NEWSLETTER

대한결핵 및 호흡기학회, 호흡기감염병 연구회

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

(요약본 외 내용은 기존 Sepsis Guideline에 따른다)

Recommendation:

1. For healthcare workers performing **aerosol-generating procedures*** on patients with COVID-19 in the ICU, we **recommend** using **fitted respirator masks** (**N95 respirators, FFP2, or equivalent)**, as opposed to surgical/medical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (best practice statement).

* Aerosol-generating procedures in the ICU include: endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, physical proning of the patient, disconnecting the patient from the ventilator, non-invasive positive pressure ventilation, tracheostomy, and cardiopulmonary resuscitation.

Respirator masks are designed to block 95 -99% of aerosol particles. The N95 type conforms to United States Federal Drug Agency standards, and the FFP2 conforms to European standards - European Committee for Standards standards). Staff should be fit tested for each different type. Surgical (also known as medical masks) are designed to block large particles, droplets and sprays, but are less effective in blocking small particle aerosols (< 5 micrometers) [14].

Recommendation:

2. We **recommend** performing **aerosol-generating procedures** on ICU patients with COVID-19 in a negative pressure room (best practice statement).

Recommendations:

3. For healthcare workers providing usual care for non-ventilated COVID-19 patients, we **suggest** using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (weak recommendation, low quality evidence).

4. For healthcare workers who are performing **non-aerosol-generating procedures** on mechanically ventilated (closed circuit) patients with COVID-19, we **suggest** using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (weak recommendation, low quality evidence).

Our recommendations are in line with the WHO guidance, and with the current evidence, which suggests that surgical/medical masks are probably not inferior to N95 respirators for providing protection against laboratory confirmed seasonal respiratory viral infections (e.g., influenza, but not measles). We updated the most recent systematic review and meta-analysis of RCTs [20], and identified one new RCT [21]. Overall, 4 RCTs (5,549 individuals) randomized healthcare workers to N95 respirators or medical masks [21-25]. The use of medical masks, as opposed to N95 respirators, did not increase laboratory-confirmed respiratory infection (OR 1.06, 95% CI 0.90 to 1.25). Although the point estimates suggest that use of medical masks was associated with increased risk of influenza-like illness (OR 1.31, 95%CI 0.94, 1.85) and clinical respiratory infection (OR 1.49, 95%CI 0.98 to 2.28), the differences were not statistically significant. A recent systematic review and meta-analysis reached similar conclusions [26].

Recommendation:

5. For healthcare workers performing **endotracheal intubation** on patients with COVID-19, we **suggest** using video-guided laryngoscopy, over direct laryngoscopy, if available (weak recommendation, low quality evidence).

There is no direct evidence comparing the use of video-laryngoscopy with direct laryngoscopy for intubation of patients with COVID-19. While SAR-CoV-2 appears to be predominantly spread by large respiratory droplets, intubation is likely a small particle (less than 5 micrometers) aerosol-generating procedure, which increases the risk of transmission to healthcare workers [29]. Intubation is particularly risky given the close contact of healthcare workers with the patient's airway and respiratory secretions. Thus, techniques that can reduce the number of attempts at endotracheal intubation and the duration of the procedure and minimize the proximity between the operator and the patient, should be prioritized, potentially reducing the risk of complications in hypoxic COVID-19 patients. In a systematic review including 64 studies and 7,044 patients, video-laryngoscopy reduced the risk of failed intubation (OR 0.35, 95%CI 0.19 to 0.65), without a significant impact upon the proportion of successful first-pass attempts (OR 0.79, 95%CI 0.48 to 1.3), hypoxia (OR 0.39, 95% CI 0.1 to 1.44), or time for tracheal intubation [30, 31]. In patients with difficult airways, the first-attempt success rate may be improved with video-laryngoscopy [32].

Recommendations:

7. For intubated and mechanically ventilated adults with suspicion of COVID-19:

   7.1. For diagnostic testing, we **suggest** obtaining lower respiratory tract samples in preference to upper respiratory tract (nasopharyngeal or oropharyngeal) samples (weak recommendation, low quality evidence).

   7.2. With regard to lower respiratory samples, we **suggest** obtaining endotracheal aspirates in preference to bronchial wash or bronchoalveolar lavage samples (weak recommendation, low quality evidence).

Lower respiratory tract specimens are considered to give a higher diagnostic yield than upper respiratory specimens in patients with pneumonia, consistent with what was observed for SARS [41], and should therefore be obtained whenever possible.

Shock and cardiac injury in COVID-19 patients

The reported prevalence of shock in adult patients with COVID-19 is highly variable (from 1% to 35%), depending on the patient population studied, the severity of illness, and the definition of shock. In a recent report summarizing the epidemiological characteristics of 44,415 Chinese patients with COVID-19, 2087 (5%) were diagnosed as critical cases, defined as severe hypoxemia and/or the presence of other organ failure, including shock [12]. In another Chinese study of 1099 patients with COVID-19 with similar severity of illness, only 12 (1.1%) developed shock [1]. In hospitalized patients, the incidence is likely higher [42] (**Table 3**), and may reach 20-35% among patients in the ICU [42, 43].

Cardiac injury (elevation of cardiac injury biomarkers above the 99th percentile upper reference limit) has been reported in 7% to 23% of patients with COVID-19 in Wuhan, China [42-45]. While the prevalence of cardiac injury may correlate with the prevalence of shock, a lack of systematic screening for cardiac dysfunction in hemodynamically stable patients means that this association cannot be taken as certain (**Table 3**).

The prognosis of patients with COVID-19 and shock has not been systematically reported. In a study of 150 patients from 2 hospitals in Wuhan, China, shock was a major reason for death in 40%, and may, at least in part, be due to fulminant myocarditis [46].

Studies on risk factors associated with shock in patients with COVID-19 are lacking. The majority of those that are available report unadjusted estimates [12, 42, 46]. Despite methodological limitations, these studies suggest that older age, comorbidities (especially diabetes and cardiovascular disease including hypertension), lower lymphocyte count, higher D-dimer level, and possibly cardiac injury are risk factors to consider.

Table 3. Epidemiological characteristics in recent COVID-19 reports.

Study	n	ICU admission	Cardiac Injury	Shock	NIPPV	Invasive MV	CFR
Huang et al. [44]	41	32%	12%	7%	24%	5%	15%
Chen et al. [65]	99	23%	-	4%	13%	4%	11%
Wang et al.[43]	138	26%	7%	9%	11%	12%	-
Guan et al.[1]	1099	-	-	1%	5.1%	2.3%	1%
Yang et al.[42]	52	100%	23%	35%	55.8%	42.3%	62%
Zhou et al.[45]	191	26%	17%	20%	14%	17%	28%

CFR: case fatality rate; ICU: intensive care unit; NIPPV: non-invasive positive pressure ventilation

The prevalence of hypoxic respiratory failure in patients with COVID-19 is 19% [12]. Recent reports from China showed that 4% to 13% of COVID-19 patients in these studies received non-invasive positive pressure ventilation (NIPPV), and that 2.3% to 12% required invasive mechanical ventilation (**Table 3**) [1, 12, 42, 43, 65]. Although the true incidence of hypoxic respiratory failure in patients with COVID-19 is not clear, it appears that about 14% will develop severe disease requiring oxygen therapy, and 5% will require ICU admission and mechanical ventilation [12]. Another study reported on 52 critically ill COVID-19 patients; 67% of these patients had ARDS, 33 (63.5%) received high-flow nasal cannula (HFNC), 56% invasive mechanical ventilation, and 42% NIPPV [42].

Risk factors for respiratory failure

Risk factors associated with respiratory failure requiring mechanical ventilation are not clearly described in published reports, although from the limited available data, risk factors associated with a critical illness/ICU admission included older age (>60 years), male gender, and the presence of underlying comorbidities such as diabetes, malignancy, and immunocompromised state [1, 12, 42, 43]. The CDC reported an overall case-fatality rate (CFR) of 2.3%, with a CFR of 14.8% in patients aged 80 years or older. In critically ill patients, the CFR was 49.0%, and it was higher than 50% in those who received invasive mechanical ventilation. The presence of pre-existing comorbid conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer were associated with higher risk of death [12].

In a cohort of Middle East Respiratory Syndrome (MERS) patients, NIPPV was not associated with improved mortality or length of stay, compared with patients who were intubated without trying NIPPV [79]. However, NIPPV was associated with a high failure rate (92.4%), leading to intubation. Patients who received NIPPV prior to intubation had increased inhaled nitric oxide requirements and increased mortality [79]. Failure rates in other pandemics, such as influenza, H1N1 and SARS, range from 10% to 70%, while demonstrations of efficacy mainly come from case series and observational studies rather than RCTs, leading to practice variation. In China, the use of NIPPV for pandemic respiratory infection is common, whereas guidelines from Europe, Hong Kong, and the US advise against NIPPV as a first-line therapy in H1N1 [84]. There are additional concerns over the use of NIPPV in respiratory pandemics like COVID-19: NIPPV may aggravate severe forms of lung injury as a result of injurious transpulmonary pressures and large tidal volumes [85, 86], and may delay initiation of invasive mechanical ventilation, leading to emergency or more unstable intubations that can increase the risk of transmission to the healthcare team [85]. In addition, NIPPV is an aerosol-generating procedure that can increase the risk of transmission of disease to healthcare workers [29]. Several other studies and meta-analyses of SARS have also highlighted the risk of nosocomial spread of the disease with NIPPV [76, 87].

If NIPPV is used, helmet NIPPV is an attractive option, if available. A single-center RCT showed decreased intubation and improved mortality from NIPPV delivered by helmet in ARDS patients [90]. Of particular importance in the setting of a pandemic such as COVID-19, NIPPV by helmet has also been shown to reduce exhaled air dispersion, whereas face masks were insufficient [91]. However, helmet NIPPV is more expensive, and without direct evidence of benefit in COVID-19 patients, resources should not be utilized to acquire this equipment if is not already available.

Recommendation:

34. For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**, we **suggest** prone ventilation for **12 to 16 hours**, over no prone ventilation (weak recommendation, low quality evidence).

Rationale:

In a series of 81 patients with COVID-19, radiographic features progressed over the first 1 to 2 weeks after symptom onset from predominant ground glass opacities to a mixed pattern of predominant basilar consolidation. This latter pattern may suggest a role for prone ventilation [110].

Recommendation:

40. In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, we **suggest** using venovenous (VV) ECMO if available, or referring the patient to an ECMO center (weak recommendation, low quality evidence).

Cytokine Storm Syndrome

Cytokine storm syndrome is a hyperinflammatory state that is characterized by fulminant multi-organ failure and elevation of cytokine levels. A recent study from China showed that COVID-19 is associated with a cytokine elevation profile that is reminiscent of secondary hemophagocytic lymphohistiocytosis (HLH) [44]. Some authors even suggest that we screen critically ill COVID-19 patients for secondary HLH using the Hscore [140], and that corticosteroids and other immunosuppressive agents can be used in patients with a high likelihood of HLH [141]. More evidence is needed before we can make recommendations on the treatment options for cytokine storm.

Recommendations

41. In mechanically ventilated adults with COVID-19 and respiratory failure (**without ARDS**), we **suggest against** the routine use of systemic corticosteroids (weak recommendation, low quality evidence).

42. In mechanically ventilated adults with COVID-19 **and ARDS**, we suggest using systemic corticosteroids, over not using corticosteroids (weak recommendation, low quality evidence).

Rationale:

There are no controlled clinical trials on the use of corticosteroids in COVID-19 patients or other coronaviruses. A published, but not peer-reviewed, report of 26 patients with severe COVID-19 reports that the use of methylprednisolone at 1-2mg/kg/day for 5 to 7 days was associated with shorter duration of supplemental oxygen use (8.2 days vs. 13.5 days; $P<0.001$) and improved radiographic findings [142]. Although interesting, we judged these preliminary reports to be an insufficient basis for formulating recommendations, due to the risk of confounding. Therefore, we used indirect evidence from community acquired pneumonia, ARDS, and other viral infections to inform our recommendation.

It is widely recognized that corticosteroids have a range of adverse effects. In viral pneumonia in the ICU, several studies showed increase in viral shedding with corticosteroid use [151-153], potentially indicating viral replication, but the clinical implication of increased viral shedding is uncertain.

Considering the above, the panel issued a suggestion against the routine use of systemic corticosteroids for respiratory failure in COIVID-19, and a suggestion to use corticosteroids in the sicker population of COVID-19 with ARDS. If clinicians use corticosteroids in ARDS, they should use lower dosing and shorter treatment courses.

Recommendation:

43. In mechanically ventilated patients with COVID-19 and respiratory failure, we **suggest** using empiric antimicrobials/antibacterial agents, over no antimicrobials (Weak recommendation, low quality evidence).

Remark: if the treating team initiates empiric antimicrobials, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology results and the patient's clinical status.

Recommendation:

44. For critically ill adults with COVID-19 who develop fever, we **suggest** using acetaminophen/paracetamol for temperature control, over no treatment (Weak recommendation, low quality evidence).

The use of non-steroidal anti-inflammatory drugs to treat fever in patients with COVID-19 continues to be debated. Until more evidence is available, we suggest using acetaminophen/paracetamol to treat fever.

Recommendation

47. In critically ill adults with COVID-19:

47.1. we **suggest against** the routine use of lopinavir/ritonavir (weak recommendation, low quality evidence).

47.2. **There is insufficient evidence to issue a recommendation** on the use of other antiviral agents in critically ill adults with COVID-19.

A recent RCT compared the use of lopinavir/ritonavir to usual care in 199 hospitalized patients with COVID-19 in China [194]. In this trial, lopinavir/ritonavir did not significantly reduce 28-day mortality (RD, -5.8%; 95% CI, -17.3 to 5.7) or time to clinical improvement (MD 1.31 days, 95% CI 0.95 to 1.80). In addition, lopinavir/ritonavir was associated with more adverse events [194]. This trial is the only available direct evidence on the use of lopinavir/ritonavir in patients with COVID-19, however, it has several limitations. The trial was unblinded and it enrolled a small number of patients (n=199) with a small number of events (44 deaths in total), which limits our confidence in its results. Nevertheless, the routine use of lopinavir/ritonavir in critically ill patients is probably not warranted, and a weak recommendation against the routine use of lopinavir/ritonavir in critically ill COVID-19 patients is reasonable.
Lopinavir/ritonavir is one of the arms in a planned WHO core treatment protocol for hospitalized patients with COVID-19, and in the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial (NCT02735707) The results of ongoing trials will help increase the precision of estimates and the certainty in the evidence.

Remdesivir is the prodrug of an adenosine analog, which incorporates into nascent viral RNA chains and results in premature termination. It was considered the most promising drug in an informal consultation on research prioritization of candidate therapeutic agents by WHO [195]. Currently, there are published case reports but no published trials on the use of remdesivir in COVID-19. Remdesivir demonstrated effective inhibition of SARS-CoV-2, MERS-CoV, and SARS-CoV in *in vitro* studies [196]. Furthermore, studies in animal models of MERS-CoV showed that it was more effective than control and superior to lopinavir/ritonavir combined with systemic IFN-β [197, 198]. Although intravenous remdesivir appears to adequately tolerated, a recent RCT showed that it was less effective than several antibody therapies in Ebola virus disease [199]. There are several ongoing RCTs that aim to examine the efficacy and safety of intravenous remdesivir for severe COVID-19 (clinicaltrials.gov NCT04257656) and for mild and moderate COVID-19 (clinicaltrials.gov NCT04252664). Another trial sponsored by the National Institute of Allergy and Infectious Diseases is recruiting patients in USA (clinicaltrials.gov NCT04280705). We will update our guidelines as new evidence emerges.

Chloroquine and its metabolite, hydroxychloroquine, are antimalarial agents that have demonstrated antiviral effects on SARS-CoV and SARS-CoV-2 *in vitro* [207-209]. Prior studies found inhibitory effects of chloroquine for multiple RNA viruses *in vitro*, but RCTs in treatment of dengue and chikungunya virus infections and of influenza prophylaxis failed to demonstrate antiviral or clinical benefits [210]. In one non-human primate model of chikungunya infection, it was shown that chloroquine's immunomodulatory effects were associated with delayed immune responses, higher levels of viral replication, and worse illness [211]. A news briefing suggested that its use in more than 100 patients showed "that it was superior to the control in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course", but the data have not been published yet [212]. A recent consensus document recommended chloroquine phosphate 500 mg twice daily for minimum of 5 days, with dose modifications if severe gastrointestinal side effects occur [213]. Since chloroquine is not available in some countries, hydroxychloroquine is an alternative. A recent study in China explored various dosing regimens of chloroquine and hydroxychloroquine using physiologically-based pharmacokinetic models [209]. The study found hydroxychloroquine to be more potent than chloroquine in inhibiting SARS-CoV-2 *in vitro*. Based on these models, a hydroxychloroquine loading dose of 400 mg twice daily followed by 200 mg twice daily for 4 days was recommended [209].