trained staff members, high-flow oxygen (up to 50 L/min) can be used in carefully selected cases of non-hypercapnic hypoxemic respiratory failure.

There are newer high-flow oxygen systems now that deliver up to 50–60 L/min flow rates using newer nasal cannula interfaces. These have shown improvement in respiratory distress and oxygenation compared with traditional facemasks[34]. A recent randomized, multi-centre trial reported that high-flow oxygen when compared to standard oxygen and non-invasive ventilation (NIV) was associated with similar intubation rates (38% vs. 47 % vs. 50%, respectively, p=0.18)[35]. Patients were excluded if they had hypercapnea ($PaCO_2$> 45 mmHg) exacerbation of obstructive lung disease, cardiogenic pulmonary oedema, hemodynamic instability or impaired level of consciousness. To date, there are no published reports on the use of high-flow oxygen in patients with MERS-CoV infection.

When high-flow oxygen is used, monitor the patient closely in an ICU. Because high-flow oxygen therapy has potential to generate aerosols, use with AIRBORNE precautions. If unsuccessful, do not delay endotracheal intubation.

Wherever available, and when staff members are trained, institute mechanical ventilation early in patients with increased work of breathing or hypoxemia that persists despite standard high flow oxygen therapy.

Choose the type of mechanical ventilation based on resource availability, staff experience and risk-benefit analysis. Options include non-invasive ventilation (NIV) administered through a tight-fitting mask or invasive mechanical ventilation administered through an endotracheal tube or tracheostomy.

In patients with SARI with non-hypercapneic hypoxemic respiratory failure, NIV should be used only in selected cases and in centres with experience with NIV.

NIV is the delivery of bi-level positive airway pressure through a tight-fitting mask. It reduces the need for endotracheal intubation in patients with severe exacerbations of chronic obstructive pulmonary disease and cardiogenic pulmonary oedema. There is, however, insufficient evidence to promote its use in patients with severe pneumonia or ARDS, unless immunosuppression is also present or disease is mild without impaired consciousness or cardiovascular insufficiency[36,37]. A case series of patients with MERS-CoV infection, found most patients treated with NIV failed this modality of therapy and endotracheal intubation was required[38].

When NIV used, it should be used as a short trial, Monitor the patient closely in an ICU. Because NIV has potential to generate aerosols, use with AIRBORNE precautions. If NIV is unsuccessful, do not delay endotracheal intubation. Some investigators have raised concerns regarding NIV's potential to cause ventilator-induced lung injury by allowing the delivery of excessively large tidal volumes[35].

Wherever available, and when staff members are trained, proceed with endotracheal intubation using a rapid sequence induction.

Patients with ARDS, especially young children those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenate patients with 100% FiO_2 for 5 minutes, via a bag-valve mask or NIV and then proceed with rapid-sequence intubation. Experienced staff members should be present. Remember to implement **AIRBORNE** precautions.

Initiate a lung-protective ventilation strategy (LPV, low volume, low pressure) for patients with ARDS after intubation

Implementing a low-volume, low-pressure ventilation strategy/protocol, which targets a tidal volume of 6 ml/kg (predicted body weight), a plateau airway pressure (Pplat) of ≤ 30 cm H_2O and SpO_2 88 – 93% or PaO_2 55-80 mm Hg (7.3-10.6 kPa) has been shown to reduce mortality in a heterogeneous population of ARDS patients of all ages[11,39]. The clinical trial's ventilator protocol is available[40].

To reach LPV targets, allow permissive hypercapnea.

To reach target SpO_2, use adequate PEEP (to keep alveoli aerated) for the degree of hypoxemia. PEEP-FiO_2 tables are available on ventilator card[40].

Consider deep-sedation targets if unable to control tidal volume.

Avoid disconnecting the patient from the ventilator. Disconnection results in loss of PEEP and lung collapse. Use in-line catheters for airway suctioning, clamp tube when disconnection is required and minimize transport.

In patients with moderate-severe ARDS, consider adjunctive therapeutics early, especially if failing to reach LPV targets.

Various interventions have been shown to reduce mortality in severe cases of ARDS when added to the LPV strategy

described above. Based on local resources and expertise, conduct a careful risk-benefit analysis (each intervention has risks), and chose the best intervention for the individual patient.

- **Place the patient in the prone position. This improves oxygenation and survival in patients with severe ARDS (PaO_2/FiO_2 < 150) when implemented early and for at least 16 consecutive hours a day[41,42]. Care must be taken to turn the patient safely[43].**
- **Administer neuromuscular blockade for initial 48 hours. This improves survival in patients with severe ARDS (PaO_2/FiO_2 < 150) and increases time off the ventilator without causing significant weakness[44].**
- **Use higher PEEP levels in patients with moderate and severe ARDS (PaO_2/FiO_2 < 200). This is associated with improved survival in a meta-analysis[45].**
- **Use a conservative fluid management strategy for all ARDS patients who are not in shock to shorten the duration of mechanical ventilation[11,46].**

6. Management of septic shock

- **Recognize sepsis-induced shock when patient develops hypotension (SBP < 90 mm Hg, MAP < 70 mm Hg, or an SBP decrease > 40 mm Hg compared to pre-morbid value, or less than two standard deviations below normal for age) that persists after adequate fluid challenge or has signs of tissue hypoperfusion (lactate > 4 mmol/L). Initiate early resuscitation.**

Standard care includes early recognition, early antimicrobial therapy (within one hour) and early initial fluid bolus followed by subsequent fluid loading as needed and vasopressor use based on clinical response[11,47-49]. The use of invasive monitors such central venous catheter and intra-arterial catheters should be based on resource availability and individual patient needs. In adults, recent clinical trials have demonstrated that strict, early resuscitation protocols targeting central venous pressure (CVP) and central venous saturation ($ScvO_2$) are not associated with improved survival when compared to standard care[47-49]. Revised resuscitation bundles are available at the Surviving Sepsis Campaign website[50]. In children, use the WHO Pocket Book of Hospital Care for Children and the American College of Critical Care Medicine Pediatric Life Support (ACCM-PALS) guidelines for the management of septic shock[13,51].

- **Give early and rapid infusion of crystalloid intravenous fluids for septic shock to achieve a minimum of 30 ml/kg in adults over one hour, or 20 ml/kg over 15-20 minutes in children**

Give crystalloid fluids, i.e., normal saline or Lactated Ringer's solution, as fluid challenge to achieve a minimum of 30 ml/kg in adults over one hour, or 20 ml/kg over 15-20 minutes in children)[11]. Determine need for further 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 mm Hg), urine output (> 0.5 ml/kg/hr in adults, 1ml/kg/hr in children), and improvement of skin mottling, capillary refill and sensorium[11]. Consider use of cardiac ultrasound or other dynamic indices of volume responsive for guidance based on local resources and experience[11].

- **Overly aggressive fluid resuscitation may lead to respiratory impairment. If there is no response to fluid loading and signs of volume overload appear (i.e. jugular venous distension, crackles on auscultation, pulmonary oedema on chest X-ray or hepatomegaly in children) then reduce or discontinue fluid administration. This is particularly important in resource-limited settings where mechanical ventilation is not available[24,52].**
- **Do not give hypotonic or starch-based solutions for resuscitation. Starches have been associated with an increased incidence of renal dysfunction and failure[11,53,54]**
- **Do not use fluid balance as a guide to administer or withhold further volume loading[24].**
- **Administer vasopressors when shock persists despite fluid resuscitation. This is to maintain adequate perfusion pressure. The initial perfusion target is MAP > 65 mmHg or SBP >90-100 mm Hg in adults and age appropriate targets in young children[11,24].**

Vasopressors (i.e. norepinephrine, epinephrine and dopamine) are most safely given through a central venous catheter at a strictly controlled rate[11]. During infusion, monitor blood pressures frequently, in order to titrate to the minimum dose necessary to maintain perfusion and prevent side effects[11]. In patients with chronic hypertension, consider individualizing MAP target to higher level (i.e. >80 mmHg) to reduce risk of renal injury[11,55]. Because of cardiac arrhythmias, consider only using dopamine in selected patients with low risk of tachyarrhythmia or those with bradycardia[11].

- **In resource-limited settings, if central venous catheters are not available, vasopressors can be given carefully through a peripheral IV placed in a large vein but closely monitor for signs of extravasation and necrosis. If extravasation occurs, stop infusion[10].**
- **If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider use of an inotrope, such as dobutamine[11].**
- **Consider administration of intravenous hydrocortisone (up to 200 mg/day, 1mg/kg 6 hourly for children) or prednisolone (up to 75 mg/day) to patients with persistent shock who require escalating doses of vasopressors[11,25]. Taper when shock resolves.**

7. Prevention of complications

Implement the following interventions (Table 3) to prevent complications associated with critical illness.

Table 3. Treatment of complications

Anticipated Outcome	Interventions
Reduce days of invasive mechanical ventilation (IMV)	• Weaning protocols that include daily assessment for readiness to breathe spontaneously[11] • Sedation protocols to titrate administration of sedation to a target level, with or without daily interruption of continuous sedative infusions[11]
Reduce incidence of ventilator-associated pneumonia	• Oral intubation is preferable to nasal intubation in adolescents and adults • Perform regular antiseptic oral care • Keep patient in semi-recumbent position • 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 days of IMV
Reduce incidence of venous thromboembolism	• Use pharmacological prophylaxis (for example, heparin 5000 units subcutaneously twice daily or a low molecular-weight heparin) in adolescents and adults without contraindications[11]. For those with contraindications, use mechanical prophylactic device such as intermittent pneumatic compression devices.
Reduce incidence of catheter-related bloodstream infection	• Use a simple checklist during insertion as reminder of each step needed for sterile insertion and daily reminder to remove catheter if no longer needed[56]
Reduce incidence of pressure ulcers	• Turn patient every two hours
Reduce incidence of stress ulcers and gastric bleeding	• Give early enteral nutrition (within 24–48 hours of admission), administer histamine-2 receptor blockers or proton-pump inhibitors[11]
Reduce incidence of ICU-related weakness	• Early mobility

8. Experimental virus-specific therapeutics

At this time, there is no conclusive evidence from rigorous clinical trials in humans to recommend any virus-specific treatments for patients with suspected or confirmed MERS-CoV infection.

Treatment with investigational therapeutic agents should use standard research treatment protocols, employ systematic clinical and virologic data collection, and occur in the context of controlled research trials and with local ethics review and approval.

Open access SARI data collection protocols and case record forms are at available at https://isaric.tghn.org/protocols/sari-bsp/

Various compounds have been found to have in vitro inhibitory activity against MERS-CoV infection. Most notable are the type 1 interferons (IFNs), with IFN–β showing the strongest inhibitory activity[57]. Others include ribavirin, mycophenolic acid, cyclosporine, chloroquine, chlorpromazine, loperamide, lopinavir, 6-mercaptopurine (6MP) and 6-thioguanine (6TG), but for many inhibition occurs at concentrations that cannot be achieved safely in humans[3,57,58]. Furthermore, in-vitro activity does not necessarily translate to efficacy in animal models or in humans. In rhesus macaques infected with MERS-CoV, combination therapy with high doses of IFN- α2b with ribavirin modestly reduced viral titres and measures of lung injury[59] but observational studies of clinical use have reported inconsistent findings (below).

Various monoclonal and polyclonal antibody preparations with neutralizing activity inhibit MERS-CoV in pre-clinical models. However, there are no data to date on the use of these preparations or of convalescent plasma to treat patients with MERS-CoV infection. A systematic review and exploratory meta-analysis of patients with SARS-CoV and influenza virus treated with convalescent plasma showed a reduction in mortality, so that it has been considered a potential treatment[60]. However, the availability of convalescent plasma, particularly with well-defined levels of MERS-CoV neutralizing and other antibodies, remains extremely limited. Also there are concerns that the therapeutic window for administration is short and that the treatment dose may cause undesired volume expansion in patients with ARDS.

Since 2013, investigators from the Kingdom of Saudi Arabia have published several retrospective observational studies using IFNs in combination with ribavirin in humans with severe MERS-CoV infection[4,61]. These studies are small, nonrandomized, and unadjusted for confounders. The most recent publication on 32 patients compared outcomes in 13 patients treated with IFN-α2a (180 μg subcutaneously once weekly) combined with ribavirin (loading dose of 2 g orally followed by 600 mg orally every 12 h) to 11 patients treated with IFN-β1a (44 μg subcutaneously three-times weekly) combined with ribavirin and found high mortality in both groups and no significant difference between them, 85% vs. 64%, p=0.24[4]. Although an earlier study of 20 patients treated with IFN- α2a combined with ribavirin found an improved survival rate at 14 days, these favorable findings were no longer significant by day 28 (70 % mortality vs. 83% in comparator group [untreated patients with confirmed MERS-CoV infection] p = 0.54)[61]. The authors suggested the lack of effectiveness could be attributed to older age, presence of co-morbid conditions and delay in treatment initiation[61]. There is only one published case study on the use of lopinavir as part of triple therapy regimen (combined with IFN and ribavarin) in a MERS-CoV infected patient that subsequently died in Greece[62].

A list of candidate therapeutics for clinical study has been compiled by Public Health England and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC)[63]. Future studies are needed to evaluate potential MERS-CoV-specific treatments, preferably using a randomized control study design and standard research treatment protocols. Such research protocols are necessary to standardize treatment interventions, including early administration, appropriate dosing regimens and adequate clinical and laboratory data collection. When data are shared with other treatment centers around the world, the power to detect efficacy or harm is strengthened.

9. Special considerations for pregnant patients

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

Experimental, virus-specific treatments should be guided by individual risk-benefit analysis based on potential benefit for mother and safety to fetus, with consultation of obstetric specialist and ethics committee.

Ribavirin has been shown to be genotoxic in vitro and teratogenic in animal models. Some other compounds considered for experimental treatments of MERS have not been tested for safety in pregnancy. Use of any of these compounds in pregnancy should be considered only when the benefit outweighs the risk of treatment.

Emergency delivery/pregnancy termination decisions are challenging and based on many factors: gestational age, maternal condition, and fetal stability. Consultations with obstetric, paediatric and intensive care specialist are essential.

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References

1. Assiri A, McGeer A, Perl TM, et al. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013;369: 407-16.
2. Oboho I, Tomczyk S, Al-Asman A, Banjar A, et al. 2014 MERS-CoV outbreak in Jeddah--a link to health care facilities. N Engl J Med 2015;372(9):846-54.
3. Zumla A, Hui D, Perlman S. Middle East respiratory syndrome. Lancet 2015; published online
4. Shalhoub S, Farahat F, Al-Jiffri A, Simhairi R et al. IFN-α2a or IFN-β1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. J Antimicrobial Chemother 2015. Epub
5. Assiri A, Al-Tawfiq JA, Al-Rabeeah AA, et al. Epidemiological, demographic, and clinical characteristics of 47 cases of Middle East respiratory syndrome coronavirus disease from Saudi Arabia: a descriptive study. *Lancet Infect Dis* 2013; **13:** 752–61.
6. Memish Z, Al-Tawfiq JA, Assiri A, AlRabiah FA, Al Hajja S, et al. Middle East Respiratory Syndrome Coronavirus Disease in Children. The Pediatric Infectious Disease 2014; 33: 904-906.
7. Al-Tawfiq JA, Hinedi K, Ghandour J, et al. Middle East respiratory syndrome coronavirus: a case-control study of hospitalized patients. *Clin Infect Dis* 2014; **59:** 160–65.
8. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med* 2014; **160:** 389–97.
9. Saad M, Omrani AS, Baig K, et al. Clinical aspects and outcomes of 70 patients with Middle East respiratory syndrome coronavirus infection: a single-center experience in Saudi Arabia. *Int J Infect Dis* 2014; **29:** 301–06
10. IMAI District Clinician Manual: Hospital Care for Adolescents and Adults. Geneva: WHO 2012. Available at http://www.who.int/influenza/patient_care/IMAI_DCM/en/index.html
11. Dellinger RP, et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012 Critical Care Medicine 2013;41:580-637. http://www.sccm.org/Documents/SSC-Guidelines.pdf
12. Global Epidemiological Surveillance Standards for Influenza. Geneva: WHO 2013. http://www.who.int/influenza/resources/documents/WHO_Epidemiological_Influenza_Surveillance_Standards_2014.pdf?ua=1
13. The Pocket Book of Hospital Care for children. Guidelines for the management of common childhood illnesses. 2nd edition. Geneva. WHO 2013. http://www.who.int/maternal_child_adolescent/documents/child_hospital_care/en/
14. The ARDS Definition Task Force. Acute Respiratory Distress Syndrome. The Berlin Definition. JAMA 2012; 2012;307(23):2526-2533.
15. Rice TW, Wheeler AP, Bernard G, Hayden D, Schoenfeld DA, Ware LB. Comparison of the Spo_2/Fio_2 Ratio and the PaO_2/FiO_2 Ratio in Patients with Acute Lung Injury or ARDS. Chest 2007; 132: 410
16. Das KM, Lee EY, Jawder SE, Enani MA, Singh R, Skakni L, Al-Nakshabandi N, AlDossari K, Larsson SG. Acute Middle East Respiratory Syndrome Coronavirus: Temporal Lung Changes Observed on the Chest Radiographs of 55 Patients. Am J Roentgenol. 23:W1-W8, 2015.
17. Kaukonen KM, Bailey M, Pilcher D, Cooper DJ, Bellomo R. Systemic Inflammatory Response Syndrome Criteria in Defining Severe Sepsis. N Engl J Med 2015;372:1629-38.

18. ACCM/SCCM Consensus Conference Committee. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. Chest 2002; 101: 1644–55.
19. Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care settings. Geneva. WHO 2014. http://apps.who.int/iris/bitstream/10665/112656/1/9789241507134_eng.pdf?ua=1
20. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. PloS One 2012;7:e35797. http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0035797
21. Laboratory Testing for Middle Eastern respiratory syndrome coronavirus. Interim recommendations. Geneva WHO. September 2014. http://www.who.int/csr/disease/coronavirus_infections/WHO_interim_recommendations_lab_detection_MERSCoV_092014.pdf?ua=1
22. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. J Infect Dis. 2014 Nov 15;210(10):1590-4
23. Drosten C et al. Transmission of MERS-coronavirus in household contacts. N Engl J Med 2014;371(9):828-35.
24. WHO. Clinical management of human infection with pandemic (H1N1) 2009: revised guidance. http://www.who.int/csr/resources/publications/swineflu/clinical_management/en/index.html
25. Dunser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. Intensive Care Medicine 2012;38:557–74.
26. WHO. Pulse oximetry training manual. http://www.who.int/patientsafety/safesurgery/pulse_oximetry/tr_material/en/
27. Lee N, Leo YS, Cao B, Chan PK, Kyaw WM, Uyeki TM, Tam WW, Cheung CS, Yung IM, Li H, Gu L, Liu Y, Liu Z, Qu J, Hui DS. Neuraminidase inhibitors, superinfection and corticosteroids affect survival of influenza patients. Eur Respir J. 2015 Jun;45(6):1642-52.
28. Zhang Y, Sun W, Svendsen ER, Tang S, MacIntyre RC, Yang P, Zhang D, Wang Q. Do corticosteroids reduce the mortality of influenza A (H1N1) infection? A meta-analysis. Crit Care. 2015 Feb 20;19:46
29. Diaz E, Martin-Loeches I, Canadell L, Vidaur L, Suarez D, Socias L, Estella A, Gil Rueda B, Guerrero JE, Valverdú-Vidal M, Vergara JC, López-Pueyo MJ, Magret M, Recio T, López D, Rello J, Rodriguez A; H1N1 SEMICYUC-CIBERES-REIPI Working Group (GETGAG). Corticosteroid therapy in patients with primary viral pneumonia due to pandemic (H1N1) 2009 influenza. J Infect. 2012 Mar;64(3):311-8.
30. Kim SH, Hong SB, Yun SC, Choi WI, Ahn JJ, Lee YJ, Lee HB, Lim CM, Koh Y; Korean Society of Critical Care Medicine H1N1 Collaborative. Corticosteroid treatment in critically ill patients with pandemic influenza A/H1N1 2009 infection: analytic strategy using propensity scores. Am J Respir Crit Care Med. 2011 May 1;183(9):12 07-14.
31. Brun-Buisson C, Richard JC, Mercat A, Thiébaut AC, Brochard L; REVA-SRLF A/H1N1v 2009 Registry Group. Early corticosteroids in severe influenza A/H1N1 pneumonia and acute respiratory distress syndrome. Am J Respir Crit Care Med. 2011 May 1;183(9):1200-6.
32. Martin-Loeches I, Lisboa T, Rhodes A, Moreno RP, Silva E, Sprung C, Chiche JD, Barahona D, Villabon M, Balasini C, Pearse RM, Matos R, Rello J; ESICM H1N1 Registry Contributors. Use of early corticosteroid therapy on ICU admission in patients affected by severe pandemic (H1N1)v influenza A infection. Intensive Care Med. 2011 Feb;37(2):272-83.
33. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med. 2006 Sep;3(9):e343.
34. Sztrymf B, Messika J, Mayot T, Lenglet H, Dreyfuss D, Ricard JD. Impact of high-flow nasal cannula oxygen therapy on intensive care unit patients with acute respiratory failure: a prospective observational study. Journal of Critical Care 2012;27:324 e9–13.
35. Frat JP, Thille A, Mercat A, Girault C. High-Flow Oxygen through Nasal Cannula in Acute Hypoxemic Respiratory Failure. NEJM 2015; 372:2185-96.
36. Keenan SP, Sinuff T, Burns KE, et al. Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. CMAJ : Canadian Medical Association Journal = journal de l'Association medicale canadienne 2011;183:E195–214.
37. Nava S, Schreiber A, Domenighetti G. Noninvasive ventilation for patients with acute lung injury or acute respiratory distress syndrome. Respiratory Care 2011;56:1583–8.
38. Arabi YM, Arifi AA, Balkhy HH, Najm H, Aldawood AS, et al. Clinical Course and Outcomes of Critically Ill Patients With Middle East Respiratory Syndrome Coronavirus Infection Ann Intern Med. 2014; 160:389-397.
39. ARDS Network. Ventilation With Lower Tidal Volumes As Compared With Traditional Tidal Volumes For Acute Lung Injury and The Acute Respiratory Distress Syndrome. NEJM; 342: 1301-1308.
40. NIH NHLBI ARDS Clinical Network's mechanical ventilation protocol card http://www.ardsnet.org/files/ventilator_protocol_2008-07.pdf
41. Guerin C, Reignier J, Richard JC, Beuret P. et al. Prone positioning in severe acute respiratory distress syndrome. NEJM 2013;368:2159-68.
42. Sud S, Friedrich JO, Taccone P, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. Intensive Care Medicine 2010;36:585–99.
43. Messerole E, Peine P, Wittkopp S, Marini JJ, Albert RK. The pragmatics of prone positioning. American Journal of Respiratory and Critical Care Medicine 2002;165:1359–63.
44. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. The New England Journal of Medicine 2010;363:1107–16.
45. Briel M, Meade M, Mercat A, Brower R. Higher Vs Lower Positive End-Expiratory Pressure In Patients With Acute Lung Injury And Acute Respiratory Distress Syndrome Systematic Review And Meta-Analysis. JAMA 2010; 303: 865-873.
46. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid-management strategies in acute lung injury. N Engl J Med 2006;354:2564–75.
47. ProCESS Investigators, Yealy DM, Kellum JA, Juang DT, et al A randomized trial of protocol based care for early septic shock. N Engl J Med 2014; 370:1683-93.
48. The ARISE Investigators and the ANZICS Clinical Trials Group. Goal directed resuscitation for patients with early septic shock. N Engl J Med 2014; 371:1496 -1506
49. Mouncey PR, Osborn TM, Power GS, et al for the ProMISe trial investigators. Trial of early, goal directed resuscitation for septic shock. N Engl J Med 2015:
50. Surviving Sepsis Campaign Updated bundles in response to new evidence http://www.survivingsepsis.org/SiteCollectionDocuments/SSC_Bundle.pdf
51. Surviving Sepsis Campaign Special considerations for paediatrics http://www.survivingsepsis.org/Guidelines/Documents/Pediatric%20table.pdf
52. Maitland K, Kiguli S, Opoka RO, Engoru C, Olupot-Olupot P, Akech SO, Nyeko R, Mtove G, Reyburn H, Lang T, Brent B, Evans JA, Tibenderana JK, Crawley J, Russell EC, Levin M, Babiker AG, Gibb DM; FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. N Engl J Med. 2011 Jun 30;364(26):2483-95

53. Perner A, Haase N, Guttormsen AB, et al. Hydroxyethyl starch 130/0.42 versus Ringer's acetate in severe sepsis. The New England Journal of Medicine 2012;367:124–34.

54. Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. The New England Journal of Medicine 2012;367:1901–11.

55. Asfar P, Meziani F., Hamel JF, Grelan F, et al. High versus Low Blood-Pressure Target in Patients with Septic Shock. The New England Journal of Medicine 2014; 370:1583-1593

56. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. The New England Journal of Medicine 2006;355:2725–32.

57. Hart BJ, Dyall J, Postnikova E, Zhou H , Kindrachuk J et al. Interferon-b and mycophenolic acid are potent inhibitors of Middle East respiratory syndrome coronavirus in cell-based assays. Journal of General Virology 2014;95: 571–577.

58. Cheng KW, Cheng SC, Chen WY, Lin MH, Chuang SJ eta al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. Antiviral Research 2015; 115: 9–16.

59. Falzarano D, de Wit E, Rasmussen AL et al. Treatment with interferon-a 2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques. Nat Med 2013;9: 1313–7.

60. Mair-Jenkins J, Saavedra-Campos M, Baillie K, Cleary P, et al. The Effectiveness of Convalescent Plasma and Hyperimmune Immunoglobulin for the Treatment of Severe Acute Respiratory Infections of Viral Etiology: A Systematic Review and Exploratory Meta-Analysis. Journal of Infectious Diseases 2015;211: 80–90.

61. Omrani AS, Saad MM, Baig K, Bahloul A, et al, Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. Lancet Infect Dis 2014 Nov;14(11):1090-5.

62. Spanakis N, Tsiodras S, Haagmans B, Raj VS, Pontikis K, et al. Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regime. International Journal of Antimicrobial Agents 2014; 44: 528–532.

63. ISARIC and Public Health England. Treatment of MERS-CoV:Information for Clinicians. Clinical decision-making support for treatment of MERS-CoV patients v2.0 14 July 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/360424/MERS_COV_information_for_clinicians_17_July.pdf