Non-invasive ventilation and heated humidified high-flow oxygen therapies for severe COVID-19: Rapid Evidence Report
4 October 2021
Prepared for Respiratory Health Section (Medicine Strategic Clinical Network™), Alberta Health Services

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Executive Summary

The Coronavirus Disease 2019 (COVID-19) pandemic has placed enormous stress on acute care systems around the world. Mild disease in adults results in influenza-like illness (fever, chills, cough, and sore throat), while severe disease results in pneumonia and acute respiratory distress that requires hospitalization and in the worst cases, intensive care with mechanical ventilation. Based on experience with non-COVID respiratory disease, patients with severe disease early in the pandemic received mechanical ventilation as soon as possible; however, as the research advanced, it became clearer that early intubation was not necessarily the best treatment for COVID-19 pneumonia and acute respiratory distress. This review was commissioned by the Respiratory Health Section of the Medicine Strategic Clinical Network (MSCN) to synthesize current evidence on non-invasive ventilation (NIV) and heated humidified high-flow oxygen (HHHFO) for severe COVID-19 to update Alberta Health Services (AHS) provincial guidance for adults hospitalized with COVID-19.

This review was initially proposed as two separate reviews; accordingly, two sets of research questions and PICOS were designed. The questions to be addressed are below.

**Heated Humidified High-Flow Oxygen and COVID**
1. Does HHHFO have clinical benefit for adult COVID-19 patients, and for how long, before the patient requires mechanical ventilation?
2. What are the characteristics of adult COVID-19 patients who may benefit from HHHFO? (Are there differences between patient subgroups associated with greater or worse outcomes)
3. What signs or symptoms indicate that an adult COVID-19 patient requires mechanical ventilation instead of receiving HHHFO?

**Non-invasive Ventilation for Acute COVID-related Hypoxemia or Respiratory Failure**
1. What is the clinical effectiveness of NIV (i.e., CPAP or Bilevel PAP), compared to HHHFO or intubation, for adult inpatients with acute COVID-related hypoxemia/respiratory failure?
2. Under what clinical conditions and in what inpatient setting is NIV more appropriate than HHHFO or intubation for managing adults with acute COVID-related hypoxemia/respiratory failure?
3. What are the risks associated with NIV for adult inpatients with acute COVID-related hypoxemia/respiratory failure compared to HHHFO or intubation?

The literature search was conducted by Knowledge Resource Services (KRS) within the Knowledge Management Department of Alberta Health Services. As this review was initially conceptualized as separate reviews, three searches were conducted with the following foci: HHHFO and COVID-19; ventilation and COVID-19; and NIV and COVID-19. KRS searched databases for English language papers published from 2020 to 2021 and included: Ovid Medline, Embase, and CINAHL. Guidelines and grey literature were limited to the United Kingdom, Australia, New Zealand, United States, Canada, European Union, and the World Health Organization. 933 articles were identified by KRS with references and abstracts provided for further review. Following two rounds of screening according to pre-determined inclusion or exclusion criteria, 15 articles from the literature search were selected for inclusion. Hand searching identified one additional primary study and four guidelines. In total, 21 articles were included in the final narrative synthesis.

This review was limited by several factors that must be considered when assessing the findings. First, this is a rapid review. The search was thorough, but not systematic. In addition, the search was limited to literature published in English in the past 2 years. For these reasons, it is possible that relevant studies were not captured in the database search.

As with most reviews of COVID-19-related evidence, this review is limited by the lack of controlled trial evidence. Observational studies cannot show causation, only association; thus, it is difficult to determine if the intervention being studied truly has clinical benefit or if benefit is due to the characteristics of the patient. These studies also suffer from the rapid pace of COVID-19 research, where studies are haphazardly designed with little attention paid to limiting bias. As a result, the studies included in this review are at high risk of bias from confounding.
With respect to the body of evidence, the terminology around high-flow oxygen is not standardized, which makes searching for grey literature challenging. The most common terms include “high flow nasal cannula”, “high flow nasal oxygen”, “heated humidified high-flow nasal cannula”, “heated humidified high-flow oxygen”, and “high-flow oxygen”. It is therefore difficult to determine if each term refers to the same systems and mode of therapy.

Based on the evidence presented in the synthesis above, the following conclusions can be made:

- The body of evidence on this topic is estimated to be of low quality. It is largely cohort studies at high risk of confounding, and guidance based on this review should acknowledge this limitation.
- No peer-reviewed RCTs were identified to address the research questions specifically relating to CPAP and Bilevel PAP as therapy for COVID-19.
- Guidelines from the WHO, Europe, UK, USA, and Australia unanimously recommend using non-invasive oxygen therapy (such as high-flow nasal cannula, CPAP, or Bilevel PAP) in hypoxemic patients requiring oxygen supplementation but for whom invasive mechanical ventilation is not yet indicated.
- The principal risk to patients arising from non-invasive oxygen supplementation in COVID-19 appears to be delayed intubation, which can be mitigated by close monitoring and not trying to rescue respiratory function with additional non-invasive therapy or positioning once therapy failure has been determined.
- One RCT found that early oxygen therapy via high-flow nasal cannula (HHHFO) resulted in significantly better respiratory rate, heart rate, and PaO₂/FiO₂ at 6 hours post treatment initiation compared to conventional oxygen therapy. Observational studies support this finding and show that non-invasive ventilation can reduce the ICU length of stay and ventilator-free days, but is not necessarily associated with a decrease in mortality.
- Benefit from non-invasive therapies is associated with early intervention, rather than with patient characteristics. The need for intubation is influenced by the patient’s physiological and biochemical characteristics. NIV as a therapy is not clearly associated with reduced need for mechanical ventilation.
- No direct evidence was identified that described best practices for identifying when to move a patient to mechanical ventilation from non-invasive ventilation. The ROX index score is a valid prognostic measure of HHHFO success or failure. ROX index values below 5.5 that do not increase over time (up to 16 hours after start of HHHFO therapy, or limited response within the first 6 hours) are strongly associated with increased risk of intubation, while patients who did not require intubation had a ROX index value above 5.5 at baseline that increased as therapy continued.
Background

The Coronavirus Disease 2019 (COVID-19) pandemic has placed enormous stress on acute care systems around the world. Mild disease in adults results in influenza-like illness (fever, chills, cough, and sore throat), while severe disease results in pneumonia and acute respiratory distress that requires hospitalization and in the worst cases, intensive care with mechanical ventilation (Alberta Health, 2021). Due to the novelty of the disease, the clinical management of COVID-19 patients has evolved rapidly as research becomes available and the natural history of the disease becomes clearer.

Based on experience with non-COVID respiratory disease, patients with severe disease early in the pandemic received mechanical ventilation as soon as possible; however, as the research advanced, it became clearer that early intubation was not necessarily the best treatment for COVID-19 pneumonia and acute respiratory distress (AHS Scientific Advisory Group, 2020). This review was commissioned by the Respiratory Health Section of the Medicine Strategic Clinical Network (MSCN) to synthesize current evidence on non-invasive ventilation (NIV) and heated humidified high-flow oxygen (HHHFO) for severe COVID-19 to update Alberta Health Services (AHS) provincial guidance for adults hospitalized with COVID-19.

Research Questions

The following research questions were formulated based on the PICO framework. These questions were used as a basis for the literature search. Initially, these two topics were proposed as two separate reviews; upon discussions with the requestor and with the manager of the Respiratory Health Section of the MSCN, it was agreed that it would be useful to package the two reviews together as they address similar questions and would use very similar searches. The research questions and PICOS frameworks are included below.

Section 1: Heated Humidified High-Flow Oxygen and COVID

1. Does HHHFO have clinical benefit for adult COVID-19 patients, and for how long, before the patient requires mechanical ventilation?
2. What are the characteristics of adult COVID-19 patients who may benefit from HHHFO? (Are there differences between patient subgroups associated with greater or worse outcomes)
3. What signs or symptoms indicate that an adult COVID-19 patient requires mechanical ventilation instead of receiving HHHFO?

<table>
<thead>
<tr>
<th>Population</th>
<th>Adult inpatients (&gt; 18) with COVID-induced hypoxemia or COVID-induced hypoxic respiratory failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Use of heated humidified high-flow oxygen therapy (i.e. OptiFlow, AIRVO, Vapotherm)</td>
</tr>
<tr>
<td>Comparator</td>
<td>Mechanical ventilation earlier in the care pathway (any therapy prior to intubation)</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Any outcomes are of value, especially prevention of intubation and/or resolution of hypoxemia</td>
</tr>
<tr>
<td>Study Types</td>
<td>Any - all experimental and quasi-experimental (RCTs, non randomized trials, before and after, time series, etc), observational (cohort and case control) as well as secondary (systematic reviews and meta analyses), guidelines</td>
</tr>
</tbody>
</table>

Section 2: Non-invasive Ventilation for Acute COVID-related Hypoxemia or Respiratory Failure

1. What is the clinical effectiveness of NIV (i.e., CPAP or Bilevel PAP), compared to HHHFO or intubation, for adult inpatients with acute COVID-related hypoxemia/respiratory failure?
2. Under what clinical conditions and in what inpatient setting is NIV more appropriate than HHHFO or intubation for managing adults with acute COVID-related hypoxemia/respiratory failure?
3. What are the risks associated with NIV for adult inpatients with acute COVID-related hypoxemia/respiratory failure compared to HHHFO or intubation?

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Non-Invasive Respiratory Therapies for Severe COVID-19

Population
Adult inpatients (stratify for medicine vs. intensive care units)

Intervention
Use of non-invasive ventilation (CPAP or Bilevel PAP) for management of COVID-related hypoxemia or respiratory failure

Comparator
Compared to HHF0 and/or intubation

Outcomes
Time to recovery, morbidity (e.g., work of or difficulty breathing), mortality

Study Types
Randomized controlled trials
Grey literature: guidelines; position statements; recommendations; guidance documents

Literature Search Strategy

The literature search was conducted by Knowledge Resources Services (KRS) within the Knowledge Management Department of Alberta Health Services. As this review was initially conceptualized as separate reviews, three searches were conducted with the following foci: HHHFO and COVID-19; ventilation and COVID-10; and NIV and COVID-19. A brief grey literature search was conducted by the librarian and was supplemented with hand-searching by the analyst.

KRS searched databases for English language papers published from 2020 to 2021 and included: Ovid Medline, Embase, and CINAHL. Guidelines and grey literature were limited to the United Kingdom, Australia, New Zealand, United States, Canada, European Union, and the World Health Organization. The full search strategy is included in the appendix of this report. Briefly, the following combinations of concepts were used to design the search:

- KRS filter for COVID-19
- Clinical outcomes (e.g. length of stay, disease progression, risk assessment)
- Respiratory support (e.g. mechanical ventilation, CPAP, BiPAP, non-invasive ventilation, high-flow oxygen)

Articles identified by KRS in their search were initially screened by title against the inclusion/exclusion criteria listed in Tables 1 and 2 below. 933 articles were identified by KRS with references and abstracts provided for further review. 738 articles were excluded from the review at the title and abstract stage. A further 180 (165 after de-duplication) were excluded after full-text review in accordance with the inclusion/exclusion criteria stated below. 15 articles from the literature search were selected for inclusion. Hand searching identified one additional primary study and four guidelines. In total, 21 articles were included in the final narrative synthesis. A flow diagram of identified studies is included in Figure 1.

Inclusion and Exclusion Criteria

The Analyst screened titles and abstracts of the search output and evaluated the selected full-text publications for final article selection using predefined inclusion and exclusion criteria. The criteria are defined below:

Table 1. Inclusion and exclusion criteria for Section 1 (HHHFO for COVID-19)
Non-Invasive Respiratory Therapies for Severe COVID-19

**Table 2. Inclusion and exclusion criteria for Section 2 (NIV for Acute COVID-related Hypoxemia or Respiratory Failure)**

<table>
<thead>
<tr>
<th>Inclusion criteria</th>
<th>Exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peer-reviewed data and grey literature (see below) published after August 1, 2020</td>
<td>Pre-prints; published before Aug 1, 2020</td>
</tr>
<tr>
<td>Adult inpatients (&gt; 18) with COVID-19 and COVID-induced hypoxemia or hypoxic respiratory failure</td>
<td>Not adults; not inpatient setting; non-COVID patients with hypoxemia or hypoxemic respiratory failure</td>
</tr>
<tr>
<td>Intervention: Non-invasive ventilation: CPAP or Bilevel PAP</td>
<td>Other oxygen therapy as intervention or comparator</td>
</tr>
<tr>
<td>Comparators: HHHFO or intubation</td>
<td></td>
</tr>
<tr>
<td>Outcomes: time to recovery, morbidity, mortality</td>
<td></td>
</tr>
<tr>
<td>Randomized controlled trials</td>
<td>Any other non-randomized experimental or observational study designs; Commentaries, Letters, Opinions, Animal Studies, modelling study, non-randomized evaluation study</td>
</tr>
<tr>
<td>Grey literature: guidelines; position statements; recommendations; guidance documents</td>
<td></td>
</tr>
</tbody>
</table>
Figure 1. PRISMA\(^1\) Flow diagram of the identified studies. 21 articles were included in this rapid review.

Evidence Summary

The database search yielded 933 citations published between 2020 and 2021. Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment. After both rounds of screening, 15 articles were retained for inclusion and six articles were identified for inclusion by hand-searching.

Although no formal quality appraisal was conducted for this review, the evidence for this topic can be estimated to be of low quality. As COVID-19 is a novel disease, clinical studies are often designed haphazardly and performed quickly. Further, the body of knowledge regarding management and treatment has evolved over time. From the evidence identified here, the effect of adjunctive steroid and antiviral treatment and prone positioning to supplement to non-invasive oxygen therapy in severe COVID-19 is unclear. Clinical trials of medications for COVID-19 were excluded from this review, and prone positioning has been previously reviewed by the AHS Scientific Advisory Group on COVID-19. In the evidence included here, patients are receiving the standard of care as determined by the medical institution providing care according to the evidence available during the study period.

As described above, the two topics addressed here were originally conceptualized as two separate reviews; accordingly, they have separate PICOS charts and inclusion/exclusion criteria. Importantly, different study types were accepted for the two topics: any study type was accepted for the research questions on HHHFO, while only RCTs and guidelines were accepted for the research questions on CPAP and Bilevel PAP.

Grey literature for non-invasive respiratory therapies

Sixteen pieces of grey literature were retrieved by the librarian for this review. Fifteen articles were excluded, and an additional five guidelines were identified by hand searching, for a total of six included guidelines in the narrative synthesis. The extracted sections from each guideline are included below in Table 4.

The principal risk to patients arising from use of non-invasive respiratory therapies in COVID-19 appears to be delayed intubation. Most of the guidelines made a specific recommendation that mechanical ventilation should be initiated without delay (i.e. without attempting to rescue respiratory function with less-invasive therapies or positioning) and should be achieved by closely monitoring the patient while they are receiving non-invasive respiratory support (Chalmers et al., 2021; National COVID-19 Clinical Evidence Taskforce, 2021; Messer et al., 2021; WHO, 2021; National Institutes of Health, 2021). The British Thoracic Society describes non-invasive respiratory support failure as: limited initial response within 6h, lack of improvement within 3 days, unchanged/increasing work of breathing, and not tolerating CPAP/NIV breaks (Messer et al., 2021). The guidance also noted the potential for COVID-19 transmission to hospital staff because of the aerosol-generating nature of some non-invasive ventilation strategies (Chalmers et al., 2021; National COVID-19 Clinical Evidence Taskforce, 2021). Appropriate personal protective equipment (PPE) should be worn by healthcare providers according to local guidance and practice.
Primary literature for non-invasive respiratory therapies

Heated Humidified High-Flow Oxygen and COVID

Fourteen articles were identified that met the inclusion criteria for the research questions regarding HHHFO treatment for COVID-19. One study was an RCT (Teng et al., 2020) and the remaining thirteen were cohort studies (7 retrospective, 6 prospective). The evidence from each article is included in Table 3 below.

Does HHHFO have clinical benefit for adult COVID-19 patients, and for how long, before the patient requires mechanical ventilation?

The RCT identified in the literature search showed that early oxygen therapy via high-flow nasal cannula (HHHFO) resulted in significantly better respiratory rate (RR), heart rate (HR) and PaO2/FiO2 at 6 hours post treatment initiation compared to conventional oxygen therapy (Teng et al., 2020). Despite no differences in patient characteristics at baseline, patients who were treated with HHHFO had a higher PaO2/FiO2 and lower respiratory rate at 24 and 72 hours compared to patients receiving conventional oxygen therapy (Teng et al., 2020).

One cohort study was identified that compared patients admitted to the intensive care unit (ICU) who received either high-flow nasal oxygen (HHHFO) within the first 24 hours or early invasive mechanical ventilation within the first 24 hours (Mellado-Artigas et al, 2021). HHHFO was associated with an increase in ventilator-free days (mean difference 8.0 days; 95% CI 4.4 to 11.7 days), a reduction in ICU length of stay (mean difference -8.2 days; 95% CI -12.7 to -3.6 days) and a 38% intubation rate (compared to an expected 100% rate in the comparator group) (Mellado-Artigas et al., 2021). In a study of elderly patients with confirmed COVID-19, those who received early HHHFO treatment (200 mmHg < PO2/FiO2 ≤ 300 mmHg) instead of conventional oxygen therapy were less likely to develop secondary infection pneumonia, or severe respiratory distress and were less likely to have an ICU stay longer than 7 days (Deng et al., 2021)

Like Mellando-Artigas (2021), Wendel Garcia et al. (2021), in an international patient cohort, found that non-invasive ventilation (NIV) was independently associated with higher overall ICU mortality (adjusted HR 2.67, 95% CI [1.14–6.25]) as well as with an increased ICU mortality rate (adjusted HR 2.96, 95% CI [1.07–8.23]) and a prolonged length of ICU stay (adjusted HR 0.57, 95% CI [0.33–0.97]) in patients failing NIV and requiring IMV. This was hypothesized by the authors to be due to longer periods of harmful spontaneous breathing and possibly delaying mechanical ventilation (Wendel Garcia et al., 2021).

No difference was observed in all-cause in-hospital mortality between groups (OR 0.64; 95% CI 0.25 to 1.64) (Mellado-Artigas et al., 2021). Likewise, the prospective cohort study by Franco et al. (2020) also found that HNFC had no significant reduction in risk of 30-day mortality, intubation, or length of hospital stay compared to other NIV modes. Conversely, another study by Palacios Chavarria et al. (2021) found that the HFNC success rate, defined as patients who did not require IMV, was 71.4% (n = 270; 95% CI 66.6–75.8) compared with 28.6% (n = 108; 95% CI 24.2–33.4) of patients who required IMV. Panadero et al. (2020) and Patel et al. (2020) also report higher mortality in patient groups requiring intubation; however, this likely reflects the severity of illness in this patient group, not an effect of the non-invasive treatment.

What are the characteristics of adult COVID-19 patients who may benefit from HHHFO? (i.e. Are there differences between patient subgroups associated with greater or worse outcomes)

Many of the cohort studies included in this review differentiated their patient groups as HFNO success and HFNO failure. Because of the study designs identified in the evidence, it is very difficult to determine if patients who are successful on high-flow therapy due to the therapy itself or because they had less severe disease. Beduneau (2021) notes that intubated patients more frequently had diabetes; however, this does not suggest that they do not benefit from HHHFO.
The RCT by Teng (2020) suggests that initiating therapy before COVID-19 pneumonia becomes too severe might be the determining factor of NIV success, as there was no difference in age, gender, onset of symptoms, or underlying disease between the two groups. This is supported by a cohort study by Long et al. (2020), who found that initiation of oxygen treatment more than 2 days after onset of hypoxia symptoms (OR, 1.92; 95% CI, 1.20 to 3.10) was significantly associated with the risk of death, and by Menga (2021), who found no difference between individuals with early or late NIV failure. Carillo Hernandez-Rubio (2020) states this clearly: physiological and biochemical factors influence a patient’s need for intubation – NIV as a therapy is not associated with reduced need for mechanical ventilation.

What signs or symptoms indicate that a COVID-19 patient requires mechanical ventilation instead of receiving HHHFO?

No direct evidence was identified that described best practices for identifying when to move a patient to mechanical ventilation from non-invasive ventilation.

Patients who were successful on HHHFO (i.e. did not require mechanical ventilation) had consistently higher PO$_2$/FiO$_2$ values at HFNC initiation (at least 100 mmHg) than those who failed HFNO (Beduneau et al., 2021; Hu et al., 2020; Vianello et al., 2020). They also had lower serum lactate dehydrogenase (LDH), higher creatinine, and lower values of PCO$_2$ and bicarbonate in the arterial-blood gas test before starting HFNC (Menga et al., 2021; Panadero et al., 2020).

The ROX index appears to be a useful measure for estimating the success or failure of high-flow oxygen therapy. ROX index values below 5.5 that do not increase over time (up to 16 hours) is strongly associated with increased risk of intubation (Palacios Chavarria et al., 2021; Panadero et al., 2020). Patients who did not require intubation had an increasing ROX index value above 5.5 at baseline and increasing as therapy continued is a good predictor of NIV success (sensitivity of 61.1%, a specificity of 84.6%, a positive predictive value of 68.8%, a negative predictive value of 79.8%) (Palacios Chavarria et al., 2021; Hu et al., 2021). ROX has been shown independently to be a valid predictor of intubation risk in patients with COVID-19 pneumonia (Suliman et al., 2021).

The SAPS II score also appears to be associated with NIV failure – patients with a higher median SAPS II score (39 (28 to 50) vs. 27 (22 to 31), P = 0.0031) (Beduneau et al., 2021) had a slightly higher risk of requiring intubation than those with a lower SAPS II score (adjusted hazard ratio per unit increase 1.039 [95% CI 1.018–1.061], P < .001) (Menga et al., 2021)

Non-invasive Ventilation for Acute COVID-related Hypoxemia or Respiratory Failure

No RCTs were identified that addressed the research questions for this review (stated below). The evidence from the identified guidelines is described above.

1. What is the clinical effectiveness of NIV (i.e., CPAP or Bilevel PAP), compared to HHHFO or intubation, for adult inpatients with acute COVID-related hypoxemia/respiratory failure?
2. Under what clinical conditions and in what inpatient setting is NIV more appropriate than HHHFO or intubation for managing adults with acute COVID-related hypoxemia/respiratory failure?
3. What are the risks associated with NIV for adult inpatients with acute COVID-related hypoxemia/respiratory failure compared to HHHFO or intubation?
Table 3. Data extraction table of included studies for the research questions respecting HHHFO. Where possible, statements were copied verbatim from the reference text.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Population</th>
<th>Intervention or Exposure</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
</table>
| Beduneau et al., 2021              | Retrospective cohort study | All consecutive patients admitted to these two ICUs during the 28 days following the first SARS-CoV-2 pneumonia admission on March 13th, 2020. Diagnosis of SARS-CoV-2 pneumonia was based on clinical characteristics, chest imaging and real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay | HFNC success (intubation not required)                                               | HFNC failure (intubation required)                                         | - Twenty-nine (67%) patients were not intubated while 14 (33%) were intubated  
- Intubated patients more frequently had diabetes (43% vs. 10%, P = 0.04).  
- Patients with extensive lesions at chest CT (≥ 25%) were more frequently intubated during ICU stay (P = 0.012).  
- Patients with higher median SAPS II and SOFA D1 scores (respectively, 39 vs. 52 and 2 to 8) vs. 2 (2 to 2.2), P = 0.0019, and a lower median PaO2/FiO2 (P/F) ratio (98 vs. 106 to 109) vs. 178 (126 to 206), P = 0.0005) were more frequently intubated.  
- Among not-intubated patients, the lowest P/F was 131 mmHg.  
- In patients with invasive ventilation, we observed more hemodynamic and kidney failure (respectively, 13 vs. 0, P = 0.002 and 5 vs. 2, P = 0.026), a longer median length of ICU stay (28 vs. 19 to 28 days, P = 0.0001) and more mortality (3 vs. 0, P = 0.013)  
- HFNC could represent a safe and effective strategy of first-line oxygenation for patients with severe hypoxemic pneumonia due to SARS-COV-2  
- The good outcome of our patients treated with HFNC was associated with a decreased risk of subsequent intubation.  
- This French clinical experience supports the use of HFNC as a first line management in patients with acute respiratory failure due to SARS-COV-2 pneumonia for whom standard face mask oxygen does not provide adequate respiratory support.  
Note: small sample size, no risk calculations; early pandemic so there were no complementary treatments (such as steroids or proning) | |
| Carrillo Hernandez-Rubio, 2020     | Prospective cohort study  | Adults with a positive PCR for SARS-CoV-2 and admitted to the Intermediate Respiratory Care Unit with tachypnea, use of accessory musculature or SpO2 <92% despite FiO2 > 0.5 | In patients presenting a SpO2 <92% despite FiO2 > 0.5 without a RR of > 30 breaths/minute or use of accessory muscles upon admission to the ICU, treatment with HFNC (AIRVO 2, Fisher and Paykel healthcare) was started with an initial flow of 60 L/min, a temperature of 37.0°C and a FiO2 between 0.5 and 1 with the objective of a SpO2 > 92% | Mechanical (endotracheal) intubation | - Median age was 60 years (range: 50.7–71.2)  
- 77.1% were male patients.  
- 55.7% of patients ascertained were obese.  
- On admission, the median PaO2/FiO2 was 83 mmHg (range: 55 to 142) and the mean SAPS II 34.3 ± 7.9 (SD).  
- 55.7% of the patients required HFNC and 27.1% required NIV in CPAP or BPAP mode, and frequent Helmet use (63.2%).  
- Physiological and biochemical factors influence a patient’s need for intubation – NIV as a therapy is not associated with reduced need for ETI  
- Regression modelling for predictive variables of ETI showed that proning was independently associated with the need for intubation (adjusted OR of 0.05, 95% CI 0.005 to 0.54, p = 0.001). (The variables age, sex, ...

N= 43

N= 70
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Type</th>
<th>Population</th>
<th>Intervention or Exposure</th>
<th>Comparator</th>
<th>Outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deng et al., 2021</td>
<td>Retrospective cohort study</td>
<td>Elderly patients (≥65 years) with confirmed SARS-CoV-2 infection, treated with HFNC between January and March 2020</td>
<td>Early HFNC: HFNC treatment when 200 mmHg &lt; $PO_2/FiO_2 \leq 300$ mmHg</td>
<td>Late HFNC: First treated with conventional oxygen therapies (e.g., low flow nasal catheter ventilation) and then HFNC when 100 mmHg &lt; $PO_2/FiO_2 \leq 200$ mmHg</td>
<td>- median age of the 110 patients was 71 (IQR 68-78; range 65 to 89) years, 65 (59.1%) were male. No significant differences on admission $SpO_2$, $PaO_2/FiO_2$, SOFA scores and APECHII scores between early and late HFNC groups. Early HFNC were less likely to have secondary infection or severe ARDS, and less likely to receive prone position ventilation and invasive mechanical ventilation than the patients who receive late HFNC. Early HFNC had a lower likelihood of developing severe pneumonia, manifested as more than 50% increase in pneumonitis foci on chest CT scan during disease progression. Early HFNC were less likely to admit to ICU, less likely to stay in ICU longer than 7 days, had less chance to develop severe ARDS and had longer time from COVID-19 onset to severe ARDS (if any).</td>
<td>- 10.5% patients in the early HFNC group converted to invasive mechanic ventilation, which is in contrast to the 52.7% in the late HFNC group. Starting HFNC or invasive mechanical ventilation at a relatively late stage of disease severity such as moderate to severe ARDS may prompt the physician to apply high $FiO_2$. Post-hoc subgroup analysis in the late HFNC group revealed that $FiO_2$ of survivors was significantly lower than that of the non-survivors and initial targeted $SpO_2$ was also relatively higher in the non-survivor subgroup. Note: possible confounding from pharmaceutical therapies (not described in methods).</td>
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<td>Franco et al., 2020</td>
<td>Prospective cohort study</td>
<td>Patients with confirmed COVID-19 referred to pulmonology units</td>
<td>High-flow nasal cannula (HFNC), continuous positive airway pressure (CPAP) or noninvasive ventilation (NIV) [Only HFNC considered for this review; n=163]</td>
<td>- After adjustment for age, baseline PaO2/FiO2 ratio, number of comorbidities and steroid usage, HFNC had no significant reduction in risk of 30-day mortality, ETI, or length of hospital stay compared to other NIV modes - Patients with a PaO2/FiO2 ratio &lt;50 presented a higher 30-day mortality rate and a higher rate of ETI (p&lt;0.001 and p&lt;0.001, respectively).</td>
<td>- HFNC success patients had higher SpO2/FiO2, PaO2/FiO2 and lower RR at 6,12 and 24h of HFNC onset - The SpO2/FiO2, PaO2/FiO2 and ROX index gradually increased in the HFNC success group, and gradually declined in the HFNC failure group - ROX index greater than 5.55 at 6h after HFNC onset, as a predictor of good prognosis has a specificity of 61.1%, a positive predictive value of 68.8%, a negative predictive value of 79.8%. - ROX index greater than 5.55 at 6h of HFNC application is the most relevant predictor of HFNC success (OR, 17.821; 95% CI, 3.741-84.903; p&lt;0.001).</td>
<td>HFNC was an effective treatment for these patients, and approximately 61.9% of patients showed improved oxygenation and were able to successfully withdraw from HFNC. - ROX index is a suitable predictor of HFNC success considering both statistical and clinical significance Note: high risk of bias from confounding; sample size decided after data collection</td>
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<tr>
<td>Hu et al., 2020</td>
<td>Retrospective cohort study</td>
<td>All patients initially admitted to the respiratory department instead of ICU and treated with HFNC were included between 1 January and 1 March 2020. N= 105</td>
<td>Success or failure of HFNC therapy (indicated for patients with SpO2≥92% and / or RR≥25 times/min under nasal tube oxygen inhalation 10L/min or mask oxygen supply)</td>
<td>- HFNC success patients had higher SpO2/FiO2, PaO2/FiO2 and lower RR at 6,12 and 24h of HFNC onset - The SpO2/FiO2, PaO2/FiO2 and ROX index gradually increased in the HFNC success group, and gradually declined in the HFNC failure group - ROX index greater than 5.55 at 6h after HFNC onset, as a predictor of good prognosis has a specificity of 61.1%, a positive predictive value of 68.8%, a negative predictive value of 79.8%. - ROX index greater than 5.55 at 6h of HFNC application is the most relevant predictor of HFNC success (OR, 17.821; 95% CI, 3.741-84.903; p&lt;0.001).</td>
<td>- HFNC was an effective treatment for these patients, and approximately 61.9% of patients showed improved oxygenation and were able to successfully withdraw from HFNC. - ROX index is a suitable predictor of HFNC success considering both statistical and clinical significance Note: risk of bias from confounding</td>
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<tr>
<td>Long et al., 2020</td>
<td>Retrospective cohort study</td>
<td>All patients diagnosed with COVID-19 were classified as having mild, severe, or critical illness according to the Guidance for Corona Virus Disease 2019</td>
<td>1. Interferon-alpha (IFN-α): 5 million U or equivalent dose per time for adults, 2 ml injection of sterile water, twice daily atomization inhalation. 2. Lopinavir/ritonavir (LPV/r): 200 mg/50 mg/capsule for adults, 2 capsules per time, twice a day, for no more than 10 days.</td>
<td>- HFNC success patients had higher SpO2/FiO2, PaO2/FiO2 and lower RR at 6,12 and 24h of HFNC onset - The SpO2/FiO2, PaO2/FiO2 and ROX index gradually increased in the HFNC success group, and gradually declined in the HFNC failure group - ROX index greater than 5.55 at 6h of HFNC application is the most relevant predictor of HFNC success (OR, 17.821; 95% CI, 3.741-84.903; p&lt;0.001).</td>
<td>- Initiation of oxygen treatment less than 2 days after onset after onset of hypoxia symptoms and the use of IFN-α among critically ill patients were significantly associated with lower risk of COVID-19 mortality.</td>
<td>Note: high risk of bias from confounding; sample size decided after data collection</td>
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<td>Mellado-Artigas et al., 2021</td>
<td>Prospective cohort study</td>
<td>Adult patients (≥ 18 years old) admitted to the ICU between March 12 and August 13, 2020. Patients were included if they had positive confirmatory nasopharyngeal or pulmonary tract sample and received support with either HFNO or intubation on the first day of ICU admission. N= 122 matched patients (61 per group)</td>
<td>HFNO as the initial oxygenation strategy in the first 24 h of ICU admission (&quot;conservative group&quot;)</td>
<td>Early invasive mechanical ventilation (within the first day of ICU admission; &quot;early intubation group&quot;)</td>
<td>- HFNO was associated with an increase in ventilator-free days (VFD) (mean difference 8.0 days; 95% CI 4.4 to 11.7 days) - HFNO associated with a reduction in ICU length of stay (mean difference - 8.2 days; 95% CI -12.7 to -3.6 days) - Intubation rate was 38% in the conservative group (compared to an expected 100% in the early intubation group) - No difference was observed in all-cause in-hospital mortality between groups (OR 0.64; 95% CI 0.25 to 1.64)</td>
<td>HFNO was associated with an increase in VFDs and shorter ICU length of stay when compared to an early intubation strategy. No significant differences were evident in all cause in-hospital mortality.</td>
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<tr>
<td>Menga et al., 2021</td>
<td>Prospective cohort study</td>
<td>All consecutive adult patients admitted to the ICU between March 12 and April 20 due to hypoxemic respiratory failure NIV used for COVID-19 hypoxemia</td>
<td>NIV for hypoxemic respiratory failure and bilateral infiltrates from other etiologies</td>
<td>- Fifty-two (61%) subjects required endotracheal intubation. All subjects were intubated due to the lack of improvement in oxygenation and dyspnea</td>
<td>- High rate of NIOS failure (61%) - In acute hypoxemic respiratory failure from other causes, NOS failure might detrimentally affect</td>
<td>Note: risk of bias from confounding drug therapies</td>
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Note: risk of bias from confounding drug therapies.
### Non-Invasive Respiratory Therapies for Severe COVID-19

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| Palacios  | Prospective cohort    | Patients aged ≥18 years who were admitted to the temporary COVID-19 hospital with a confirmed diagnosis of COVID-19 [as verified by PCR and hypoxemic respiratory failure (PaO2 ≤ 60 mmHg)] | HFNO treatment success (did not require IMV) | HFNO failure (required IMV) | - HFNC success rate, defined as patients who did not require IMV, was 71.4% (n = 270; 95% CI 66.6–75.8) compared with 28.6% (n = 108; 95% CI 24.2–33.4) of patients who required IMV.  
- Patients with HFNC success rarely required admission to the ICU and had shorter lengths of hospital stay [19/270 (7.0%) and 15.0 days, respectively] than those who required IMV [104/108 (96.3%) and 26.5 days, respectively.  
- In patients with HFNC success, Rox index values increased from 5.98 at baseline to 6.41, 6.83, 7.02, 7.37, 7.87, and 8.20 after 1, 2, 4, 6, 12, and 16 hours, respectively.  
- In patients with HFNC failure, Rox index values remained low from 5.40 at baseline to 5.70, 5.88, 5.76, 5.93, 5.74, and 5.62 after 1, 2, 4, 6, 12, and 16 hours, respectively. | clinical outcomes by delaying intubation and allowing self-inflicted lung injury during treatment  
- It is possible that nonventilatory features (eg, the microvascular involvement of the disease and the unavailability of etiologic treatments) play an important role in determining NIOS treatment outcome in COVID-19 disease  
Notes: early pandemic prior to evidence of steroid effectiveness as a treatment. |

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| Panadero et al., 2020 Spain | Retrospective cohort study | Patients included in the analysis were between the ages of 18 and 80, who had PaO2/FiO2 <200mmHg or SpO2/FiO2 ratio <240, and who were treated with high-flow oxygen therapy through nasal cannula N= 40 | Successful HFNO treatment | Failed HFNO treatment | - In patients with HFNC success, the median (IQR) ratio of SpO2 over FiO2 (SPFI) increased from 135.7 (115.3, 160.0) after 2 hours to 158.4 (127.2, 192.2) after 16 hours of HFNC.  
- In patients with HFNC failure, the median (IQR) SPFI ratio decreased from 115.0 (98.0, 140.0) after 2 hours to 110.4 (96.5, 134.9) after 16 hours of HFNC.  
- CALL score at admission (adjusted HR 1.27; 95% CI 1.09–1.47; p < 0.01), Rox index at 1 hour (adjusted HR 0.82; 95% CI 0.70–0.96; p = 0.02), and absence of treatment with steroids (adjusted HR 0.34; 95% CI 0.19–0.62; p < 0.0001) were all significant predictors of HFNC failure | - Mean age was 58.9 years, and 70% were men (21 experienced therapy failure)  
- Overall mortality rate was nine patients (22.5%), all of whom were in the failed HFNC therapy group  
- The patients who did not require intubation had lower serum LDH levels and higher creatinine levels. They also presented lower values of PCO2 and bicarbonate in the arterial-blood gas test before starting HFNC  
- SpO2/FiO2 ratio after starting HFNC was significantly higher in the group that did not require intubation (113.4±6.6 vs 93.7±6.7; p=0.020), as was the ROX index (5.0±1.6 vs 4.0±1.0; p=0.018)  
- ROX value of less than 4.94 at 2-6 hrs post-initiation was associated with increased risk of intubation (HR 4.03 [95% CI 1.18 – 13.7]; p=0.026) | - HFNC enabled us to treat ARDS successfully in a high proportion of patients (47.5%) without requiring invasive ventilatory support and with low mortality  
- Patients with a ROX <4.94 after HFNO initiation may benefit from closer monitoring or early intubation |
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<td>Patel et al., 2020</td>
<td>Retrospective cohort study</td>
<td>Patients tested positive for COVID-19 using nasopharyngeal RT-PCR or patients with high clinical suspicion and findings suggestive of COVID-19 based on high-resolution CT of the chest, with moderate-to-severe hypoxaemic respiratory failure and were on oxygen delivery via HFNT</td>
<td>Successful HFNO treatment (&quot;non-intubation group&quot;)</td>
<td>Failed HFNO treatment (&quot;intubation group&quot;)</td>
<td>- The average age was 60.66 (±13.50) years, 49 (47.12 %) were female, 53 (50.96%) were African-American, 23 (22.12%) Hispanic. - Mortality was 14.44% (n=15) in our cohort with 13 (34.4%) in the intubation group and 2 (2.9%) in the non-intubation group (p=0.0018) - SF ratios were significantly different between the two groups at baseline, with the intubation group having much lower SF ratios compared with those who remained on HFNT (111.03±34.09 vs 127.9±43.47, p&lt;0.004) - ICU LOS was higher for the intubation group (10.45 days±6.12 vs 4.05 ± 2.64 days, p=0.0008)</td>
<td>- Of 104 patients (23.3%) treated initially with HFNT, 64.4% remained on HFNT and were able to avoid escalation to non-invasive and IMV. - Survival advantage cannot be attributed to HFNT based on the study’s retrospective design. Use of HFNT did not result in worsened outcomes either.</td>
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<td>Teng et al., 2020</td>
<td>RCT</td>
<td>Adults &gt;18 years; the patients met the diagnostic criteria for patients with severe COVID-19 in the COVID-19 Diagnosis and Treatment Plan</td>
<td>HFNC oxygen therapy. Initial parameters: temperature was 37°C, flow rate was 50 L/min, and oxygen concentration was 50%. Parameters were adjusted according to blood oxygen saturation level (SpO2), blood gas and tolerance, maintaining SpO2 above 93%.</td>
<td>Conventional oxygen therapy (COT); oxygen utilizing a nasal catheter or a common mask. Initial oxygen absorption flow set at 5 L/min, adjusted according to the condition of SPO2; maintaining SpO2 above 93%</td>
<td>- Age, gender, interval from onset to diagnosis and underlying diseases between the two groups were not significantly different - Differences in HR, RR and PaO2/FiO2 at 0 hours of treatment between the two groups were not significant - At 6 hours after treatment with the two oxygen therapies, HR, RR and PaO2/FiO2 were better in the HFNC oxygen therapy group than in the COT group (P &lt; .05) - At 24 and 72 hours after treatment, PaO2/FiO2 was better in the HFNC oxygen therapy group than in the COT group (P &lt; .05) - At 6, 24 and 72 hours after treatment, RR was lower in the HFNC oxygen therapy group than in the COT group, and PaO2/FiO2 was higher in the HFNC</td>
<td>Compared with COT, early application of HFNC oxygen therapy in patients with severe COVID-19 can improve oxygenation and RR, and HFNC oxygen therapy can improve the infection indexes of patients and reduce the length of stay in the ICU of patients.</td>
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### Non-Invasive Respiratory Therapies for Severe COVID-19

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<td>Vianello et al., 2020</td>
<td>Retrospective cohort study</td>
<td>Italy</td>
<td>(1) laboratory-confirmed COVID-19 infection; (2) PaO2/FIO2 ratio &lt;300 mm Hg, FIO2 being determined as previously described; (3) failure of conventional O2-therapy delivered through a non-rebreathing mask with a reservoir bag to maintain SaO2 ≥92%; N= 28 (consecutively admitted)</td>
<td>Success: patients who had a successful outcome from HFNO therapy, as defined by reversal of hypoxemia (SaO2 ≥92%), no need for NIV and/or invasive mechanical ventilation (IMV), discharge from RICU, with the patient alive and conscious for at least 48 hours after discharge. Failure group: patients who had an unsuccessful outcome, defined as the need for NIV or IMV by ETI and/or death while on HFNC support</td>
<td>Male:female ratio was 3 to 1 (21 vs 7). The patients were classified, in accordance with the WHO criteria, as showing moderate (17 cases) or severe (11 cases) acute respiratory distress at admission - Nineteen (67.8%) succeeded HFNC as hypoxemia was reversed and they were discharged from the RICU and were still alive on day 15 after discharge. Nine patients (32.2%) failed HFNC and received NIV (five required IMV) - All nine failing patients had lower PaO2/FIO2 (76 (53–190) vs 126 (52–296) mm Hg; p=0.0194) and higher serum C reactive protein level (130 (110–270) vs 110 (29–180); p=0.01277) than HFNO success group. - Patients with PaO2/FIO2 at admission ≤100 mm Hg showed a greater rate of treatment failure (7/9 (77.8%)), as opposed to those with PaO2/FIO2 &gt;100 mm Hg (6/21 (31.6%); p=0.0246), with an OR of failure of 7.6 (95% CI 1.2 to 48.1).</td>
<td>- PaO2/FIO2 at admission had prognostic relevance - patients with PaO2/FIO2 values ≤100 mm Hg had an increased risk of treatment failure.</td>
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<td>Wendel Garcia et al., 2021</td>
<td>Prospective cohort study</td>
<td>International</td>
<td>Patients were included in the present substudy if they required standard oxygen therapy (SOT) (&gt;10 L/min), HFNC, NIV, or IMV at the</td>
<td>(1) SOT group: patients receiving SOT with an oxygen flow of ≥10 L/min (FiO2 was approximated based on the delivered oxygen flow)</td>
<td>- After matching, 351 patients (85 SOT, 87 HFNC, 87 NIV and 92 IMV) were included in the final analysis - ICU mortality rate was higher (p = 0.016) in patients initially ventilated with NIV</td>
<td>- Compared to the other respiratory support strategies, NIV was associated with higher ICU mortality rates.</td>
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<td>time point of admission to the ICU defined as day 0. N=351</td>
<td>(2) HFNC group: patients receiving HFNC, defined as a device delivering humidified and heated oxygen at a flow rate above 30 L/min&lt;br&gt;(3) NIV group: patients receiving NIV, irrespective of interface, mode and ventilator type employed&lt;br&gt;(4) IMV group: intubated patients receiving IMV</td>
<td>than in the other groups (SOT: 18%, HFNC: 20%, NIV: 37%, IMV: 25%)&lt;br&gt;- median duration of the in-hospital stay until intubation was longer (p&lt;0.001) in the NIV group (4 [IQR, 3–7] days) compared to the other three groups (SOT: 3 [1–5] days, HFNC: 3 [2–6] days, IMV: 1 [0–3] days)&lt;br&gt;- Patients who were initially treated with HFNC and NIV, and later required IMV, had longer (p = 0.018) ICU lengths of stay than patients under initial SOT when compared to early IMV&lt;br&gt;- NIV was independently associated with a higher overall ICU mortality (adjusted HR 2.67, 95% CI [1.14–6.25]) as well as with an increased ICU mortality rate (adjusted HR 2.96, 95% CI [1.07–8.23]) and a prolonged length of ICU stay (adjusted HR 0.57, 95% CI [0.33–0.97]) in patients failing NIV and requiring delayed IMV, as opposed to the other respiratory support strategies</td>
<td>- The excess mortality observed in patients treated with NIV in this study might thus be explained by the longer period of harmful spontaneous breathing in patients failing NIV therapy, exacerbated by an increased respiratory rate and disproportionate tidal volumes induced by NIV therapy</td>
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- We suggest high flow nasal cannula oxygen (HFNC) or non-invasive continuous positive airway pressure (CPAP) delivered through either a helmet or a face-mask for patients with COVID-19 and hypoxaemic acute respiratory failure in the absence of immediate indications for invasive mechanical ventilation (conditional recommendation, very low quality of evidence).
- Signs of CPAP/HFNO/NIV failure include: limited initial response within 6h, lack of improvement within 3 days, oxygen saturation ≤ 92%.
- HFNC and non-invasive CPAP should not delay mechanical ventilation in patients who are not responding to treatment.
- Prone positioning may improve oxygenation in non-intubated patients with acute hypoxaemic respiratory failure and is widely used for mechanically ventilated patients with COVID-19.

- [Consensus Recommendation]: Guiding principles of care: For patients with COVID-19 and hypoxaemic acute respiratory failure in the absence of immediate indications for invasive mechanical ventilation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place. Closed circuit NIV should be used.
- [Conditional recommendation]: Consider using HFNO therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If HFNO is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only. Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.
- [Conditional recommendation]: Consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If NIV is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only.
- [Consensus recommendation]: Consider using HFNO/NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring endotracheal ventilation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.
- [Conditional recommendation]: For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning for at least 3 hours per day as tolerated. When positioning a patient in prone, ensure it is used with caution and accompanied by close monitoring of the patient. Use of prone positioning should not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised less invasive respiratory therapies.

- The trigger for consideration for escalation of patients on general wards to an RSU should be the inability to maintain oxygen saturations ≥94% on an inspired oxygen <40%.
- Signs of CPAP/HFNO/NIV failure include: limited initial response within 6h, lack of improvement within 3 days, unchanged/increasing work of breathing, not tolerating CPAP/NIV breaks.
- CPAP and NIV impact on suitability for ECMO support so it is important to consider critical care early when appropriate.
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| World Health Organization, 2021 | International | 2021 | **Severe Pneumonia from COVID-19**  
- We recommend immediate administration of supplemental oxygen therapy to any patient with emergency signs during resuscitation to target SpO2 ≥ 94% and to any patient without emergency signs and hypoxaemia (i.e. stable hypoxemic patient) to target SpO2 > 90% or ≥ 92–95% in pregnant women. Deliver oxygen flow rates using appropriate delivery devices (e.g. use nasal cannula for rates up to 5 L/min; Venturi mask for flow rates 6–10 L/min; and face mask with reservoir bag for flow rates 10–15 L/min).  
- Patients hospitalized with COVID-19 require regular monitoring of vital signs (including pulse oximetry) and, where possible, utilization of medical early warning scores (e.g. NEWS2, PEWS) that facilitate early recognition and escalation of treatment of the deteriorating patient  
- **Conditional recommendation**: We suggest awake prone positioning of severely ill patients hospitalized with COVID-19 requiring supplemental oxygen (includes high-flow nasal oxygen) or non-invasive ventilation (conditional, low certainty evidence).  
- Applying the agreed values and preferences, the GDG inferred that almost all well-informed patients would want to undergo prone positioning if awake, requiring oxygen or non-invasive respiratory support, given the lack of harm from the observational studies and panel experience  
- **ARDS from COVID-19**  
- Patients with hypoxemic respiratory failure and haemodynamic instability, multiorgan failure or abnormal mental status should not receive HFNO or NIV in place of other options such as invasive ventilation  
- We recommend prompt recognition of progressive acute hypoxemic respiratory failure when a patient with respiratory distress is failing to respond to standard oxygen therapy and adequate preparation to provide advanced oxygen/ventilatory support |
| National Institutes of Health, 2021 | United States | 2021 | **Nonmechanically Ventilated Adults with Hypoxic Respiratory Failure**  
- For adults with COVID-19 and acute hypoxic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (BIIa).  
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxic respiratory failure and for whom HFNC is not available (BIIa).  
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation (CIIa).  
- The Panel recommends against using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (AIII).  
- The optimal oxygen saturation (SpO2) in adults with COVID-19 is uncertain. However, a target SpO2 of 92% to 96% seems logical considering that indirect evidence from experience in patients without COVID-19 suggests that an SpO2 <92% or >96% may be harmful. |
Non-Invasive Respiratory Therapies for Severe COVID-19

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| National Institute for Health and Care Excellence, 2021 | England | 2021 | [Conditional recommendation] Consider offering continuous positive airway pressure (CPAP) to people with COVID-19 when: 1) They have hypoxaemia that is not responding to supplemental oxygen with a fraction of inspired oxygen of 0.4 (40%) or more, and 2) escalation to invasive mechanical ventilation would be an option but it is not immediately needed, or 3) it is agreed that respiratory support should not be escalated beyond CPAP.  
[Conditional recommendation against] Do not routinely offer high-flow nasal oxygen as the main form of respiratory support for people with COVID-19 and respiratory failure in whom escalation to invasive mechanical ventilation would be appropriate.  
For people with COVID-19 having continuous positive airway pressure, ensure: 1) there is access to critical care providers for advice, review and prompt escalation of treatment if needed (such as when treatment has failed) 2) regular review by an appropriate senior clinician (such as every 12 hours) and more frequent review if needed, in line with the British Thoracic Society guidance on respiratory support units and the Faculty of Intensive Care Medicine guidelines on the provision of intensive care services, and 3) regular assessment and management of symptoms alongside non-invasive respiratory support. |
Limitations

This review was limited by several factors that must be considered when assessing the findings. First, this is a rapid review. The search was thorough, but not systematic. In addition, the search was limited to literature published in English in the past 2 years. For these reasons, it is possible that relevant studies were not captured in the database search.

As with most reviews of COVID-19-related evidence, this review is limited by the lack of controlled trial evidence. Observational studies cannot show causation, only association; thus, it is difficult to determine if the intervention being studied truly has clinical benefit or if benefit is due to the characteristics of the patient. These studies also suffer from the rapid pace of COVID-19 research, where studies are haphazardly designed with little attention paid to limiting bias. As a result, the studies included in this review are at high risk of bias from confounding.

With respect to the body of evidence, the terminology around high-flow oxygen is not standardized, which makes searching for grey literature challenging. The most common terms include “high flow nasal cannula”, “high flow nasal oxygen”, “heated humidified high-flow nasal cannula”, “heated humidified high-flow oxygen”, and “high-flow oxygen”. It is therefore difficult to determine if each term refers to the same systems and mode of therapy.

Conclusions

Based on the evidence presented in the synthesis above, the following conclusions can be made:

- The body of evidence on this topic is estimated to be of low quality. It is largely cohort studies at high risk of confounding, and guidance based on this review should acknowledge this limitation.
- No peer-reviewed RCTs were identified to address the research questions specifically relating to CPAP and Bilevel PAP as therapy for COVID-19.
- Guidelines from the WHO, Europe, UK, USA, and Australia unanimously recommend using non-invasive therapies (such as HHHFO, CPAP, or Bilevel PAP) in hypoxemic patients requiring oxygen supplementation beyond what conventional oxygen therapy can provide, but for whom invasive mechanical ventilation is not yet indicated.
- The principal risk to patients arising from non-invasive oxygen supplementation in COVID-19 appears to be delayed intubation, which can be mitigated by close monitoring and not trying to rescue respiratory function with additional non-invasive therapy or positioning once therapy failure has been determined.
- One RCT found that early oxygen therapy via high-flow nasal cannula (HHHFO) resulted in significantly better respiratory rate (RR), heart rate (HR) and PaO\textsubscript{2}/FiO\textsubscript{2} at 6 hours post treatment initiation compared to conventional oxygen therapy. Observational studies support this finding and show that HHHFO can reduce the ICU length of stay and ventilator-free days, but is not necessarily associated with a decrease in mortality.
- Benefit from non-invasive ventilation or HHHFO therapies is associated with early intervention, rather than with patient characteristics. The need for intubation is influenced by the patient’s physiological and biochemical characteristics. NIV as a therapy is not clearly associated with reduced need for mechanical ventilation.
- No direct evidence was identified that described best practices for identifying when to move a patient to mechanical ventilation from non-invasive ventilation. The ROX index score is a valid prognostic measure of HHHFO success or failure. ROX index values below 5.5 that do not increase over time (up to 16 hours after start of HHHFO therapy, or limited response within the first 6 hours) is strongly associated with increased risk of intubation, while patients who did not require intubation had a ROX index value above 5.5 at baseline that increased as therapy continued.
References


Appendix

List of Abbreviations
AHS: Alberta Health Services
CI: Confidence Interval
COVID-19: Coronavirus Disease 2019
CPAP: Continuous Positive Airway Pressure
HFNC: High Flow Nasal Cannula
HFNO: High Flow Nasal Oxygen
HHHFO: Heated Humidified High-Flow Oxygen
HR: Heart Rate
ICU: Intensive Care Unit
KRS: Knowledge Resource Services
LDH: lactate dehydrogenase
MSCN: Medicine Strategic Clinical Network
NICE: National Institute for Health and Care Excellence
NIV: Non-invasive Ventilation
OR: odds ratio
PAP: Positive Airway Pressure
PPE: Personal Protective Equipment
RCT: Randomized Controlled Trial
RR: Respiratory Rate
UK: United Kingdom
US: United States
WHO: World Health Organization

Included Studies


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Excluded Studies

HHHFO Search

<table>
<thead>
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<th>Reference</th>
<th>Reason for Exclusion</th>
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Table 1: Literature Review on NIV for COVID-19 Patients

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<th>Findings/Conclusions</th>
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### Non-Invasive Respiratory Therapies for Severe COVID-19 - 33

No ventilation outcomes

O2 requirement, not ventilation. No outcomes for ventilation

No NIV, no outcomes

No outcomes from HHHFO

No ventilation outcomes

Case report + narrative review

No outcomes from ventilation type

Small case series (n=4)

Article retracted

No outcomes of ventilation

No ventilation outcomes reported

No outcomes from ventilation

No outcomes from ventilation

Analysis not specific to HHHFO or NIV – strategy includes upgrading and downgrading

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Non-Invasive Respiratory Therapies for Severe COVID-19


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No ventilation outcomes


No ventilation outcomes


Wrong comparator (proning)

General ventilation search

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Non-Invasive Respiratory Therapies for Severe COVID-19 - 39


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<td>JAMA. 2021;325(17):1731-43</td>
<td>Narrative review</td>
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<td>Sykes D, Parthasarathy A, Brown O, Crooks M, Faruqi S. COVID-19 progression, frailty, and use of prolonged continuous positive airway pressure as a ward-based treatment: Lessons to be learnt from a case.</td>
<td>Lung India. 2021;38(7 Supplement 1):S64-S8</td>
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Search Strategy

Search 1: HHHFO

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2 exp Oxygen/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (10826)
3 exp Oxygen Inhalation Therapy/m, st, sn, th [Methods, Standards, Statistics & Numerical Data, Therapy] (5508)
4 exp Respiratory Insufficiency/th [Therapy] (17135)
5 exp Respiratory Distress Syndrome/th [Therapy] (12221)
6 exp Noninvasive Ventilation/is, mt [Instrumentation, Methods] (1183)
7 exp Cannula/ (1134)
8 "high-flow oxygen".ti,ab. (622)
9 airvo.ti,ab. (12)
10 optiflow.ti,ab. (55)
11 Vapotherm.ti,ab. (32)
12 "high-flow nasal cannula".ti,ab. (1324)
13 "high-flow nasal oxygen".ti,ab. (268)
14 or/2-13 (45582)
15 1 and 14 (1122)
16 exp Treatment Outcome/ (1128781)
17 exp Disease Progression/ (192863)
18 exp Time Factors/ (1212142)
19 exp "Severity of Illness Index"/ (267175)
20 exp "Length of Stay"/ (94610)
21 exp Risk Assessment/ (289008)
22 exp Monitoring, Physiologic/ (183070)
23 exp Biomarkers/an, bl [Analysis, Blood] (324575)
24 or/16-23 (3162803)
25 15 and 24 (402)
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Non-Invasive Respiratory Therapies for Severe COVID-19 - 43

Database: Embase <1996 to 2021 Week 29>
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2 exp Oxygen/ad, tu, th [Administration & Dosage, Therapeutic Use, Therapy] (991)
3 exp Oxygen Inhalation Therapy/ (64247)
4 exp Respiratory Insufficiency/th [Therapy] (13124)
5 exp noninvasive ventilation/ (14930)
6 exp cannula/ (19771)
7 exp oxygen therapy/ (64247)
8 "high-flow oxygen".ti,ab. (1229)
9 Airvo.ti,ab. (64)
10 Optiflow.ti,ab. (178)
11 Vapotherm.ti,ab. (105)
12 "high-flow nasal cannula".ti,ab. (2374)
13 "high-flow nasal oxygen".ti,ab. (458)
14 or/2-13 (102440)
15 exp treatment outcome/ (1804695)
16 exp disease exacerbation/ (137146)
17 exp time factor/ (40474)
18 exp disease severity/ (1768868)
19 exp "length of stay"/ (206737)
20 exp risk assessment/ (600593)
21 or/15-20 (3945183)
22 1 and 14 (1012)
23 21 and 22 (483)
Non-Invasive Respiratory Therapies for Severe COVID-19

24. limit 23 to (human and english language and yr="2020 -Current") (455)
25. limit 24 to exclude medline journals (114)
26. limit 25 to (adult <18 to 64 years> or aged <65+ years>) (83)
27. remove duplicates from 26 (83)

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Database: Ovid MEDLINE(R) ALL <1946 to July 27, 2021>
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3. exp "Severity of Illness Index"/ (267175)
4. exp Risk Assessment/ (289008)
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6. exp Ventilators, Mechanical/ (9562)
7. exp Intubation, Intratracheal/ (40422)
8. or/5-7 (120917)
9. 1 and 8 (2548)
10. or/2-4 (698129)
11. 9 and 10 (452)
12. limit 11 to (english language and humans and yr="2020 -Current") (446)
13. limit 12 to ("all adult (19 plus years)" or "young adult (19 to 24 years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)") (339)
14. limit 13 to (case reports or clinical trial or comparative study or controlled clinical trial or evaluation study or guideline or meta analysis or multicenter study or observational study or practice guideline or pragmatic clinical trial or randomized controlled trial or "review" or "scientific integrity review" or "systematic review") (179)

Database: Embase <1996 to 2021 Week 29>
Search Strategy:

1. COVID-19/ or SARS-CoV-2/ or coronavirinae/ or betacoronavirus/ or Coronavirus infection/ (32310)
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3. exp disease exacerbation/ (137146)
4. exp disease severity/ (176868)
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Search 3: NIV

Database: Ovid MEDLINE(R) ALL <1946 to September 10, 2021>
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4  exp Time Factors/ (1214954)
5  exp "Severity of Illness Index"/ (269119)
6  exp "Length of Stay"/ (95490)
7  exp Risk Assessment/ (291461)
8  effect*.ti. (2072468)
9  exp Monitoring, Physiologic/ (184240)
10  exp Biomarkers/an, bl [Analysis, Blood] (326457)
11  or/2-10 (4994814)
12  exp Continuous Positive Airway Pressure/ or CPAP.ti. (9064)
13  "Bilevel Positive Airway Pressure".ti. (85)
14  exp Noninvasive Ventilation/ (2809)
15  or/12-14 (11633)
16  1 and 11 and 15 (95)
17  limit 16 to (english language and humans and ("all adult (19 plus years)" or "adult (19 to 44 years)" or "young adult and adult (19-24 and 19-44)" or "middle age (45 to 64 years)" or "middle aged (45 plus years)" or "all aged (65 and over)" or "aged (80 and over)")) (69)
18  limit 17 to (english language and yr="2020 -Current") (67)
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Database: Embase <1996 to 2021 Week 36>
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5  exp "Severity of Illness Index"/ (19322)
6  exp "Length of Stay"/ (209577)
7  exp Risk Assessment/ (607793)
8  effect*.ti. (1676845)
9  exp Monitoring, Physiologic/ (7706)
10  exp Biomarkers/an, bl [Analysis, Blood] (8456)
11  or/2-10 (4153429)
12  exp Continuous Positive Airway Pressure/ or CPAP.ti. (7839)
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<tr>
<td>S13</td>
<td>(MH &quot;Morbidity+&quot;)</td>
<td>178,537</td>
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<tr>
<td>S12</td>
<td>(MH &quot;Disease Progression+&quot;)</td>
<td>51,149</td>
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<tr>
<td>S11</td>
<td>(MH &quot;Severity of Illness&quot;)</td>
<td>31,437</td>
</tr>
<tr>
<td>S10</td>
<td>(MH &quot;Treatment Outcomes+&quot;) OR (MH &quot;Outcome Assessment&quot;)</td>
<td>442,971</td>
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<tr>
<td>S9</td>
<td>(MH &quot;Outcomes (Health Care)+&quot;)</td>
<td>526,278</td>
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<tr>
<td>S8</td>
<td>(MH &quot;Risk Assessment&quot;)</td>
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<td>S7</td>
<td>(MH &quot;Length of Stay&quot;)</td>
<td>45,665</td>
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<tr>
<td>S6</td>
<td>(MH &quot;Time Factors&quot;)</td>
<td>179,115</td>
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<tr>
<td>S5</td>
<td>S2 OR S3 OR S4</td>
<td>6,543</td>
</tr>
<tr>
<td>S4</td>
<td>TI noninvasive ventilation</td>
<td>1,055</td>
</tr>
<tr>
<td>S3</td>
<td>TI bilevel positive airway pressure</td>
<td>37</td>
</tr>
<tr>
<td>S2</td>
<td>(MH &quot;Continuous Positive Airway Pressure&quot;)</td>
<td>5,591</td>
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