Public Health England

Protecting and improving the nation's health

ISARIC

Treatment of MERS-CoV: Information for Clinicians

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

5 September 2015
v3.0

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 world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Prepared by: Colin Brown
For queries relating to this document, please contact: colin.brown@phe.gov.uk

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Contents

About Public Health England 1
1. Document Scope 4
2. Literature 4
3. SARS-CoV Approximation of MERS 5
4. Evidence Base 5
5. Management of Cases 6
Table 1: Benefit is likely to exceed risk 8
Table 1: Data is inadequate for assessment 10
Table 1: Risk is likely to exceed benefit 11
Feedback 14
Useful Links 14
Document Authors 14
Consultation 15
Bibliography: articles of interest 16

1 Document scope

This evolving 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 Infection 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, SARS: Systematic review of treatment effects, published in PLoS Med (2006;3(9):e343). A further useful review of SARS is: Cheng VCC et al, Clinical management and infection control of SARS: lessons learned, published in Antiviral Research (2013;100:407-419).

There are two useful summaries of MERS treatment options: 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), and Chan JFW et al, Middle East Respiratory Syndrome Coronavirus: Another Zoonotic Betacoronavirus Causing SARS-Like Disease, published in Clinical Microbiology Reviews (2015;28(2):465-521). Colleagues with experience of managing MERS-CoV patients in affected countries have also reviewed treatment options for MERS-CoV (see Section 10 Bibliography - general).

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, up to date as of August 2015 using the search strategy detailed in Momattin et al (2013) searching across Pubmed, Embase, Scopus and the Web of Science.

A further manual review of all recent MERS-related papers in Pubmed was performed for each therapeutic option. Some information contained herein is unpublished *in vitro* and animal model work on MERS-CoV from several international groups to whom we are indebted. The experts consulted are listed in Section 9 - Consultation.

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 some differences in *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 possible 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 of MERS-CoV replication, and some have demonstrated an inhibitory effect at serum 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. Such therapies have therefore not been included.

There has been no significant change in recommedations of therapeutic agents since the last published version (v2.0) in July 2014 based on available evidence, except that mycophenolic acid (mycophenolate mofetil or MMF) has been downgraded to ‘red’ based on recent marmosrt model data suggesting increased replication and worse outcomes on administration compared to controls. One patient also developed MERS while on MMF treatment. There has also been recent progress in the rapid development and testing of monoclonal and polyclonal human neutralizing antibodies in small animal models. These may be options for compassionanate use and preferably for study in controlled trials in the near future.

Treatment with specific therapeutic agents should ideally occur in the context of formal observational studies or controlled intervention trials (see https://isaric.tghn.org/articles/adapted-study-documents-protocols/ for open access protocols).

5 Management of cases

5.1 Infection control

Effective infection control is essential to protect staff and patients. Instigate measures as described in the PHE guidelines (https://www.gov.uk/government/publications/merscov-infection-control-for-possible-or-confirmed-cases).

5.2 Routine investigations

PHE will advise clinicians on samples for clinical and infection control purposes. We recommend that initial sampling from confirmed positive cases includes blood for viral load monitoring, and possibly serial respiratory tract sampling in severe cases for monitoring response to therapy and possible resistance. Viral sampling for research purposes could include serial upper and lower respiratory tract, blood, stool and urine samples for monitoring of viral load and persistence within body compartments.

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 updated WHO Interim Guidance on MERS: http://www.who.int/csr/disease/coronavirus_infections/case-management-ipc/en.

The Surviving Sepsis Campaign guidelines also offer standards of care for the critically ill.

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/articles/adapted-study-documents-protocols/ 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 containing MERS-CoV antibodies, interferon and lopinavir may be considered for specific treatment of MERS-CoV patients. Interferon and lopinavir remain 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 advanced pre-clinical development at the time of writing and initial clinical studies are anticipated shortly, but significant progress has been made recently. UK physicians should contact PHE (Professor Maria Zambon's office, + 44 20 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, particularly in MERS patients. 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, ribavirin monotherapy, and mycophenolate mofetil (MMF). 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 the WHO Interim Guidance on MERS and Surviving Sepsis International Guidelines).

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 viral load sampling with PCR testing should be performed in any patients who do receive steroids for any indication.

5.5 Combination therapies

Therapeutic agents were used in multiple combinations for treatment of SARS patients, and increasingly in MERS patients, but there remain inadequate data to disentangle the effects of individual agents from the possible benefits of any combinations. The vast majority of experience is from restrospective observational studies. 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. Ribavirin has also been associated with significant adverse effects in both SARS and MERS patients. 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 (see https://isaric.tghn.org/articles/adapted-study-documents-protocols/ for open access protocols).

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

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

Therapy	Studies * Performed	Data: SARS and other respiratory viruses	Data: MERS	Safety Profile	UK feasibility
GREEN: Benefit is likely to exceed risk					
Convalescent plasma (or high neutralizing antibody titre products)	SIV; SA; SC; MIV; MA	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 based on levels of MERS-CoV specifc antibodies, and high-titer camel serum improved viral clearance in infected mice. No MERS-CoV human studies have been published, but studies have been in progress since 2014. A mouse model for candidate vaccine design induces potent humoral and cellular immune responses. There may be wide variation in the amount of neutralizing antibody depending on illness severity, timing of plasma collection in relationship to convalescene, with waning titres over time.	Good safety profile in UK, risks as for other blood products. Convalescent plasma should be tested to have documented specific MERS antibody before use.	Availability depends on UK epidemiological situation. Please contact PHE for an update on availability.
Interferons	SIV; SA; SC; MIV; MA; MC	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	*In vitro*, MERS-CoV appears to be more sensitive to Type I IFNs than SARS-CoV, especially IFN-β. Some animal evidence from marmoset model in severe	Well established agent. Clinicians experienced in managing side effects	Injectable recombinant interferon β1b is currently first choice and is routinely

		studies.	disease with IFN-β1b. Animal studies with Poly IC topical IFN inducer suggest efficacy. Type 1 IFNs are among the most active drugs at clinically achievable serum levels. IFN-α in combination with ribavirin shows some efficacy in non-human primates, but this animal model does not accurately reflect severe MERS illness seen in humans.	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.	available. Inhaled interferon β is currently in Phase 2 trials but has not been adequately studied in severe lower respiratory tract infections.
Lopinavir	SIV; SA; SC; MIV; MA; MC	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). Good *in vivo* evidence from marmoset model for improved outcomes. Use in one patient alongside IFN and ribavirin.	Well established agent with favourable toxicity profile. Gastrointestinal side effects are common but self-limiting.	Routinely available (as lopinavir and ritonavir combination preparation).
Monoclonal and polyclonal neutralising antibodies	SIV; SA; MIV; MA	Strong *in vitro* neutralising effect against the SARS-CoV spike protein.	Novel monoclonal antibodies to MERS-CoV spike protein have strong neutralising effect. Potent MERS-CoV–neutralizing antibody have recenty been isolated from memory B cells of an infected individual and polycloncal human neutralizing antibodies have been	No human studies have yet been conducted. In those products which have satisfied UK regulatory safety requirements, benefit is likely to exceed risk. Monoclonal antibody resistant	Contact PHE for an update on availability. Use should be within a trial, or if not possible, through a compassionate use

			produced in transchromosomal bovines. Camel antibodies have been successful in prophylactic and therapeutic use in murine models. Human mAbs have been successfully trialled as both therapy and prophylaxis in murine models.	mutants (MARMS) selected *in vitro* are not inhibited *in vivo* and show little loss of fitness.	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-α2b 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 some clinical, radiographic and virological improvements. IFN/ribavirin combination therapy given late in illness to 5 MERS patients did not prevent death, and was not helpful in a further 3 out of 6 cases. Some case reports of apparent benefit when used for early therapy or post-contact prophylaxis, but there have been case studies that show little effect on mortality. One retrospective cohort	Adverse effects of ribavirin were frequent in SARS clinical studies (see ribavirin, below). In combination studies, the experimental ribavirin concentrations were higher than those achieveable clinically during treatment of hepatitis C. One restropective cohort of 20 patients showed no increase in adverse effects apart from greater haemoglobin reduction**.**	Routinely available. Data are inadequate to decide whether any benefit conferred by possible interferon and ribavirin synergy outweighs the risk of ribavirin toxicity.

			study showed improved outcomes in severe MERS-CoV infection in those given ribavirin and IFN-α2a at 14 days but not 28. IFN- α2a may give worse outcomes than IFN-α2b due to higher $IC_{50.}$		
Nitazoxanide	MIV	No SARS data. Two RCTs show benefit in childhood respiratory infections and uncomplicated influenza in adults, respectively. Inhibitory for two non-human CoVs *in vitro.*	No activity *in vitro* against MERS-CoV. No animal model data available.	Well established agent with defined safety profile.	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, described in several papers.	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; MC	A SARS-CoV animal study suggests early anti-inflammatory effects but found ongoing administration may enhance viral replication in the lung. SARS clinical	No studies available. Given to many MERS patients under uncontrolled circumstances with limited outcome data.	SARS studies found no mortality benefit and evidence for adverse effects of systemic steroids, with both acute and long-term harms,	Routinely available.

		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.		including delayed viral clearing reported, and increased opportunistic infections. Osteonecrosis was observed following pulsed methylprednisolone, more commonly in male, young patients, and in those receiving more than one type of steroid administration.	
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 the effects of other therapies.	MERS-CoV is inhibited by ribavirin at very high concentrations *in vitro*. These exceed concentrations achievable during clinical use, except possibly for 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	Studies of ribavirin in large numbers of SARS patients found frequent adverse effects including haemolysis, metabolic disturbances, and liver function test derangement.	Routinely available.

			prevent death. One recent review suggests that decreased mortality at 14 days seen in combination therapy may be associated with the use of oral ribavirin, but this is specuative.		
UK intravenous human normal immunoglobulin (IVIG)	SC; MIV MC	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. Local IVIG given to correct platelet imbalance in one Saudi study, with favourable outcome.	Commercial IVIG products have been associated with rare acute renal failure and thromboembolic events.	Routinely available.
Mycophenolic acid / mycophenolate mofetil (MMF)	SIV; SA; MIV; MA; MC	No effect on SARS-CoV *in vitro* or in a murine model.	Inhibits MERS-CoV *in vitro*, with a concentration achievable by standard clinical oral dosing. Synergy in vitro with IFN-β1b. MERS-CoV marmoset studies indicate that MMF used alone may increase viral replication and worsen outcomes. One patient acquired infection while on MMF following renal transplantation but survived with reduction in dose.	Effect of transient immunosuppressive activity in this context is uncertain. Established treatment with multiple well characterised side effects.	Routinely available.

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 maria.zambon@phe.gov.uk.

7 Useful links

PHE – https://www.gov.uk/government/collections/middle-east-respiratory-syndrome-coronavirus-mers-cov-clinical-management-and-guidance

ISARIC – http://www.isaric.org

WHO – http://www.who.int/emergencies/mers-cov/en/

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

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

8 Document authors

Dr Colin Brown[1,2]
Dr Gail Carson[3]
Dr Meera Chand[1,5]
Dr Jake Dunning[1,3,4]
Professor Maria Zambon[1]

[1] National Infection Service, Public Health England, UK
[2] Hospital for Tropical Diseases & Department of Clinical Microbiology, University College London Hospital, UK
[3] International Severe Acute Respiratory & Emerging Infection Consortium (ISARIC), UK
[4] Centre for Respiratory Infection, Imperial College London, UK
[5] Guy's & St Thomas' Hospitals NHS Foundation Trust, UK

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. this is a document intended for continual update.

Contributors involved in literature review, documentation, and draft development:
Ken Baillie, University of Edinburgh, UK & ISARIC Working Group 3 chair
Nick Barrett, Guy's & St Thomas' Hospitals NHS Foundation Trust
Katrina Barlow, Public Health England, UK
Nichola Goddard, Public Health England, UK
Eli Harris, Oxford University, UK
Kajsa-Stina Longuere, ISARIC Coordinating Centre, UK
Nick Phin, Public Health England, UK
John Watson, Public Health England, UK

International experts invited to comment on basis of experience of SARS/H5N1/critical care, or to contribute unpublished data:
Neil Adhikari, Sunnybrook Research Institute, Canada
Yaseen Arabi, King Saud Bin Abdulaziz University for Health Sciences, Saudi Arabia
Abdullah Brooks, Johns Hopkins University, US & ISARIC chair
Janet Diaz, California Pacific Medical Center, US
Jeremy Farrar, when he was Director of Oxford University Clinical Research Unit, Vietnam
Heinz Feldman, National Institute of Allergy and Infectious Diseases, National Institutes of Health, US
Ron Fouchier, Erasmus Medical Center, The Netherlands
Rob Fowler, University of Toronto, Canada & ISARIC
Bart Haagmans, Erasmus Medical Center, The Netherlands
Frederick Hayden, University of Virginia School of Medicine, US & ISARIC past chair
David Hui, Chinese University of Hong Kong, China
Michael Ison, Northwestern University Feinberg School of Medicine, US
Eric Snijder, University Medical Center Leiden, The Netherlands

WHO staff:
Nikki Shindo, World Health Organization, Switzerland

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