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Antiviral Treatment Guidelines for Middle East Respiratory Syndrome

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Middle East respiratory syndrome (MERS) is an acute infectious disease of the respiratory system caused by the new betacoronavirus (MERS coronavirus, MERS-CoV), which shows high mortality rates. The typical symptoms of MERS are fever, cough, and shortness of breath, and it is often accompanied by pneumonia. The MERS-CoV was introduced to Republic of Korea in May 2015 by a patient returning from Saudi Arabia. The disease spread mostly through hospital infections, and by the time the epidemic ended in August, the total number of confirmed diagnoses was 186, among which 36 patients died. Reflecting the latest evidence for antiviral drugs in the treatment of MERS-CoV infection and the experiences of treating MERS patients in Republic of Korea, these guidelines focus on antiviral drugs to achieve effective treatment of MERS-CoV infections.

Key Words: MERS; Coronavirus; Antiviral; Treatment

1. Background and purpose

Middle East respiratory syndrome (MERS) is an acute respiratory disease caused by the MERS coronavirus (MERS-CoV). The first case was confirmed in Saudi Arabia in 2012; since then, cases have primarily occurred in countries near the Arabian Peninsula. The typical symptoms of MERS are fever, cough, and shortness of breath, and it is often accompanied by pneumonia. It is also sometimes accompanied by digestive symptoms such as diarrhea. The clinical manifestations of MERS-CoV infection range from asymptomatic infection to pneumonia with acute respiratory distress syndrome and even multi-organ failure resulting in death. In the majority of patients, the disease progresses rapidly to pneumonia within 1 week of symptom onset, for which mechanical ventilation or intensive care treatment is often required. The MERS-CoV is a zoonotic virus transmitted from animals to humans, and the major reservoir host is thought to be dromedary camels; human-to-human transmission is known not to commonly

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occur [1]. When human-to-human transmission does occur, it is usually the result of close contact with MERS patients, either within the family or within health-care facilities. As of August 2015, there were a total of 1,401 confirmed patients with MERS-CoV infections worldwide; of them, 500 died (mortality rate, 36%) [2]. The vast majority of cases (>85%) occurred in Saudi Arabia. In Republic of Korea, since the first confirmed MERS patient returned from Saudi Arabia in May 2015, there were a total of 186 confirmed cases, most of whom were infected during hospital outbreaks, and to date (15 August 2015), 36 patients died (mortality rate, 19%) [3].

During the domestic MERS-CoV epidemic, there was concern that mortality would be high. Hence, the Korean Society of Infectious Diseases (KSID) and the Korean Society for Chemotherapy (KSC) collaborated to produce and distribute simple recommendations for the use of antiviral drugs based on antiviral treatment data from a previous epidemic of the severe acute respiratory syndrome coronavirus (SARS-CoV), which is similar to the MERS-CoV, and recent data on the treatment of MERS-CoV. Now that the South Korean MERS-CoV epidemic terminates , we have compiled antiviral MERS-CoV treatment guidelines for based on the recent domestic experience of treating patients with MERS in an effort to achieve a more effective MERS treatment in the future.

2. Scope and subjects

The present treatment guidelines only address MERS-CoV antiviral drugs and certain adjuvant treatments that can help in the treatment of patients with MERS. Because there are also plans to publish guidelines for the diagnosis and infection control of MERS-CoV, these are not discussed in the present guidelines. In addition, the use of prophylactic antiviral drugs for MERS-CoV exposure is not addressed in these guidelines due to a lack of related evidence. The patients targeted in these antiviral treatment guidelines are adults, including pregnant women and the elderly, and the information is intended for use by all general and specialist practitioners treating patients with MERS.

3. Composition of the committee developing the guidelines

In July 2015, under the guidance of the Korean Society of Infectious Diseases (KSID) and Korean Society for Chemotherapy (KSC), the committee developing the antiviral MERS-CoV treatment guideline was formed by including five specialist physicians in infectious diseases.

4. Framing key questions

Nine key questions on antiviral drugs and adjuvant treatments were selected following the collection and evaluation of evidence relating to the treatment of MERS-CoV and the similar virus SARS-CoV as well as a review of overseas MERS-CoV treatment guidelines.

5. Searching for evidence

We performed a search of the literature relating to MERS-CoV and SARS-CoV treatment guidelines published after 2002. We searched the literature from the past 20 years for details of the doses and adverse effects of antiviral drugs including interferon, ribavirin, and lopinavir/ritonavir. Searches were performed on PubMed (www.pubmed.gov) using combinations of the following search terms: Middle East respiratory syndrome, severe acute respiratory syndrome, coronavirus, treatment, therapy, and antiviral. Because the number of original articles on MERS-CoV treatment is small, we reviewed all articles including case reports.

6. Clarifying the recommendation strength and evidence

To determine the strength and evidence of the recommendations, we followed the guidelines of the Infectious Diseases Society of America with minor modification (Table 1). Written recommendations for each of the key questions were determined through a panel conference among the five specialists. Once the key recommendations were decided, they were sent by email to the committee for guideline development as well as to external infectious disease specialists, who assessed the appropriateness of each recommendation on a scale of 1-9. Following a review of the results and the issues raised, the rec-

Table 1. Recommendation of evidentiary strength and quality

Strength of recommendation	Quality of evidence for recommendation
A: Should always be offered	I: One or more properly designed randomized, controlled trials
B: Should generally be offered	II: One or more well-designed, nonrandomized trial, cohort, or case-controlled analytical studies (preferably from more than one center), or dramatic results from uncontrolled experiments
C: Optional	III: Expert opinion or descriptive studies

ommendations were amended to produce the guidelines.

7. External specialists review

A draft of the antiviral MERS-CoV treatment guidelines was reviewed by specialists in infectious disease from the MERS Rapid Response Team of the Public-Private Joint MERS Task Force. This review was then reflected in the guidelines.

MERS-CoV antiviral treatment guidelines

Key question 1. Which patients should be administered antivirals?

- Although the role of antivirals in the treatment of MERS or the similar disease SARS have not been clearly proven, considering the high mortality and morbidity rates, antiviral treatment should be considered in addition to the appropriate supportive care (BIII).
- Important risk factors predicting the progression to severe disease and death include old age, underlying diseases (cardiac disease, chronic pulmonary disease, diabetes, chronic renal disease, etc.), breathing difficulties, and bilateral pneumonia (II). When such risk factors are present in confirmed or suspected MERS-CoV cases, active antiviral treatment is recommended (BIII).
- Even in patients without risk factors related to the progression to severe disease or death, respiratory failure and multi-organ failure may develop rapidly (III). Therefore, in patients with suspected or confirmed MERS-CoV infection with symptoms (fever or shortness of breath) or pulmonary infiltrate on a chest x-ray, antiviral treatment is recommended as long as the risk of adverse effects is not too high (BIII).

During the SARS epidemic of 2002-2003, antivirals such as interferon-α, ribavirin, and lopinavir/ritonavir were used in a large number of patients, and the results were reported in cohort studies. However, there was no clear conclusion about the efficacy of antivirals [4]. There is a serious lack of clinical data to demonstrate the effects of antiviral treatment in patients with MERS. The data that exists were derived from retrospective cohort studies including a small number of patients, and they do not show a clear therapeutic effect [5, 6]. In one retrospective study analyzing the effects of antiviral treatment in 44 patients with MERS, the 14-day survival rate of the treatment group was significantly higher than that of the control group (70% vs. 29%, $P = 0.004$), but there was no significant difference in 28-day survival (30% vs. 17%, $P = 0.054$) [5]. However, because patients with MERS show a high mortality rate (approximately 36% in reports from the Middle East, and 19% in the South Korean epidemic), antiviral treatment can be actively considered since their efficacy has been confirmed in laboratory studies and they have shown some degree of efficacy in retrospective clinical studies.

In MERS-CoV infection, the important risk factors factors for death are old age (>50-65 years, depending on the study), underlying diseases (cardiac disease, chronic pulmonary disease, diabetes, chronic renal disease, etc.), bilateral pneumonia, and low cycle threshold (C_t) values in real-time reverse transcription polymerase chain reaction at diagnosis [6-10]. The risk factors predicting progression to severe disease are also similar [7, 9, 10]. In data analyzing 108 patients during the South Korean epidemic, age >50 years and shortness of breath were significant risk factors on multivariate analysis, while on univariate analysis, underlying diseases and bilateral pneumonia were also associated with death (unpublished data). In a retrospective study by Omrani et al. [5], antiviral treatment significantly improved 14-day survival in patients with severe MERS requiring mechanical ventilation. Therefore, in patients with risk factors for death or progression to severe MERS, active antiviral treatment is recommended.

Retrospective cohort studies have shown that there are also cases of healthy medical workers or patients without underlying diseases who die or progress to severe disease [10, 11]. An analysis of 108 domestic patients with MERS showed the deaths of two patients without any particular underlying diseases (unpublished data). Therefore, even in patients without underlying diseases, if there are clear symptoms or signs of pneumonia, antiviral treatment should be considered as long as the risk of adverse effects is not considered high.

Key question 2. When is the most appropriate time for antiviral administration?

- Antiviral administration should be considered as soon as possible after diagnosis (BIII).

In retrospective studies of the effects of antiviral treatment for MERS-CoV infection, it is highly likely that the therapeutic effects of antivirals were unclear because the majority of patients were critically ill due to severe pneumonia and multi-organ failure [5, 12]. Also, looking at several observational studies of SARS-CoV treatment, there was no therapeutic effect in reports in which antiviral treatment (ribavirin) was started at 6-14 days after after the onset of symptomes, but there was a

therapeutic effect in reports in which antivirals were administered within 48 hours of hospitalization or a SARS diagnosis [4, 13, 14]. Considering all of these facts, a therapeutic effect of antivirals against MERS-CoV can only be expected when the treatment is administered as soon as possible after diagnosis.

Key question 3. Which antiviral regimens can be used in South Korea?

- A combination regimen of type 1 interferon + ribavirin + lopinavir/ritonavir is recommended for antiviral therapy (BIII).
- The use of ribavirin alone is not recommended for antiviral therapy, whereas combined administration with type 1 interferon is recommended (AIII).
- In cases in which it is difficult to use ribavirin for antiviral therapy, a combination regimen of type 1 interferon + lopinavir/ritonavir should be considered first (AIII).
- The dose of ribavirin for MERS-CoV treatment has not been standardized, but the drug can be used at the same doses as in previous clinical trials or the treatment of other respiratory viruses. Dose adjustment may be required in patients showing signs of a decline in renal function (AIII) (Table 2).

There are currently no antiviral drugs with a clearly proven clinical effect in the treatment of MERS-CoV infection. Antiviral studies reported to date have mostly been laboratory studies, and so the actual clinical data for the use of antivirals are limited. There are data from animal experiments and a small amount of clinical data for type 1 interferon, ribavirin, and lopinavir/ritonavir. Type 1 interferons include interferon-α2a, -α2b, and -β1a. In an animal experiment in rhesus macaques, a combination regimen of interferon-α2b and ribavirin showed clinical improvements and reduced severity [15]. There have been clinical case reports of patients who improved after combination therapy with interferon-α2b and ribavirin [16]. However, room remains for debate due to the lack of sufficient clinical studies on combination therapy using type 1 interferon and ribavirin. In one retrospective comparative analysis of cases treated with ribavirin + interferon-α2a or interferon-β1a, neither regimen was effective [6]. In another retrospective clinical study of the effects of a combination regimen of interferon-α2a and ribavirin, 14 of 20 patients (70%) who received this treatment survived beyond 14 days, whereas only seven of 24 patients (29%) in the non-treatment group survived, seemingly demonstrating an effect of the combination regimen (P = 0.004). However, the interpreta-

Table 2. Antiviral treatment for MERS-CoV

Medication[a]	Normal renal function (CrCl > 50 mL/min)	Impaired renal function[b] (CrCl 20-50 mL/min)	Hemodialysis or CrCl < 20 mL/min
A. Ribavirin, high dose[c]	2,000 mg po loading dose → 1,200 mg po q8h for 4 days → 600 mg po q8h for 4-6 days	2,000 mg po loading dose → 600 mg po q8h for 4 days → 200 mg po q8h for 4-6 days	2,000 mg po loading dose → 200 mg po q6h for 4 days → 200 mg po q12h for 4-6 days
Ribavirin, alternative intermediate dose[d]	2,000 mg po loading dose → 10 mg/kg po q8h for 10 days	2,000 mg po loading dose → 200 mg po q8h for 10 days	2,000 mg po loading dose → 200 mg po q12h for 10 days[e]
B. Interferon-α2a[f]	180 μg per week for 2 weeks	Same dose	Same dose
C. Lopinavir/ritonavir[g]	Lopinavir/ritonavir 400 mg/100 mg po q12h for 10 days	Same dose	Same dose
D. Convalescent plasma	300-500 mL of full plasma (3-5 mL/kg)		

[a]In the case of adverse effects caused by ribavirin, the dose should be reduced or its use should be suspended.
[b]If continuous renal replacement therapy is being administered, the ribavirin dose should be adjusted according to the plasma removal rate, and when calculation is difficult, consider using a dose that maintains the creatinine clearance rate (CrCl) at 20-50 mL/min.
[c]This is the dose typically used in the treatment of severe acute respiratory syndrome coronavirus or Middle East respiratory syndrome.
[d]This is a reduced dose due to concerns of adverse effects caused by ribavirin, such as cytopenia or hemolytic anemia. Based on the evidence that ribavirin + interferon-α combination therapy shows a synergistic effect *in vitro*, this follows the dose typically used for the treatment of respiratory syncytial virus treatment to ensure safety.
[e]In dialysis patients or those with severe renal dysfunction, use of ribavirin is usually not recommended due to concerns of fatal hemolytic anemia. Therefore, if ribavirin is to be used, the patient should be closely monitored for hemolytic anemia and other major adverse effects.
[f]Pegylated interferon-α2a (Pegasys®; Roche Pharmaceuticals) is administered by subcutaneous injection (SC). It can be replaced by interferon-β1a (Rebif®, 44 μg SC three times per week). Although there have been no clinical trials using interferon-α2b (Pegintron®), its administration can be considered at the treatment dose for hepatitis C, which is 1.5 μg/kg SC once per week.
[g]Lopinavir/ritonavir (Kaletra®) is mostly metabolized by the liver, so care should be taken in patients with severe liver dysfunction.

tion of the results remains under debate because there was no statistically significant difference for 28-day mortality, with the treatment group showing 30% survival and the non-treatment group showing 17% survival ($P = 0.054$) [5]. Both studies have limited ability to provide statistical proof due to the small number of patients. However, since there was an overall trend for improvement in the type 1 interferon + ribavirin combination therapy group, until the lack of an effect has been shown conclusively, combination therapy is recommended. Evidence for the use of lopinavir/ritonavir as an antiviral for MERS-CoV infection is based on its efficacy in the treatment of SARS-CoV [17, 18]. In an animal experiment of common marmosets, the administration of lopinavir/ritonavir alone significantly reduced the numbers of MERS-CoV colonies in the lungs compared to the non-treatment group, and this effect was identical to that of interferon-β1b [19]. Indeed, one report showed that patients administered lopinavir/ritonavir at the same time as type 1 interferon + ribavirin combination therapy showed improved viremia after 2 days [20]. Hence, if possible, the use of lopinavir/ritonavir in addition to type 1 interferon + ribavirin combination therapy is recommended. As for type 1 interferons, *in vitro* studies showed a stronger effect of interferon-β than interferon-α. Moreover, of these options, the median effective inhibitory concentration (EC_{50}) to maximum serum concentration ratio of interferon-β1b was lower than those of interferon-α2a, interferon-α2b, and interferon-β1a [21, 22]. However, because clinical studies are lacking, no particular type 1 interferon can yet be concluded to be superior to the others [6].

In one *in vitro* study, ribavirin and interferon-α2b separately inhibited MERS-CoV proliferation [23]. However, MERS-CoV proliferation was not inhibited at the typical concentrations of ribavirin used clinically, and inhibition was only confirmed at concentrations that show toxicity in humans [21]. Therefore, monotherapy with ribavirin at typical doses is expected to show a reduced clinical effect. Nevertheless, when interferon-α2b and ribavirin are administered in combination, they showed a synergistic effect and a reduced dose of ribavirin was required [23]. Therefore, its combined administration with interferon is recommended.

As mentioned above, lopinavir/ritonavir was comparable with interferon β1b in an animal experiment of common marmosets [19]. Hence, in cases in which ribavirin cannot be used due to renal dysfunction or other adverse effects, monotherapy with interferon-β1b or lopinavir/ritonavir can be considered. Nevertheless, since there are still no antivirals with a clearly proven clinical effect for the treatment of MERS-CoV infection, as long as there are no contraindications, a combination regimen of type 1 interferon + lopinavir/ritonavir should first be considered.

There are no studies of the dose-dependent differences in therapeutic efficacy for ribavirin in the treatment of MERS-CoV infection. Hence, the dose used in the retrospective study of Omrani et al. [5] is recommended. This dose is the same as that typically used in SARS-CoV treatment [13]. However, if there are concerns about ribavirin-induced adverse effects, including cytopenia and hemolytic anemia, a reduced dose could be used. This reduced dose is based on the synergistic effect of combined type 1 interferon + ribavirin in an *in vitro* study, and it follows the dose used in the treatment of respiratory syncytial virus to ensure safety [24]. Nevertheless, since the suppression of virus proliferation showed a dose-dependent pattern in an *in vitro* study, the dose choice needs to be carefully considered [22, 25]. Dose adjustment is required for ribavirin according to renal function, so creatinine clearance (CrCl) requires monitoring throughout treatment. As there is an increased risk of adverse effects if renal function declines, care must be taken.

Key question 4. How long should antiviral drugs be administered?

- Antiviral treatment is generally recommended for 10-14 days in patients with MERS-CoV infection (BIII).

Antiviral treatment was previously administered for 10-14 days in patients with SARS-CoV infection; accordingly, the same antiviral treatment duration has been applied for patients infected with MERS-CoV [5, 6, 13, 26]. In a retrospective cohort study of patients ≥16 years old with MERS-CoV pneumonia in Saudi Arabia, when combined interferon-α2a and ribavirin treatment was continued for 10-14 days, 14-day survival increased significantly [5]. Although the difference did not reach statistical significance, 28-day survival showed a positive trend in the treatment group also. However, even after approximately 10 days of antiviral therapy, MERS-CoV remained detectable in the respiratory secretions of some patients for up to 2-3 weeks [6]. Since the clinical significance of this finding is unclear, further studies are required for the appropriate duration of antiviral treatment. Treatment extension can be considered when immune deficiency leads to persistent viral shedding, whereas if a patient shows rapid recovery and there are concerns about adverse drug effects, the antiviral treatment duration might be shortened. Antiviral treatment is generally recommended for 10-14 days in pa-

tients with MERS-CoV infection, but the optimal duration should be decided according to the patient's condition.

Key question 5. Should antiviral drugs be used by pregnant women?

- Considering the physiological adaptations to pregnancy, pregnant women should be treated conservatively. Any decision to use antiviral drugs requires the consideration of ethical issues and a consultation with an obstetric specialist (AIII).

Pregnant women are conventionally considered a high-risk group for the progression to severe disease or death, and a case was reported of stillbirth in the second trimester of pregnancy for a woman infected with MERS-CoV [27]. Of the antiviral drugs recommended, ribavirin is in Category X for safety in pregnant women, while lopinavir/ritonavir and type 1 interferon are in Category C. Given the lack of clinical studies on antiviral treatment in pregnant women, it is difficult to recommend these drugs. Considering the physiological adaptations to pregnancy in pregnant women, conservative treatment should be provided [28]. When treating pregnant women infected with human immunodeficiency virus (HIV), the preferred protease inhibitor is lopinavir/ritonavir [29]. Among type 1 interferons, there is evidence supporting the safe use of interferon-β1a, which is used to treat multiple sclerosis, in pregnant women. Although one report showed that the incidence of spontaneous abortion increased in pregnant women who used interferon-β1a, there was no statistically significant difference with the incidence in control individuals [30, 31]. Therefore, the use of antiviral drugs can be considered after a comparison of risks and benefits of the drugs. Possible antiviral treatment would be combination therapy with interferon-β1a and lopinavir/tironavir, but there is no case report of this being used in pregnant women with MERS. Any decision to use antiviral drugs requires the consideration of ethical issues and a consultation with an obstetric specialist.

Key question 6. What are the adverse reactions and points of caution for different antiviral drug classes?

- Care must be taken to prevent the occurrence of hemolytic anemia when using ribavirin, while changes in complete blood count (CBC), reticulocyte, haptoglobin, and bilirubin levels should be monitored closely. If hemolytic anemia occurs, dose reduction or cessation should be considered (AIII).
- Type 1 interferon can cause myeloid dysfunction, so CBC changes must be closely monitored. If anemia, leukopenia, or thrombocytopenia occurs, dose reduction or cessation should be considered (BIII).

Of 110 patients infected with SARS-CoV, hemolytic anemia reportedly occurred in 67 patients (61%) during ribavirin treatment [32]. This could occur 3-5 days after the start of treatment, and on average occurred 10 days after the start of treatment. It mostly occurred when the dose exceeded a normal dose of 1,000-2,000 mg, so it could occur at the doses used to treat MERS-CoV. Hence, during ribavirin use, changes in hemoglobin, bilirubin, haptoglobin, and reticulocyte levels require close monitoring. If hemolytic anemia does occur, a dose reduction or cessation should be considered; if necessary, the use of lopinavir/ritonavir instead of ribavirin could be considered. Dose reduction is required in the case of impaired renal function, and ribavirin use is not recommended for patients on dialysis or those with severe renal dysfunction due to concerns of fatal hemolytic anemia. Other common adverse effects of ribavirin include bradycardia (<55/min), hypomagnesemia, and hypocalcemia [33]. In addition, since ribavirin shows teratogenicity, male and female patients should both use contraception for 6 months after treatment [34].

Fatigue and flu-like symptoms can occur during type 1 interferon use; in these cases, the patient should be given supportive care [34]. Care is required since 20% of patients taking type 1 interferons show anemia, leukopenia, and thrombocytopenia due to bone marrow suppression. If anemia does occur, the ribavirin dose first needs to be reduced or ceased if it is administered in combination, and if there is still no improvement, the use of recombinant erythropoietin can be considered. If leukopenia or thrombocytopenia occurs, the interferon dose needs to be reduced in accordance with the manufacturer's recommendations [35, 36].

Key questions 7. Are there any other drugs with an antiviral effect against MERS-CoV?

Mycophenolic acid, chloroquine, chlorpromazine, and loperamide have a demonstrated antiviral effect against MERS-CoV in laboratory tests, and amiodarone had an antiviral effect against SARS-CoV infection (III). In addition to an immunosuppressive action through the inhibition of T/B lymphocyte differentiation, mycophenolic acid is known to show a broad antiviral effect against West Nile, Japanese encephalitis, yellow fever, dengue, and chikungunya viruses in *in vitro* animal experiments. Some authors have suggested the possi-

bility of clinical trials of the short-term use of mycophenolic acid and interferon-β1b in combination against MERS-CoV infection by lowering its EC_{50} value [37]. Chloroquine inhibited MERS-CoV replication at an EC_{50} of 3.0 μM, and it is predicted to inhibit infection in the early stages. Chlorpromazine suppresses viral invasion in the early stages by inhibiting clathrin-mediated endocytosis, and it is predicted to have an antiviral effect by inhibiting other later processes. Loperamide has also been suggested as a possible treatment since it inhibits two other coronaviruses at low micromolar concentrations (4-6 μM) [38, 39]. The effects of amiodarone on MERS-CoV infection have not been confirmed, but it is known to inhibit SARS-CoV proliferation at the post-endosomal level by altering the endocytic pathway, so it is predicted to have a similar effect against MERS-CoV infection [40]. One key functional receptor during host cell infection by MERS-CoV is the transmembrane protein dipeptidyl peptidase 4 (DPP4). Adenosine deaminase is a protein that binds to DPP4, thereby competing with MERS-CoV for DPP4 binding, and it has been confirmed to act as an antagonist to MERS-CoV infection *in vitro* [41]. DPP4 breaks down incretin through its enzymatic function, and the DPP4 inhibitor gliptin, which is used as a hypoglycemic agent, interferes with this enzymatic action. Therefore, DPP4 inhibitors (such as gliptin) may not interfere with MERS-CoV binding to DPP4, nor experimental studies have been conducted to date.

Key question 8. Does convalescent plasma therapy help?

- Convalescent plasma therapy could be administered experimentally for patients with severe MERS-CoV infection that is refractory to antiviral drugs (BIII).
- The appropriate time for convalescent plasma therapy in patients with MERS-CoV infection is within 2 weeks after disease onset (BIII).

There is insufficient evidence to ascertain the safety and efficacy of convalescent plasma therapy in patients with MERS-CoV infection, but SARS-CoV treatment experiences would be helpful. According to the results of a meta-analysis examining eight observational studies of convalescent plasma therapy in patients with SARS-CoV infection, mortality rates were lower when patients were given the treatment and no major adverse effects were reported [42]. In terms of convalescent plasma administration timing, when a subgroup analysis was performed on 48 patients, the results were only positive when the treatment was given within 14 days of symptom onset [42]. Also, in an analysis of 80 patients with SARS in Hong Kong who were treated with convalescent plasma, treatment timing was significantly earlier for the group with positive results compared to the group with poor results (11.7 days vs. 16.0 days, $P = 0.012$) [43].

Considering the hypothesis that an inappropriate antibody response could lead to poor clinical results in MERS-CoV infection, convalescent plasma therapy could help some patients with severe disease. In fact, in serum collected from patients who died of MERS-CoV infection, no specific antibodies were detected in the serum collected on the 26th and 32nd days after infection [11]. Convalescent plasma therapy in patients with MERS-CoV infection could be performed experimentally with the patient's consent (or a guardian's consent, in cases in which the patient lacks the capacity to give consent) in patients with severe disease that is refractory to antiviral therapy. Considering SARS-CoV treatment experiences to date, the appropriate timing for treating MERS-CoV infection with convalescent plasma therapy is likely to be within 2 weeks after the disease onset [4].

Key question 9. What about other adjuvant therapies?

The long-term use of high-dose steroids can cause adverse effects such as the development of opportunistic infections, avascular necrosis, secondary bacterial infections, and persistent viral replication, and since its efficacy is has not been clearly proven for SARS, its routine use in MERS patients should be avoided [4, 29, 44, 45]. However, in a state of severe shock requiring vasopressors, the administration of low-dose steroids may be considered [46]. In patients with severe SARS, high-dose steroids were often used when fever persisted or respiratory failure/radiological findings worsened, but it has been difficult to evaluate the efficacy [4, 46]. Some authors expressed the opinion that the combined administration of steroids and antiviral drugs would be helpful in some special cases, such as those of acute respiratory distress syndrome caused by SARS-CoV infection [46, 47]. If high-dose steroids are to be used in patients with MERS-CoV infection, step-down dosing of methylprednisolone can be considered as has been used in SARS treatment [48].

Since there is a lack of evidence of the efficacy of intravenous immunoglobulin (IVIG), its routine use for the treatment of MERS is not recommended. Moreover, on rare occasions, IVIG can lead to acute renal failure or thrombosis. Although one study compared the effects of antiviral therapy and IVIG in patients with SARS, its result was inconclusive [4].

In one analysis, pneumonia was confirmed in 60% of 108 patients during the South Korean MERS-CoV infection epidemic (unpublished data). Although the majority of these cases are thought to be viral pneumonia, further data are needed to show how many of these cases actually had concurrent bacterial pneumonia. According to the previous report, there are cases of MERS accompanied by other viruses such as parainfluenza, rhinovirus, influenza virus, and herpes simplex virus. Some mechanically-ventilated patients were complicated by secondary bacterial pneumonia, which was caused by *Klebsiella pneumoniae*, *Staphylococcus aureus*, or *Acinetobacter* spp. [1]. Antibacterial treatment for the combined bacterial pneumonia should be determined according to the patient's clinical condition.

Notes

1. Limitations

To produce treatment guidelines that are appropriate to the domestic situation, evidence must be supplied by data from the recent domestic MERS-CoV epidemic. However, because the domestic clinical experience has not yet been published in the form of academic papers, this could not be fully reflected in these guidelines. In the future, as various studies are published on the clinical features and treatment of MERS-CoV in South Korea, these guidelines will require amendment. In addition, due to the lack of sufficient evidence, these guidelines are mostly recommendations reflecting the opinions of specialists. Hence, it should be noted that these are in no way absolute standards, and that when applied to the treatment of an individual patient, the recommendations may differ according to the patient's condition and the opinions of the clinicians involved.

2. Plan for guideline updates

These guidelines are to be reformed with the addition of the latest evidence once a sufficient amount of data has been accumulated regarding treatment experiences both in Republic of Korea and overseas.

3. Potential conflicts of interest

These treatment guidelines have been compiled with the support of the KSID and the KSC. The committee for the development of the guidelines did not receive any form of payment in relation to the development herein, nor was any influence received from any other for-profit organizations.

Supplementary material

Guideline Korean version.

Supplementary material can be found with this article online http://www.icjournal.org/src/sm/ic-47-212-s001.pdf.

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