



Public Health
England



Treatment of MERS-CoV: Decision Support Tool

**Clinical Decision Making Tool for Treatment of MERS-CoV v.1.1,
29 July, 2013**

ISARIC = International Severe Acute Respiratory & Emerging Infection Consortium

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NB Note version - living document that will be regularly updated as new research becomes available

Decision Support: Treatment of MERS-CoV

Document scope

This document reviews the available evidence regarding treatment of Middle East Respiratory Syndrome Coronavirus (MERS-CoV), largely based on recent experience in treating SARS and pandemic influenza, and following Public Health England (PHE) discussions with international experts convened through the International Severe Acute Respiratory & Emerging Infection Consortium (ISARIC). Though informed by the views of clinicians who have first-hand experience of treating patients with SARS-CoV and other novel respiratory pathogens, it is intended to provide an overview of the evidence rather than be proscriptive in suggesting therapeutics, or as guidelines from the review group.

Treatment cornerstone

The most important recommendation remains that general supportive care continues to be the keystone of management, as similarly expressed in the Surviving Sepsis Campaign guidelines for the care of the critically ill, and that any additional benefit of novel pharmacological agents remains uncertain, through lack of evidence, rather than lack of plausibility. Treatment with other therapeutic agents should ideally occur in the context of systematic data collection (patient characteristics, severity of illness, other treatments and outcomes), formal observational studies or in controlled trials.

Literature

A list of references is given at the end of this document. This document takes much of the SARS information from the systematic review of SARS treatment performed by Lauren Stockman, Richard Bellamy and Paul Garner published in PLoS Medicine in 2006:

- Stockman LJ, Bellamy R, Garner P (2006) SARS: Systematic review of treatment effects. PLoS Med 3(9): e343. DOI: 10.1371/journal.pmed.0030343

Some information contained herein is unpublished *in vitro* and animal investigatory work on MERS-CoV from several international groups to whom we are indebted. Experts consulted are listed at the end.

SARS approximation of MERS-CoV

Despite inferences that can be drawn from SARS, a recent study comparing gene expression changes following SARS-CoV and MERS-CoV infection in a human lung epithelial cell line demonstrates that the viruses induce similar activation of certain pathways *in vitro*, but that MERS-CoV downregulates expression of several genes associated with the antigen presentation pathway, suggesting that host adaptive responses may be diminished in MERS-CoV compared to SARS-CoV. Furthermore, information on the pathogenesis and clinical spectrum of disease in human infections caused by MERS-CoV is very modest at present. Both of these coronaviruses can cause severe viral pneumonia and sometimes multi-organ failure in association with protracted viral replication in the lower respiratory tract and detection of virus in blood and sometimes other fluids. However, many unanswered fundamental questions exist regarding routes of transmission and sites of infection, incubation period, viral dynamics, host factors, and innate and adaptive immune responses for MERS-CoV infections.

Reviewed agents

The following agents are considered on the basis of plausibility to be most worth consideration of experimental intervention treatment. By reference to other serious viral infections e.g. SARS, influenza, Ebola, it is believed that the strongest evidence for intervention exists for use of convalescent plasma or other preparations (hyperimmune globulin, monoclonals) that possess neutralizing antibodies. Limited and in some cases no, support exists for the use of the remaining agents being trialed. For any chosen intervention, we advocate that use should be accompanied by an appropriately planned evaluation of effectiveness that includes sequential virologic, clinical, and biomarker measurements.

Routine investigations

We recommend that routine specimens include blood, stool, urine, and upper and lower respiratory tract. ISARIC has developed a generic biological sampling protocol: <http://www.prognosis.org/isaric> and case report forms: <http://www.prognosis.org/isaric/crf.php>.

Convalescent plasma

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Convalescent plasma obtained from an individual who has recovered from MERS-CoV contains high levels of neutralising antibody (PHE unpublished data). Though potentially very limited in availability, if it can be accessed the evidence suggests this is likely to be the best therapy to neutralize extracellular virus. Use should be accompanied by an appropriately planned evaluation of effectiveness.

Intravenous Immunoglobulin (IVIG)

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Though IVIG may work in a similar manner to convalescent plasma if cross-reactive antibodies were present, there is no evidence at present to suggest current non-selected batches have any anti-MERS-CoV effect. Use is not recommended outside of an appropriately planned evaluation of effectiveness.

Interferon (IFN)

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Practicalities likely dictate that IFN will be more accessible than plasma. There is *in vitro* (MERS-CoV, SARS) and animal model (SARS) evidence that IFN inhibits viral replication, particularly early in clinical course, as well as limited observational human data suggesting clinical benefit (SARS). Use is not recommended outside of an appropriately planned evaluation of effectiveness.

HIV Protease Inhibitors (PIs)

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There is limited, inconsistent evidence that certain HIV PIs have *in vitro* anti-SARS effect, and may have possible clinical benefit in patients, though the scientific rationale is unclear. Use is not recommended outside of an appropriately planned evaluation of effectiveness.

Ribavirin

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Ribavirin may have a CoV antiviral effect, however many adverse effects were seen during SARS therapy. Expert opinion suggests withholding ribavirin for MERS-CoV, even when other therapeutic options have failed. Use is not recommended outside of an appropriately planned evaluation of effectiveness.

Corticosteroids

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Corticosteroids may act as immunomodulatory agents, but there is no mortality benefit and contrary evidence for any benefit, including delayed viral clearing in SARS. Use is not recommended outside of an appropriately planned evaluation of effectiveness, except for those in whom other proven clinical benefits may outweigh harms (such as in minimisation of long-term end organ damage). If used, early intervention during the period of maximal viral shedding and acute inflammatory response may be important. Accumulating evidence suggests that viral shedding may continue for some time (over 30 days), and the possible impact of corticosteroids on clearance, as with SARS, should be closely monitored.

Nitazoxanide (NTZ) & Others

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NTZ's safety profile, *in vitro* activity (canine CoV), and reported antiviral and clinical effect on other respiratory viruses (influenza) is encouraging, though no clinical CoV studies exist. Early *in vitro* evidence suggests cyclosporin A, a potential pan-CoV inhibitor, demonstrates *in vitro* effect against MERS-CoV, though no clinical or animal studies exist. siRNA to several targets in SARS-CoV showed activity in rhesus model. Use is not recommended outside of an appropriately planned evaluation of effectiveness.

Combination therapy

N/A

Therapeutic agents were used in multiple combinations during SARS but there is inadequate data to disentangle the effects of individual agents from the possible benefits of any combinations. There is limited data from MERS animal models concerning IFN and ribavirin dual therapy, and for this reason

we have included this below.

Strength of evidence

	Study Focus: *	Quality of Best Available Evidence®	Order of Recommendation¥
Convalescent plasma ≠	SIV; SA; SC; MIV	SC (Moderate)	1
Interferon	SIV; SA; SC; MIV	MIV (Low)	2
Protease Inhibitors	SIV; SA; SC	SIV (Very Low)	2
Intravenous Immunoglobulin	SIV; SA; SC; MIV	Nil	3
Nitazoxanide	Nil	Nil	3
Others e.g. Cyclosporin A	SIV; MIV	MIV (Very Low)	3
Ribavirin	SIV; SA; SC	SIV (Very Low)	4
Corticosteroids	SIV; SA; SC	SA (Low)	4
Interferon plus ribavirin	SIV; SC; MIV; MA	MA (Very Low)	4

≠ Hyperimmune globulin or human neutralising monoclonals when available. The latter were shown active in SARS animal models.

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

¥ Recommendations

1 (Consider for use) = Probable Clinical Effect

2 (Do Not Consider for use outside of an appropriately planned evaluation of effectiveness) = Potential Clinical Effect or Proven *In Vitro* Effects with Some Potential Side Effects

3 (Do Not Consider for use at this time outside of an RCT) = Little or No Evidence of Either *In Vitro* or Clinical Effect

4 (Do Not Consider for use at this time outside of an RCT) = Suggested Clinical Effect or Proven *In Vitro* Effect with Potential Serious Side Effects

Choice of agent

From the above table, convalescent plasma could be used - if both available and safe – but this should, at a minimum, be accompanied by daily dynamic sampling and data collection using the standardised ISARIC/WHO protocols and record forms.

Ideally, this would be part of systematic prospective observational studies including similar data collection and sampling in patients treated without the use of convalescent plasma. Where possible, this would be in the context of a randomised controlled trial (RCT) involving other interventions such as IVIG or placebo.

IFN and PIs could potentially be trialed, but only with daily dynamic sampling and collection of data using the ISARIC/WHO standardized proformas and preferably as part of an RCT.

Only use NTZ and cyclosporin as part of an RCT, as even though they are unlikely to have worrying adverse effects, there is little or no SARS or MERS-related evidence.

We recommend not using ribavirin or corticosteroids outside of an RCT (unless for some other clinical indication) due to potential worrying adverse side effects.

Decision Support: Treatment of MERS-CoV with Convalescent Plasma

- **Proposed MOA** – Neutralization of extracellular virus and possibly other effects (e.g. antibody-dependent cell-mediated cytotoxicity, preventing cell-cell spread of virus).
- ***In vitro* and animal model activity for SARS** – Plasma contains neutralising antibodies against the S-spike protein inhibited virus replication within *in vitro* and animal models.
- ***In vitro* activity in MERS-CoV** – Some evidence that convalescent SARS sera may contain cross-reactive antibodies against MERS-CoV (neutralizing antibody titre of >1:10).
- **Human virologic and clinical effectiveness in SARS-CoV and other viruses** – A SARS systematic review highlighted two studies of convalescent plasma given in addition to steroids and ribavirin. Both were inconclusive - the effect was not distinguishable from other treatment, comorbidities, or illness stage. However, observational data suggested potential efficacy, though the timing of antiviral effects after administration was not documented.
 - In Hong Kong, 80 non-randomised recruited patients were given convalescent plasma: the discharge rate at day 22 was 58.3% for patients (n=48) treated within 14 days of illness onset compared to 15.6% for those (n=32) treated beyond 14 days.
 - Reductions (three log¹⁰) in blood viral load was seen in small numbers of SARS patients.
 - Timing in relation to SARS onset was dependent on peak viraemia (day 10) – it was only effective within 14 days of onset. MERS-CoV viral kinetics remain unknown, including date of peak viral load and replication duration, and thus best treatment timing. Limited UK data indicated detectable virus up to day 30 in at least two body compartments.
 - Three Taiwanese healthcare workers infected with SARS were treated with convalescent plasma; all survived after severe progression and failure to respond to other treatments.
- In one 2009 observational study of patients with H1N1pdm09 in Hong Kong, 500mls convalescent plasma with an antibody titre of >1:160 was infused intravenously to 20 patients over four hours. Reduced mortality (crude mortality 20% vs 55% in controls) and more rapid virus clearance were seen compared to critically ill patients given NAI therapy alone. More recent RCT evidence in 17 patients with H1N1pdm09 given hyperimmune globulin versus 18 given IVIG showed significantly lower respiratory viral loads in the former.
- **Safety profile** – Risk of transfusion related acute lung injury (TRALI) and incompatibilities.
- **Key PK properties** – Recovered SARS healthcare workers had neutralising antibody levels between 1:160 and 1:2560. 600-900ml screened donated plasma recovered by apheresis and cell separation; 200ml aliquots stored at -70C; and 200-400ml given to each patient.
- **Current approval status** – Named patient basis following ethical approval and sampling - early treatment is likely to be better. Ethical approval should be sought as an urgent issue.
- **Current availability** – Not currently available. The UK PHE and WHO EMRO-affiliated countries with convalescent patients are investigating the possibility of obtaining hyperimmune plasma. This document will be updated as this situation becomes clearer.

SUMMARY: No evidence from randomised trials to suggest a mortality benefit. Observational data points to possible efficacy in SARS and severe influenza. As MERS-CoV viral replication kinetics unclear, convalescent plasma treatment can be considered in patients who are deteriorating, despite other specific and supportive therapy, and in whom virus remains detectable. Use should be accompanied by an appropriately planned evaluation of effectiveness.

Decision Support: Treatment of MERS-CoV with Intravenous Immunoglobulin (IVIG)

- **Proposed MOA** – If cross-reactive neutralising antibodies are present, as with convalescent plasma, neutralization of extracellular virus and possibly other effects.
- ***In vitro* and animal model activity for SARS** – Theoretically, if neutralising antibodies present in the pooled sera from exposure to other coronaviruses cross-react with MERS-CoV, IVIG would act in the same way as those present in convalescent plasma.
- ***In vitro* activity in MERS-CoV** – Investigation of pooled IVIG for interaction with MERS-CoV in culture has been undertaken by PHE (HPA), with no evidence of reactivity (PHE unpublished data).
- **Human virologic and clinical effectiveness in SARS-CoV** – The same systematic review of SARS detailed five studies that included IVIG as part of the therapeutic regime given to some non-randomised patient groups, in addition to steroids, interferon and ribavirin. Again, all were inconclusive, as any improvement could not necessarily be attributed to IVIG administration.
 - In Hong Kong, 12 non-randomised recruited patients who had deteriorated despite corticosteroid and ribavirin therapy were given 5 ml/kg/day Pentaglobin, with improvements seen in chest imaging and oxygenation, though there was no control group for comparison.
 - In a Taiwanese cohort, IVIG was administered if severe leukopenia ($<2 \times 10^9/L$), thrombocytopenia ($<100 \times 10^9/L$), or both occurred, at a dose of 1 g/kg/day for 2 days. IVIG appeared effective in controlling both blood parameters, though again without a control group.
 - In another Taiwanese review of a variety of treatment options, 40 patients were given IVIG, though its effect was not commented on separate from additional interventions.
 - Two Chinese articles also describe its administration to SARS patients, but again do not comment on any effect on treatment outcome.
- **Safety profile** – Though rare, commercial intravenous immunoglobulin products have been associated with acute renal failure and thromboembolic events.
- **Key PK properties** – The only doses reported are mentioned above, with no further mention of pharmacokinetic properties.
- **Current approval status** – Available in most countries.
- **Current availability** – Currently available from a variety of commercial suppliers, though there are current concerns regarding scarcity of supply.

SUMMARY: No randomised evidence suggests that there is mortality benefit with the use of IVIG plasma. Limited observational data suggest it was associated with improvements in some clinical markers of disease severity. Initial laboratory testing suggests there is no activity against MERS-CoV, and therefore its use is not recommended as a specific anti-coronavirus agent outside of an appropriately planned evaluation of effectiveness.

Treatment of MERS-CoV with Interferon (IFN)

- **Proposed MOA** – Inhibition of viral replication (protection of non-infected cells) and immunomodulatory effects (NK cell activation).
- ***In vitro* and animal model activity for SARS** – IFNs type I (α , β), type II (γ), and type III (λ) have been tested for their SARS-CoV antiviral activities *in vitro* and in animals.
 - IFN- β and IFN- γ synergistically inhibit SARS-CoV replication. 12 *in vitro* studies for IFN type I have been reported, and all demonstrated an antiviral effect against SARS-CoV.
 - Effects demonstrated in monkey and human cell lines. IFN- α and - β consistently active *in vitro* (INF- β most active). Synergistic effects seen with ribavirin, and combined IFN- β and - γ . Pegylated IFN- α 2b 3mg/kg reduced SARS replication and lung injury in monkeys.
 - Exogenous IFN- α inhibits SARS-CoV replication in murine lungs. Viruses causing target cell lysis are effectively inhibited by IFNs through antiviral activity in non-infected cells. IFNs may thus have greatest effect in prophylaxis or early post-exposure management.
 - INF- λ controlled infections in murine epithelial cells (respiratory; gastrointestinal).
- ***In vitro* and animal model activity activity in MERS-CoV** – PegIFN- α was 50-100 times more effective for MERS-CoV than SARS-CoV. Early unpublished data suggests this is the most active agent *in vitro* of various compounds screened. Type I and III IFN efficiently reduced MERS-CoV replication in HAE cultures. MERS-CoV appears to be 50-100 times more sensitive to IFN- α than SARS-CoV. 16-hr subcut administration (with ribavirin) in MERS-CoV infected macaques led to improvements in clinical signs, radiographic changes, and viral load.
- **Human virologic and clinical effectiveness in SARS-CoV** – In a small uncontrolled clinical study in Toronto, corticosteroid use (13 patients) with interferon alfacon-1 (a synthetic interferon- α ; used in nine patients) showed improvements in oxygenation and oxygen dependence, and more rapid resolution of lung radiograph abnormalities. In SARS patients, two studies of IFN- α given with steroids and/or ribavirin were also reported. No significant difference was seen in outcome between IFN- α treatment group and those treated with other regimens. Results of both studies were inconclusive due to a lack of a consistent treatment regimen or suitable control group. One additional Chinese study reported IFN- α use alongside ribavirin and steroids. The Stockman review determined this to be inconclusive because the variety of treatments given may have masked the effect of IFN- α alone.
- **Safety profile** – Significant side effects need managed from those experienced in its use e.g. those that treat hepatitis C virus (HCV) infection. Given tolerability concerns, consideration should be given to shorter-acting preparations compared to peg-IFNs.
- **Key PK properties** – Different brands vary by formulation and dosage. Though IFN binds to specific cellular receptors and induces a variety of cellular responses that mediate the antiviral effects, *In vitro* levels are likely beyond what can be achieved clinically. A recent MERS-CoV study suggests lower concentrations of combined IFN- α 2b and ribavirin achieved comparable endpoints. Cytostatic effects may account for the inhibition of replication.
- **Current approval status** – IFN- α is approved for treatment of HCV in many countries.
- **Current availability** – Available for selected countries.

SUMMARY: There is *in vitro* and limited animal and observational experience that IFN, particularly early use, has efficacy against SARS, in addition to *in vitro* activity against MERS-CoV. Early treatment of severe disease with ongoing viral replication could occur in the context of controlled trials. Use is not recommended outside of an appropriately planned evaluation of effectiveness.

Treatment of MERS-CoV with HIV Protease Inhibitors

- **Proposed MOA** – CoV protease inhibitor.
- **In vitro and animal model activity for SARS** – Proteases have many diverse families e.g. HIV/retrovirus (aspartic); coronavirus (cysteine).
 - Structure, active site residues, substrate binding pockets and proteolysis mechanism are different, with HIV protease inhibitors tailored to block a specific HIV enzyme.
 - Some inhibitory effect has been reported for SARS-CoV; the mechanism is unclear e.g. intermediates from lopinavir synthesis were reported to be better inhibitors than the final product.
 - Of three studies, two demonstrated that lopinavir inhibits cytopathic effects of SARS in fetal rhesus monkey kidney cells. One study showed detectable but reduced activity in Vero-E6 cells, and another concluded that Lopinavir/ritonavir (L/r) had no effect.
 - A synergistic effect of lopinavir with ribavirin has been reported.
- **In vitro activity in MERS-CoV** – 80% inhibition at 8uM with lopinavir; 20uM is toxic. The same experiment reproduced inhibition of SARS-CoV at 16uM. The evolutionary distance between SARS-CoV and MERS-CoV is considerable. Work on new PIs specifically targeted against MERS-CoV is underway, but remains at a very preliminary stage.
- **Human virologic and clinical effectiveness in SARS-CoV and other viruses** – Non-randomized observational reports found reductions in steroid use and nosocomial infections in L/r treated patients, who had decreasing viral loads and rising blood lymphocyte counts.
 - 75 SARS patients treated with L/r plus ribavirin in Hong Kong had lower mortality, intubation, and steroid use than ~1000 matched controls receiving only ribavirin.
 - 41 other Hong Kong patients given L/r plus ribavirin had less ARDS, nosocomial infection, use of corticosteroids and death than 111 matched patients treated with ribavirin. They had lower viral loads in nasopharyngeal aspirates and higher peripheral lymphocyte counts compared with historical controls who had received ribavirin. The reductions in NPA viral loads might have been due to decreased use of steroids and not a direct antiviral effect. No effect was seen for salvage therapy for progressive lung disease.
 - Darunavir not tested, though extrapolation could suggest a potential therapeutic effect.
- **Safety profile** – L/r: Diarrhoea, and inhibitor of CYP3A, therefore potential drug interactions. Darunavir: use with caution in moderate hepatic impairment (no PK data for severe hepatic impairment, so avoid use); no renal adjustment needed. Contra-indicated with statins.
- **Key PK properties** – L/r: Multiple dosing with 400/100 mg L/r twice daily gives mean peak plasma lopinavir of 9.8 µg/mL and mean morning trough concentration of approximately 7.1 µg/mL. Principally metabolized and eliminated by the liver. Darunavir: no data for SARS.
- **Current approval status** – Approved for HIV treatment in most countries.
- **Current availability** – Widely available.

SUMMARY: There is limited, inconsistent evidence that L/r has *in vitro* anti-SARS-CoV effect and possible clinical benefit in patients, though the scientific rationale for these effects is unclear. It is unclear whether the observed inhibition *in vitro* derives from CoV protease inhibition, or whether other viral or cellular function may be targeted. These agents have a favourable toxicity profile, but ongoing *in vitro* studies with MERS-CoV are not yet conclusive, so that there is no solid evidence that administration would be beneficial. Use is not recommended outside of an appropriately planned evaluation of effectiveness.

Decision Support: Treatment of MERS-CoV with Ribavirin

- **Proposed MOA** – CoV antiviral effect and an immunomodulatory agent.
- ***In vitro* and animal model activity for SARS** – The systematic review detailed six studies describing the *in vitro* antiviral effect of ribavirin; of these, four demonstrated an antiviral effect. Two studies, performed in human cell lines and Vero cell lines, showed a synergistic antiviral effect between ribavirin and Type I IFN (IFN- β 1a or leukocytic IFN- α). No virological effects in animal models were seen when used as monotherapy. **A synergistic effect was seen *in vitro* when combined with IFN- β .**
- ***In vitro* activity and animal model activity in MERS-CoV** – A recent article suggests that though MERS-CoV was sensitive to both IFN-a2b and ribavirin alone in Vero and LLC-MK2 cells, this was at relatively high (cytostatic) concentrations. When combined, lower concentrations could be used, with similar *in vitro* outcomes. Administration **with IFN** in MERS-CoV infected macaques led to improvements in clinical signs, radiographic changes, and viral load. Ribavirin was administered as a loading dose intravenously followed by subsequent intramuscular doses every 8 hours.
- **Human virologic and clinical effectiveness in SARS-CoV** – The systematic review found 30 studies describing ribavirin treatment that was given to ten or more patients, often in combination therapy with other treatments such as corticosteroids.
 - The effect of ribavirin could not be distinguished from the effects of other treatments (such as steroids and antiviral drugs), and many did not have control groups or randomised allocation of treatment, and the review classified most as ‘inconclusive’. Where outcomes could be determined, adverse effects were reported.
 - Doses used varied across studies, though most commonly used was either 8 mg/kg IV 3 times/day or 1.2 g oral 3 times/day.
- **Safety profile** – There is evidence of adverse side effects and possible increased viral replication due to immunomodulatory effects. Four studies demonstrated some evidence of possible harm. Three large trials that included over 100 patients in each showed decreased haemoglobin levels after ribavirin treatment compared to levels in the same patients before ribavirin had been administered. Haemolytic anaemia was common, with estimates ranging from 36 to 61%; whether SARS had a contributory role was not possible to determine. One study noted that ~ 30% of patients had higher ALT levels than normal during SARS infection. In patients who were also treated with ribavirin, higher ALT levels were seen in >75%.
- **Key PK properties** – There is no standardized regimen of ribavirin in the treatment of SARS. *In vitro* inhibitory levels are likely to be unachievable clinically; intravenous dosing is unlikely to reach the inhibitory levels reported, although a recent MERS-CoV article suggests lower concentrations of combined IFN-a2b and ribavirin achieved comparable endpoints. Cytostatic effects may account for the inhibition seen.
- **Current approval status** – Approved for the treatment of a variety of viral infections (including HCV) in many countries.
- **Current availability** – Available in selected countries.

SUMMARY: Ribavirin alone is highly unlikely to possess substantial antiviral activities at clinically used dosages. Given the many adverse effects noticed during therapy for SARS, expert opinion suggests that ribavirin should not be used to treat MERS-CoV even when other therapeutic options have failed, outside of an appropriately planned evaluation of effectiveness.

Treatment of MERS-CoV with Corticosteroids

- **Proposed MOA** – Immunomodulatory agent.
- ***In vitro* and animal model activity for SARS** – A porcine model suggests six days early administration of high-dose 2 mg/kg dexamethasone may reduce early pro-inflammatory responses, but longer administration for a period may enhance viral replication in the lung.
- ***In vitro* activity in MERS-CoV** – None available.
- **Human virologic and clinical effectiveness SARS-CoV and other lung injuries** – Pulsed or high dose steroids, generally reserved for patients with worsening hypoxemia, dyspnoea, or radiographic progression and used alongside ribavirin and/or IFN, did not appear to improve survival in patients with ALI/ARDS, though smaller observational studies suggest benefit on some outcome measures. Most studies were deemed inconclusive by the review.
 - Pulsed, low, intermediate and tapered doses were used: most studies were inconclusive. SARS treatment duration varied from early administration of 2-3 days high-dose methylpred (up to 1g per day), sometimes followed by low dose steroids or pulsed methylpred (e.g. 500mg for 3-5 days), and lasted up to 4 weeks in Chinese literature.
 - One observational study from Hong Kong found the use of high-dose dexamethasone was associated with clinical improvement, though another suggested that early corticosteroid treatment was associated with a higher subsequent plasma viral load. One case series suggested more rapid clearing of chest radiographic abnormalities with pulse dosing. Another Chinese study, which randomised patients to four therapeutic options, showed more rapid resolution of fever, respiratory symptoms, and radiographic changes with pulse dosing but no differences in survival or length of hospital stay were noted.
 - Hong Kong data suggested that convalescent plasma therapy was associated with a more favourable outcome in SARS patients who deteriorated despite ribavirin and high-dose steroid therapy than continuing high-dose methylprednisolone.
- **Safety profile** – Evidence of adverse side effects and possible increased viral replication due to immunomodulatory effects were seen in a double-blind RCT. In addition to increased risk of nosocomial infections, systemic corticosteroids were associated with other acute and chronic complications in SARS patients, including psychosis, diabetes, dose-related avascular necrosis of the hip, osteoporosis and long-term morbidity including disabling muscle weakness and neuropathy. Increased complications and mortality were seen in pandemic 2009 H1N1 influenza patients with pneumonia or ARDS given steroids in several studies. Little benefit was seen in a meta-analysis of steroid use in late-stage ARDS (≥ 7 days), though one group weakly supports low-to-moderate-dose steroids if ARDS <2 weeks duration; this use was associated in other meta-analyses with multiple outcome benefits, particularly with early administration. If used, during maximal viral shedding (accumulating evidence this continues for >30 days) the possible impact on viral clearance should be closely monitored.
- **Key PK properties** – There is no standardized regimen for steroid use.
- **Current approval status** – Widely approved for the treatment of a variety of illnesses.
- **Current availability** – Widely available.

- **SUMMARY:** There is no mortality benefit and contrary evidence for a beneficial role of steroids, with both acute and long-term harms, including delayed viral clearing reported in SARS patients. Therefore, corticosteroid use for MERS-CoV is not recommended outside of an appropriately planned evaluation of effectiveness, except for those where other proven clinical benefits may outweigh harms (e.g. long-term end organ damage minimisation).

Treatment of MERS-CoV with Nitazoxanide (NTZ)

- **Proposed MOA** – Purported interferon inducer (or other mode of action), and inhibitor of influenza HA maturation (main mode of action is anti-parasitic for cryptosporidium).
- ***In vitro* and animal model activity for SARS-** NTZ has not been tested either *in vitro* or in animal models for SARS, though it has an inhibitory effect against canine CoV at 1-1.5 ug/ml.
- ***In vitro* activity in MERS-CoV** – No effect in either Vero or Huh7 cells, and toxic above 16µM.
- **Human virologic and clinical effectiveness SARS and other** – No evidence for SARS; a randomised, double-blind placebo trial in childhood viral respiratory infection showed NTZ was safe and reduced symptom duration. Phase 2 RCT in uncomplicated influenza reported significant antiviral and clinical effects (600mg twice daily for 5 days compared to placebo).
- **Safety profile** – Good safety profile; dose-related diarrhoea and other GI disturbances.
- **Key PK properties** – Mean peak plasma levels of about 4 ug/ml and trough of about 1 ug/ml for tizoxanide (active metabolite) on 600 mg BID with food regimen (influenza trial).
- **Current approval status** – Approved for cryptosporidium and giardia in many countries.
- **Current availability** – Widely available.

SUMMARY: No clinical evidence exists. Its safety profile and IFN-inducing effects suggest NTZ use is not recommended outside of an appropriately planned evaluation of effectiveness.

Treatment of MERS-CoV with other agents

- Cyclosporin A (CyA) has been shown *in vivo* to affect the replication of many coronaviruses (at 8-10µM), and it affects the function of several members of the 277 cyclophilin family, blocking functional interactions between viral proteins of cyclophilin family members. Though cyclophilins are suggested as pan-CoV inhibitors targets, no clinical/animal studies performed. Recent testing of 96 clinical compounds has shown that as well as IFN, CyA may demonstrate the best *in vitro* effect against MERS-CoV. Non-immunosuppressive analogues of CyA e.g. Debio 025 have been developed in HCV treatment. Steady-state levels in humans are generally targeted at 100-400 ng/ml or 83-333 nmol/L, in order to avoid nephrotoxicity.
- Chloroquine (entry inhibitor) inhibits MERS-CoV CPE in Vero cells at 32uM (IC50 15µM) and Huh7 cells (IC50 5µM; for SARS-CoV 3µM). No toxicity was seen at these concentrations, however a similar *in vitro* effect has been shown in dengue and influenza. In clinical trials for Dengue, the therapeutic levels required in humans were never achieved, and for influenza, chloroquine was ineffective in animal models and as prophylactic agent in humans.
- Chlorpromazine (entry inhibitor): IC50 for MERS-CoV 10µM on Vero and 6µM on Huh7 cells, with an inhibitory effect on SARS-CoV. It is toxic at 16µM.
- Loperamide: IC50 for MERS-CoV 8uM in Vero cells, though it is toxic at 16µM. On Huh7 cells, the IC50 is 5µM, but again it is toxic above 16µM.
- Mannose-binding lectin to SARS may interfere with other early pre- or post-receptor-binding events necessary for efficient viral entry. These results suggest that MBL contributes to the first-line host defense against SARS-CoV and that MBL deficiency is a susceptibility factor for acquisition of SARS. The availability of recombinant human MBL is currently uncertain.
- Short interfering RNA (siRNA) directed to conserved gene sequences in SARS potentially inhibit *in vitro* and macaque model replication, and, alone or in combination with other drugs, may have potential for the prevention and treatment of SARS. Again, no clinical evidence exists for their use at present and specific siRNA for MERS-CoV-EMC are not currently available.

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Convalescent plasma

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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 front-line 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.

Useful links

PHE – <http://www.hpa.org.uk/Topics/InfectiousDiseases/InfectionsAZ/NovelCoronavirus2012/>

ISARIC – <http://www.isaric.org>

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

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

CDC – <http://www.cdc.gov/features/novelcoronavirus/>

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Many thanks to all who participated in the variety of PHE and ISARIC/WHO-led teleconferences for sharing their valuable input.