The optimal management of the patient with COVID-19 pneumonia: HFNC, NIV/CPAP or mechanical ventilation?

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Background. The recent pandemic has seen unprecedented demand for respiratory support of patients with COVID-19 pneumonia, stretching services and clinicians. Yet despite the global numbers of patients treated, guidance is not clear on the correct choice of modality or the timing of escalation of therapy for an individual patient.

This narrative review assesses the available literature on the best use of different modalities of respiratory support for an individual patient, and discusses benefits and risks of each, coupled with practical advice to improve outcomes.

On current data, in an ideal context, it appears that as disease severity worsens, conventional oxygen therapy is not sufficient alone. In more severe disease, i.e. PaO_2/FiO_2 ratios below approximately 200, helmet-CPAP (continuous positive airway pressure) (although not widely available) may be superior to high-flow nasal cannula (HFNC) therapy or facemask non-invasive ventilation (NIV)/CPAP, and that facemask NIV/CPAP may be superior to HFNC, but with noted important complications, including risk of pneumothoraces.

In an ideal context, invasive mechanical ventilation should not be delayed where indicated and available. Vitally, the choice of respiratory support should not be prescriptive but contextualised to each setting, as supply and demand of resources vary markedly between institutions. Over time, institutions should develop clear policies to guide clinicians before demand exceeds supply, and should frequently review best practice as evidence matures.

Keywords. COVID-19; mechanical ventilation; high-flow nasal cannula; continuous positive airway pressure; non-invasive ventilation.

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1. Introduction

Respiratory support for the spectrum of patients with hypoxic COVID-19 pneumonia has included: oxygen delivered via facemask or nasal cannula (or both simultaneously – so-called 'double-barrel oxygen'); high-flow nasal cannula (HFNC); continuous positive airway pressure (CPAP); non-invasive ventilation (NIV); and invasive mechanical ventilation (IMV). Despite widespread use of each modality, definitive and evidence-based guidelines informing when each is best utilised are varied and inconsistent.[1] Each modality has unique benefits and drawbacks, and decisions regarding selection of therapy for any individual COVID-19 patient, as well as when to escalate therapy, have largely been based on clinical experience, expert opinion, pre-COVID-19 literature, and gradually emerging evidence from the COVID-19 pandemic. In particular, the optimal timing of intubation and invasive mechanical ventilation remains a key, yet inadequately addressed, question for clinicians.[2]

The COVID-19 pandemic has placed unprecedented demands on global critical care services, resulting in the use of HFNC, NIV and CPAP outside an intensive care or high-care setting, posing novel challenges to healthcare staff and with potential risks to patients.[3] The challenges involved in providing appropriate ventilatory support to patients are further amplified in Africa by a lack of resources including critical care beds, equipment, trained intensivists, and the world's lowest vaccination rates.[4,5] Given these difficulties, guidance on the optimal use of limited resources, such as HFNC and NIV/CPAP, is important. However, it is impossible to provide blanket guidance on the use of such modalities without careful consideration of the context in which they are required.

The purpose of this narrative review is to assist clinicians with best-practice decisions in the respiratory support of critically ill patients with COVID-19 pneumonia, by summarising the available evidence and comparing the use of the different modalities of ventilation, namely conventional HFNC, NIV/CPAP and IMV. Evidence is supplemented by expert opinion from the authors where knowledge gaps remain and, importantly, taking into account the large variability in resources between institutions, regions and nations, as well as demand for those resources during COVID-19 waves. Thus, while providing guidance for best practice, the review concludes with the importance of contextualisation in decision making.

2. High-flow nasal cannula oxygen therapy (HFNC)

HFNC had not been widely adopted as a means of respiratory support prior to the COVID-19 pandemic. It is an oxygen-delivery method capable of supplying high inspired partial pressures of warmed and humidified oxygen. The device consists of a flow generator which provides gas flow rates of up to 60L/min, an air-oxygen blender that can vary the inspired oxygen fraction (FiO_2) ranging from 21% to 100% irrespective of flow rate, and a humidifier that saturates the gas mixture. Certain devices lack an air-oxygen blender and the inspired oxygen fraction is set manually by the adjustment of a separate oxygen flowmeter. The disadvantage of this is that when flow is altered, the inspired fraction of oxygen is changed.

Humidification temperatures can range from 31°C - 37°C and are adjusted to patient comfort. To minimise condensation, the heated humidified gas flows through insulated and heated tubing and is delivered to the patient via a soft and pliable nasal interface, offering advantage over conventional nasal cannulae, or venturi and reservoir mask systems. HFNC has an added advantage of allowing the patient to talk, eat and drink during treatment.

The main physiological effect of HFNC in improving oxygenation is due to the very high flow rates of gas delivered. These flow rates better match the inspiratory demands of patients in respiratory failure. In conventional oxygen interfaces (e.g. venturi masks), the FiO_2 is reduced by entrainment of room air at the mouth, proportional to the patient's minute ventilation and peak inspiratory flow (PIF) – both of which are increased in respiratory distress.[6-8] HFNC delivers a flow which far exceeds the patient's minute ventilation and PIF, thus offsetting room air entrainment, and delivering a reliable FiO_2. A separate but related mechanism is that HFNC washes out the nasopharyngeal dead space. This purges the CO_2 (and nitrogen if high FiO_2) from exhaled breath in the upper airways, reducing rebreathing and thereby increasing both the alveolar partial pressure of oxygen and the fraction of minute ventilation participating in gas exchange.[9] Lastly, the high flow rates increase positive end-expiratory pressure (PEEP), which can decrease the work of breathing, and improve oxygenation. However, this effect is likely to be modest at best, with the increase in PEEP estimated to be only ~1 cmH_2O of PEEP for every 10 L/min of high-flow delivered, with changes through the respiratory cycle, and is reduced with open mouth-breathing.[10]

2.1. HFNC compared with conventional oxygen therapy (COT)

The term COT includes oxygen delivered via reservoir facemask, venturi mask (40% FiO_2) and nasal cannula.

At face value, HFNC has many benefits over COT, yet there is surprisingly little evidence for its use in respiratory failure in adults, particularly prior to the COVID-19 pandemic.[11] The initial preference for HFNC in many parts of the world was based on indirect data from patients with non-COVID-19 causes of hypoxaemic respiratory failure which, on balance, favoured HFNC compared with CPAP, as well as studies that suggested a high failure rate of CPAP in patients with Middle East respiratory syndrome (MERS).[12]

The effectiveness of HFNC in a resource-limited setting was established by Calligaro *et al.*[13] during the first wave of COVID-19, and included 293 consecutive patients with COVID-19-related severe respiratory failure. The median (IQR) arterial oxygen partial pressure to fraction inspired oxygen ratio (PaO_2/FiO_2) was 68. Of these, 47% of patients were successfully weaned from HFNC. The median duration of HFNC was 6 days in those successfully treated v. 2 days in those who failed ($p<0.001$). A higher ratio of oxygen saturation/FiO_2 to respiratory rate within 6 h (ROX-6 score) after HFNC commencement was associated with success. One limitation to this study was that there was no control group.

It may be expected that, in COVID-19 pneumonia, HFNC would have better outcomes compared with COT, given the reduced work of breathing and improved mechanisms of oxygenation discussed above. However, the data for definitive conclusions are not yet mature. Equally, in resource-divergent contexts, one must consider if these modalities are an 'end in themselves' (i.e. are an indication of what is available) or a 'bridge' to more invasive support.

A recent, predominantly pre-COVID-19 Cochrane review that included 31 studies (22 parallel-group and nine cross-over designs) with 5 136 patients, concluded that HFNC in general may lead to less treatment failure when compared with COT, but probably makes little or no difference to treatment failure when compared with CPAP or nasal intermittent positive pressure ventilation (NIPPV) in hypoxic respiratory failure.[14] However, the authors rated the evidence to be of low or very low certainty. Another meta-analysis that included 25 randomised clinical trials (3 804 participants), concluded that HFNC was associated with a reduced need for intubation compared with COT (risk ratio 0.76).[15]

In patients with severe COVID-19 pneumonia, a retrospective report from France found reduced rates of intubation and mechanical ventilation with HFNC compared with other modalities. The mean PaO_2/FiO_2 ratio was 126 (97 - 195) in the patients who received HFNC and 130 (86 - 189) in those who did not.[16] In contrast, the authors of the recently concluded RECOVERY-respiratory support (RS) trial concluded that 'HFNC provided no benefit compared with COT' in the primary outcome of intubation or death within 30 days.[17] It should be noted that the mean PaO_2/FiO_2 was 135 for patients treated with COT and 139 for those offered HFNC (much higher than in the study by Calligaro *et al.*[13]). Moreover, the median time to intubation was one day for both groups, suggesting that the investigators opted for an 'early intubation' strategy, which significantly limits the interpretation of the results for contexts where escalation to invasive mechanical ventilation is not feasible.

In a recent randomised controlled trial (RCT) of 199 patients who were randomly assigned HFNC or COT (median PaO_2/FiO_2 ratios 104 and 105, respectively) for COVID-19, HFNC significantly reduced the need for IMV (HR 0.62; 95% confidence interval (CI) 0.39 - 0.96) as well as reducing the time to clinical recovery.[18] Thus, it is possible that the benefit of HFNC over COT may be maximal in patients with more severe disease and lower PaO_2/FiO_2 ratios.

The choice between HFNC and COT is context specific and needs to be carefully considered, with many questions remaining. It remains probable that HFNC is a better modality than COT where escalation to mechanical ventilation is not possible, and for patients with more severe acute respiratory distress syndrome (ARDS) (e.g. PaO_2/FiO_2 ratios <150). It is not known if the same holds true in settings where invasive ventilation is readily available, or for less severe ARDS (e.g. PaO_2/FiO_2 ratios >200). Further, the modality in which COT is administered should be considered, and HFNC may have less benefit over reservoir facemask oxygen than venturi mask and nasal cannula oxygen therapy. These questions remain unanswered.

Additionally, concerns have been raised about prolonged HFNC delaying invasive ventilation, when indicated and available. HFNC has been anecdotally observed to result in significant atelectasis when prolonged over a number of days. This is probably due to a combination of factors including: inadequate PEEP, washout of nitrogen splinting of alveoli with high FiO_2, reduced lung compliance resulting in smaller tidal volumes at high respiratory rates, and patient immobility. This progression to atelectasis in severe COVID-19 pneumonia may theoretically make delayed invasive ventilation less successful.

2.2. Tips and tricks for HFNC

HFNC should ideally be initiated in an awake and co-operative patient once the saturation drops below 92% despite receiving oxygen.[13] HFNC is not an appropriate modality for patients with a rising arterial partial pressure of carbon dioxide ($PaCO_2$), nor with an altered mental state, nor very high work of breathing.[13]

HFNC can be administered by non-ICU specialists in non-critical care environments without the use of invasive monitoring or intensive patient-to-nurse ratios.[13,19] This has important implications for resource-constrained settings where access to intensive care for patients with severe COVID-19 pneumonia is limited. The minimum monitoring requirement for HFNC is pulse oximetry. Ideally, and if available, patients should be cohorted in high-care areas or COVID-19 wards, with the hope that economies of scale and increased access to HFNC-trained staff may reduce costs and improve outcomes. The degree to which HFNC can be scaled up is highly dependent on local oxygen capacity, the delivery infrastructure within hospitals, and the robustness of the oxygen supply chain.

HFNC can also be combined with awake self-proning, which itself has been shown to improve oxygenation and reduce the need for intubation in COVID-19 pneumonia.[20] HFNC should be initiated at a flow rate of 45 - 60 L/min, with titration of the FiO_2 to maintain adequate oxygenation. The nasal interface should be an appropriate size for the patient and adjusted to ensure a proper fit. Common complications that can cause rapid desaturation, and even death, are tube kinking and interface malpositioning. Malpositioning, or so-called interface disconnections, occur when the nasal interface either dislodges from the patient's nose or if the interface occludes against the side of the nasal cavity, thus obstructing the flow of oxygen. Patients should be instructed to keep their mouths closed as far as possible in order to maximise the beneficial effects of HFNC including PEEP, dead space washout, and decreasing room air entrainment.

The addition of facemask oxygen to patients on HFNC (all PaO_2/FiO_2 <98) improved oxygen saturation by a mean of 5.1% (95% CI 3 - 7.2%) in a small study of 18 patients. The mechanism for this is not entirely understood; however, the authors hypothesised that a facemask may limit the entrainment of room air, especially when the patient breathes with their mouth open.[21] While this is encouraging, especially in countries where escalation of care beyond HFNC may be limited, one caution should be exercised: where poor nurse:patient ratios exist, the facemask may obscure possible disconnections of the HFNC interface.

Patients should be reassessed regularly after HFNC initiation to determine the need for escalation of respiratory support; the oxygen saturation/FiO_2 divided by respiratory rate (ROX score) is a useful tool for the early prediction of treatment outcome.[13,22,23] The timing of intubation remains a difficult decision which relies on a composite clinical assessment of respiratory effort, patient exhaustion, rising arterial partial pressure of carbon dioxide ($PaCO_2$) or altered mental state. The ROX score and ROX score trends are objective measures that utilise easily measured respiratory parameters and can potentially reassure the clinician about the safety of continuing with HFNC. Sudden deterioration in a patient's condition should precipitate rapid reassessment of the equipment and interfaces, as patients frequently have limited physiological reserve. The electricity supply should be checked, as many devices do not contain an in-built back-up power supply. Additionally, humidifier irrigation fluid should be checked regularly, as a lack of humidification can cause airway desiccation and decrease tolerance of the device.

An overlooked aspect of patient monitoring is the effect that ethnicity has on pulse oximeter readings. A recent article highlighted that in the crucial SpO_2 bracket of 85 - 89%, pulse oximeters record the SpO_2 of black patients as 3.9% higher than the true value. This is in comparison with white patients, where the pulse oximeter overestimates the true SpO_2 to a lesser degree (the pulse oximeter reading is 2.4% higher than the true SpO_2 on average). Using a mixed-effects linear model, in comparison with white patients, pulse oximetry overestimated the true SpO_2 in black patients by 1.8%. Thus, using SpO_2 monitoring alone, the severity of hypoxia in black patients may be underestimated in comparison with white patients.[24]

There has been concern that HFNC may increase bio-aerosol dispersion in the environment owing to the high gas flow, with the potential for nosocomial transmission to other patients and healthcare workers. However, this risk seems to be considerably overstated.[25,26] Dispersion studies have shown that, compared with oxygen therapy with a mask, the utilisation of HFNC does not increase either dispersion or microbiological contamination into the environment. This is particularly so as the patient can wear a surgical mask over the HFNC to reduce aerosol transmission during coughing or sneezing, which represents an additional benefit.

3. NIV/CPAP (including helmet CPAP)

In clinical medicine, the terms NIV and CPAP are often used (incorrectly) interchangeably. For the purposes of this review, NIV

is defined as the application of bi-level positive pressure and CPAP is defined as the application of a single level of positive pressure throughout the respiratory cycle. These modalities may be delivered via a facemask or helmet apparatus (CPAP only).

3.1. Benefits and risks

Although evidence for the efficacy of NIV and CPAP in COVID-19 is limited,[27-30] it may be considered in the management of acute respiratory failure. Their benefits are well documented in patients with chronic obstructive pulmonary disease (COPD) and cardiogenic pulmonary oedema.[31] However, they have been associated with a failure rate exceeding 70% in viral pneumonias in general[32] and, before COVID-19, a higher mortality rate was reported in ARDS patients with a PaO_2/FiO_2 ratio <150 mmHg compared with IMV.[33]

A lack of randomised controlled trials on the use of NIV/CPAP in COVID-19 has resulted in significant variations in international guidelines[34] and clinical practice,[35] reflecting existing uncertainty of benefits and harm, and a variety of factors influencing use, including availability of critical care beds[35] and the theoretical risk of nosocomial infections.

The potential to avert intubation[18,27,36] and the considerable morbidity and mortality associated with IMV[37,38] makes NIV/CPAP appealing modalities in COVID-19. Additionally, NIV/CPAP has emerged as feasible modalities outside the ICU. In a systematic review and meta-analysis of 17 studies and 3 377 patients with COVID-19 outside an ICU setting, 26% (21 - 30%) failed NIV and required intubation, with an overall mortality of 36% (30 - 41%).[3] The converse argument remains that modified care outside a critical care unit may be detrimental. Without appropriate monitoring and nursing care, inadvertent disconnection from the ventilator circuit in the agitated patient, device intolerance, suboptimal delivery of nutrition, and delayed recognition of clinical deterioration are substantial risks.

Of concern, patients with COVID-19 who have failed NIV and require intubation have a higher risk of mortality.[3,27,39] Benefits related to the avoidance of IMV must be balanced with the risk of NIV/CPAP failure and potentially worse outcomes that follow. In a retrospective cohort of 61 patients, Avdeev *et al.*[28] reported a mortality rate of 88% in the 28% of patients who failed NIV and required IMV, as compared with the 72% where NIV was deemed successful, although probable confounding limits interpretation. Delayed intubation and patient self-inflicted lung injury (P-SILI) are postulated to contribute to these adverse outcomes. Elevated respiratory drive, high tidal volume and increased fluctuations in pleural pressure during spontaneous breathing may exacerbate lung injury[3,40,41] and a higher incidence of pneumomediastinum has been reported.[17] Extrapolated from IMV, measures to mitigate P-SILI in NIV currently being considered include limitation of tidal volume,[42] application of PEEP[43] and a reduction of spontaneous effort.[40] However, to date, no ventilatory NIV strategy has been identified that might limit the risk and improve patient outcomes.[40]

If available, helmet CPAP is a preferred option over facemask NIV, having the benefits of improved patient comfort and tolerance, the ability to deliver higher levels of PEEP than facemask NIV and HFNC,[44] and decreased aerosol dispersion.[45] Interestingly, a single-centre RCT of 83 patients which compared facemask NIV with helmet CPAP (median PaO_2/FiO_2 ratio of 144 in the facemask NIV group, 118 in the helmet CPAP group) showed that helmet CPAP reduced the need for intubation (61% v. 18%) and decreased mortality[46] compared with facemask NIV, despite lower PaO_2/FiO_2 ratios. Moreover, helmet CPAP negates the need for a ventilator and may be connected to an oxygen system in a ward, which may be particularly desirable in a pandemic setting.

Although helmet CPAP is not available in many places, a single-centre, pre-COVID-19 study from Canada suggests that helmet CPAP is more cost-effective than facemask CPAP.[47] It remains to be seen if this benefit may be extrapolated to other contexts.

4. Outcome benefits of NIV/CPAP

There are copious pre-COVID-19 data supporting the use of NIV/CPAP in patients with acute exacerbations of COPD and acute cardiogenic pulmonary oedema.[48,49] However, data defining the benefit of NIV/CPAP in patients with acute respiratory failure due to other causes have historically been less clear.[50]

A network meta-analysis[15] was conducted which consisted of 25 pre-COVID-19 studies comparing helmet CPAP, facemask NIV and HFNC with COT. Intubation rates were significantly lower in the three non-invasive groups compared with COT (helmet CPAP: RR 0.26, 95% CI 0.14 - 0.46; facemask NIV: RR 0.76, 95% CI 0.62 - 0.90; HFNC, RR 0.76, 95% CI 0.55 - 0.99). When compared with HFNC, helmet CPAP was associated with a significantly decreased risk of intubation (RR 0.35, 95% CI 0.18 - 0.66) while facemask NIV was not (RR 1.01, 95% CI 0.74 - 1.38). In comparison with COT, the risk of death was lower in the helmet CPAP and facemask NIV groups (helmet CPAP: RR 0.40, 95% CI 0.24 - 0.6; facemask NIV: RR 0.83, 95% CI 0.68 - 0.99) but was not significantly different for the HFNC group (RR 0.87, 95% CI 0.62 - 1.15). Importantly, the mortality benefit in the facemask NIV group was not significant in patients with severe disease (mean PaO_2:FiO_2 <200 mmHg). COPD and congestive cardiac failure were excluded from the analysis, implying these were the most likely groups to benefit from NIV/CPAP. However, the heterogeneity of the patient groups in the included studies was an important limitation in this meta-analysis.

In the setting of COVID-19, data do not consistently demonstrate superior outcomes of one or other of NIV/CPAP and HFNC v. COT.[16,29,36,51-53]

Helmet CPAP has further been compared with HFNC in a randomised trial from Italy of 109 COVID-19 infected patients with moderate or severe acute hypoxaemic respiratory failure. Patients receiving helmet CPAP experienced lower rates of intubation (30% v. 51%) as well as more days free of invasive mechanical ventilation (28 v. 25 days).[36]

The RECOVERY-RS Trial[17] is the largest clinical trial to date to compare CPAP, HFNC and COT in patients with moderate or severe COVID-19. The CPAP group had a reduced composite outcome risk of endotracheal intubation or death within 30 days (OR 0.72, 95% CI 0.53 - 0.96, p=0.03). However, the CPAP group experienced a higher rate of adverse events such as haemodynamic instability, pneumothorax and pneumomediastinum.

Although there is a lack of robust data to inform the choice of the best non-invasive modality, current evidence suggests that helmet

CPAP may have an advantage over facemask NIV/CPAP,[15] while either facemask or helmet NIV/CPAP may hold benefit over HFNC.[17] However, more data are needed both to confirm this evidence, as well as to determine which modality is best for which level of disease severity. For example, do patients with lower PaO_2/FiO_2 ratios (<150) or higher work of breathing do better on NIV/CPAP compared with HFNC, or vice versa?

When to initiate NIV/CPAP

Clinical trials and published guidelines have varied in the criteria used to initiate NIV/CPAP.[17,29,36,54] Similar to HFNC, ongoing hypoxaemia (SpO_2<94% at sea level) while on COT (10 - 15 L/min) and respiratory fatigue (RR>30/min, accessory muscle use, hypercapnia) should be used as indicators for initiating NIV/CPAP. Once a trial of NIV/CPAP is considered, it should be commenced as soon as possible and closely monitored for worsening respiratory fatigue. As inspiratory effort has been associated with the development of P-SILI,[32,55] it should be considered in patient monitoring.

In terms of evaluating for NIV/CPAP failure, the ROX score utilises respiratory rate as a surrogate for respiratory effort, but does not fully account for respiratory muscle exertion. An alternative monitoring tool is the HACOR score (a composite score of heart rate, acidosis, consciousness, oxygenation and respiratory rate)[56] which has been shown to predict NIV/CPAP failure accurately. However, this score has the same limitation as the ROX score in terms of not considering respiratory effort (only rate), and has not been shown to be better than PaO_2/FiO_2 ratio in predicting NIV/CPAP failure.[57]

Who is the ideal candidate for NIV/CPAP?

With current data available, there is no 'ideal' candidate for NIV/CPAP. In addition to hypoxaemia, patients with a high work of breathing are most likely to derive benefit from NIV/CPAP,[15] but this should be balanced against a patient's tolerance for the modality.

Evidence supports the use of NIV/CPAP in acute exacerbation of COPD and cardiogenic pulmonary oedema,[32,48,49] and these conditions are incorporated into clinical algorithms for COVID-19,[50] with logic suggesting that NIV/CPAP may be the preferred modality.

Who should not be placed on NIV/CPAP?

Patients who have an emergent need for endotracheal intubation should not be placed on NIV/CPAP, e.g. owing to imminent cardiac or respiratory arrest. Other relative contra-indications to NIV/CPAP include: diminished level of consciousness; patients who are unable to co-operate; those with compromised upper airways owing to obstructions; inability to clear secretions; and patients with non-respiratory organ failure (e.g. severe encephalopathy, severe upper gastrointestinal bleeding, haemodynamic instability, or unstable cardiac arrhythmias).[34,58]

4.1. Tips and tricks for NIV/CPAP

A variety of interfaces through which NIV/CPAP is delivered are available, each with its own benefits and pitfalls. Careful selection for proper fit, optimal seal and patient tolerance is essential for success, and is an essential part of therapy initiation. Patients should be 'coached' through initiation of NIV/CPAP and, to avoid feelings of claustrophobia, patients can be asked to self-apply (i.e. hold) the facemask, before the head straps are attached. Additionally, initiation at lower levels of pressure is advised, with gradual escalation over the following few hours.[59] Regular pressure care of the nasal bridge is needed in patients receiving prolonged NIV/CPAP.

During COVID-19, some clinicians have used intermittent NIV/CPAP to address the basal atelectasis that invariably occurs with prolonged HFNC and high FiO_2. Although there is physiological rationale for this approach, and reduction in FiO_2 has anecdotally been observed in some patients, the objective effectiveness of this strategy is not known, and should not delay IMV when available.

NIV/CPAP has an added benefit of using less oxygen compared with HFNC, which may allow safer transfer of patients between healthcare facilities, or within facilities (e.g. transport for imaging). As with HFNC, NIV/CPAP does not appear to result in increased bio-aerosol dispersion in comparison with COT via nasal prong or facemask.[60]

5. Invasive mechanical ventilation (IMV)

5.1. Benefits and risks

The risks and benefits of ventilation in the setting of COVID-19 pneumonia are not dissimilar to the risks and benefits of ventilation in critical care in general. Unfortunately, the literature gives neither evidence of a direct comparison of NIV/CPAP or HFNC to IMV in the setting of COVID-19, nor as to the ideal timing to transition to IMV.

For reasons of resource limitation, most institutions have followed a stepwise increase in respiratory support for hypoxic patients with COVID-19 pneumonia: initiating with COT via nasal prongs; increasing the inspired FiO_2 progressively with various facemask devices; and thereafter either to NIV/CPAP or HFNC; and finally to IMV.

It would be useful if there were prospective randomised trials to guide clinicians as to the optimal timing for IMV. The point at which patients are referred for IMV has been driven by availability of staff and ventilators, and also by various triage mechanisms. There are some differences with respect to the ventilation of patients with COVID-19 pneumonia that are worth considering. For example, severely hypoxic patients with COVID-19 pneumonia frequently require the use of neuromuscular blockers in combination with prone positioning and high ventilator pressures, and these have their own specific considerations, risks and benefits. The use of neuromuscular blockers brings the risk of awareness in the face of inadequate sedation, as well as an increased risk for the development of both deep vein thrombosis and pressure sores.[61]

The ventilation of patients in the prone position reduces access to the airway and central venous lines and carries the risk of accidental displacement of invasive devices with repetitive changing of position from supine to prone and back again. While patients ventilated with COVID-19 pneumonia are not phenotypically identical from the perspective of pulmonary mechanics,[62] many patients are exposed to ventilatory parameters that are far from ideal. Persistently high FiO_2 in combination with high driving and plateau pressures together with large ventilatory power, tend to make some degree of ventilator-induced lung injury (VILI) unavoidable.[63,64]

Every effort should be made to provide non-injurious ventilation. In order to achieve this, both permissive hypercapnoea and permissive hypoxia have been utilised to avoid hypoxia (delivery) and VILI.

Despite the potentially negative consequences of IMV, the

alternative of patients remaining on non-invasive support in the face of poor lung mechanics and inadequate oxygenation is dire. Clinicians around the world have had to face the terrible situation of providing palliative care to patients who refuse IMV or where resources and triage criteria make ventilation not an option. South African data give a ventilated survival rate of 30.8%.[65]

The ideal point in time at which IMV should be instituted remains a vexed question. Should all resources be available, and all patients candidates for IMV (no triage reason for exclusion), it should be instituted when other means of non-invasive support fail. The point at which failure occurs is difficult to identify. It appears that patients who have had prolonged non-invasive respiratory support have a less favourable outcome with IMV compared with patients who are intubated earlier. For an individual patient, both the current severity and trajectory of disease need to be repeatedly assessed, and late intubations avoided.[66] An earlier identified intubation time point would be ideal, to discriminate early from late intubations. Although anecdotal, in our experience this point is reached at approximately two weeks following the need for respiratory support; however, better data are needed. Patients with incidental COVID-19 presenting for another indication (e.g. for trauma) should probably be considered for IMV using the same criteria for their primary (non-COVID-19) condition, and appear to have a much better outcome.

Ideal candidates for invasive ventilatory support are those who are younger, have little or no comorbidity and low sequential organ failure assessment (SOFA) scores. Conversely, those with poorer outcomes are older, have more comorbidity, higher SOFA scores and require IMV late in their illness.[67] This should not, however, exclude them from consideration should resources be available. The requirement for either vasopressor or renal support around the time of initiation of ventilation is associated with a poor outcome.

Tips and tricks for IMV

It has been our collective experience that many patients with COVID-19 pneumonia deteriorate on IMV despite usual lung protective ventilation, with escalating oxygen requirement and declining PaO_2/FiO_2 ratios. In the absence of ECMO, the following strategies can be attempted to improve ventilation and outcomes.

Recruitment manoeuvres

Recruitment manoeuvres in severely hypoxaemic patients may transiently increase oxygenation but no outcome studies demonstrate mortality benefit. They may, however, be considered as a rescue therapy although the step-wise manoeuvre is not recommended as it may cause harm.[68,69]

Airway pressure release ventilation (APRV)

Lung elastance is not homogeneous, and application of positive pressure results in regional over- and under-distention. Early initiation of APRV may reduce the incidence of ARDS and mortality and, in a pre-COVID-19 comparison with conventional low tidal volume ventilation, oxygenation, compliance, need for sedation and vasopressor use, all favoured the APRV.[70-73]

APRV applies CPAP with time-cycled releases to a lower pressure, usually zero, while allowing uninterrupted spontaneous respiration to occur. Accordingly, there are four settings: pressure high (P high), pressure low (P low), time high (T high) and time low (T low). T low is usually 0.35 - 0.8 seconds, depending on lung elastance, and the end expiratory lung volume that results can be manipulated by changing the duration of T low and observing the expiratory flow pattern with the next cycle initiating at between 50 and 75% of the peak expiratory flow rate. The auto-PEEP so generated allows slow non-traumatic recruitment to occur, despite differing alveolar re-expansion time constants.[71-76] Spontaneous ventilation also frequently allows sedation or neuromuscular blockade (NMB) to be reduced or avoided.

Avoidance of fluid overload

Inflammatory processes are associated with capillary leak and non-cardiogenic pulmonary oedema which is exacerbated by fluid overload. This worsens oxygenation and is associated with worse outcome.[77,78] Fluid overload predicts longer mechanical ventilation, prolongs ICU and hospital stay, and increases mortality.[79,80]

Careful fluid management from the start, consisting of restrictive fluid administration and judicious use of diuretics, may reduce time on the ventilator and reduce mortality.[81] However, a de-resuscitation protocol in patients who have already been fluid overloaded also improves outcome and reduces mortality safely, the one caveat being that de-resuscitation should not be too rapid such that intravascular volume is depleted with subsequent hypoperfusion.[82,83]

Proning

Pre-COVID-19, proning had been associated with improved outcome and gas exchange owing to reduced ventilation perfusion mismatch.[84-86] Whereas there are copious data on awake proning with COVID-19, there is less on its use in mechanically ventilated patients. Recent studies have demonstrated that oxygenation improves but the effect on outcome remains less clear. A recent study utilised data from the STOP-COVID study to emulate a hypothetical 'target trial' which analysed observational data to guide practice.[87] Of 2 338 patients included, 702 (30.0%) were proned and had a lower adjusted risk of death with a hazard ratio of 0.84 (95% CI 0.73 - 0.97).[88] Another large study of 1 057 patients, with ARDS of varying severity of whom 61% were proned, assessed mortality based on disease severity and whether oxygenation improved. Of the proned patients, 78% responded to proning (defined as an increase in the PaO_2/FiO_2 ratio of at least 20 mmHg after proning) and were termed O_2-responders. O_2-responders, had a mortality rate of 38% compared with non-O_2-responders who had a mortality rate of 65% (p=0.039). This study was limited by the fact that the proned patients had more severe disease and a higher mortality rate overall in comparison with those who were not proned.[89] In addition, patients with lower driving pressures had a greater increase in PaO_2/FiO_2 ratio after proning. This study correlated with the findings of another study in which response to proning was independently associated with liberation from IMV at 28 days and this was proportional to the extent of the response.[90]

As stated, it is difficult to determine if proning is actually associated with improved outcome. It is possible that response merely predicts increased likelihood of survival.[91]

Neuromuscular blockade (NMB)

Early reports indicated that NMB, particularly with cis-atracurium, may be beneficial in patients with severe ARDS and possibly may

function as a rescue therapy.[92] Subsequent studies have not always supported the concept and benefit has not always been observed.[93] In addition, a meta-analysis of five studies did not show survival benefit.[94] NMB is still utilised with refractory hypoxaemia in an attempt to decrease the metabolic rate and energy expenditure and to reduce the likelihood of unplanned extubation.

Permissive hypoxaemia

If ECMO is unavailable and there is profound hypoxaemia despite maximal ventilatory support, permissive hypoxaemia may be necessary rather than using injurious mechanical ventilation.[95] Saturations as low as 80% are survivable so long as oxygen delivery is maintained, as measured by serial measurements of central venous oxygen saturation, central venous-to-arterial partial pressure of carbon dioxide difference, or lactate.[96]

Bronchoscopy

Although there is a risk to both operator and assistants, occasional patients, particularly those who have not had access to physiotherapy, may develop mucus plugs which may be present without obvious atelectasis on imaging. Removal of these has been shown to improve oxygenation.[97]

6. Contextualisation for settings where resources are limited

It is important to appreciate that the above discussion highlights the choice of mode of ventilation for an individual patient with COVID-19 pneumonia regardless of resources. However, resources vary considerably between countries, regions and institutions, and therefore the discussion presented above needs to be contextualised to the clinician's own environment. In reality, choice of management is often determined not only by best practice guidelines, but also by resource availability and resource demand. The COVID-19 pandemic to date has demonstrated that demand for those resources varies markedly over time as the various waves wax and wane. This can quickly lead to demand outstripping resource availability, even in the most well-resourced environments.

Clinicians and healthcare planners working in low- and middle-income countries (LMICs) are not unfamiliar with making triage decisions, yet the sheer numbers of patients simultaneously requiring triage decisions has affected the mental health of many healthcare workers during the COVID-19 pandemic, given the consequences of choices made. It is therefore important for institutions to plan in advance, and decide on: modalities of respiratory support they will offer, thresholds and criteria for escalation of care, as well as criteria for withdrawal of therapy. Advanced planning and effective communication to all staff will reduce the real-time stress to frontline workers, who are able to refer back to institutional policies. Any institutional planning needs to anticipate fluctuations between demand and supply of resources, and update frequently as new data emerge. Institutional plans should involve medical ethicists and, where possible, emergency 'ethics teams' should be available during times of peak need to assist with decision making, especially regarding termination-of-care decisions. Unfortunately, this planning is best done between waves, when most frontline workers are exhausted, recovering and naturally avoidant of such topics.

When planning for care, a number of technical factors need to be considered. The potential institutional demand for resources should be estimated by determining both the population to be served, as well as whether alternative institutions for patient care are available in the geographical vicinity. The equipment needed or available to provide various ventilation options should be assessed. This includes assessment not only as to what equipment is required, but additionally whether the sophistication of this equipment is appropriate to the context of the institution, whether maintenance and sterilisation of the equipment is feasible, and whether a continual supply of disposables is secured.

Equally important is consideration of the human resources required for each modality of respiratory support. In LMICs, there is a dire shortage of trained and qualified critical care personnel, such as physicians, nurses and technologists.[98] Of necessity, during the COVID-19 pandemic, staff not *au fait* with equipment or advanced patient management, were frequently required to manage patients above their level of expertise, placing them at risk of disease transmission and long-term mental health disorders.[99] Further, where there is lack of knowledge or supervision, minor technical problems (e.g. interface kinking or disconnection) can result in unnecessary patient death. To improve outcomes, critical care physicians need to embrace the continual role of trainer for inexperienced staff, as well as to monitor, support and audit the care being provided.

Additionally, one needs to consider the space required for different modalities offered. Where no dedicated ICU or high-care beds are available, will the same care be provided in general wards, or will lesser care be offered? In most contexts, institutions have elected to offer lower levels of care in general wards, but this need not hold true for well-resourced institutions. It is strongly recommended that severely ill patients be cohorted together as far as possible, e.g. in 'high-flow wards'. One caveat that should be added is that oxygen and power supply requirements need to be met in those locations, and engineers need to be consulted.

While a comprehensive review of infection prevention and control (IPC) pertaining to COVID-19 pneumonia is outside the scope of this review, important barriers in the prevention of transmission of SARS-CoV-2 to healthcare workers in LMICs include availability of personal protective equipment (PPE), lack of both trained medical staff and staff trained in the usage of PPE, and a limited environmental infrastructure to allow for isolation and containment of patients with COVID-19. The development of IPC guidelines with implementation through proper IPC training remains a cornerstone in preventing the nosocomial transmission of SARS-CoV-2.[100] Other measures to improve IPC that are applicable in LMICs include isolating and cohorting patients if individual isolation is not possible, forming dedicated teams of healthcare workers who work exclusively with COVID-19 patients, and limiting non-essential visitors to hospitals.[101]

Summary

On the currently available evidence, for the individual patient, in an ideal context, as COVID-19 pneumonia severity worsens, it appears that COT is not as good as other modalities. With increasing severity of disease (especially PaO_2/FiO_2 ratios below approximately 200) helmet-CPAP may be superior to HFNC or facemask CPAP, and facemask

CPAP may be superior to HFNC, but with the noted complications. IMV should not be delayed where indicated.

However, these recommendations need to be strongly tempered and contextualised to the setting where care is being given, and the issues of supply and demand of human and other resources. Further, the data are rapidly evolving and these conclusions will most likely need to be amended as better data emerge.

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