Therapeutic Options for Middle East Respiratory Syndrome Coronavirus (MERS-CoV) – possible lessons from a systematic review of SARS-CoV therapy

Hishom Momattin a, Khurram Mohammed a, Alimuddin Zumla b, Ziad A. Memish c, Jaffar A. Al-Tawfiq d,e

a Pharmacy Services Division, Saudi Aramco Medical Services Organization, Dhahran, Saudi Arabia
b Division of Infection and Immunity, University College London, London, and University College London Hospitals NHS Foundation Trust
c Deputy Minister for Public Health, and Director WHO Collaborating Center for Mass Gathering Medicine Ministry of Health, and Professor, Al-Faisal University, Riyadh, Saudi Arabia
d Specialty Internal Medicine, Saudi Aramco Medical Services Organization, Dhahran, Saudi Arabia, and Indiana University School of Medicine, Indiana, USA

A R T I C L E   I N F O

Corresponding Editor: Eskild Petersen, MD, DMSc, MBA, Editor-in-Chief, International Journal of Infectious Diseases

Keywords:
MERS-CoV
Interferon
Ribavirin
SARS

A B S T R A C T

The Middle East Respiratory Syndrome coronavirus (MERS-CoV) has been detected in a number of countries in the Middle East and Europe with an apparently high mortality rate. It is phylogenetically related to the SARS coronavirus and has also been associated with severe respiratory illness as well as nosocomial transmission in healthcare settings. Current international recommendations do not support any specific therapies; however, there are a number of agents, which were used during the SARS epidemic of 2003. It is possible that these might be active against the related MERS coronavirus. We have reviewed the literature on the safety and efficacy of therapies used in patients with SARS with a view to their potential use in patients with MERS-CoV infections.

© 2013 International Society for Infectious Diseases. Published by Elsevier Ltd. All rights reserved.

1. Introduction

Coronaviruses are RNA viruses which usually cause mild upper respiratory illnesses. The emergence of SARS (severe acute respiratory Syndrome) MERS (Middle East respiratory syndrome) has focussed global attention on the clinical significance of coronaviruses.

The current Middle East Respiratory Syndrome Novel coronavirus (MERS-CoV) was first isolated in June 2012 from the respiratory tract of a businessman in the Bisha area of Saudi Arabia, who subsequently died of pneumonia and renal failure.1 As of 28 July 2013 MERS-CoV has caused 91 laboratory confirmed cases and 46 deaths, representing a high case fatality rate of 50%.2 The high case fatality rate is likely related to the pattern of the disease as we probably are seeing only the tip of the iceberg of critically ill and admitted patients. The high fatality rate is likely to decline as milder clinical cases emerge. Similar to SARS, common symptoms in patients with MERS-CoV include fever, cough, shortness of breath, and gastrointestinal symptoms. Most patients have had pneumonia and the majority was reported to have multiple co-morbid conditions.3,4

The rapid deployment of effective therapeutics is a high priority as there is currently no specific therapy or vaccine for MERS-CoV. The clinical experience from SARS suggests that a number of interventions including ribavirin with and without corticosteroids, interferon alfa with corticosteroids, ribavirin with lopinavir and ritonavir, and convalescent plasma may improve the outcome in patients but the data are not conclusive.5

The purpose of this review is first to summarize the effectiveness of these treatments, in an attempt to identify a therapeutic approach that could help select the most appropriate therapeutic options for patients with MERS-CoV infections.

2. Methods

We systematically searched the literature databases (PubMed, Science Direct and the Cochrane database) for published studies. We used the key words “SARS”, “coronavirus”, in combination with “treatment”, human studies, randomized controlled trials (RCT), prospective or retrospective cohort designs, case-control designs,
| Reference # | Type of study | Dose | # patients | Time of administration | Outcome |
|-------------|---------------|------|------------|------------------------|---------|
| 8           | Observational (LOE, III) | IV loading dose 2g then 1 g IV q6h x 4 days then 500 mg IV Q8h x 4-6 days | 7 | Upon admission to a medical ward | translucent |
|             |               |      |            |                        | Outcome  |
|             |               |      |            |                        | N=7     |
|             |               |      |            |                        | Died    2 |
|             |               |      |            |                        | Improved within 5 days 5 |
|             |               |      |            |                        | - Recovered completely 3 |
|             |               |      |            |                        | - mild dyspnea with 3 weeks follow-up 2 |
| 9           | Observational (LOE, III) | 9 patients on 8mg/kg IV q8H 1 patient on 1.2 g po Q8h (Duration of therapy not mentioned) | 10 | Upon admission | translucent |
|             |               |      |            |                        | Outcome  |
|             |               |      |            |                        | N=10    |
|             |               |      |            |                        | Died with respiratory failure 2 |
|             |               |      |            |                        | Resolution of fever and improvement in heart rate within 2 days 8 |
|             |               |      |            |                        | Recovered completely 1 |
|             |               |      |            |                        | Able to walk on the level without apparent restriction 4 |
|             |               |      |            |                        | Able to walk 3-5 steps on the level 3 |
|             |               |      |            |                        | Mild dry cough 4 |
| 10          | Retrospective case series (LOE, II) | Loading dose of 2 g IV, then 1 g IV q6h for 4d, then 500 mg q8h for 3d The median treatment was 6d. 40% received steroids; Most patients received approximately 20 to 50 mg/d of hydrocortisone for 10 days. One patient received pulse steroid. | 111 | 91% started on ribavirin within the first 48hr of hospitalization. <20% received steroid in the first 48 hours. | translucent |
|             |               |      |            |                        | Outcome  |
|             |               |      |            |                        | Ribavirin was associated with significant toxicity |
|             |               |      |            |                        | N=111   |
|             |               |      |            |                        | Hemolysis (%) 76 |
|             |               |      |            |                        | Decrease in hemoglobin of 2 g/dL (%) 49 |
|             |               |      |            |                        | Admitted to the ICU (%) 20 |
|             |               |      |            |                        | 21-day mortality 6.5% |
|             |               |      |            |                        | Possible harm |
| 11          | Retrospective cohort study (LOE,II) | PO 20 mg/kg TID versus Osel tamivir, 75 mg BID | Ribavirin (n=14) Osel tamivir (n=6) | Most of patients at day 10-14 of symptoms. | translucent |
|             |               |      |            |                        | Outcome  |
|             |               |      |            |                        | Oseltamivir N=6 Ribavirin N=14 |
|             |               |      |            |                        | improved sufficiently to be extubated required mechanical ventilation 2 0 |
|             |               |      |            |                        | died of progressive respiratory failure 6 3 |
|             |               |      |            |                        | Inconclusive |
|             |               |      |            |                        | Inconclusive |
|             |               |      |            |                        | There is no obvious response to ribavirin, and several patients deteriorated in spite of its use. In contrast, a number of patients recovered without use of ribavirin. |
| 12          | Prospective observational study (LOE, II) | IV 8mg/kg Q8h for 14days + hydrocortisone 200 mg IV Q8h over 10 days, then PO prednisolone 1mg/kg for 5 days, 0-5 mg/kg for 3 days, and 0-25 mg/kg for 3 days. pulses of methylprednisolone 500 mg IV OD for 2-3 doses | 75 | After diagnosis of SARS | translucent |
|             |               |      |            |                        | Outcome  |
|             |               |      |            |                        | Worsening in week 2 is unrelated to uncontrolled viral replication but may be related to immunopathological damage. |
|             |               |      |            |                        | Outcome  |
|             |               |      |            |                        | Oseltamivir N=6 Ribavirin N=14 |
|             |               |      |            |                        | Death* 5 (7%) |
|             |               |      |            |                        | Convalescence at home or at rehabilitation facility 27 (36%) |
|             |               |      |            |                        | Hospital admission 29 |
|             |               |      |            |                        | In general ward 29 (39%) |
|             |               |      |            |                        | In intensive-care unit for ARDS 13 (17%) |
|             |               |      |            |                        | Inconclusive |
|             |               |      |            |                        | Inconclusive |
|             |               |      |            |                        | *Two patients died of acute myocardial infarction, one of clinical sepsis, and two of clinical sepsis and ARDS |
### 13 Randomized control trial (LOE, II)

| Group | Patients | Ribavirin | Interferon-alpha | Antibiotics | Resolution of pyrexia (days) | Respiratory improvement (days) | Require mechanical ventilation | Deaths |
|-------|----------|-----------|------------------|-------------|-------------------------------|-------------------------------|------------------------------|--------|
| A (40) | 190      | No        | Yes              | AZ, FQ, LF  | 9.4 ± 3.6                     | 10.9 ± 7.3                   | Yes                          | 2      |
| B (30) |           | Some      | Some             | AZ, FQ, LF  | 6.7 ± 1.9                     | 9.8 ± 5.1                    | Yes                          | 2      |
| C (60) |           |           | Yes              | AZ, FQ, LF  | 7.2 ± 2.8                     | 7.8 ± 3.9                    | Yes                          | 7      |
| D (60) |           |           | No               | AZ, FQ, LF  | 3 ± 1.4                       | 5.9 ± 2.6                    | Yes                          | 0      |

At the time of admission:

| Group | Patients | Ribavirin | Interferon-alpha | Antibiotics | Resolution of pyrexia (days) | Respiratory improvement (days) | Require mechanical ventilation | Deaths |
|-------|----------|-----------|------------------|-------------|-------------------------------|-------------------------------|------------------------------|--------|
| A (40) | 190      | No        | Yes              | AZ, FQ, LF  | 9.4 ± 3.6                     | 10.9 ± 7.3                   | Yes                          | 2      |
| B (30) |           | Some      | Some             | AZ, FQ, LF  | 6.7 ± 1.9                     | 9.8 ± 5.1                    | Yes                          | 2      |
| C (60) |           |           | Yes              | AZ, FQ, LF  | 7.2 ± 2.8                     | 7.8 ± 3.9                    | Yes                          | 7      |
| D (60) |           |           | No               | AZ, FQ, LF  | 3 ± 1.4                       | 5.9 ± 2.6                    | Yes                          | 0      |

Resolution of pyrexia and respiratory improvement was significantly better in group D (p > 0.05)

### 14 Prospective cohort study (LOE, II)

| Group | Patients | Cefotaxime + PO levofloxacin or clarithromycin + Oseltamivir or PO ribavirin loading dose 2.4 g then 1.2 g TID + prednisolone 0.5–1 mg/kg/day, patient with dyspnea were treated with IV ribavirin 400 mg Q8h + hydrocortisone 10 mg Q8h, or Pulses of methylprednisolone 0.5 g IV infusion for 3 days. | After 48h of persistent fever | Broad spectrum antimicrobial (n = 138) | Ribavirin + steroid (n = 138) | Methylprednisolone IV (n = 107) |
|-------|----------|-------------------------------------------------|-------------------------------|-------------------------------------|-------------------------------|-------------------------------|
| A (40) | 156      | Sustained response: 0 (0)                         | Ribavirin: 9 (6.5%)           | Methylprednisolone: 50 (46.7%)     |
| B (30) |           | Partial response: 0 (0)                          | 16 (11.6%)                   | 45 (42.1%)                        |
| C (60) |           | No response: 138 (100%)                          | 9 (6.5%)                     | 12 (11.2%)                        |
| D (60) |           | Possible harm: 113 (81.9%)                        |                              |                                   |

### 15 Retrospective cohort study (LOE II)

| Group | Patients | Treatment consisted of Ribavirin with either intravenous or oral hydrocortisone with or without one pulsed steroid regime (intravenous methylprednisolone 500 mg per day for 3–5 days) | Outcome | Use of ribavirin did not confer any benefit for patients with SARS. Use of ribavirin did not confer any benefit for patients with SARS. |
|-------|----------|-------------------------------------------------|---------|----------------------------------------------------------------------------------------------------------------------------------|
| A (40) | 40       | Mean time of 3.4 days ± 3.6 (median, 2 days; range, 1–19 days) after admission | Non-ribavirin (%) | Ribavirin (%) | P-value |
| B (30) |           | Mean time of 3.4 days ± 3.6 (median, 2 days; range, 1–19 days) after admission | 17 (12.9) | 10 (10.3) | 0.679 |
| C (60) |           | Mean time of 3.4 days ± 3.6 (median, 2 days; range, 1–19 days) after admission | 27 (20.5) | 19 (19.6) | >0.999 |
| D (60) |           | Mean time of 3.4 days ± 3.6 (median, 2 days; range, 1–19 days) after admission | 132 (100%) | 132 (100%) | 1.000 |
or case series; agents included were ribavirin, interferon, Lopinavir and ritonavir (LPV/r), and convalescent plasma. We exclude corticosteroid studies as this was beyond the scope of this review and the management of severe pneumonia has been well covered in the WHO guideline.6

Data extracted from these publications include: authors name, publication year, type of study, level of evidence, sample size, interventions dose, duration, indication, route, and time of administration, number of patients, and efficacy and safety outcome of these interventions. The outcomes of interest included mortality rate, measures of morbidity and adverse effects. The outcomes reported in the selected studies included death, mechanical ventilation, improvement of symptoms, admission to the intensive care unit, infectious complications, successful discharge and adverse effects.

3. Assessment of study quality

The clinical studies were all critically appraised. Aspects that were assessed included study design, the possibility of bias in the selection of the control group and treatment allocation, and whether the treatment regimen and reporting of outcomes were consistent. The studies were tabulated and summarized in a narrative way, and were grouped by the treatment strategy. We categorized each article depending on which drug was used. We tabulated results as type of study, dose, duration, time of administration, and indication of medication, number of patients included in that study, plus the final outcomes.

The studies were scored using the US Preventive Services Task Force scoring system7, where Level of Evidence.

LOE, I: Evidence obtained from at least one properly designed randomized controlled trial.
Level II-1: Evidence obtained from well-designed controlled trials without randomization.
Level II-2: Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
Level II-3: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
Level III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

4. Results

We identified 54 studies about SARS or coronavirus and we included 19 studies only. We excluded 35 studies since 14 of them were in vitro studies, 15 corticosteroid studies, and 6 were non-therapeutic studies. Overall, we analyzed 19 studies, nine used ribavirin alone or with interferon (Table 17–19, two used lopinavir and ritonavir (Table 20, six used convalescent plasma (Table 3)21–23, there was one study of Interferon alpha (Table 4)24 and one study comparing Interferon alpha versus ribavirin13. Summaries of the different studies are presented in Tables 1–4.

Table 2
Lopinavir/Ritonavir studies

| Reference # | Type of study | Regimen | # patients | Indication | Time of administration | Outcome |
|-------------|---------------|---------|------------|------------|-----------------------|---------|
| 17          | Cohort study (LOE, II) | Ribavirin for 14 days (24 mg PO loading dose, followed by 1.2 g PO Q8h, or 8 mg/kg IV Q8h, if the patient could not tolerate oral treatment), + corticosteroid therapy for 21 days (hydrocortisone 100-200 mg Q 6-8 hours, or methylprednisolone 3 mg/kg/day, depending on severity). If no response pulses of methylprednisolone 500-1000 mg IV QD were used as rescue therapy, then + lopinavir 400 mg/ritonavir 100 mg PO Q12h for 10 to 14 days | 1052 patients | SARS | In newly diagnosed patient; or as rescue therapy later in the course of the illness when patients had worsening symptoms | The addition of lopinavir/ritonavir to a standard treatment protocol as an initial treatment appeared to be associated with improved clinical outcome and reduce death rate |
| 18          | Cohort (LOE, II) | Historical group: Ribavirin for 14 days (4 g PO loading dose followed by 1.2 g Q8h, or 8 mg/kg IV Q6h) + corticosteroid for 21 days (starting dose: hydrocortisone 100-200 mg Q 6-8 hours or methylprednisolone 3 mg/kg/day). Pulses of IV methylprednisolone (0.5-1 g/day up to 4 g) if needed; Treatment group: + lopinavir (400 mg)/ritonavir (100 mg) PO Q12h for 14 days | 41 patients treated, 111 Historical (152) | SARS | Newly diagnosed SARS patients with no ARDS | Patients treated with lopinavir/ritonavir appeared to run a milder disease course in terms of diarrhea, recurrence of fever, and worsening of chest radiographs. A reduction in the viral load, reduction in steroid usage and nosocomial infections was seen in patients initially treated with lopinavir/ritonavir |

| Evidence | LOE | r, cohort number | n44 | n634 |
|----------|-----|-----------------|-----|------|
| Death rate (%) | 2.3 | 15.6 |
| Intubation rate (%) | 0 | 11 |
| Desaturation rate (%) | 68.2 | 84.5 |
| Proportion requiring pulse methylprednisolone (%) | 27.3 | 55.4 |
| Mean pulse methylprednisolone dose (G) | 1.6 | 3.0 |

| Development of ARDS or death within 21 days | p value |
|---------------------------------------------|---------|
| n111 | 32 (28.8%) | 1 (2.4%) |
| n41 | < 0.001 |

| Death/ARDS at day 21 | n7 | n(6.3%)25 (22.5) |
|----------------------|-----|-----------------|
| % | 0 (0%) | (2.4%) |
| Reference # | Type of study        | Regimen                                                                 | # patients | Indication | Time of administration | Outcome                                                                                      |
|------------|----------------------|-------------------------------------------------------------------------|------------|------------|------------------------|--------------------------------------------------------------------------------------------|
| 19         | Cohort study (LOE,II)| Convalescent plasma (500 mL) was obtained from each of three SARS patients and transfused into the 3 infected HCW. | 3 patients | SARS       | No date was given      | All three patients survived. One healthcare worker became pregnant subsequently, delivering 13 months after discharge. |
| 20         | Case report (LOE, III)| infusion of plasma collected (200ml) from a convalescent patient with SARS to treat, in combination with ribavirin and corticosteroids | One patient | SARS       | On day 14 of hospitalization | The clinical outcome was successful, despite the relatively low volume of plasma infused; furthermore, no side-effects were observed |
| 21         | Cohort (LOE, II)     | 200-400ml (4-5ml/kg) of ABO compatible convalescent plasma              | 80 patients |            | On day 14 of starting symptoms | Mortality rate 12.5% compared to 17% of SARS patient |
| 22         | Retrospective cohort study (LOE, II) | ribavirin + methylprednisolone 3 doses (500 mg each) of pulsed methylprednisolone 200-400 ml of convalescent plasma (plasma group) or further pulses of methylprednisolone (steroid group) 200-400 ml of | 30         | SARS       | At the discretion of the attending clinicians and according to the availability of convalescent plasma. | Discharge rate by day 22 Following onset of illness: Plasma group (n= 19) 73.4% N= 14, Steroid group (n= 21) 19% N= 4, P value 0.001. Discharge rate by day 22 after adjustment for co-morbidities: Plasma group (n= 19) 77.8% (14/18), Steroid group (n= 21) 23% (3/13), P value 0.004. Death rate: Plasma group (n= 19) 0%, Steroid group (n= 21) 23.8% (3/13), P value 0.049. Inconclusive |
Table 4
Interferon alpha studies

| Reference n | Type of study | Regimen | # patients | Indication | Time of administration | Outcome |
|-------------|---------------|---------|------------|------------|------------------------|---------|
| 23          | Retrospective cohort study (LOE,II) | Prednisone PO 50mg BID or IV methylprednisolone 40mg Q12h if not control IV methyl/prednisolone 500mg OD for 3 days then taper and step down to PO prednisone to complete 20days SQ interferon alfacon-1 for 10 days starting with 9mcg/d if at least 2 days then 15 mcg/d if no response for 8-13 days | 28 | SARS | When health Canada approval for interferon alfacon-1 use in SARS treatment (may 29, 2003) | Resolution of fever and lymphopenia were similar between groups corticosteroid interferon alfacon-1 s alone (n=13) transferred to the intensive care unit required intubation and mechanical ventilation died | 68.5% |

5. Discussion

There has been a lot of concern worldwide about the emergence of the MERS-CoV. Although infection control, molecular diagnostics and international public health have improved considerably since the 2003 SARS epidemic, there are still no proven or licensed therapies for any coronavirus infection. The high mortality associated with MERS-CoV led us to conduct this systematic review to summarize the available options for treatment for novel coronavirus infection based on previous reports of therapy of SARS, a related coronavirus.

The most commonly used agent was the broad spectrum antiviral ribavirin. There were seven reports of the use of ribavirin in SARS patients although only four reported control groups. The mortality benefit was inconsistent with mortality rates of between 5% and 42.8%, 8-14 two studies showed improvements of symptoms in 71.4%-80% of patients, and ICU admission rates of 13%-20%.8,9 The major problem with ribavirin was the significant incidence of adverse events especially hemolysis which was reported in 68.5%.10

The timing of the start of antiviral agents is important in most virus infections. One study compared oseltamivir versus ribavirin and showed no obvious response to ribavirin, however, the treatment were started after 10-14 days of symptoms which might have lead to the poorer outcomes.11

There was only one randomized controlled trial: this compared ribavirin versus interferon-1x and showed no advantage of ribavirin over interferon in patients with SARS.12,13 In addition, there were observational studies comparing Interferon-1x versus untreated controls.23 Interferon led to improvements in clinical and laboratory parameters compared with control patients.23

However, there was no standard regime used and adverse events were not well documented.

The addition of lopinavir/ritonavir to ribavirin regimen was associated with improved clinical outcome and reduces the death rate comparing to ribavirin regimen alone in observational studies.17,18 These studies are detailed in Table 2.

Few studies addressed the effect of convalescent plasma.19-22 These studies were mainly case reports which limit the generalizability of their findings. In three studies of SARS patients, patients

| Medication | Normal dose Crc > 50ml/min | Impaired renal function Crl (20-50 ml/min) | ESRD (Hemodialysis) Crc< 20ml/min |
|------------|-----------------------------|------------------------------------------|---------------------------------|
| Ribavirin oral | 2000 mg loading dose then 1200mg q8h for 4 days, then 600mg po q8h for 4-6 days | | |
| Peg interferon alfa 2b | 1.5mcg/kg once per week x 2 | Same dose | Same dose |
| Lopinavir 400 mg; ritonavir 100 mg oral | Lopinavir 400 mg/ ritonavir 100 mg twice daily for 10 days. May be given in combination with Ribavirin | Same dose | Same dose |
| convalescent plasma | 300–500 ml of full plasma (3 – 5 ml/kg) With a rate of 2ml/min for one time in day 2 of ICU admission. | Same dose | Same dose |
in the plasma group had a shorter hospital stay (58.3% - 73.4% versus 15.6% - 19%; P < 0.001) and lower mortality than the comparator group (0% - 12.5% versus 17% - 23.8%).

Intriguingly, in a vitro study showed that convalescent plasma from SARS patients might contain cross-reactive antibodies against other beta-coronavirus including MERS-CoV. Of 27 sera, 7 (25%) had antibodies anti-MERS-CoV neutralizing antibodies at low titers. Convalescent sera was recommended in a recent study by the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC). Cross-reactive antibodies may be present in convalescent plasma from SARS patients against other beta-coronavirus and may be associated with a better outcome, reduced mortality, and shorter hospital stay. There are considerable technical hurdles to overcome before convalescent sera can be widely recommended as a therapeutic agent in the modern era. Currently, there is a need to establish a serology test to diagnose patients with mild disease and thus identify those patients as possible donors of convalescent sera.

We conclude that the use of ribavirin may improve the outcome and reduce mortality as shown in a number of studies. One of the reasons for the failure of ribavirin in some reports may have been the timing for the use of ribavirin, after 6–14 days of symptom, compared to studies which showed benefits when ribavirin was started within 48 hours of hospitalization or after diagnosis of SARS was established.

Among the limitations of this review are the heterogeneity of the reviewed studies in terms of the wide range of treatment dosages, frequency, and route of administration, duration, and timing of administration. The reported treatment effects should be interpreted with caution due to the lack of randomized, controlled trials.

Also, while we have drawn on the SARS literature, and SARS is a closely related virus, there are clearly differences between SARS and the MERS-CoV and the data might not be able to be directly extrapolated to MERS-CoV infected patients. The use of the discussed agents would require monitoring hematological and biochemical parameters during treatment to detect and prevent adverse effects associated with therapy. Possible dosages of discussed agents especially with unavailability of intravenous ribavirin are listed in Table 5. The table also includes the possible dosage of pegylated interferon-α (PegIFN-α) that is commonly used in the treatment of hepatitis C virus infection. PegIFN-α was 50–100 times more effective in vitro for MERS-CoV than SARS-CoV. The long half-life of PegIFN-α and the associated adverse effects calls for extra attention for the use of shorter-acting interferon.

The use of interferon therapy with ribavirin is not recommended in patients with hepatitis C virus infection and renal dysfunction (Clcr < 50 ml/minute).

With the emergence of MERS-CoV and the lack of high quality clinical evidence to support recommendations for the use of available therapeutic options, there is a clear need for developing protocols to be used in randomized-controlled trials in order to determine the most effective therapies for this novel emerging pathogen.

Acknowledgements

The authors (HAM, MK, and JAT) wish to acknowledge the use of Saudi Aramco Medical Services Organization (SAMSO) facilities for the data and study, which resulted in this paper. Opinions expressed in this article are those of the authors and not necessarily of SAMSO. Professor Zuma acknowledges support from the University College London Hospitals NHS Foundation Trust, the National Institute of Health UCLH Biomedical Research Centre, the EDCTP and the EC-FW7. Authors thank Dr. Paul Anantharajah Tambyah from National University of Singapore’s Department of Medicine for his critical review of the manuscript.

References

1. AlBarrak AM, Stephens CM, Hewson R, Memish ZA. Recovery from severe novel coronavirus infection. Saudi Med J 2012;33:1265–9.
2. CDC. Middle East Respiratory Syndrome. Available at: http://www.cdc.gov/coronavirus/mers/faq.html last accessed July 27, 2013.
3. Assiri A, McGee A, Perl TM. Hospital outbreak of Middle East respiratory syndrome coronavirus. N Engl J Med 2013;369:5:407–16.
4. Assiri A, Al-Tawfiq JQA, Al-Rabeah 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; published online July 26. http://dx.doi.org/10.1016/S1473-3099(13)70204-4.
5. Stockman LJ, Bellamy R, Garner P. SARS: systematic review of treatment effects. PLoS Med 2008;5:3.e543.
6. World Health Organization. Clinical management of severe acute respiratory infections when novel coronavirus is suspected: What to do and what not to do. Available at: http://www.who.int/csr/disease/coronavirus_infections/Interim-Guidance_ClinicalManagement_NovelCoronavirus_11Feb2013.pdf.
7. U.S. Preventive Services Task Force August 1998: Guide to clinical preventive services: report of the U.S. Preventive Services Task Force. DIANE Publishing, pp 24–
8. Poutanen SM, Low DE, Henry B, Finkelstein S, Rose D, Green K, et al. Identification of severe acute respiratory Syndrome in Canada. N Engl J Med 2003;348:1995-2005.
9. Tsang KW, Ho PL, Ooi CC, Yee WK, Wang T, Chan-Yeung M, et al. A Cluster of Cases of Severe Acute Respiratory Syndrome in Hong Kong. N Engl J Med 2003;348:1977–85.
10. Booth CM, Matukas LM, Tomlinson GA, Rachlis AR, Rose DB, Dwoish HA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. JAMA 2003;290:334.
11. Hsu LY, Lee CC, Green JA, Ang B, Paton NI, Lee L, et al. Severe acute respiratory syndrome (SARS) in Singapore: clinical features of index patient and initial contacts. Emerg Infect Dis 2003;9:713–7.
12. Peiris JS, Chu CM, Cheng VC, Chan KS, Hung IF, Poon LL, et al. Clinical progression and viral load in a community outbreak of coronavirus-associated SARS pneumonia: a prospective study. Lancet 2003;361:1767–72.
13. Zhao Z, Zhang F, Xu M, Huang K, Zhong W, Cai W, et al. Description and clinical treatment of an early outbreak of severe acute respiratory syndrome (SARS) in Guangzhou, PR China. J Med Microbiol 2003;52:715–20.
14. Sung JJ, Wu A, Joynt GM, Yuen KY, Lee N, Chan PK, et al. Severe acute respiratory syndrome: report of treatment and outcome after a major outbreak. Thorax 2004;59:414–20.
15. Ooi GC, Khong PL, Ho JC, Lam B, Wong WM, Yiu WC, et al. Severe Acute Respiratory Syndrome: Radiographic Evaluation and Clinical Outcome Measures. Radiology 2003;229:500–6.
16. Leung TN, Ang R, Earnest B, Tech C, Xu W, Leo YS. Investigational use of ribavirin in the treatment of severe acute respiratory syndrome, Singapore. 2003. Trip Med Int Health 2004;9:923–7.
17. Chan KS, Lai ST, Chu CM, Tsui E, Tam CY, Wong MM, et al. Treatment of severe acute respiratory syndrome with ribavirin/interferoni: a multicentre retrospective matched cohort study. Hong Kong Med J 2003;9:399–406.
18. Chu CM, Cheng VC, Hung IF, Wong MM, Chan KH, Chan KS, et al. Role of ribavirin/interferon in the treatment of SARS: initial virological and clinical findings. Throm 2004;59:525–6.
19. Yeh KM, Chiuieh TS, Siu KL, Lin JC, Chan PK, Peng MY, et al. Experience of using convalescent plasma for severe acute respiratory syndrome among healthcare workers in a Taiwan hospital. J Antimicrob Chemother 2005;56:919–22.
20. Burnout T, Radosvich M. Treatment of severe acute respiratory syndrome with convalescent plasma. Hong Kong Med J 2003;9:309. author reply 310.
21. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. Eur J Clin Microbiol Infect Dis 2005;24:44–6.
22. Soo YO, Cheng Y, Wong R, Hui DS, Lee CK, Tsang KK, et al. Retrospective comparison of convalescent plasma with combining high-dose methylprednisolone treatment in SARS Patients. Clin Microbiol Infect 2004;10:676–8.
23. Loutfy MR, Blatt LM, Siminovich KA, Ward S, Wolff B, Lho H, et al. Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. JAMA 2003;290:3222–8.
24. Chan KH, Chan JF, Tse H, Chen H, Lau CC, Cai JP, et al. Cross-reactive antibodies in convalescent SARS patients’ sera against the emerging novel human coronavi rus EMC (2012) by both immunofluorescent and neutralizing antibody tests. J Infect 2013;67:130–40.
25. ISARIC. International Severe Acute Respiratory & Emerging Infection Consor tium. Clinical Decision Making Tool for Treatment of MERS-CoV v1.0, 18 June 2013. Available at: http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1317139281416 last accessed July 26, 2013.
26. Raj VS, Mos H. Dipetidyl peptidase 4 is a functional receptor for the emerging human coronavirus-EMC. Nature 2013;495:251–4.