The use of high-flow nasal oxygen in COVID-19

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The key healthcare challenge of the coronavirus disease 2019 (COVID-19) pandemic is the safe delivery of respiratory support on a large scale. The care of critically ill COVID-19 patients is guided by our knowledge and experience with acute respiratory distress syndrome (ARDS), but this crisis is pushing patients and their clinicians into unchartered territories. One of the key decisions faced by healthcare systems is in selecting the appropriate devices for oxygen administration. The use of high-flow nasal oxygen (HFNO) in COVID-19 is the subject of much debate, relating to the benefits and harms that may result for patients and healthcare workers alike.

In recent years, HFNO has become a commonly used therapy for patients with acute hypoxaemic respiratory failure. Frat et al. conducted a multicentre randomised controlled trial (RCT) of 310 patients assessing the efficacy of HFNO, non-rebreather facemask or non-invasive ventilation (NIV) in the treatment of type 1 respiratory failure [1]. The primary outcome of tracheal intubation rate was 38% in the HFNO group, 47% in the non-rebreather facemask group and 50% in the NIV group ($p = 0.18$ for all comparisons). However, the study was only powered to demonstrate an absolute difference of 20% between groups. The hazard ratio for death at 90 days was 2.01 (95%CI 1.01–3.99) with facemask vs. HFNO and 2.50 (95%CI 1.31–4.78) with NIV versus HFNO. The authors proposed that the lower mortality observed in the HFNO group resulted from the cumulative benefit of a lower tracheal intubation rate in those patients with severe hypoxaemia (P_aO_2:$F_IO_2 \leq 200$ mmHg), and a slightly lower mortality among intubated patients who were initially treated with HFNO.

Rochwerg et al. published a systematic review and meta-analysis comparing HFNO with conventional oxygen therapy in patients with acute hypoxaemic respiratory failure [2]. Nine RCTs involving 2093 patients were reviewed, including the aforementioned Frat et al. study. No difference in mortality was observed in patients treated with HFNO (relative risk (RR) 0.94, 95%CI 0.67–1.31) compared with conventional oxygen therapy. The use of HFNO resulted in a decreased requirement for tracheal intubation (RR 0.85, 95%CI 0.74–0.99) and a lower risk of escalation of oxygen therapy (RR 0.71, 95%CI 0.51–0.98) when compared with conventional therapy. Escalation of oxygen therapy was defined as initiation of non-invasive ventilation or invasive mechanical ventilation in either group, and additionally as crossover to HFNO in the conventional therapy group. The authors declared a low level of certainty to both benefits.

The extent to which these outcomes in ARDS populations of undifferentiated aetiology are applicable to COVID-19 patients is unknown. If the above benefits are attainable in this

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population, then HFNO would warrant consideration as an early method of respiratory support even if the provision of other forms of support was not limited. However, a narrative has emerged that HFNO use should be greatly restricted or even contraindicated in the treatment of COVID-19. This is multifactorial, but driven largely by a unique concern that did not feature in the above studies: the potential for aerosolisation of virus particles and a heightened risk that healthcare workers could become infected with coronavirus.

At the time of this writing (27 March, 2020), joint guidance issued by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists states that "*high-flow nasal oxygen or similar devices should be avoided*," remarking that there is "*no survival benefit compared to conventional oxygen therapy, and the risk of environmental viral contamination may be higher"* [3]. The World Health Organization (WHO) recommends that HFNO should only be used in selected patients with hypoxaemic respiratory failure [4]. The guideline lists hypercapnia, haemodynamic instability, multi-organ failure and abnormal mental status as scenarios that render it generally inappropriate for use. It recommends that patients are cared for in a monitored setting and by experienced personnel capable of performing tracheal intubation in the event of an acute deterioration or failure to improve after a short trial (*"about 1 hour"*). The COVID-19 guidelines of the Australian and New Zealand Intensive Care Society (ANZICS) state that HFNO is a *"recommended therapy"* for hypoxia associated with COVID-19 illness, as long as staff are wearing optimal airborne personal protective equipment (PPE) [5]. The COVID-19 guidelines of the Surviving Sepsis Campaign recommend using HFNO over conventional oxygen therapy in patients with acute hypoxemic respiratory failure despite conventional oxygen therapy [6]. An additional recommendation is made that HFNO is used over NIV in these patients.

Evidence for aerosolisation

Leung et al. evaluated the effects of HFNO use on environmental contamination by bacteria in 19 critically ill patients with Gram-negative bacillus pneumonia [7]. Four experimental conditions were created for each patient in single occupancy rooms. Oxygen was administered by HFNO at 60 $l.min^{-1}$ or via simple facemask and each mode was examined separately under two conditions of room ventilation (6 or 12 air changes per hour). The F_IO_2 of HFNO or the flow rate of facemask oxygen were adjusted to maintain oxygen saturation ≥ 92%. Three sets of air samples were collected for each experimental condition, at three locations ≥ 1 m from the patient. Surface contamination was also assessed by placing Petri-dishes between 0.4 m and 1.5 m from the patient's nose. For the primary outcome, no difference was observed in Gram-negative bacillus count between the HFNO and facemask groups for air samples or settle plates at both rates of air change. On post-hoc analysis, the total bacterial count on settled plates was higher at 0.4 m than at 1.5 m from the patient for both methods of oxygen delivery and at the lower air change rate.

Loh et al. simulated patient coughing while using HFNO to assess maximum distance of droplet dispersion [8]. Five volunteers gargled 10 ml of diluted red then blue food die. From a seated position, they inhaled to vital capacity and coughed with an open mouth after each gargle. This process was then repeated following application of HFNO at 60 $l.min^{-1}$. The furthest distance that a visible food dye droplet travelled on the ground was measured in each scenario. Droplet spread with coughing occurred at a mean (SD) distance of 2.48 (1.03) m at baseline and 2.91 (1.09) m with HFNO. A maximum cough distance of 4.50 m was measured when using HFNO.

Hui et al. demonstrated an increase in droplet dispersion with increasing flow rates with HFNO through use of a smoke-laser illumination technique on a human patient simulator [9]. When flow rates were increased from 10 $l.min^{-1}$ to 60 $l.min^{-1}$, non-cough exhaled air distances increased from 6.5 (1.3) cm to 17.2 (3.3) cm in the sagittal plane. Leakage up to 620 mm occurred in the lateral plane when the cannulae and the interface tube became loose. The authors concluded that exhaled air dispersion during HFNO therapy and continuous positive airway pressure (CPAP) is limited when used correctly.

Kotoda et al. assessed dispersal of thickened water and fresh yeast solutions by HFNO at 60 $l.min^{-1}$ on a manikin over a 10-minute period [10]. These solutions aimed to mimic saliva and nasal mucus secretions. Liquid dispersal was assessed by suspending water-sensitive paper at 30 cm intervals above the supine manikin's face. Spots of water were detected on the paper at a 30 cm distance but not at a 60 cm distance. Yeast dispersal was detected by suspending Petri dishes at 30 cm intervals above the supine manikin's face, followed by incubation. Similar to the liquid dispersal experiment, colony formation was observed only on the dish closest to the manikin's face. The experiment was then repeated to determine the effect of manually re-adjusting the cannula once during the 10-minute period in an effort to mimic the effect of a patient touching and repositioning the cannula. This movement increased both water dispersion and colony formation. Use of this study as supportive evidence for the acceptability of HFNO in COVID-19 is potentially problematic. In this study, the manikin is supine but patients are not. The points of detection are suspended above the manikin's face, but the vertical distance of spread will be less than all other directions as the droplets must rise against gravity. Examination of droplet spread in anterior and lateral directions, in upright and semi-recumbent positions, and in a human rather than a manikin model, would be more reflective of clinical practice.

It is clear that the evidence-base for our understanding of aerosolisation with HFNO is sparse and the extent to which we can apply this knowledge to use of HFNO in COVID-19 illness is unknown. For example, these studies relate to bacterium or yeast aerosolisation rather than aerosolisation of virus. The manikin and simulation studies discussed above report shorter distances of particle spread when compared to the human studies. Overall, these studies offer us some limited reassurance. One systematic review suggested that during the severe acute respiratory syndrome (SARS) outbreaks, healthcare workers exposed to HFNO were not at increased risk of transmission, based on a low quality of evidence [11]. Whilst HFNO flow rate appears to influence aerosol spread, this does not inherently mean that flow rates should be reduced as a safety measure. Statistically significant increases in spread might not necessarily indicate a linear increase in clinical risk. Furthermore, it is well-demonstrated that some HFNO benefits are determined by flow rate, such as positive airway pressure generation and reducing flow rates will reduce these effects [12].

The risk of infection

The question is perhaps not whether HFNO can aerosolise particles, but whether this translates into significant infection risk, how this risk compares to alternative respiratory supports, and perhaps most importantly, whether we can adequately protect ourselves from such aerosolisation. Adequate PPE is foremost in risk mitigation - another finite resource that will influence risk-benefit appraisal (Table 1).

A negative pressure room is regarded as *"preferable"* for patients receiving HFNO in ANZICS guidelines [5]. These guidelines list HFNO as an aerosol-generating procedure and state more broadly that these procedures should be undertaken in a single room if a negative pressure room is not available. The WHO recommends use of a negative pressure room

when using HFNO *"whenever possible"* [4]. Surviving Sepsis Campaign guidelines recommend use of a negative pressure room for aerosol-generating procedures, though they do not list HFNO in a non-exhaustive list of examples of aerosol-generating procedures [6]. Where this is not feasible, these guidelines recommend that a portable high-efficiency particulate air filter should be used in the room of an aerosol-generating procedure *"wherever possible".* Guidelines that support the option of HFNO use in COVID-19 therefore regard a negative pressure room as desirable but not essential. No recommendations are offered regarding locations of HFNO use by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists, as these institutions recommend that HFNO should be avoided [3].

Unnecessary patient interactions with healthcare workers should be avoided and necessary ones should occur at a distance where possible. Other measures, such as a superimposed facemask (either oxygen mask or surgical facemask), can provide a cover over the nose and mouth. This may be of benefit in trapping some aerosols, provided the patient is tolerant of the mask and that a path for gas egress is ensured for the avoidance of barotrauma.

In clinical practice, HFNO is occasionally used for pre-oxygenation and apnoeic oxygenation at the time of tracheal intubation. These interventions are associated with closer clinician proximity to the patient's airway than that which is observed when HFNO is used for respiratory failure. The WHO COVID-19 guideline lists HFNO as an appropriate method of pre-oxygenation but does not support its inclusion with evidence [4]. Conversely, the ANZICS guidelines recommend that HFNO is avoided for pre-oxygenation [5]. Joint guidance issued by the Faculty of Intensive Care Medicine, Intensive Care Society, Association of Anaesthetists and Royal College of Anaesthetists states that HFNO is not currently recommended for COVID-19 patients *"around the time of intubation"* [13]. Given that there is evidence that HFNO is inferior to facemask pre-oxygenation, there is little basis for its inclusion as a pre-oxygenation method in the WHO guidelines.

Suggested approaches

If a patient is receiving HFNO therapy before pre-oxygenation, the anaesthetist should consider a reduction in flow rate and select an F_IO_2 of 1.0 when they are positioning the patient and preparing equipment at the head of the bed, as this may reduce aerosolisation during the preparatory phase of intubation. When the clinician is ready to commence pre-oxygenation, we advise that the HFNO device should be turned off before removal of the cannulae from the nares, followed by quick application of a facemask. The cannulae themselves should not be handled as this is likely where the greatest density of viral particles reside on the device. Instead, grasp the strap on either side and raise it from posterior to anterior over the head, such that the cannulae are gently removed away from the operator and the patient. The cannulae should then be deposited in a clinical waste bag which can later be used for other contaminated materials such as a disposable videolaryngoscope blade or suction catheter.

The benefit of HFNO in achieving apnoeic oxygenation of the critically ill patient during airway management has also been inconsistently demonstrated [14]. In this context, and given that aerosolisation concerns are heightened by airway instrumentation, it is difficult to advocate for broad use of apnoeic oxygenation with HFNO. Its use in patients with an anticipated difficult airway warrants greater consideration.

The human factor challenges of rapid sequence intubation are almost certainly magnified by the perfect storm of suboptimal staffing, equipment and locations of care. This risk is

compounded by a fatigued anaesthetist who has been bombarded with advice on how to optimise their practice in preceding weeks, much of which may be unfamiliar to them: from use of PPE to avoidance of techniques like facemask ventilation that are enshrined in traditional anaesthesia practice. In light of these concerns, if HFNO can avert tracheal intubation of some patients, it may paradoxically confer a protective benefit to the clinician, as a well as a therapeutic benefit to the patient and a resource-protecting benefit to the broader population.

Prone positioning is a widely used therapy in ARDS and COVID-19. Whilst mechanical ventilation is typically undertaken as a prelude to proning, it is not a pre-requisite. For proning of the awake patient, HFNO may be a more practical and comfortable alternative than NIV, though use of both has been described [15]. Early use of HFNO and of awake prone positioning has been speculated by some clinicians as a cause for the reduced mortality from COVID-19 observed in Jiangsu Province compared to Hubei Province in China [16].

Severe acute respiratory syndrome coronavirus 1 (SARS-CoV-2) ribonucleic acid (RNA) detection in the upper and lower respiratory tracts can persist for weeks [17]. However, the magnitude of viral shedding is thought to vary throughout the illness period [18]. During the SARS outbreak in 2003, one study estimated peak shedding in the nasopharynx at 6–11 days after the onset of illness [19]. If intubated patients with COVID-19 have reduced levels of viral shedding by the time of extubation then this would offer additional reassurance for the safety of HFNO as a method of post-extubation respiratory support.

Oxygen for healthcare use is a finite, albeit replenishable, resource. High-flow nasal oxygen consumes oxygen to a greater extent than other methods of respiratory support. The Faculty of Intensive Care Medicine recommends avoidance of high-flow oxygen delivery devices in order to conserve oxygen [3]. Ongoing assessment of on-site oxygen supplies and robustness of the oxygen supply chain should negate this concern sufficiently to enable HFNO use. In the unlikely event that oxygen supply issues arise, then the extent of HFNO use within the hospital would require re-appraisal.

Triage and prognostication are important components of clinical decision-making during a pandemic. Not all patients will be regarded as suitable for all therapies, irrespective of our capacities to initiate them. In circumstances where tracheal intubation may be deemed inappropriate, such as advanced age and co-morbidities, clinicians may look to alternative methods of respiratory support to aid recovery or merely to achieve symptomatic relief. Withholding such therapy solely on the basis of speculation regarding aerosolisation risks to healthcare staff seems ethically questionable.

Conclusions

The COVID-19 pandemic has evoked an understandable sense of vulnerability in healthcare workers. Emotion influences care: our fear of the unknown, and central to that, our fear that we as clinicians could become patients ourselves. It is understandable how an intervention such as HFNO that has been speculated to increase healthcare worker risk of COVID-19 could lead to a reflex abandonment of its use.

Clinicians should remain open-minded that HFNO may be an appropriate therapy for many patients for whom tracheal intubation has not yet become a necessity but for whom low-flow nasal oxygen or facemask oxygen is not providing adequate respiratory support. After

all, HFNO is a technique that aims to oxygenate patients, and that is at the heart of what we are trying to achieve. Any decision, replicated at this magnitude of global disease burden, has scope for significant impact on patient outcomes, for better or for worse. The discordant views expressed by different societies throughout the world reflect uncertainty, but patients with COVID-19 exhibit no discordance in their universal need for respiratory support. It is simplistic to suggest that in avoiding HFNO we are erring on the side of caution. This is only true if the alternatives have a better risk-benefit profile - for healthcare workers and patients. In our institutions and in our dialogue, let us no longer speak in absolute terms of favour or opposition to HFNO in COVID-19. We must make every practicable effort to protect both ourselves from infection and our patients from dogma. We must acknowledge the unknowns but prevent them from commandeering the care we provide.

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Table 1. Summary of the current role and understanding of HFNO in the management of patients with COVID-19.

- Based on knowledge of HFNO use in acute respiratory distress syndrome, this method of respiratory support may reduce the requirement for invasive mechanical ventilation of patients with COVID-19.
- Guidelines on respiratory support provided by multiple national bodies differ significantly in their stance on HFNO use in COVID-19.
- An evidence-gap exists between the demonstration of aerosolisation and its impact upon infection risk to the healthcare worker, particularly when wearing adequate personal protective equipment.
- Clinicians should make every effort to mitigate risk to themselves and other healthcare workers through appropriate use of personal protective equipment.
- Whilst a negative pressure room is preferable for HFNO use, resources may be limited. Single rooms, or as a last resort, cohorting COVID-19 patients together, may be more appropriate than contraindicating the therapy.
- In deciding not to use HFNO due to aerosolisation concerns, the clinician is committing to alternative therapies that have their own associated risks.
- For patients deemed unsuitable for tracheal intubation but who are deteriorating despite standard nasal oxygen or facemask oxygen, HFNO and CPAP are the only remaining options in active management and should be considered.
- Widespread use of HFNO requires ongoing monitoring of oxygen supply and an understanding of the robustness of the oxygen supply chain.

HFNO, high-flow nasal oxygen; CPAP, continuous positive airway pressure.