Public Health England

ISARIC

Treatment of MERS-CoV: Information for Clinicians

Clinical decision-making support for treatment of MERS-CoV patients

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About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through advocacy, partnerships, world-class science, knowledge and intelligence, and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

This document was created by PHE and the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC) as a resource for use by UK healthcare professionals, and is made available internationally through ISARIC. It is a living document that will be updated regularly.

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Contents

1 Document scope

This document is intended to provide an overview of available evidence and experience on investigational therapeutics for clinicians treating confirmed cases of MERS-CoV.

It was produced by PHE and the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) for the use of UK clinicians.

It is informed by literature concerning SARS, pandemic 2009 H1N1 influenza and MERS, as well discussions with international experts convened through ISARIC.

2 Literature

This document takes much of the SARS information from the following systematic review of SARS treatment: Stockman LJ, Bellamy R, Garner P (2006) SARS: Systematic review of treatment effects. PLoS Med 3(9): e343. DOI: 10.1371/journal.pmed.0030343.

Two recent reviews are also available: Cheng VCC et al, Clinical management and infection control of SARS: lessons learned, published in *Antiviral Research* (2013;100:407-419) and Momattin H et al, Therapeutic Options for MERS-CoV – possible lessons from a systematic review of SARS-CoV therapy, published in the *International Journal of Infectious Diseases* (2013;17:e792–e798). Colleagues with experience of managing MERS-CoV patients in affected countries have also reviewed treatment options for MERS-CoV (see bibliography and Momattin H et al, 2013)

A list of references used in this analysis is given at the end of this document. A regular literature review has been performed to ensure that evolving evidence is captured. Some information contained herein is unpublished *in vitro* and animal model work on MERS-CoV from several international groups to whom we are indebted. Experts consulted are listed at the end.

3 SARS-CoV approximation of MERS-CoV

Although we draw inferences from SARS in this document, there are important differences between SARS and MERS coronaviruses (CoVs), and some areas in which MERS-CoV data is not yet sufficient to enable comparison. MERS- and SARS-CoV infections demonstrate different in vitro virological and immunological characteristics but the clinical relevance of these are unknown.

The limited evidence available on viral dynamics and clinical course suggest that MERS-CoV patients have shorter time from illness onset to clinical presentation and requirement for ventilatory support (median seven days; range 3-11) than SARS-CoV patients, as well as associated higher respiratory tract viral loads during the first week of the illness. Some therapeutic options that showed apparent clinical effects in observational human trials of SARS-CoV patients have not demonstrated in vitro inhibition of MERS-CoV.

4 Evidence base

Therapies that are plausible and supported by reasonable in vitro, animal and/or clinical data from MERS-CoV or other respiratory virus infections are shown in Table 1. A large number of other compounds have been evaluated for in vitro inhibition against MERS-CoV and some have demonstrated an inhibitory effect at concentrations that might be achieved in patients.

However, without animal studies or well-documented experience of clinical use in comparable contexts, these are not currently ready for clinical use in MERS-CoV patients.

5 Management of case

5.1 Infection control

Effective infection control is essential to protect staff and patients. Instigate measures as described in the PHE guidelines (www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317136232722).

5.2 Routine investigations

PHE will advise clinicians on samples for clinical and infection control purposes. We recommend that routine specimens include upper and lower respiratory tract, blood, stool and urine.

For organisations considering studies, ISARIC has developed a generic biological sampling protocol (www.prognosis.org/isaric) and case report forms (www.prognosis.org/isaric/crf.php).

5.3 Approach to treatment

The most important recommendation remains that high-quality supportive care is the keystone of management, as expressed in the Surviving Sepsis Campaign guidelines for the care of the critically ill and the WHO Interim Guidance on MERS: www.who.int/csr/disease/coronavirus_infections/InterimGuidance_ClinicalManagement_NovelCoronavirus_11Feb13u.pdf?ua=1.

Any additional benefit of investigational pharmacological agents is uncertain, because of lack of evidence, rather than lack of plausibility. Treatment with specific therapeutic agents should ideally occur in the context of formal observational studies or controlled intervention trials (see https://isaric.tghn.org/protocols/sari-bsp/ for open access protocols).

In the UK, two centres have experience of managing severely ill patients with MERS. Consultation with staff in these centres may be helpful. PHE will facilitate communications if required.

5.4 Specific therapies

Based on the evidence presented in Table 1, convalescent plasma, interferon and lopinavir may be considered for specific treatment of MERS-CoV patients. Interferon and lopinavir are likely to be the most accessible initial treatments. PHE will advise on

the availability of convalescent plasma once a case is identified. Specific MERS-CoV monoclonal and polyclonal antibodies are in development at the time of writing. UK physicians should contact PHE (Professor Maria Zambon's office, 020 8327 6810) for information about the current availability of monoclonal or polyclonal antibodies.

Other agents described in Table 1 have demonstrated antiviral effects in vitro, but without documented in vivo efficacy or sufficient clinical data. Some are associated with concerns about safety in clinical practice. Many require safety studies, animal studies, or both before clinical trials can be initiated. Expert consensus is to avoid those agents classified as "red", ie corticosteroids for specific treatment of MERS, and ribavirin. In some patients corticosteroids may be considered for other indications according to local policy, for example exacerbations of asthma/COPD, suspected or documented adrenal insufficiency or refractory septic shock (in line with Surviving Sepsis International Guidelines and WHO Interim Guidance on MERS).

The effect of steroids on viral clearance in MERS is unknown, although systemic corticosteroid administration delayed clearance of SARS-CoV and has been associated with prolonged replication of other respiratory viruses. Consequently, serial sampling with PCR testing should be performed in any patients who do receive steroids for any indication.

5.5 Combination therapy

Therapeutic agents were used in multiple combinations for treatment of SARS patients but there are inadequate data to disentangle the effects of individual agents from the possible benefits of any combinations. Limited data from in vitro and animal studies of MERS-CoV infection suggests a possible synergistic effect from combining interferon (IFN) and ribavirin. However, the concentrations of ribavirin used are much higher than those used to treat hepatitis C virus infection. Available data is inadequate to decide whether any benefit conferred by an interferon/ribavirin synergy outweighs the risk of ribavirin toxicity. Therefore, this combination is not recommended unless it is used in an appropriately planned clinical trial.

Table 1. Evidence base for specific therapies for MERS-CoV infection

Therapy	Studies conducted	Data: SARS and other respiratory viruses	Data: MERS	Safety profile	UK feasibility
GREEN: Benefit is likely to exceed risk					
Convalescent plasma (or high neutralising antibody titre products)	SIV; SA; SC; MIV	RCT not performed in SARS. One RCT supports use of hyperimmune globulin in severe A(H1N1)pdm09 influenza. Observational data suggests efficacy in SARS, A(H1N1)pdm09 and other influenza virus infections. A pooled meta-analysis including SARS-CoV and influenza studies showed a significantly lower risk of mortality in those treated with convalescent plasma or serum.	*In vitro* neutralizing effect. No MERS-CoV animal or human studies have been published, but studies are in progress in 2014.	Good safety profile in UK, risks as for other blood products.	Availability depends on UK epidemiological situation. Please contact PHE for an update on availability.
Interferons	SIV; SA; SC; MIV; MA	Type I (α, β), type II (γ), and type III (λ) interferons show activity against SARS in extensive *in vitro* and limited animal and observational clinical studies.	In vitro, MERS-CoV appears to be more sensitive to Type I IFNs than SARS-CoV, especially IFN-β. Animal studies with Poly IC topical IFN inducer suggest efficacy. IFN-α in combination with ribavirin shows some efficacy in non-human primates, but this animal	Well established agent. Clinicians experienced in managing side-effects should be consulted eg those treating hepatitis C virus (HCV) infection and multiple sclerosis. Consideration should be given to shorter-acting preparations compared to peg-IFNs.	Injectable interferon β is currently first choice and is routinely available. Inhaled interferon β is currently in Phase 2 trials.

			model does not accurately reflect severe MERS illness seen in humans.		
Lopinavir	SIV; SA; SC; MIV	Limited data that HIV protease inhibitors have in vitro anti-SARS-CoV effect. Observational studies suggest clinical benefits in SARS patients treated with lopinavir/ritonavir, including a reduction in mortality reported in one study.	Lopinavir inhibitory for MERS-CoV in vitro at concentrations observed in blood during clinical use. (Note other HIV PIs tested, atazanavir and ritonavir, were inactive).	Well established agent with favourable toxicity profile. Gastrointestinal side-effects are common but self-limiting.	Routinely available (as lopinavir/ritonavir combination preparation)
Monoclonal and polyclonal neutralising antibodies	SIV; SA; MIV	Strong in vitro neutralising effect against the SARS-CoV spike protein.	Novel monoclonal antibodies to MERS-CoV spike protein have strong neutralising effect.	Human safety studies will be conducted before individual products made available. In those products which have satisfied UK regulatory safety requirements, benefit is likely to exceed risk.	Contact PHE for an update on availability. Use should be within a trial, or if not possible, through a compassionate use arrangement.

YELLOW: Data is inadequate for assessment					
Interferon + ribavirin (combination therapy)	SIV; SA; SC; MIV; MA; MC	Synergistic effect in vitro and in animal model when ribavirin combined with IFN-β. Effect of combination could not be distinguished from other concurrent treatments in SARS patients. Where outcomes could be determined, adverse effects were reported.	IFN-a2b and ribavirin combined in vitro had anti-MERS-CoV effect at lower concentration than when used separately. Combination IFN-α2b and ribavirin in MERS rhesus macaque model led to clinical, radiographic and virological improvements. IFN/ribavirin combination therapy given late in illness to 5 MERS patients did not prevent death. Recent case reports of apparent benefit when used for early therapy or post-contact prophylaxis.	Adverse effects of ribavirin were frequent in SARS clinical studies (see ribavirin, below). In combination studies, the experimental ribavirin concentrations were higher than those observed clinically during treatment of hepatitis C.	Routinely available. Data is inadequate to decide whether any benefit conferred by possible interferon/ribavirin synergy outweighs the risk of ribavirin toxicity.
Nitazoxanide	MIV	No SARS data. Two RCTs show benefit in childhood respiratory infections and uncomplicated influenza in adults, respectively. Inhibitory for one non-human CoV in vitro.	No activity in vitro against MERS-CoV. No animal model data available.	Well established agent with defined safety profile.	Routinely available.

Mycophenolic acid	SIV; SA; MIV	No effect on SARS-CoV in vitro or in murine model.	Inhibits MERS-CoV in vitro, with a concentration achievable by standard clinical oral dosing. Synergy in vitro with IFN-β1b. MERS-CoV animal studies are in progress. No MERS clinical studies.	Effect of transient immunosuppressive activity in this context is uncertain. Established treatment with multiple well characterised side-effects.	Routinely available.
Chloroquine	SIV;MIV	Inhibitory in vitro for multiple viruses including influenza. No consistent activity in animal models of influenza and negative results in one influenza RCT of seasonal prophylaxis.	Inhibits MERS-CoV in vitro, with a concentration achievable by standard clinical oral dosing.	Well established agent with defined safety profile.	Routinely available

RED: Risk is likely to exceed benefit					
Corticosteroids (as specific therapy for MERS-CoV infection)	SA; SC;	A SARS-CoV animal study suggests early anti-inflammatory effects but found ongoing administration may enhance viral replication in the lung. SARS clinical studies found no mortality benefit. Some observational studies found clinical improvements after treatment, but one RCT found increased viral load associated with corticosteroid treatment Use of systemic corticosteroids in patients with severe influenza A(H1N1)pdm09 was also associated with increased risks of prolonged lower respiratory tract viral replication, nosocomial infections, ventilator-associated pneumonia, and higher mortality in observational studies.	No studies available. Given to many MERS patients under uncontrolled circumstances.	SARS studies found no mortality benefit and evidence for adverse effects of systemic steroids, with both acute and long-term harms, including delayed viral clearing reported, and increased opportunistic infections. Osteonecrosis was observed following pulsed methylprednisolone.	
Ribavirin – monotherapy	SIV; SA; SC; MIV; MC	Four of six in vitro SARS studies found an antiviral effect. No virological effects were found on SARS in animal models as monotherapy. In SARS clinical studies, the effect of ribavirin could not be distinguished from	MERS-CoV is inhibited by ribavirin at very high concentrations in vitro. These exceed concentrations achievable during clinical use, except possibly for	Studies of ribavirin in large numbers of SARS patients found frequent adverse effects including haemolysis, metabolic disturbances, and liver function test	

		the effects of other therapies.	high IV dosages. No animal monotherapy studies have been conducted. Combination therapy including ribavirin was given to five MERS patients late in the illness and did not prevent death.	derangement.	
UK intravenous human normal immunoglobulin IVIG)	SC; MIV	Five SARS studies conducted; all inconclusive as used IVIG as part of combination therapy. In one uncontrolled study in Hong Kong, 12 patients who had deteriorated despite other therapies were given IVIG as an additional therapy, with evidence of subsequent improvement.	PHE evaluation shows that UK IVIG has no evidence of MERS-CoV neutralising activity. IVIG from endemic countries requires separate evaluation.	Commercial intravenous immunoglobulin products have been associated with rare acute renal failure and thromboembolic events.	

* SARS in vitro (SIV); SARS animal (SA); SARS clinical (SC); MERS-CoV in vitro (MIV); MERS animal (MA); MERS clinical (MC)

6 Feedback

As this is a document intended for continual update, we are particularly interested in the views of those who may be using it on the frontline of service. Please send thoughts or suggestions for improvement, or any other comments, to colin.brown@phe.gov.uk and meera.chand@phe.gov.uk.

7 Useful links

PHE – www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/NovelCoronavirus2012/

ISARIC – http://www.isaric.org

WHO – www.who.int/csr/disease/coronavirus_infections/update_20130517/en/index.html

ECDC – www.ecdc.europa.eu/en/healthtopics/coronavirus-infections/pages/index.aspx

CDC – www.cdc.gov/features/novelcoronavirus/

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9 Consultation

The following coronavirus experts and clinicians and scientists with experience of SARS, MERS-CoV, and other respiratory viruses were involved in PHE or ISARIC teleconferences or commented on drafts of this document. We are most grateful to them all for their valued input.

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Clinicians, virologists, health professionals, and public health experts involved in managing MERS-CoV patients:
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