GUIDELINE

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Severe influenza treatment guideline

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INTRODUCTION

Background and purpose

Severe influenza is defined as influenza with a severe symptom or syndrome such as respiratory distress or deceased consciousness or accompanying a severe complication such as encephalopathy or renal failure. In contrast to mild influenza, for which patients recover mostly by ambulatory care, severe influenza requires hospital admission in most cases or intensive treatment in the intensive care unit in some cases. In particular, the elderly, infants, and chronic patients are known to be at high risk for severe influenza because they may have accompanying complications such as exacerbation of an underlying disease, development of pneumonia, and another organ dysfunction or they may die.

Therefore, there is an increasing need for an effective treatment method applicable to severe influenza. Severe influenza treatment methods, which have been recently discussed, include high-dose, long-term antiviral therapy, combination antiviral therapy, administration of antibiotics, application of extracorporeal membrane oxygenation (ECMO), administration of a corticosteroid, administration of intravenous immunoglobulin (IVIG), application of plasmapheresis, and administration of a statin. However, no comprehensive, specific expert guideline for these methods is available yet. The Transgovernmental Enterprise for Pandemic Influenza in Korea published in 2012 a guideline for the use of an antiviral agent for seasonal influenza. But the guideline deals with only the use of an antiviral agent, not the various treatment methods which can be applied to severe influenza [1].

Therefore, this guideline was developed by analyzing and evaluating domestic and international literature and guidelines with respect to the various treatment methods so that severe influenza could be effectively treated.

Scope and subjects

The subjects of this guideline are all patients including infants and the elderly. The subject disease is severe seasonal influenza infection. This guideline adapts the general definition of severe influenza from influenza-related severe acute respiratory illness. Quoting the 2010 guideline of the World Health Organization (WHO), severe influenza is defined as follows [2].

- Definition of severe influenza: influenza corresponding to the definition of influenza-like illness (ILI; sudden onset of fever and cough or sore throat) and presenting at least one of the following clinical presentations:

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- Dyspnea, tachypnea, or hypoxia
- Radiological signs of lower respiratory tract disease
- Central nervous system involvement (e.g., encephalopathy, encephalitis)
- Severe dehydration
- Acute renal failure
- Septic shock
- Exacerbation of underlying chronic disease, including asthma, chronic obstructive pulmonary disease (COPD), chronic hepatic or renal insufficiency, diabetes mellitus, or other cardiovascular conditions
- Any other influenza-related condition or clinical presentation requiring hospital admission

Users of this guideline are all general practitioners and medical specialists who treat severe influenza patients. This guideline includes information on not only on antiviral agents but also on antibiotics, ECMO, corticosteroids, IVIG, plasmapheresis, statins, etc. The recommendations included in this guideline could be changed according to future study results.

METHOD OF DEVELOPMENT

Constitution of the guideline development committee

For the development of this guideline through a multidisciplinary discussion, the guideline development committee was constituted with nine members that included an infectious disease specialist, a pediatrics specialist, and a methodology specialist.

Derivation of key questions based on guidelines previously developed

To define key questions for the treatment guideline, clinical practice guidelines previously developed were first reviewed. The reviewed clinical practice guidelines were those that were published between 2009 and 2013 which included ones written in both English and Korean.

The reviewed guidelines were limited to those that were developed by a central or local government or by academic societies. The guidelines were searched for in four databases. Table 1 shows the database and key words used in the search. Two of the Development Committee members reviewed the treatment guidelines and selected 23 guidelines appropriate to the scope of this guideline (Appendix 1). To derive the key questions, the key questions included in each guideline were listed, compared, and reviewed. Then, a total of 10 key questions were chosen.

Determination of the development method

After reviewing the 10 key questions, a systematic literature review was performed for the questions which had not been dealt with in previous guidelines or which needed additional searching. Other key questions were reviewed with the evidence and the degree of recommendations provided by the previous guidelines. If necessary, domestic evidence and recent literature were added.

Literature search

Evidence in the guidelines previously developed

The quality of the selected treatment guidelines was not evaluated. The newness was verified by determining the year of publication and the year of the basis search. The recommendations for each of the selected key questions provided by the individual guidelines were compared by making a recommendation comparison table for each key question.

Additional literature search

According to the selection of the key questions, an additional literature search was carried out for eight key

Table 1. Database and search terms for the clinical guideline

Database	Homepage	Search terms
National Guideline Clearinghouse	www.guideline.gov	influenza
NHS Evidence	www.evidence.nhs.uk	influenza
Guideline International Network	www.g-i-n.net	influenza
PubMed	www.ncbi.nlm.nih.gov/pubmed	influenza AND systematic[sb]

NHS, National Health Service.

questions (Appendix 2). The search was performed with research articles published in English and Korean between January 1970 and May 2013 which included clinical studies but excluded case reports. Two databases, OVID MEDLINE and Cochrane Controlled Trial Registers, were used. The articles were finally chosen by two of the Development Committee members for each of the key questions. Table 2 shows the selected articles for each of the key questions.

Determination of recommendation grade for recommendations

The grade of the recommendations was determined by reviewing the design method of the selected clinical studies. The grade of the recommendations was determined by carefully considering whether the recommendation could be generalized and whether the recommendation could be consistently applied to actual clinical settings. When the domestic basis was not sufficient, the degree was determined by the entire Guideline Development Committee reaching a consensus.

The Development Committee used the evidence and recommendation grades of the Infectious Diseases Society of America (Table 3).

The statement for each recommendation was determined by a specialist panel meeting. Nine specialists participated in the panel meeting and they evaluated the appropriateness of each recommendation on a 1 to 9 point scale (1 point-most inappropriate; 9 points-most appropriate). The panel meeting was held as a face to face meeting. The results and problems were reviewed in the first evaluation. The recommendations were revised and evaluated again in the second evaluation.

External review and approval

The recommendations were reviewed by five specialists and their comments were reflected in the guideline. To collect opinions of the stakeholders, approval was acquired from the Korean Society of Infectious Diseases and the Korean Society for Chemotherapy.

ANTIVIRAL AGENTS

Key question 1: what is the optimal dose of oseltamivir for the treatment of severe influenza?

- Standard-dose oseltamivir is recommended for the treatment of severe influenza (BI).

Table 2. Number of selected references for each key question

Key question	No. of reference	Study design		
		RCT	Observational study	Etc.
IVIG	5	0	5	0
ECMO	17	0	17	0
Macrolide	4	0	4	0
Statin	2	0	2	0
Steroid	15	0	15	0
High dose therapy	3	1	2	0
Combination therapy	3	0	3	0
Plasmapheresis	2	0	2	0

RCT, randomized controlled trial; IVIG, intravenous immunoglobulin; ECMO, extracorporeal membrane oxygenation.

Table 3. Recommendation of strength and evidence for recommendations

Strength of recommendation	Quality of evidence for recommendation
A: should always be offered	I: one or more properly designed randomized, controlled trial
B: should generally be offered	II: one or more well-designed, nonrandomized trial
C: optional	III: expert opinion, descriptive studies

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Many studies have been conducted to compare and evaluate the effects of treatment using a standard- and high-dose of antiviral agent with mild influenza infection patients without any complications. However, each study showed clinically and virologically different results [3-6].

Although the data are not sufficient regarding high-dose antiviral agent treatment in patients with severe influenza, double-dose oseltamivir treatment (two times a day at 150 mg each) has been recommended for the treatment of A/H5N1 avian influenza infection considering the decreased oral absorption rate and the safety data for high-dose administration. However, a large-scale prospective cohort study in China conducted with patients infected by the pandemic influenza A (H1N1) in 2009 (3,066 patients presenting pneumonia) showed that high-dose oseltamivir treatment (> 3.8 mg/kg per day) did not improve the survival rate compared with the standard-dose treatment [7]. A multi-institutional, double blind, randomized study conducted in Southeast Asia showed that high-dose oseltamivir treatment (two times a day at 150 mg each) in patients with severe influenza did not have a particular therapeutic advantage over the standard-dose treatment (two times a day, 75 mg each) [8]. Specifically, there was no difference in the virus repression effects and in the clinical therapeutic reactions (the period of time requiring mechanical ventilation, the duration of intensive care unit admission, mortality, etc.) on the fifth day after starting the treatment. A recently published study, which was conducted on adult influenza inpatients aged 18 or higher in Hong Kong, compared the therapeutic effects of standard- and high-dose oseltamivir treatments [9]. In this study, there was no significant difference between the standard- and high-dose groups in the viral RNA detection rate, fever duration, and admission duration on the fifth day after starting the treatments. The study is limited in the sense that severe, critical patients were not included in the study subjects. However, the maximum and minimum blood oseltamivir concentrations were measured in the study, indicating that the administration of the standard-dose oseltamivir treatment, two times a day at 75 mg each, also showed a blood oseltamivir concentration which was about eight to 18 times higher than the 90% inhibitory concentration. Therefore, treatment using oseltamivir with the standard-dose is recommended also for patients with severe influenza infection (BI). It is recommended that the actual dose of oseltamivir according to age, weight, or underlying diseases should follow the Clinical Practice Guideline for Antiviral treatment and Chemoprophylaxis of Seasonal Influenza [1].

Domestic data with regard to treatment with a high-dose antiviral agent is very limited. Kim et al. [10] reported that an oseltamivir administration at a high dose, which was two times more than the standard dose, showed a clinical improvement in a pediatric severe influenza patient who had a graft-versus-host disease. Kang et al. [11] evaluated the therapeutic reactions of high dose oseltamivir treatment in severe adult patients who were infected by the pandemic influenza in 2009 and reported that six out of the eight severe patients with accompanying pneumonia survived and no virus was detected in five out of the six surviving patients on the fifth day after starting the treatment.

Although a few important studies may provide a basis for whether to recommend standard- or high-dose oseltamivir treatment for severe influenza infection, additional studies are required in the future. In addition, there are insufficient data to establish a recommendation for a high-dose therapy with intravenous peramivir or a zanamivir inhaler.

Key question 2: what is the optimal duration of the antiviral treatment for a severe influenza patient?

- If the clinical course remains severe or progressive, the duration of the antiviral treatment is recommended to be extended longer than the usual treatment duration (e.g., 5 days for oseltamivir).

No clinical studies have evaluated the effectiveness of a longer duration of antiviral treatment for treating severe influenza patients. However, one study showed that hospitalized patients with influenza can shed detectable virus beyond the 5-day period [12] and many experts have expressed their opinion that a longer duration of antiviral treatment may be helpful in patients with severe influenza. At the time of the H1N1 pandemic in 2009, the WHO influenza antiviral therapy guideline also recommended that the antiviral treatment should be maintained without a break until the virus infection is resolved or there is satisfactory clinical improvement. [2]. The Centers for Disease Control and Prevention

guideline also stated that a longer use of an antiviral agent may be considered if a severe state continues even after using an antiviral agent for 5 days [13]. Therefore, if the clinical course remains severe or progressive, the duration of the antiviral treatment is recommended to be extended longer than the usual treatment duration (e.g., 5 days for oseltamivir) (BIII). Furthermore, the usual antiviral treatment duration is recommended to follow the Clinical Practice Guideline for Antiviral Treatment and Chemoprophylaxis of Seasonal Influenza [1]. However, if the clinical course remains severe or progressive even after administering an antiviral agent for the usual treatment duration, antiviral drug susceptibility testing will be needed.

Key question 3: should antiviral combination therapy be used in a severe influenza patient?

- Antiviral combination therapy is not generally recommended for the treatment of severe influenza (BII).

Data with respect to the combined use of antiviral agents are very limited. Prospective studies that compared the effects of oseltamivir monotherapy, zanamivir monotherapy, and oseltamivir and zanamivir combination therapy with patients who were infected by mild seasonal influenza without any complications in the 2008 to 2009 season showed that the therapeutic effect of the oseltamivir and zanamivir combination treatment was rather lower compared to that of the oseltamivir single treatment and not significantly different from that of the zanamivir single treatment [14,15].

Although the data with respect to a combined use of the antiviral agents in a severe influenza patient are not sufficient, a study showed that the synergic effect of an oseltamivir and amantadine combination therapy could be helpful in a severe patient [16]. A recent report showed that a triple therapy with oseltamivir, amantadine, and ribavirin, having different active sites, provided not only an *in vivo* synergic effect on a seasonal influenza virus but also a synergic effect on a seasonal influenza virus presenting resistance to one drug [17]. With regard to the clinical usefulness of such a triple combination therapy, a retrospective study that compared the treatment result of oseltamivir monotherapy with that of oseltamivir, amantadine, and ribavirin combination therapy in severe influenza patients admitted to an intensive care unit during the epidemic period of the pandemic H1N1 in 2009 showed that the 14-day mortality and 90-day mortality were lower in the case of the combination therapy compared to the case of the monotherapy, but the difference was not significant [18]. In another study conducted with H1N1 infected patients who were admitted to an intensive care unit in 2009, a combination of antiviral agents did not show a better survival rate than that of a monotherapy [19,20]. Therefore, according to the research results available until now, because the combined administration of antiviral agents to a severe influenza patient may not be considered more effective and the indiscriminate application of a combined administration of antiviral agents to all severe influenza patients is not recommended (BII).

However, because various combinations of currently available antiviral agents have not been sufficiently evaluated and a number of animal test reports have shown that a combined use of antiviral agents is effective, the recommendation with respect to a combined use of antiviral agents to a severe influenza patient may need to be revised by additional studies in the future. In addition, considering that such a combined therapy does not present many drug side effects, a limited application of a combined use of antiviral agents may be taken into consideration for a severe influenza patient who is suspected to have resistance to an antiviral agent or who does not respond to a conventional treatment.

ANTIBIOTICS

Key question 4: should an antibiotic be administered to a severe influenza patient?

- An antibiotic along with an antiviral agent is recommended to be administered from the beginning of the treatment to a severe influenza patient with accompanying pneumonia (BII).
- An antibiotic is recommended to be administered to a patient with severe influenza complicated by acute otitis media or sinusitis (BII).

Key question 5: when an antibiotic is considered for a severe influenza patient, which antibiotics are recommended?

- Antibiotics such as ampicillin/sulbactam, amoxicillin/clavulanate, third-generation cephalosporins, and respiratory

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quinolones that show an antibacterial activity to *Staphylococcus aureus*, *Streptococcus pneumonia*, *Streptococcus pyogenes*, and *Moraxella catarrhalis* are recommended (BII).

Some studies have shown that the prescription of an antibiotic in acute sore throat patients alleviate the symptom a little and decrease the suppurative complications such as acute otitis media. However, such an effect was more distinctive in a patient group in which throat swabs were positive for *Streptococcus* [21], and more side effects were found in a group in which an antibiotic was prescribed for upper respiratory infection [22], and there was no difference in the time taken until loss of symptoms between the group in which an antibiotic was immediately administered and the group in which an antibiotic was administered only after a secondary bacterial infection was verified [23]. Considering these results, it is not generally recommended to administer an antibiotic to all influenza patients [24]. Therefore, the use of an antibiotic is recommended only in cases where the influenza infection is complicated by pneumonia, acute otitis media, sinusitis, and other infections (BII).

The most frequent and serious complication of influenza is secondary bacterial pneumonia. In cases of influenza complicated by pneumonia, it is difficult to distinguish whether the pneumonia is from an influenza virus or a secondary bacterial infection. However, once the influenza is complicated by pneumonia, a secondary bacterial infection is identified in many of the cases. Many studies were conducted regarding the etiologic bacteria of pneumonia in patients with severe influenza complicated by pneumonia during the 2009 H1N1 pandemic. A study conducted in the United States with 36 dead pediatric patients in 2009 showed that 10 of the 36 subjects (43%) were definitely diagnosed with a secondary bacterial infection microbiologically or pathologically [25]. A study which was conducted later also showed that 17 out of 53 dead pediatric patients (32%) were verified to have had a secondary bacterial infection microbiologically [26].

The bacteria frequently isolated from patients with pneumonia by influenza infection included *Staphylococcus aureus*, *Streptococcus pneumonia*, *Streptococcus pyogenes*, and *Moraxella catarrhalis*. Because secondary bacterial pneumonia often accompanies influenza, the early use of an antibiotic with an antibacterial activity specific to the bacteria mentioned above is recommended in the cases of patients with influenza complicated by pneumonia [26]. Therefore, according to the Treatment Guideline for Community-acquired Pneumonia, an empiric antibiotic for pneumonia due to influenza infection such as ampicillin/sulbactam, amoxicillin/clavulanate, third-generation cephalosporins, and respiratory quinolones could be used as the primary drug [27]. However, because atypical bacteria such as *Mycoplasma* and *Legionella* are not likely to accompany influenza, there could be a low need to use a macrolide in influenza patients although it is the primary drug for general community-acquired pneumonia. In the cases of otitis media and sinusitis, antibiotics such as amoxicillin and amoxicillin/clavulanate are used as the primary drug [28]. When the culture test result shows that the bacteria, which has caused a secondary bacterial infection, has resistance to the primary drug or that the clinical condition of the patient is not improved, the used antibiotic should be replaced by another according to the susceptibility test result and the treatment guideline for each infectious disease. In a case where hospital-acquired pneumonia seems to have developed because of a long period of admission for a severe influenza patient, it is recommended to treat that patient with an appropriate antibiotic according to the culture test result from the patient's respiratory sample and to the antibiotic resistance pattern of respiratory pathogens in each institution.

EXTRACORPOREAL MEMBRANE OXYGENATION

Key question 6: should extracorporeal membrane oxygenation be applied to a severe influenza patient?

- ECMO is recommended to be applied to an influenza patient presenting continued hypoxia which does not respond to a conventional treatment (BIII).

Application of ECMO to a severe influenza patient is a supportive method to acquire time for the patient to recover, rather than a direct treatment of influenza. Thus, ECMO application is one of the rescue therapies which should be considered when a patient is having respiratory failure from influenza who does not respond to a

conventional therapy [29-31]. There is no prospective study on the effect of ECMO in a severe influenza patient. Most of the studies are case studies most of which are about the pandemic H1N1 in 2009. Reports have shown different mortality rates of severe influenza in which ECMO was applied between 8% and 75%, but the average mortality rate was 32%, indicating a relatively good effect [32-49]. Therefore, it is recommended to apply ECMO to an influenza patient presenting continued hypoxia which does not respond to a conventional treatment (BIII). Indications and contraindications for consideration or implementation of ECMO are shown in Table 4 [31].

STEROIDS

Key question 7: should a corticosteroid be administered to a severe influenza patient?

- Systemic corticosteroid administration should not performed for the treatment of a severe influenza patient (BII).
- The exception is that a corticosteroid could be administered for the treatment of a disease for which the therapeutic effect of a steroid has already been proven, such as asthma, COPD, and adrenal insufficiency (BIII).

Administration of empirical corticosteroids as a first line or salvage treatment was reported in more than half of the severe patients including acute respiratory distress syndrome during the pandemic influenza in 2009 [50]. However, the effect of corticosteroids in a severe influenza patient has not been studied sufficiently and thus, is still controversial.

Quispe-Laime et al. [51] suggested the use of a low to moderate dose of a steroid because a corticosteroid may significantly improve lung injuries. However, this study result has limitations due to its research design and the small size of the study populations. Kil et al. [52] reported that the duration of fever and the duration of oxygen therapy were significantly shorter, and the number of patients whose pneumonia was resolved at the time of discharge was greater in the severe pediatric influenza patient group where a steroid was adminis-

Table 4. Indication and contraindication of extracorporeal membrane oxygenation for influenza patients with acute respiratory distress syndrome

The status of consideration for ECMO
$PaO_2/FiO_2 < 150$ with $FiO_2 > 90\%$
$PaO_2/FiO_2 < 100$ with PEEP ≥ 10 cmH_2O
Murray score 2–3
Oxygenation index > 25
Hypercapnia and respiratory acidosis with pH < 7.25
Indication of ECMO
$PaO_2/FiO_2 < 80$ with FiO2 > 90%
$PaO_2/FiO_2 < 70$ with PEEP ≥ 15 cmH_2O
Murray score > 3–4
Oxygenation index > 30
Hypercapnia and respiratory acidosis with pH < 7.25 for at least 6 hours
Contraindication of ECMO
Absolute contraindications
Cerebral hemorrhage or other absolute contraindications to anticoagulation
Moribund patient
Decision to limit therapeutic effort
Prior functional dyspnea grade IV
Terminal chronic disease
Established multiorgan failure (≥ 2 organs without including respiratory apparatus, with ≥ 2 points on the SOFA scale)
Severe aortic insufficiency (in the case of venous-arterial ECMO)
Relative contraindications
Mechanical ventilation for more than 7 days; age > 65 years
Body mass index > 40 kg/m^2
Aortic dissection (in the case of venous-arterial ECMO)

ECMO, extracorporeal membrane oxygenation; PEEP, positive end-expiratory pressure; SOFA, sequential organ failure assessment.

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tered. Sohn et al. [53] also reported that the administration of a corticosteroid within 48 hours to 37 pediatric patients presenting exacerbating influenza pneumonia resulted in the recovery of all the patients without a sequela. However, these two studies also should be carefully interpreted because the size of the study population was small and the subjects were limited to pediatric patients. There is a considerable number of clinical case series and case reports in which severe patients with encephalopathy or with respiratory complications such as pneumonia improved after the use of a corticosteroid [54-67].

However, all the studies that analyzed the effect of corticosteroids during the pandemic H1N1 infection in 2009 showed a negative result. A study conducted by the European Society of Intensive Care Medicine showed that the use of a corticosteroid was not helpful to the treatment of a patient and rather, increased the risk of hospital-acquired pneumonia [68]. Mady et al. [69] conducted a study with patients admitted to an intensive care unit at the time of the pandemic influenza in 2009 and reported that use of a corticosteroid increased the mortality three times. Linko et al. [70] prospectively observed the mortality of patients who were administered a corticosteroid and the patients who were not among the influenza confirmed patients admitted to an intensive care unit during the pandemic influenza in 2009 and reported that there was no significant difference in the mortality between the two groups. Han et al. [71] compared the prognosis of an early corticosteroid administration group in which a steroid was administered within 72 hours after onset of influenza symptoms, a delayed administration group, and a nonadministration group and reported that the percentage of patients who progressed to a severe disease and the mortality were higher in the early administration group. Maravi-Poma et al. [72] analyzed the severe influenza treatment results among pregnant women and reported that the mortality tended to be higher in the corticosteroid administration group than in the nonadministration group although the difference was not statistically significant. A study conducted in Japan by Kawashima et al. [73] in which a survey was given to medical doctors who had treated pediatric influenza encephalopathy showed that the administration of a corticosteroid did not affect the treatment results. Brun-Buisson et al. [74] analyzed 208 acute respiratory failure patients who had no other indication for corticosteroids other than acute respiratory failure and showed that the administration of a corticosteroid increased the mortality and the risk of hospital-acquired pneumonia, and particularly, early administration within 3 days after mechanical ventilation was correlated with increased mortality. Similar to the results of other studies, a study on viral pneumonia did not show a therapeutic effect for a steroid [76].

There has not yet been a well-designed randomized controlled study to evaluate the effect of corticosteroid administration in severe influenza. Some clinical case series and case reports showed that the corticosteroid had a therapeutic effect. On the contrary, prospective cohort studies and retrospective comparative studies, which were conducted with larger study populations, showed that corticosteroid administration did not decrease mortality but rather increased complications. Therefore, in general, systemic corticosteroid administration for treatment of a severe influenza patient is not recommended (BII). The exception is that a corticosteroid could be considered for treatment of a disease for which the therapeutic effect of a corticosteroid has already been proven, such as asthma, COPD, and adrenal insufficiency (BIII).

OTHER TREATMENTS

Key question 8: should intravenous immunoglobulin or statin injection or plasmapheresis be implemented for treatment of a severe influenza patient?

- There is not sufficient evidence to recommend implementation of IVIG, statin, or plasmapheresis for treatment of a severe influenza patient.

No randomized controlled study has been conducted with respect to whether the administration of IVIG may improve the prognosis of a severe influenza patient. Only a few case reports are available [60,77-80]. Therefore, there is not sufficient evidence to recommend the administration of IVIG to a severe influenza patient. However, because all the case reports showed good prognosis after the administration of IVIG, according to the clinician's judgment based on the case reports, the administration of IVIG to a severe influenza patient could be considered.

A statin, which is an inhibitor of 3-hydroxy-3-methylglutaryl-CoA reductase, blocks intracellular signal transduction via isoprenoid showing an anti-inflammatory effect, regulating immune response, and inhibiting cell growth. It has been known by many clinical studies that a statin is helpful in a pneumonia patient or sepsis patient because of its anti-inflammatory effect [81]. Vandermeer et al. [82] analyzed with COPD patients showed that death by influenza and pneumonia and death by COPD were significantly lower in patients who used a moderate dose of statin (≥ 4 mg/day) [84]. However, a retrospective case-control study conducted in the UK with the Influenza Clinical Information Network at the time of the pandemic H1N1 in 2009 showed that preadmission statin use did not affect the prognosis [85]. A retrospective study conducted in Mexico with a small number of influenza patients admitted to an intensive care unit showed that the survival rate was higher in the cases where a statin was administered (pravastatin 40 mg/day) [86]. However, a prospective cohort study conducted in Spain with patients presenting pneumonia showed that any anti-inflammatory therapy did not improve the prognosis [87]. Therefore, at present, there is not sufficient evidence to recommend statin use for severe influenza patients. However, according to a clinician's judgment based on the anti-inflammatory effect and several small-scale studies, statin use in a severe influenza patient could be considered.

There are only a couple of clinical case reports with pediatric patients as the subjects in which plasmapheresis was conducted for the purpose of treating severe influenza in a severe influenza patient, not for the purpose of treating a complication such as thrombotic thrombocytopenic purpura (TTP), hemolytic anemia, Guillain-Barre syndrome, acute renal failure, and rhabdomyolysis. Patel et al. [88] reported that three pediatric patients who had been clinically exacerbated despite application of an antiviral agent, mechanical ventilation, ECMO, and vasopressor all recovered because plasmapheresis was performed. Kawashima et al. [65] performed plasmapheresis with three pediatric patients presenting influenza encephalopathy in parallel with steroid administration or glucose and insulin combined treatment and reported that all the patients had recovered without a sequela. All the clinical case reports showed that plasmapheresis was effective, but the number of subjects was too small and the effect has not been analyzed by a large-scale prospective randomized controlled study. Therefore, at present, there is not sufficient evidence to recommend implementation of plasmapheresis for a severe influenza patient. However, implementation of plasmapheresis could be considered in a case presenting a complication for which plasmapheresis has already been proven as an effective therapeutic method, such as TTP, hemolytic anemia, Guillain-Barre syndrome, acute renal failure, and rhabdomyolysis.

CONCLUSIONS

Limitations

This guideline was designed to provide recommendations by searching as many studies as possible with a systematic literature review and by evaluating various therapeutic methods for severe influenza. However, there were not many study results which could be used as a basis for the recommendations, and domestic literature was particularly insufficient. Therefore, this guideline may need to be revised by continuously conducting relevant studies in the future. In addition, when this guideline is applied to the treatment of individual patients, the application range of this guideline may be dependent on the state of each patient. In addition, specialists may have different opinions about the application of this guideline depending on each situation.

Plan for revision

Up-to-date results with respect to the recommendations in this guideline will be periodically reviewed every 3 years. The guideline will be revised if there are new research results which may provide an appropriate basis for the recommendations.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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This guideline provides the basic treatment principles appropriate to the circumstances in Korea as of November 2013 for the treatment of severe seasonal influenza. Therefore, rather than applying the suggestions provided in this guideline to all patients having severe influenza, it is appropriate to determine a treatment method according to the final decision of a physician depending on the clinical situation of individual patients based on this guideline.

This guideline can be used individually for diagnosis, treatment, and education, but it should not be used for commercial purposes or for a review on the diagnosis and treatment of severe influenza.

To use this guideline for another purpose, an agreement should be acquired by submitting a written request to the Transgovernmental Enterprise for Pandemic Influenza in Korea (TEPIK).

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Appendix 1. Characteristics of the selected clinical guidelines

Number	Nation	Publishing institute	Year	Title
1	Canada	AMMI	2012	The use of antiviral drugs for influenza: recommended guidelines for practitioners
2	USA	CDC	2011	Antiviral agents for the treatment and chemoprophylaxis of influenza
3	UK	NICE	2009	Amantadine, oseltamivir and zanamivir for the treatment of influenza
4	USA	AAP	2013	Recommendations for prevention and control of influenza in children, 2012–2013
5	Australia	ASID	2009	ASID position statement: infection control guidelines for patients with influenza-like illnesses, including pandemic (H1N1) influenza 2009, in Australian health care facilities
6	Italy	GDG	2009	Italian evidence-based guidelines for the management of influenza-like syndrome in adults and children
7	USA	IDSA	2009	Seasonal influenza in adults and children-diagnosis, treatment, chemoprophylaxis, and institutional outbreak management: clinical practice guidelines of the Infectious Diseases Society of America
8	-	WHO	2010	WHO guidelines for pharmacological management of pandemic influenza A (H1N1) 2009 and other influenza viruses
9	USA	ACOEM	2011	Pandemic Influenza Guidance for Corporations
10	Singapore	Hospital Influenza Workgroup	2009	Management of novel influenza epidemics in Singapore: consensus recommendations from the Hospital Influenza Workgroup (Singapore)
11	UK	Health Protection Agency	2012	HPA guidance on use of antiviral agents for the treatment and prophylaxis of influenza
12	Canada	Government of Alberta	2011	Alberta Health and Wellness Public Health Notifiable Disease Management Guidelines
13	Australia	CDNA	2012	Influenza Infection CDNA national guidelines for public units
14	USA	AST, TTS, CST	2010	Guidance on Novel Influenza A/H1N1 in Solid Organ Transplant Recipients
15	-	WHO EMR	2011	Clinical management guidelines for pandemic (H1N1) 2009 virus infection in the Eastern Mediterranean region: technical basis and overview
16	China	Chinese Ministry of Health	2011	Chinese Guidelines for Diagnosis and Treatment of Influenza (2011)
17	Europe	ECIL	2013	European guidelines for prevention and management of influenza in hematopoietic stem cell transplantation and leukemia patients:
18	Taiwan	-	2010	Recommendations for the management of children with H1N1 novel influenza infection
19	Spain	SEMICYUC	2011	Recommendations of the Infectious Diseases Work Group (GTEI) of the Spanish Society of Intensive and Critical Care Medicine and Coronary Units (SEMICYUC) and the Infections in Critically Ill Patients Study Group (GEIPC) of the Spanish Society of Infectious Diseases and Clinical Microbiology (SEIMC) for the diagnosis and treatment of influenza A/H1N1 in seriously ill adults admitted to the Intensive Care Unit

AMMI, Association of Medical Microbiology and Infectious Diseases Canada; CDC, Centers for Disease Control and Prevention; NICE, National Institute for Health and Clinical Excellence; AAP, American Academy of Pediatrics; ASID, Australian Society for Infectious Diseases; GDG, Guideline Development Group; IDSA, Infectious Diseases Society of America; WHO, World Health Organization; ACOEM, American College of Occupational and Environmental Medicine; CDNA, Communicable Disease Network Australia; AST, American Society of Transplantation; TTS, The Transplantation Society; CST, The Canadian Society of Transplantation; EMR, Eastern Mediterranean Region; ECIL, The European Conference on Infections in Leukemia; SEMICYUC, Spanish Society of Intensive and Critical Care Medicine and Coronary Units.

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Appendix 2. Search strategy for key questions

Key question	Search terms
IVIG	1. ivig.mp. or exp Immunoglobulins, Intravenous/ 2. influenza.mp. or exp Influenza, Human/ 3. 1 AND 2
ECMO	(influenza OR h1n1 OR pandemic OR epidemic) AND (ards OR (acute AND respiratory AND distress AND syndrome) OR ali OR (acute AND lung AND injury) OR arf (acute AND respiratory AND failure) OR (pulmonary AND failure) OR (pulmonary AND insufficiency) OR (respiratory AND failure) OR (respiratory AND insufficiency)) AND (ecmo OR (extracorporeal AND membrane AND oxygenation))
Macrolide	1. exp Macrolides/ 2. (macrolide* or clarithromycin* or troleandomycin* or erythromycin* or josamycin* or azithromycin* or roxithromycin*).tw. 3. influenza.mp. or exp Influenza, Human/ 4. (1 OR 2) AND 3
Statin	1. statin.mp or exp statin/ 2. influenza.mp. or exp Influenza, Human/ 3. 1 AND 2
Steroid	1. exp corticosteroids/ 2. exp glucocorticoids/ 3. ?steroid$.tw. 4. ?corticoid$.tw. 5. exp prednisolone/ 6. exp prednisone/ 7. (prednisolone or prednisone).tw. 8. 1 or 2 or 3 or 4 or 5 or 6 or 7 9. influenza.mp. or exp Influenza, Human/ 10. 8 AND 9
High dose therapy	1. antiviral.mp. or exp Antiviral Agents/ 2. peramivir.mp. or exp Neuraminidase/ 3. oseltamivir.mp. or exp Oseltamivir/ or exp Neuraminidase/ 4. dose.mp. 5. influenza.mp. or exp Influenza, Human/ 6. ((1 OR 2 OR 3) AND 4)) AND 5
Combination therapy	1. exp Drug Therapy, Combination/ or combination.mp. 2. influenza.mp. or exp Influenza, Human/ 3. 1 AND 2
Plasmapheresis	1. plasmapheresis.mp. or exp Plasmapheresis/ 2. plasma exchange.mp. or exp Plasma Exchange/ 3. plasmaphoresis.mp. 4. influenza.mp. or exp Influenza, Human/ 5. (1 OR 2 OR 3) AND 4

IVIG, intravenous immunoglobulin; ECMO, extracorporeal membrane oxygenation.