Evidence Summary on High-Flow Nasal Cannula Oxygen Therapy for the Treatment of Acute Hypoxemic Respiratory Failure for COVID-19

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Background

What is COVID-19?

Novel coronavirus disease (COVID-19) is a disease caused by severe acute respiratory coronavirus 2 (SARS-CoV-2). Its symptoms include fever or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle or body aches, headache, loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, and diarrhea ([1]US Centers for Disease Control and Prevention, 2020). These symptoms may appear in people with COVID-19 after 2-14 days from exposure to the virus. COVID-19 can also be passed on through respiratory droplets and through surfaces. This then raises the concern for airborne spread during procedures that can generate aerosols which transmit infectious viral particles.

What are the possible complications of COVID-19?

Symptoms of COVID-19 may range from mild to critical COVID-19 infection. Within a week's time, the symptoms of a patient may progress to severe infection and several complications of COVID-19 may appear. A patient with COVID-19 may be further complicated with respiratory failure, specifically acute respiratory distress syndrome. This major complication can manifest shortly after the onset of dyspnea or difficulty in breathing. For critically ill COVID-19 patients, researchers found that they may be prone to have acute hypoxemic respiratory failure (or AHRF). AHRF prevents enough oxygen from going to the lungs and the blood.

Two respiratory support strategies may help COVID-19 patients with AHRF in their breathing, namely invasive and non-invasive ventilation. Invasive respiratory support delivers air directly to the lungs by inserting a tube through the mouth or the nose. Examples include mechanical ventilation or intubation. On the other hand, non-invasive respiratory support delivers air through a sealed mask, nasal prong, or cannula placed over the mouth, nose, or whole face. Some examples would be conventional oxygen therapy, high-flow nasal cannula, bi-level airway positive airway support, and continuous positive airway pressure.

What is a high-flow nasal cannula?

High-flow nasal cannula (HFNC) is a type of non-invasive equipment which supplies high flow rates of oxygen to improve breathing and respiratory support. By delivering high volumes of air, this displaces the excess carbon dioxide in the lungs with oxygen. The normal flow rates during quiet breathing is 30 liters per minute. Conventional oxygen

therapies can give flow rates of 15 liters per minute at a maximum, while high-flow nasal cannulas can provide up to 60 liters per minute.

Rapid review on high-flow nasal cannula

As evidence on COVID-19 rapidly evolve, the Health Technology Assessment Unit conducted a rapid review to synthesize the most recent information on the clinical effectiveness and safety, resource requirements and associated costs, and ethical and social impacts of high-flow nasal cannula when compared with other non-invasive ventilations for the treatment of acute hypoxemic failure in both COVID-19 and non-COVID-19 patients.

Policy Question

Should high-flow nasal cannula oxygen therapy for the treatment of acute hypoxemic respiratory failure among COVID-19 patients be recommended for expansion or investment by DOH and PhilHealth?

Research Questions

1. **Clinical Performance**

   ### Clinical effectiveness

   Among COVID-19 patients, is HFNC oxygen therapy more effective than other non-invasive ventilation in treating acute hypoxemic respiratory failure based on the following outcomes?

   - Mortality
   - Failure of respiratory support (escalation to invasive ventilation)
   - Length of hospital stay
   - Length of intensive care unit (ICU) stay

   ### Clinical safety

   Among COVID-19 patients, is HFNC oxygen therapy safer than other non-invasive ventilation in treating acute hypoxemic respiratory failure based on risk of aerosolization of respiratory droplets?

   ### Clinical guidelines and evidence synthesis on use of HFNC

   Which countries have implemented HFNC oxygen therapy for the treatment of acute hypoxemic respiratory failure among COVID-19 patients?

What is the current position and/or recommendation of HTA agencies regarding the use of HFNC oxygen therapy for the treatment of acute hypoxemic respiratory failure among COVID-19 patients?

2. **Resource Requirements and Associated Costs**

   What are the resource requirements and associated costs on the use of HFNC or other non-invasive ventilation in treating COVID-19 patients with acute hypoxemic respiratory failure?

3. **Ethical and Social Impact Assessment**

   What are the ethical and social issues on the use of HFNC among COVID-19 patients with acute hypoxemic respiratory failure?

Responsiveness to Disease Magnitude, Severity, and Equity

COVID-19 Situational report

In early 2020, the World Health Organization (WHO) declared COVID-19 as a global pandemic affecting more than 220 countries and regions. As of 30 November 2020, they have recorded at least 62,363,527 COVID-19 cases and 1,456,687 confirmed deaths worldwide. In the Philippines, there have been 429,864 COVID-19 cases with 8,373 deaths as of 30 November 2020. To date, there is no known treatment for SARS-CoV-2.

As scientists draw near to discovering the cure for COVID-19, different respiratory support strategies are currently used to manage COVID-19 complicated with acute respiratory distress syndrome. The Health Professional Alliance Against COVID-19 (HPAAC), an alliance of different medical societies, came up with a way to determine when to use non-invasive or invasive respiratory support for COVID-19. In its unified algorithm dated 7 November 2020, HPAAC advised to start oxygen support therapy to an adult patient with COVID-19 pneumonia with respiratory symptoms or distress.

PhilHealth covers additional medical services needed by COVID-19 patients with critical pneumonia. In addition, the Department of Health recently funded the purchase of 200 units of HFNC in an effort to address the needs of COVID-19 patients.

Key findings of rapid review: Ethical and social impact

Participants of an online survey and small group discussion are more comfortable to undergo a respiratory support procedure recommended by their doctors. Regardless of the defined clinical benefit of HFNC, they showed willingness to pay for a non-invasive respiratory strategy such as HFNC. Moreover, they are willing to pay an additional cost, even out of pocket spending, to prevent early intubation. Some individuals prefer transferring facilities or hospitals to receive their preferred procedure. Their decision-making may have been affected by the fear of intubation, and the fear of immobility which would entail additional expenses for the family and a decreased quality of the patient's life.

It is important to communicate and educate patients on different respiratory support strategies, and ensure family support to alleviate the patient's fear and anxiety in using these interventions. From a patient group's perspective, the government should fund HNFC and should only disinvest when there is proof that HFNC is not effective.

Overall, participants of the survey and small group discussion have not identified any legal, religious, or cultural issues which can stop a patient from receiving a non-invasive respiratory procedure.

Safety and Effectiveness

The HTA Unit collected information based on review of rapid and systematic reviews, locally conducted studies not covered in rapid and systematic reviews, and evidence from expert consultation.

Key findings of rapid review: Review of Evidence on Clinical Safety and Effectiveness

1. **Review of Reviews**

Clinical Effectiveness

Mortality outcome

COVID-19 patients: One local review by Villanueva et al. (2020) reported lower mortality (range of values: 0-81%) among COVID-19 patients given HFNC when compared to those using other non-invasive ventilation (range of values: 4.5- 92.0%). The review also noted that the included studies have variable study designs, lacked comparison groups, controls for confounders, and have potentially unequal baseline patient characteristics. Because of these limitations, they reported that results are inconclusive.

Non-COVID-19 patients: Among immunocompromised patients, a 2018 study by Sklar et al. reported a pooled risk ratio on mortality rate of 0.60 (95% confidence interval: 0.37-0.97, p=0.04) when compared to other non-invasive ventilation. Given this, HFNC use has significantly reduced (40%) the risk for mortality when compared with other non-invasive strategies. The authors also reported moderate heterogeneity (52%) of the subgroup analysis done for HFNC and other non-invasive ventilation. They also did not report results for publication bias and assessment using the GRADE tool. Caution should be taken in the interpretation of the pooled estimates since the included studies differ in study design.

Outcome for failure of respiratory support (escalation to invasive ventilation)

COVID-19 patients: There is a higher failure of initial respiratory support in the group given HFNC compared to patients given other non-invasive strategies, according to the 2020 study by Villanueva et al. The review also noted that the included studies have variable study designs, lacked comparison groups, controls for confounders, and have potentially unequal baseline patient characteristics. Because of these limitations, they reported that results are inconclusive.

Non-COVID-19 patients:

- Among immunocompromised patients, the 2018 study by Sklar et al. reported a pooled risk ratio of 0.67 (95% confidence interval: 0.43-1.04, p=0.07) on the intubation rate when HFNC is compared to other non-invasive ventilation. Given this, HFNC use was considered tending to benefit but not statistically significant. The authors also reported high heterogeneity (68%) of the subgroup analysis done for HFNC and other non-invasive ventilation. Caution should be taken in the interpretation of the pooled estimates since the included studies differ in study design.

- Regardless of the pre-existing conditions of patients, the 2018 study by Xu et al. reported a pooled odds ratio of 0.57 (95% confidence interval: 0.36-0.92, p=0.02) for groups given HFNC versus those given non-invasive strategies. The HTA Unit noted this to be statistically significant.

Outcome for length of hospital stay

For both COVID-19 and non-COVID-19 groups, the HTA Unit did not find any study comparing the length of hospital stay for patients given HFNC as compared to those given other non-invasive ventilation.

Outcome for length of ICU stay

For both COVID-19 and non-COVID-19 groups, the HTA Unit did not find any study comparing the length of ICU stay for patients given HFNC as compared to those given other non-invasive ventilation.

Critical Appraisal in rapid review

COVID-19 patients: The studies did not report the results of the risk of bias assessment, and the quality of studies for COVID-19 patients is generally unknown.

Non-COVID-19 patients: The randomized controlled trials for the non-COVID-19 patients reported a highly varied risk of bias using the Cochrane Risk of Bias (RoB) tool. Observational studies, on the other hand, have generally low risk of bias based on the Newcastle-Ottawa Scale for Observational Studies.

The HTA Unit performed a critical appraisal on included systematic reviews using AMSTAR 2 and reported their quality to be critically low. Included studies failed to explicitly report on the following:

- Protocol registration before review commencement
- Justifications for exclusion of individual studies.
- Risk of bias considerations for results interpretation
- Assessment of presence and likely impact of publication bias

They also devised a checklist based on the Cochrane Rapid Review Interim Guidance to see if the rapid review by Villanueva et al. (2020) is aligned with the DOH HTA Methods Guide. The said rapid review was reported to adhere to the guidelines on the study objectives,

search and information sources, data extraction, and synthesis of results, fulfilling four out of nine items in the checklist.

At present, the HTA Unit reported that there is insufficient evidence showing the conclusive advantage of HFNC for treating AHRF among COVID-19 patients when compared to other non-invasive ventilation. For the non-COVID-19 groups, HFNC use shows a lower risk of mortality based on one systematic review for immunocompromised patients, versus the use of other non-invasive ventilation. Evidence remains conflicted on the ability of HFNC to lower the rate of intubation based on two systematic reviews. The included studies did not report on the length of hospital and ICU stay.

Clinical safety against aerosol generation

COVID-19 patients: The HTA Unit did not find any reviews on the safety of HFNC based on the aerosolization of respiratory droplets.

Non-COVID-19 patients: At present, the HTA Unit reported that there is insufficient evidence establishing the clinical safety of HFNC. The rapid review also mentioned a study that reported that the increase of pressure (for CPAP) or flow rate (for HFNC) would also increase the distance traveled by respiratory droplets.

The quality of evidence in the systematic review by Agarwal et al. 2020 was also found to be critically low. The reviewers also observed similar commonly reported critical flaws for the studies, as discussed above.

2. Review of Local Studies

COVID-19 patients: The HTA Unit did not find any local studies which show the relative treatment effects of HFNC versus other non-invasive modalities. The studies on the HFNC being conducted by four public hospitals is expected to be completed by December 2020 or early 2021.

Non-COVID-19 patients: The randomized clinical trial by See et al. from the Philippine Heart Center reported that HFNC did not demonstrate superior advantage over non-invasive positive pressure ventilators, in terms of ICU mortality, rate of intubation, and length of hospital stay. Following a critical appraisal of the clinical trial, the reviewers reported a high risk of bias.

3. **Evidence from Expert Opinion**

Most local experts (8 of 12 experts) consulted use HFNC for COVID-19 patients with AHRF that do not need immediate intubation. They also observed that patients are more comfortable with HFNC use than mechanical ventilation.

The assessment team also collected slightly varied opinions on risk of aerosol generation spread with HFNC use, and on the need for negative pressure rooms. The team reports that one expert does not see the risk for aerosol generation, while two experts said that HFNC use poses this risk relatively lower than for the risk for other non-invasive ventilation. Due to perceived risk of aerosolization, three experts also recommend using negative pressure system rooms with a heating, ventilation, and air conditioning system, or isolating COVID-19 patients in a single room.

Key findings of rapid review: Clinical Guidelines on HFNC Use

The rapid review reported that the treatment guidelines from China, the Philippines, the United States, and Vietnam positively recommended HFNC, but with conditions for its use. The treatment guidelines from the United Kingdom did not recommend the use of HFNC. Meanwhile, the WHO, Canada, Indonesia, Japan, Australia, and Malaysia listed several conditions where HFNC should be or should not be used.

Key findings of rapid review: Findings and Recommendations of HTA Agencies

Of the 13 HTA agencies reviewed by the HTA Unit, none have completed assessing HFNC for COVID-19 patients with AHRF.

Household Financial Impact

Evidence not reviewed.

Cost-effectiveness

Evidence not reviewed.

Affordability and Viability

Key findings of rapid review: Resource requirements and associated costs

Based on the responses of private and public hospitals in a standard questionnaire and an online consultation on the requirements for human resource, training, consumables, infrastructure, projected costs and implementation concerns of HFNC, they identified the following resources in using HFNC:

- Support of a pulmonologist, nurse and respiratory therapist. Minimal training is required.
- Machines, consumables (such as heated tubes and autofill chamber kit, nasal cannula, sterile water, sterile mask, complete personal protective equipment, ultraviolet light, and humidifier), and oxygen supply
- Facilities equipped with separate wards and isolation rooms, and disinfection procedures to prevent spread due to the possible risk of aerosol generation.

Oxygen source: Wall-mounted versus tank-pipe system

There are mixed expert opinions on the recommended oxygen source for HFNC. Some experts noted that the oxygen source should be wall-mounted; however, one expert shared that the HFNC machine can also be connected to a standard oxygen cylinder (tank).

Negative pressure room system

Two hospitals require that COVID-19 patients be placed in a separate room with a negative pressure system. However, for one hospital which does not have negative pressure rooms, such special rooms were not made a requirement for the use of HFNC.

Costs

Costs for HFNC differ depending on the severity of a patient and the duration of treatment. Established evidence on the treatment duration is still limited. The reviewers cannot directly compare the costs of HFNC versus other non-invasive modalities.

Patients may need to pay a projected initial cost ranging from Php 10,000.00 to Php 13,000.00. Meanwhile, the use of other non-invasive respiratory strategies may cost from Php 6,754.00 to 14,549.25. One public hospital charges the same rates for HFNC with flow rates of 9-10 liters per minute and flow rates greater than 10 liters per minute.

Patients may also need to pay for daily costs for consumed oxygen, rental fees for machine use, and consumed sterile water for injection. The daily rate of HFNC machine use ranges from Php 1,100.00 to 2,030.00. On the other hand, the daily rental of machines used for other non-invasive ventilatory support amounts from Php 1,840.00 to Php 2,860.00. For non-

invasive respiratory strategies, bacterial filters will need to be replaced every 2 to 3 days, and its cost can add on the charged expenses.

HTA Council Interim Recommendation

Based on currently available evidence, the HTA Council **recommends to continue funding** high-flow nasal cannula. It may be used as a treatment option for COVID-19 patients with acute hypoxemic respiratory failure, **provided that these requirements are met:**

- In recognition of limited clinical evidence on the use of HFNC for COVID-19 patients, all patients on HFNC should be enrolled in a national registry and be part of a national study. This will support generation of evidence in the local setting.
- In view of the limited evidence on the aerosol generation potential of HFNC, facilities should be equipped with negative pressure rooms and adequate personal protective equipment (PPEs) for all frontline carers.
- Facilities should have a wall-mounted oxygen source.

The HTA Council shall update its recommendation once the ongoing local studies become available regarding its clinical effectiveness and safety.

References

[1] US Centers for Disease Control and Prevention. (2020, May 13). *Symptoms of Coronavirus*. https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html

Note: Other references cited in this summary document are lifted from the adopted report.