Noninvasive Respiratory Support

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Despite its life-saving nature, invasive mechanical ventilation does not come without risk, and the avoidance of invasive mechanical ventilation is the primary goal of noninvasive respiratory support. Noninvasive respiratory support in the form of continuous or bi-level positive airway pressure were considered the only viable options to accomplish this for many years. Innovation and research have led to high-flow nasal cannula being added to the list of specialized therapies clinically shown to reduce escalation of care and intubation rates in patients presenting with acute respiratory failure. The amount of research being performed in this clinical space is impressive, to say the least, and it is rapidly evolving. It is the responsibility of the clinicians trained to use these therapies in the management of respiratory failure to understand the currently available evidence, benefits, and risks associated with the type of noninvasive respiratory support being used to treat our patients.
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Introduction

Prior to the introduction of pressure support ventilation, the options for invasive ventilatory assistance were to have controlled pre-set volume delivered or completely unassisted breathing. This made the process of complicated weaning and muscle conditioning problematic. The addition of pressure support ventilation increased patient comfort and reduced work of breathing while effectively maintaining gas exchange.[1,2] With evidence that spontaneous breathing with pressure support could support gas exchange and reduce inspiratory effort, the concept of providing a form of inspiratory support with a face mask was next to be tested. In 1990, Brochard and colleagues[3] provided inspiratory pressure support via mask to subjects with an exacerbation of COPD. The study evaluated the physiological effects of inspiratory support by mask in 11 subjects and the effectiveness of the therapy in 13 subjects. The authors had designed a "noninvasive ventilatory-assistance apparatus" capable of delivering the inspiratory pressure when demanded by the patient, and it could cycle off at adjustable criteria based on flow deceleration. This study reported significant improvements in arterial pH, P_{aCO_2}, and a significant reduction in breathing frequency. Additionally, when compared to a retrospective

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cohort, the subjects followed for treatment efficacy had significantly fewer intubations ($P < .001$) and a significantly shorter ICU length of stay ($P < .01$).

Building upon their previous work, Brochard et al[4] conducted a randomized controlled trial comparing standard therapy with noninvasive ventilation (NIV) in 85 subjects with a COPD exacerbation. This study reported a significant reduction in the need for intubation (26% vs 74%, $P < .001$) and in-hospital mortality (9% vs 29%, $P = .02$) for subjects treated with NIV. This began the steady growth in research assessing the various conditions that might benefit from the use of NIV with the outcome of avoiding intubation.

Physiological Benefits of NIV in Adults

The physiological benefits of NIV are realized through the augmentation of tidal volume and reduction in the work of breathing. This can easily be conceptualized when considering the work required to breathe (ie, the basic equation of motion). An individual must generate the muscular pressure required to overcome any resistive and/or elastic forces imposed on the airways and lungs. NIV provides an inspiratory pressure that can offload (mostly share) the work required to overcome these forces. Additionally, expiratory pressure can assist with increased elastic forces due to atelectasis by providing pressure aimed at maintaining stable alveoli during exhalation.

The use of NIV involves the use of a mask interface. In the adult acute care environment, this generally involves an interface that covers both the mouth and the nose. Early studies found that intolerance of therapy due to the mask interface could lead to treatment failure.[5,6] The common issues related to NIV interfaces include skin pressure sores (particularly on the bridge of the nose), claustrophobia, and general mask discomfort.[7] Although mask interfaces have improved significantly over the years, the effects of skin breakdown are always monitored and concerning when NIV use is prolonged, and especially when high levels of support are being used (when masks are generally applied more tightly). The helmet interface does not apply pressure to the face, but the neck and under the arms (where straps are used to stabilize the helmet) need to be monitored for any skin integrity issues. While there may be differences in practice regarding humidification during NIV,[8] humidification improves comfort and may have a positive impact on tolerance of therapy.[9]

Physiological Benefits of High-Flow Nasal Cannula in Adults

Standard oxygen therapy devices such as nasal cannula, simple masks, and masks with reservoirs have a similar limitation when oxygen delivery is 15 L/min or less; as the inspiratory flow demand of the individual in distress increases, the delivered F_{IO_2} of these devices can be diluted through room-air entrainment.[10] This is the reason for using devices with the ability to deliver higher flow; they allow a more accurate and consistent delivery of gases. Air-entrainment devices are the most common types of high-flow devices (eg, Venturi style devices) and are traditionally delivered via face mask. Additionally, the comfort of high-flow oxygen devices is increased with the addition of heated humidity.[11] The concept of meeting the inspiratory flow demand of the patient, combined with improving comfort and tolerance of therapy, are 2 of the mechanisms responsible for the clinical benefits of high-flow nasal cannula (HFNC).[12]

In addition to comfort and improved F_{IO_2} delivery, HFNC can significantly reduce work of breathing, breathing frequency, and minute ventilation while maintaining P_{aCO_2}.[13,14] Considering HFNC does not provide the same inspiratory support or tidal volume augmentation as NIV, this finding strongly suggests improvements in alveolar ventilation through reduction in anatomical dead space leading to increased efficiency of ventilation. HFNC has potential to generate positive pressure in the airways, particularly during exhalation, but it is dependent upon cannula size, flow, cannula/naris ratio, and whether the mouth is open or closed.[15] These limitations regarding the generation of positive pressure may explain the larger improvements in P_{aO_2} observed by Vargas et al[14] during delivery of CPAP of 5 cm H_2O compared to HFNC set to 60 L/min, despite having similar effects in reducing inspiratory effort and work of breathing when compared to a non-rebreathing mask.

Treatment of Respiratory Failure: NIV

The most recent clinical practice guidelines for NIV in acute respiratory failure were published in 2017 by Rochwerg and colleagues.[16] The strongest recommendations continue to be for patients presenting with a COPD exacerbation or cardiogenic pulmonary edema. Further recommendations are shown in Table 1.

While many of the acute conditions that have supportive evidence to use NIV can have associated hypoxemia, the treatment of de novo respiratory failure (ie, hypoxemic failure in the absence of underlying chronic lung disease or cardiac failure) has no recommendation.[16] An example condition that could be classified as de novo respiratory failure would be community-acquired pneumonia in patients without COPD or cardiac failure. A study by Confalonieri and colleagues[17] compared subjects with and without COPD presenting with community-acquired pneumonia and found that subjects with COPD avoided intubation when treated with NIV, whereas those without COPD did not. Treatment of hypoxemic respiratory failure with NIV does have some supportive evidence when a helmet-style NIV interface is

Table 1. Clinical Recommendations for NIV and HFNC

Noninvasive Ventilation	High-Flow Nasal Cannula
Strong recommendation for:	Strong recommendation for:
Hypercapnia with COPD exacerbation	Hypoxemic respiratory failure
Cardiogenic pulmonary edema	
Conditional recommendation for:	Conditional recommendation for:
Immunocompromised	Immediately after extubation (prophylaxis)
Postoperative patients	Postoperative high-risk and/or obese patients following cardiac or thoracic surgery
Palliative care	
Trauma	
Immediately after extubation in high-risk patients (prophylaxis)	
Weaning in hypercapnic patients (early extubation)	
Conditional recommendation against:	
Prevention of hypercapnia in COPD exacerbation	
Postextubation respiratory failure	
No recommendation for or against:	No recommendation for or against:
Acute asthma exacerbation	Peri-intubation period
De novo respiratory failure	
Pandemic viral illness	

Adapted from References 16 and 27.

used. A systematic review and meta-analysis comparing the helmet interface to face mask in the treatment of acute respiratory failure indicated that the helmet reduced intubation rates and mortality in subjects with hypoxemic respiratory failure, although the authors concluded that larger, more rigorous, randomized controlled trials are needed as the available scientific evidence is not yet strong enough to recommend its use for this purpose.[18] A meta-analysis by Xu et al[19] published in 2017 also indicated that although there appears to be decreased intubation rates and hospital mortality (mainly due to the helmet interface) in subjects treated with NIV for hypoxemic respiratory failure without underlying chronic respiratory or cardiac disease, the data are insufficient to make a recommendation for its use, and large randomized trials are required to determine true efficacy.

The overall lack of recommendation to use NIV for de novo hypoxemic respiratory failure is due to the fact that evidence is very mixed, there are many known risk factors for failing NIV, and significant hypoxemia ($P_{aO_2}/F_{IO_2} <$ 150 mm Hg) is one of these factors. Other risk factors include etiologies such as community-acquired pneumonia, ARDS, and immunosuppression. In a study published using data collected for the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure (LUNG SAFE) study, Bellani and colleagues[20] reported NIV was used in 16% of subjects with varying degrees of ARDS severity. Failure of NIV occurred in 22.2% of mild, 42.3% of moderate, and 47.1% of subjects with severe ARDS. The mortality was 45.4% for subjects with ARDS who failed NIV. When subjects with ARDS treated with NIV were matched by $P_{aO_2}/F_{IO_2} <$ 150 mm Hg with those who were invasively ventilated (ie, no NIV) mortality was higher for those treated with NIV (25% vs 36%, $P = .033$).

A score designed to predict NIV failure in hypoxemic subjects was developed by Duan et al[21] using heart rate, acidosis, consciousness, oxygenation, and respiratory rate (HACOR). The authors found that a HACOR score > 5 at 1 h after NIV initiation was able to predict failure of NIV with excellent diagnostic accuracy (area under the curve 0.91 [95% CI 0.88–0.94]; sensitivity 75.9%; specificity 92.6%). The diagnostic accuracy was also excellent across different subgroups of clinical diagnoses and different time points (1 h, 12 h, 24 h, 48 h). A separate validation study assessed the diagnostic accuracy of a HACOR score > 5 in a retrospective study of > 2,000 subjects; the results indicated excellent diagnostic accuracy at 1 h and revealed that a HACOR score of > 6 had the best diagnostic accuracy at 6 h, 12 h, 24 h, and 48 h.[22] The ability to predict NIV failure early in patients with hypoxemic respiratory failure could help avoid delays in intubation. Both delaying intubation and failure of NIV are associated with higher mortality.[21,23] In addition to hypoxemic respiratory failure, Duan et al[24] utilized an adjusted HACOR score to predict NIV failure in hypercapnic subjects. A HACOR score > 5 at 1–2 h after start of NIV displayed excellent diagnostic accuracy in their internal validation and acceptable accuracy in their external validation. When they compared subjects with a HACOR score > 5 at 1–2 h who were intubated early (< 48 h) to those who were intubated late (≥ 48 h), hospital mortality was 35.9% and 79.3%, respectively ($P < .01$).[24]

Treatment of Respiratory Failure: HFNC

The use of HFNC in adults increased significantly after the publication of the FLORALI trial.[25] The FLORALI trial failed to demonstrate a reduction in intubation as their primary outcome comparing HFNC to standard oxygen therapy and NIV, but the secondary outcome of 90-d mortality was significantly lower for subjects treated with HFNC. This finding was likely due to the significant reduction in intubation found in subjects with more severe hypoxemia ($P_{aO_2}/F_{IO_2} \leq 200$ mm Hg). A systematic review and meta-analysis of studies in adults reported a significant reduction in escalation of care and the need for intubation (4.4% absolute risk reduction).[26] However, overall there was no significant reduction in mortality in the analysis. This systematic review and meta-analysis provided the basis for publishing clinical practice guidelines for the use of HFNC as respiratory support.[27] The guideline recommendations for HFNC can be found in Table 1.

While clinical practice guidelines support the use of HFNC to treat hypoxemic respiratory failure, there is insufficient evidence to provide recommendations for the treatment of hypercapnic respiratory failure.[27] A systematic review and meta-analysis of HFNC in hypercapnic respiratory failure by Huang and colleagues[28] reported no difference in intubation or mortality when HFNC and NIV were compared, which might suggest similar effectiveness. However, a major limitation with the 5 randomized controlled trials included in the review is that they included 3 randomized controlled trials of postextubation subjects. Subjects with hypercapnia who met criteria for extubation were assumed to be recovering from an acute illness rather than presenting with it. Additionally, one of the included studies had no failure in either group therefore provided no risk data to the analysis.

Non-inferiority trials are performed when a new therapy is compared to a therapy already considered to be the accepted standard (ie, NIV for exacerbation of COPD). While these types of trials are important for establishing therapies with similar effectiveness, they can be difficult to interpret at times. For example, a non-inferiority randomized controlled trial by Cortegiani et al[29] randomly assigned 79 subjects with mild to moderate COPD exacerbation (arterial pH 7.25–7.35, $P_{aCO_2} \geq 55$ mm Hg before ventilatory support). The primary end point was the mean difference in P_{aCO_2}, with a non-inferiority margin of 10 mm Hg from baseline (start of therapy) to 2 h. Their secondary end points were non-inferiority of HFNC to NIV at 6 h. The authors reported that treatment with HFNC was statistically non-inferior to NIV for decreasing P_{aCO_2} after 2 h and 6 h in both the per-protocol and intention-to-treat analysis. However, 32% of the subjects randomized to HFNC required NIV by 6 h, and 57% required NIV at least once during hospitalization and required a longer duration than subjects randomized to NIV. It is important to understand that non-inferiority in this example does not suggest HFNC is as good as the accepted standard of NIV, as many subjects required escalation to NIV at some point. Large superiority trials would be required to determine true safety and clinical effectiveness of HFNC as a primary treatment option for the management of COPD exacerbation. Other studies are underway to assess the combined use of HFNC and NIV in the management of acute on chronic respiratory failure rather than comparing one against the other.[30]

Another non-inferiority randomized controlled trial published by Doshi et al[31] randomly assigned 204 subjects presenting to the emergency department with undifferentiated respiratory failure. The non-inferiority margin for treatment failure was 20% and 15% for intubation. There were 7% more intubations in the NIV group than the HFNC group. The challenge in interpreting this study is that although it appears that HFNC was non-inferior to NIV, treatment failure while in the emergency department was 5% higher (95% CI –4 to 15) for HFNC. In total, 27 subjects failed HFNC, and 20 of them (75%) were successfully rescued with NIV and subsequently avoided intubation. It is common practice to include the patients who crossed over to the treatment arm in their intended arm, something referred to as an intention-to-treat analysis. However, doing so in this example can lead to misinterpretation of treatment effectiveness. Clearly, HFNC in this study should not be viewed as a replacement for NIV because NIV allowed the avoidance of intubation in the HFNC group when the therapy failed.

The timing of HFNC failure and its association with clinical outcomes was explored by Kang et al in 2015.[32] They used a propensity-matched score analysis of subjects treated with HFNC who failed HFNC early ($\leq$ 48 h) compared to late ($\geq$ 48 h). The authors reported that late failure was associated with higher ICU mortality, poor weaning from mechanical ventilation, and less successful extubations.[32] This was a single-center, retrospective study and further studies should confirm these findings. However, the concept of predicting failure of HFNC failure to avoid delaying intubation has been the subject of ongoing research. In 2019, Roca and colleagues published a validation study following their previous work with the ROX index.[33,34] The ROX index is calculated as $\frac{S_{pO_2}/F_{IO_2}}{\text{breathing frequency}}$.

The ROX index validation study was a study of subjects presenting with hypoxemic respiratory failure secondary to pneumonia who met criteria for HFNC and were followed until death or hospital discharge.[34] The ROX index was not used to decide intubation, rather it was calculated after study completion to determine the diagnostic accuracy of the ROX index to predict success of HFNC to avoid invasive mechanical ventilation. Intubation criteria were predetermined in this study, and included a breathing frequency threshold of 30 breaths/min, which may limit accuracy of the scores in general practice. This is an important

Table 2. Example of Intubation Criteria

The Following Clinical or Respiratory Criteria are Met
Clinical criteria
Decreased level of consciousness (Glasgow coma score ≤ 12)
Cardiac arrest/arrhythmias
Hemodynamic instability (mean arterial blood pressure ≤ 65 mm Hg despite fluid loading bolus and/or vasopressor use)
Respiratory criteria: Persistent or worsening respiratory failure, including at least 2 of:
P_{aO_2} < 60–65 mm Hg or S_{pO_2} < 90% despite F_{IO_2} ≥ 0.60
S_{pO_2} < 90% for > 5 min
Evidence of high work of breathing
Respiratory acidosis (pH < 7.25-7.35)
Breathing frequency > 30 breaths/min*
Inability to clear secretions

* Breathing frequency thresholds vary across studies.

consideration because breathing frequency is the denominator of the ROX index and would greatly affect the threshold values associated with success or failure. Examples of intubation criteria used in studies of HFNC can be found in Table 2. The diagnostic accuracy of the ROX index of 4.88 or greater to predict success of HFNC improved over time, and accuracy was best at 12 h, 18 h, and 24 h (area under the receiver operating characteristic curve of 0.759, 0.755, and 0.801, respectively). The authors also provided ROX values with the highest specificity to predict failure at 2 h, 6 h, and 12 h (area under the curve of 2.85, 3.4, and 3.85, respectively).[34] Using values that predict failure with the highest specificity attempts to avoid false positives that would result in patients meeting failure criteria (and being intubated) who would have otherwise not required invasive ventilation.

External validation of the study performed on data from the FLORALI trial[25] found a statistically similar diagnostic accuracy of the ROX index at 2 h, 6 h, and 12 h, but all of the area under the curve values were < 0.70, which could be considered clinically unacceptable.[35] However, they[34] did find a statistically different change in ROX index from 1 h to 12 h between those who failed HFNC and those who were successful with a mean change of –0.32 (95% CI –1.10 to 0.46) for those who failed HFNC, and a mean change of 1.01 (95% CI –0.05 to 2.08) for those who were successfully managed with HFNC ($P = .02$). There are 2 study differences that could have contributed to the weakened performance of the ROX index in the FLORALI cohort. First, the ROX index study included only subjects with pneumonia as the cause of respiratory failure. The FLORALI trial was not exclusively pneumonia patients, although the majority of subjects enrolled in the study did have a diagnosis of pneumonia. Second, and likely most importantly, is that the FLORALI trial included similar intubation criteria but with a breathing frequency > 40 breaths/min as one of the criteria. The ROX index includes breathing frequency as the denominator; using a higher threshold with intubation criteria would lead to different predictive values, as previously mentioned.

Additional studies have assessed the diagnostic accuracy of the ROX index to predict HFNC success with mixed results. In immunosuppressed subjects, Lemiale and colleagues[36] found the ROX index was significantly different between those who failed HFNC and those who did not (ROX index 4.79 [95% CI 3.69–7.01] versus ROX index 6.10 [95% CI 4.48–8.68], $P < .001$); however, the overall diagnostic accuracy of the ROX index at 6 h (area under the curve of 0.623 [95% CI 0.557–0.689]) and performance of the threshold value of 4.88 were poor. The authors performed a multivariate analysis indicating that at 6 h, the ROX index was associated with a lower risk of intubation (odds ratio 0.89 [95% CI 0.82–0.96], $P = .04$) for every point of increase.

The ROX index has also been assessed in patients with COVID-19 alone, and as part of larger nomogram to predict success and failure of noninvasive respiratory support. In a research letter, Zucman and colleagues[37] reported that a ROX index ≥ 5.37 at 4 h had good discrimination for predictive success of HFNC in subjects with COVID-19 (area under the curve of 0.75 [95% CI 0.6–0.9]; sensitivity 0.66, specificity 0.83). Hu et al[38] reported that a ROX index > 5.55 at 6 h was predictive of HFNC success in both a univariate and multivariate analysis (odds ratio 8.6 [95% CI 3.342–22.354], $P < .001$, and odds ratio 16.821 [95% CI 3.741–84.903], $P < .001$, respectively). A nomogram and online calculator was developed by Liu and colleagues[39] to predict failure of noninvasive respiratory support (HFNC and NIV) in subjects with COVID-19. The nomogram uses age, Glasgow coma scale, ROX index, number of comorbidities, and vasopressor use. The online calculator then calculates a noninvasive respiratory support failure risk (http://www.china-critcare.com/covid/risk_prediction.html, *Accessed May 11, 2021*). The nomogram was stable through internal and external validation with a C-statistic (equal to area under the curve) of 0.88 (95% CI 0.72–0.96) for NIV and 0.86 (95% CI 0.72–0.93) for HFNC in the external validation.

A final note with the ROX index is that flow can impact the ROX index. Mauri and colleagues[40] enrolled 57 hypoxemic respiratory failure subjects with pulmonary infiltrates on chest radiograph to start with either 30 L/min or 60 L/min of high-flow for 20 min and then cross over to the alternative flow after the 20-min study phase. The authors reported that subjects with a low ROX index at 30 L/min were more likely to respond to higher flow with an increase in the ROX index.[40] This observation could be considered in 2 ways: if you begin patients on a lower flow setting, consider a "flow challenge" by increasing flow for 20 min

Table 3. Clinical Factors Considered High Risk for Extubation Failure

Age > 65 y
Heart failure as cause of intubation
Pneumonia as the cause of intubation
COPD (moderate to severe)
Body mass index > 30 kg/m^2
Airway patency issues
≥ 2 comorbidities
≥ 2 failed spontaneous breathing trials
Invasive ventilation > 7 d

to see if the ROX index improves; alternatively, after HFNC initiation, consider using the highest flow tolerated by the patient that is within manufacturer recommendations for maintaining humidification effectiveness (ie, some devices may not provide optimal humidification at certain flow levels).

Avoiding Re-Intubation

Several studies have compared the use of HFNC and NIV to standard oxygen therapy immediately following extubation to reduce the rate of re-intubation.[41-47] In subjects with low risk of re-intubation, Hernández et al[45] reported a significant reduction in re-intubation within 72 h when using HFNC compared to standard oxygen therapy, with an absolute difference of 6.1% (95% CI 0.7–11.6%). In high-risk patients, the application of NIV immediately postextubation has been included in NIV clinical guideline recommendations for several years.[16,48] In a multicenter, randomized, noninferiority clinical trial of 604 subjects, Hernández et al[45] compared HFNC to NIV immediately after extubation in subjects meeting high-risk criteria with primary outcomes of all-cause re-intubation and postextubation respiratory failure (as the cause of re-intubation). Using a noninferiority threshold of 10%, the all-cause re-intubation rate had a difference of –3.7%, which was well within the 10% threshold. The difference for postextubation respiratory failure was 12.9%, but in the direction favoring HFNC and therefore still non-inferior. It should be noted that "high risk for extubation failure" does not have a universally accepted definition. However, many studies include similar criteria; examples of these criteria are found in Table 3.

A systematic review and meta-analysis of 8 randomized controlled trials compared HFNC, standard oxygen, and NIV use postextubation.[49] Compared to standard oxygen therapy, HFNC reduced the rate of re-intubation (absolute risk reduction 8.1%) and postextubation respiratory failure (absolute risk reduction 9.4%). The authors[49] found no difference in mortality between subjects treated with HFNC versus standard oxygen therapy immediately following extubation. Compared to NIV, there was no difference in the rate of re-intubation, postextubation respiratory failure, or mortality in subjects treated with HFNC versus NIV immediately following extubation. However, when compared to NIV immediately following extubation, HFNC reduced the ICU length of stay and was associated with improved patient comfort.

In a multicenter randomized controlled, Thille and colleagues[50] compared HFNC alone to the combination of HFNC+NIV immediately following extubation in subjects at high risk of extubation failure. Therapy was provided for a minimum of 48 h in both groups. In the HFNC+NIV group, NIV was the initial therapy for a minimum of 4 h after extubation, and a minimum of 12 h of total NIV therapy was required in a 24-h period, including the use of NIV overnight. The primary outcome was reintubations at day 7, which occurred in 18% of subjects treated with HFNC alone and 12% in subjects treated with HFNC+NIV (absolute difference −6.4 [95% CI −12.0 to −0.9], $P = .02$). The secondary outcomes of postextubation respiratory failure at day 7, re-intubation at 48 h, 72 h, and prior to ICU discharge, all were significantly lower in subjects treated with HFNC+NIV. The authors further investigated the influence of hypercarbia in a subgroup analysis. Subjects with $P_{aCO_2} > 45$ mm Hg demonstrated a significant difference in re-intubation rates favoring HFNC+NIV, whereas there was not a significant difference in re-intubation rates in subjects with P_{aCO_2} of ≤ 45 mm Hg.

Summary

The treatment of hypercarbic respiratory failure with NIV has been strongly recommended for decades. At this time, NIV is still considered a first-line therapy for patients presenting with COPD exacerbation or cardiogenic pulmonary edema. Hypoxemic respiratory failure can have many causes, some of which have supportive evidence for using NIV, but hypoxemic respiratory failure in the absence of underlying chronic lung or cardiac disease (de novo) currently has no recommendation for using NIV because of associations with high failure rates potentially leading to worse outcomes. Clinicians should be cautious when using NIV in this subgroup of patients. As a general approach to treating hypoxemic respiratory failure, HFNC has been shown to reduce escalation of care (to NIV), may reduce intubation rates, and currently holds a strong recommendation for use. For the avoidance of re-intubation, HFNC is superior to standard oxygen therapy in low-risk patients and similar to NIV in high-risk patients. However, the use of HFNC in combination with NIV further reduces the risk of re-intubation in patients with $P_{aCO_2} > 45$ mm Hg. Since the initial studies of NIV in the early 1990s, many advances

in equipment and interfaces have immensely improved tolerance of therapy. The inclusion of HFNC as a noninvasive option for providing respiratory support has led to improved outcomes for our patients, and future studies will continue to provide useful guidance for which patient populations receive the most benefit for each therapy.

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