ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure

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Shareable abstract (@ERSpublications)
This guideline provides evidence-based recommendations for the use of high-flow nasal cannula alongside other noninvasive forms of respiratory support in adults with acute respiratory failure
https://bit.ly/3mgwO8h


Abstract

Background High-flow nasal cannula (HFNC) has become a frequently used noninvasive form of respiratory support in acute settings; however, evidence supporting its use has only recently emerged. These guidelines provide evidence-based recommendations for the use of HFNC alongside other noninvasive forms of respiratory support in adults with acute respiratory failure (ARF).

Materials and methodology The European Respiratory Society task force panel included expert clinicians and methodologists in pulmonology and intensive care medicine. The task force used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methods to summarise evidence and develop clinical recommendations for the use of HFNC alongside conventional oxygen therapy (COT) and noninvasive ventilation (NIV) for the management of adults in acute settings with ARF.

Results The task force developed eight conditional recommendations, suggesting the use of 1) HFNC over COT in hypoxaemic ARF; 2) HFNC over NIV in hypoxaemic ARF; 3) HFNC over COT during breaks from NIV; 4) either HFNC or COT in post-operative patients at low risk of pulmonary complications; 5) either HFNC or NIV in post-operative patients at high risk of pulmonary complications; 6) HFNC over

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COT in nonsurgical patients at low risk of extubation failure; 7) NIV over HFNC for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV; and 8) trialling NIV prior to use of HFNC in patients with COPD and hypercapnic ARF.

Conclusions
HFNC is a valuable intervention in adults with ARF. These conditional recommendations can assist clinicians in choosing the most appropriate form of noninvasive respiratory support to provide to patients in different acute settings.

Introduction
High-flow nasal cannula (HFNC) is a respiratory support device, which is used during early noninvasive management of acute respiratory failure (ARF), alongside conventional oxygen therapy (COT), and noninvasive ventilation (NIV). The benefits of HFNC, which are both clinical (e.g. patient comfort and ease of use) and physiological (e.g. high oxygenation, alveolar recruitment, humidification and heating, increased secretion clearance, reduction of dead space) [1], can prevent deterioration of lung function and endotracheal intubation [2–4].

However, there is limited evidence on the most appropriate form of noninvasive respiratory support in the different ARF scenarios. While HFNC is more comfortable and tolerated when compared to COT and to NIV, its ability to unload respiratory muscles in ARF may be lower than that provided by NIV. Moreover, prolonging noninvasive respiratory support in patients failing with either HFNC and NIV may result in delayed intubation and worsen hospital mortality [2, 5]. Risks and benefits may vary in different scenarios (e.g. hypoxaemic and hypercapnic ARF, post-operative and post-extubation ARF, coronavirus disease 2019 (COVID-19) pneumonia).

The European Respiratory Society (ERS) created a task force to provide evidence-based recommendations on HFNC in adults with ARF.

Materials and methods
Scope and purpose of the document
This document is intended to help clinicians, policy-makers and patients in making evidence-based decisions on HFNC in adults with ARF in different settings. For the most part, the perspective of individual clinicians in high-resourced settings was considered, being reflective of the ERS membership. Nevertheless, feasibility of HFNC in lower-resourced countries has been considered (table 1) [6]. Due to limitations in the certainty of evidence and the variation in available resources, all recommendations were weak/conditional.

Composition of the task force panel
The task force consisted of 18 clinicians with expertise in respiratory and acute care medicine. The leadership team consisted of clinical chairs (BE, RS) along with the methodology team (SO, GS) and ERS

<table>
<thead>
<tr>
<th>TABLE 1 Interpretation of strong and conditional recommendations</th>
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<tr>
<td><strong>Strong recommendation</strong></td>
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methodologist (TT) who had experience in guidelines development using Grading of Recommendations, Assessment, Development and Evaluation (GRADE) methodology. The European Lung Foundation provided a representative to give a patient’s perspective.

**Conflict of interest declaration and management**

All task force members were required to disclose any financial conflicts and sign a confidentiality agreement in accordance with the ERS policy.

**Formulation of questions**

An initial list of eight questions was developed by the task force chairs (BE, RS) and submitted to the ERS for approval. The questions were structured in PICO (population, intervention, comparison, outcomes) format and, together with a list of outcomes, were approved by the task force panellists and the methodology team (table 2). The task force planned two *a priori* subgroups for PICO questions on hypoxaemic respiratory failure and immunocompetent and immunocompromised patients. With the advent of the COVID-19 pandemic in March 2020, the task force included a third subgroup: COVID-19 patients.

**Literature searches**

With the assistance of a medical librarian, the methodology team conducted systematic searches of the medical literature. We searched up to January 2021 in MEDLINE, Embase (database inception onwards) and Cochrane CENTRAL (2006 onwards) for relevant observational studies and randomised clinical trials (RCTs) (supplementary material).

The retrieved references were screened in duplicate using Covidence reference management software (www.covidence.org). We included English-language RCTs and observational studies comparing HFNC to COT or NIV (supplementary figure S1). Data were extracted into a pilot-tested data extraction form, and entered into RevMan software (version 5.3; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) for meta-analysis. For each PICO question, the methodology team, with input from the task force chairs, rated the certainty of evidence for each outcome using standard GRADE methods and created evidence summaries [7, 8]. Certainty of evidence was rated as “high”, “moderate”, “low” or “very low”, with RCTs starting as “high” certainty and observational evidence as “low” certainty [9]. Evidence could be rated down one or two levels based upon whether the included studies were judged to be at high risk of bias [10]; results were inconsistent between studies [11]; or the evidence was indirect [12], imprecise [13] or at high risk of publication bias [14].

<table>
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<th>TABLE 2</th>
<th>Population, intervention, comparison, outcomes (PICO) questions and recommendations</th>
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<tr>
<td>1. Should HFNC or COT be used in patients with acute hypoxaemic respiratory failure?</td>
<td>The ERS task force suggests the use of HFNC over COT in patients with acute hypoxaemic respiratory failure (conditional recommendation, moderate certainty of evidence)</td>
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<tr>
<td>2. Should HFNC or NIV be used in patients with acute hypoxaemic respiratory failure?</td>
<td>The ERS task force suggests the use of HFNC over NIV in acute hypoxaemic respiratory failure (conditional recommendation, very low certainty of evidence)</td>
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<tr>
<td>3. Should HFNC or COT be used during breaks from NIV in patients with acute hypoxaemic respiratory failure?</td>
<td>The ERS task force suggests the use of HFNC over COT during breaks from NIV in patients with acute hypoxaemic respiratory failure (conditional recommendation, low certainty of evidence)</td>
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<tr>
<td>4. Should HFNC or COT be used in post-operative patients after extubation?</td>
<td>The ERS task force suggests the use of either COT or HFNC in post-operative patients at low risk of respiratory complications (conditional recommendation, low certainty of evidence)</td>
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<tr>
<td>5. Should HFNC or NIV be used in post-operative patients after extubation?</td>
<td>The ERS task force suggests the use of either HFNC or NIV in post-operative patients at high risk of respiratory complications (conditional recommendation, low certainty of evidence)</td>
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<tr>
<td>6. Should HFNC or COT be used in nonsurgical patients after extubation?</td>
<td>The ERS task force suggests the use of HFNC over COT in nonsurgical patients after extubation (conditional recommendation, low certainty of evidence)</td>
</tr>
<tr>
<td>7. Should HFNC or NIV be used in nonsurgical patients after extubation?</td>
<td>The ERS task force suggests the use of NIV over HFNC for patients at high risk of extubation failure, unless there are absolute or relative contraindications to NIV (conditional recommendation, moderate certainty of evidence)</td>
</tr>
<tr>
<td>8. Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?</td>
<td>The ERS task force suggests a trial of NIV prior to use of HFNC in patients with COPD and acute hypercapnic respiratory failure (conditional recommendation, low certainty of evidence)</td>
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HFNC: high-flow nasal cannula; COT: conventional oxygen therapy; NIV: noninvasive ventilation; ERS: European Respiratory Society.
The task force was asked to prioritise the initial list of outcomes, rating their clinical importance from 1 to 9, with mean scores of 1–3 indicating “low importance”, 4–6 “important but not critical” and 7–9 as “critical” [15]. The panel prioritised as “critical” mortality, intubation and escalation of treatment.

A virtual meeting was held during the ERS Congress in September 2020 to discuss PICOs and the literature search results. The leadership team met virtually in November 2020 to work through the GRADE evidence-to-decision framework and develop draft recommendations. The evidence-to-decision framework considers balance of desirable and undesirable effects, certainty of effects, patient values and preferences, resource use, cost-effectiveness, health equity and acceptability and feasibility of an intervention in order to develop an overall recommendation [16]. Recommendations were designated as “weak/conditional” or “strong” using the wording “we suggest” and “we recommend”, respectively [17].

The task force panel reviewed the evidence and draft recommendations, and voted on both using the GRADEpro PanelVoice system (wwwGRADEpro.org/panelvoice) between December 2020 and January 2021. For a weak/conditional recommendation a majority vote was sufficient to approve the recommendation; for a strong recommendation, stronger agreement (>70%) was required. Questions for which consensus were not reached were re-evaluated by the leadership team based upon feedback from the task force, revised, and had additional rounds of voting to reach consensus.

Results
All recommendations had consensus except for PICO questions 7 and 8, for which a second round of voting was conducted. Evidence summaries (including forest plots from meta-analyses) and evidence-to-decision framework summaries for each PICO can be found in the supplementary material.

HFNC for hypoxaemic acute respiratory failure
PICO question 1: Should HFNC or COT be used in patients with acute hypoxaemic respiratory failure?
Recommendation 1
We suggest the use of HFNC over COT in adults with acute hypoxaemic respiratory failure (conditional recommendation, moderate certainty of evidence).

Background
Acute hypoxaemic respiratory failure (AHRF) is caused by a wide range of aetiologies including pulmonary infection, inflammation or exacerbation of chronic heart or lung disease. The clinical spectrum of AHRF ranges from mild hypoxaemia to full-blown acute respiratory distress syndrome (ARDS). In this question, de novo AHRF was addressed, rather than established ARDS, as there is not yet consensus on whether nonintubated patients can be diagnosed with ARDS [18]. Noninvasive respiratory support aims to improve hypoxaemia, reduce work of breathing, enhance comfort, avoid intubation and provide time to effectively treat the triggering condition, thereby reducing mortality [19]. Unfortunately, many patients with AHRF require escalation to invasive mechanical ventilation (IMV) [20]. The most common noninvasive respiratory treatment in AHRF is COT, which increases the fraction of inspired oxygen (FiO2), using simple interfaces including nasal prongs, facemask with reservoirs or Venturi mask. Potential mechanisms of COT failure include ineffective support matching patient ventilatory needs due to altered respiratory mechanics, unreliable FiCO2 delivery, lack of humidification and patient self-inflicted lung injury (P-SILI) [21, 22].

HFNC is a noninvasive, high-concentration oxygen delivery interface which addresses some of the limitations of COT. By providing airflow as high as 50–60 L·min⁻¹, HFNC closely matches the inspiratory demands of dyspnoeic patients with AHRF, and reliably achieves an FiO2 as high as 100%, while also providing a low level of positive end-expiratory pressure (PEEP) in the upper airways, facilitating alveolar recruitment [2]. Other potential benefits of HFNC over COT include decreased risk of P-SILI, avoiding harmful changes in transpulmonary pressure, carbon dioxide washout of upper airways, improved ventilation and provision of reliable humidification, which may result in increased patient comfort and enhanced secretion clearance [1, 23–25]. These clinical and physiological benefits constitute a strong rationale for early use of HFNC to prevent the need for noninvasive and invasive positive-pressure ventilation, and to reduce the risk of mortality mostly correlated with ventilator-associated complications. This is particularly true for immunocompromised patients who are more likely to develop complications correlated to IMV, such as ventilator-associated pneumonia (VAP) [26, 27].

Evidence summary
12 parallel-group RCTs [28–39] and four crossover RCTs [24, 40–42] comparing HFNC to COT were selected. In general, the evidence is limited by imprecision. Mortality is similar in the short term (hospital,
intensive care unit (ICU) or 28 days) (risk ratio 0.99, 95% CI 0.84 to 1.17; risk difference −0.3%, 95% CI −4.1 to 4.3; moderate certainty) or 90 days (risk ratio 0.97, 95% CI 0.83 to 1.13; risk difference −1.0, 95% CI −5.7 to 4.4; moderate certainty). 11 studies evaluated the effect of HFNC on intubation, finding that HFNC may reduce intubation (risk ratio 0.89, 95% CI 0.77 to 1.02; risk difference −3.1%, 95% CI −6.4% to 0.6%; moderate certainty) and escalation to NIV (risk ratio 0.76, 95% CI 0.43 to 1.34; risk difference −2.9%, 95% CI −6.9% to 4.1%; moderate certainty) [29–35, 37–39]. HFNC reduces patient discomfort (standardised mean difference (SMD) 0.54 lower, 95% CI 0.86 lower to 0.23 lower; high certainty), dyspnoea (SMD 0.32 lower, 95% CI 0.66 lower to 0.03 higher; moderate certainty), and slightly lowers respiratory rate (mean difference (MD) 2.25 breaths·min\(^{-1}\), 95% CI 3.24 breaths·min\(^{-1}\) lower to 1.25 breaths·min\(^{-1}\) lower; high certainty). The impact of HFNC upon gas exchange is generally small, with HFNC increasing partial pressure of oxygen in arterial blood (\(P_{\text{aO}_2}\)) values (MD 16.72 mmHg, 95% CI 5.74 mmHg higher to 27.71 mmHg higher; high certainty) and, possibly, the \(P_{\text{aO}_2}/F_{\text{O}_2}\) ratio (MD 25.01 mmHg, 95% CI 14.21 mmHg lower to 64.24 mmHg higher; low certainty); without a substantial effect on arterial carbon dioxide tension (\(P_{\text{aCO}_2}\)) values (MD 0.01 mmHg, 95% CI 1.17 mmHg lower to 1.2 mmHg higher; high certainty).

Impact upon length of stay is inconsistent, suggesting an increased ICU stay by 1.97 days (95% CI 1.02 days higher to 2.93 days higher; moderate certainty), with a small overall reduction in hospital length of stay of 0.72 days (95% CI 1.54 days lower to 0.1 days higher; moderate certainty).

For the subgroup of immunocompromised patients, effects are similar, with no impact upon mortality [30, 31, 35, 39], although without the reduced intubation rate between HFNC and COT. No RCTs evaluating HFNC versus COT in patients with COVID-19 were found.

**Justification**

The guideline task force panel makes a conditional recommendation for HFNC over COT as the evidence suggested that the balance of effects, particularly a reduction in intubation, probably favours HFNC over COT. However, the panel’s certainty is limited by imprecision. The impact on mortality is probably small (<1%). Thus, HFNC is most likely to benefit patients who are at high risk of intubation; its use should be favoured in patients with more severe disease rather than patients requiring low oxygen flow rates, or in those with severe symptoms, given the improvements in patient comfort, dyspnoea, respiratory rate, and gas exchange. The panel notes that AHRF, particularly ARDS, is heterogeneous: identifying patients most likely to benefit from HFNC requires clinician judgement [43].

The task force does not identify any major trade-offs in which patient values would be likely to play a role, as both the increased comfort of HFNC along with lower intubation rates would probably be preferred by most patients.

There is limited evidence on resource utilisation. While material cost, set-up and oxygen use of HFNC are probably higher than COT, avoiding intubation may save money and ancillary costs (i.e. sedation, ventilators, monitors). Conversely, during times of resource scarcity other considerations (avoiding intubation versus limiting oxygen versus human resources) may influence the choice of HFNC versus COT. While the existing evidence suggests an increased ICU length of stay, the panel is uncertain, as hospital policies differ whether or not HFNC requires ICU, intermediate care and respiratory high-dependency unit (step-down/step-up unit), or general ward [44]. Overall hospital length of stay may be unaffected by use of HFNC. The task force identified one study evaluating cost-effectiveness of HFNC in the pre-intubation phase in the UK [45]. It found that HFNC resulted in overall cost-savings of GBP 156 compared to COT, and higher savings of GBP 727 in high-risk patients. In low-income countries, HFNC may reduce health equity (e.g. the device may not be available to all persons, and high oxygen use by HFNC may limit availability of oxygen to other patients). Widespread use of HFNC in ICUs demonstrates feasibility of the device, even in resource-constrained settings during a pandemic [46].

**Subgroup considerations**

Data for both immunocompetent and immunocompromised subgroups were estimated and similar for mortality, but showing a smaller magnitude for intubation and escalation to NIV in the immunocompromised subgroup. There is no evidence of increased harm in the use of HFNC versus COT. Given this residual uncertainty, the panel decided there are insufficient data to make a separate recommendation.

There are few high-quality data to guide effectiveness of HFNC in COVID-19; however, given the heterogeneity of patients, which may include other viral pneumonias and ARDS, it is reasonable to make the same conditional recommendation. Use of HFNC requires separate consideration of resources,
including protective personal equipment and ventilation, given the currently unknown risks of transmissibility from patients using HFNC versus COT [47–50]. The panel does not make a recommendation regarding the use of awake prone position in HFNC, recognising that there is little evidence and few RCTs to address the question [51–54].

**PICO question 2: Should HFNC or NIV be used in patients with acute hypoxaemic respiratory failure?**

**Recommendation 2**

We suggest the use of HFNC over NIV in patients with acute hypoxaemic respiratory failure (conditional recommendation, very low certainty of evidence).

**Background**

HFNC and NIV are used more frequently in patients with progressive or moderate to severe AHRF ($P_{aO2}/F_{iO2} \leq 200$ mmHg), when the risks of intubation and death are higher [20, 21]. In more severe AHRF ($P_{aO2}/F_{iO2} < 100$ mmHg), clinicians aim to balance the benefits of maintaining spontaneous breathing and averting intubation together with its complications (i.e. VAP and ventilator-induced lung injury) versus the harms of delayed intubation, including high inspiratory effort, increased lung stress and risk of lung injury during noninvasive respiratory support [55]. HFNC is an attractive alternative to NIV for treating patients with AHRF and high respiratory demand.

While NIV provides higher mean airway pressures than HFNC and assists ventilation by effectively unloading respiratory muscles, treatment failure is frequent. NIV failure occurs more frequently in patients with more severe ARF: $P_{aO2}/F_{iO2} < 200$ mmHg before treatment and higher Simplified Acute Physiology Score II (≥35) are associated with a two-fold risk of intubation [56]. Improvement in gas exchange provided by NIV may help identify patients at greatest risk of treatment failure, as $P_{aO2}/F_{iO2} < 175$ mmHg after 1 h of NIV is associated with need for intubation [20]. Finally, expired tidal volume exceeding 9–9.5 mL·kg$^{-1}$ predicted body weight while undergoing NIV delivered in pressure support mode with a low level of assistance can predict treatment failure with good specificity and sensitivity [57, 58].

There are practical differences between HFNC and NIV, which may impact patient comfort and tolerance. While HFNC devices use a similar interface, NIV can be delivered using either a facemask or helmet interface. To date, the most frequently used interface in RCTs has been facemask NIV, although helmet NIV may be more comfortable and allow the application of a more “protective” ventilation with higher PEEP (i.e. 8–12 cmH$_2$O) and lower pressure support values with fewer air leaks and interruptions [59, 60]. Clinicians now have the option of HFNC and NIV with a variety of interfaces for use in AHRF; however, the recent ERS/American Thoracic Society (ATS) task force did not offer a recommendation on the use of NIV for de novo AHRF, noting that the majority of the studies used COT as a comparator [20].

**Evidence summary**

We identified five parallel-group RCTs [30, 61–64] and two crossover RCTs [65, 66] comparing HFNC to NIV in AHRF. Three RCTs reported short-term mortality (hospital, ICU or 28-day), finding that HFNC may reduce mortality (risk ratio 0.77, 95% CI 0.52 to 1.14; risk difference $-$4.5%, 95% CI $-$9.4% to 2.7%; very low certainty); however, this is limited by imprecise and inconsistent effects between the studies. One trial reported a possible large reduction in mortality with use of HFNC (risk ratio 0.43, 95% CI 0.25 to 0.78; risk difference $-$16.1%, 95% CI $-$21.4% to $-$6.2%; low certainty). In both, the panel raised concerns that the NIV used does not reflect current real-world practice (lower intensity and duration of only 8 h·day$^{-1}$), and thus the evidence is rated down for indirectness. Five RCTs evaluated effect of HFNC on intubation, demonstrating that HFNC may reduce intubation (risk ratio 0.84, 95% CI 0.61 to 1.16; risk difference $-$4.1%, $-$10.1% to 4.1%; low certainty), but this result is limited by indirectness and imprecision [30, 61–64].

HFNC may have a small impact on length of stay, potentially decreasing ICU stay by 0.55 days (95% CI $-$2.0 days to 0.89 days; low certainty) and increasing overall hospital stay by 0.8 days (95% CI $-$0.59 days to 2.19 days; very low certainty). Pooled analysis of four RCTs shows that HFNC may improve patient comfort (SMD $-$0.23, 95% CI $-$0.55 to 0.09; moderate certainty), but results in greater degree of perceived dyspnoea than NIV (SMD 0.19, 95% CI $-$0.01 to 0.40; very low certainty) [30, 41, 62, 66].

Looking at the physiological effects of HFNC, pooled analysis of four [30, 41, 64, 66] and three RCTs [30, 64, 66] shows that HFNC results in slightly lower $P_{aO2}$ values (MD $-$19.98 mmHg, 95% CI $-$11.97 mmHg to $-$28.0 mmHg; moderate certainty) and $P_{aO2}/F_{iO2}$ ratio (MD $-$43.26, 95% CI $-$29.48 to $-$57.04; moderate certainty), respectively, with little difference in $P_{aCO2}$ values (MD 0.45 mmHg, 95% CI 1.94 mmHg lower to 1.05 mmHg higher; low certainty) or respiratory rate (MD 0.83 breaths·min$^{-1}$, 95% CI $-$1.04 breaths·min$^{-1}$ to 2.7 breaths·min$^{-1}$; low certainty).
The panel judged that the existing evidence generally supports the use of HFNC over NIV as first-line treatment for AHRF, but this evidence is limited by imprecision, and there is still uncertainty as to the true effect of NIV, given concerns about the indirectness of the comparison NIV as used in the studies. In particular, the trial by FRAT et al. [30] demonstrated the largest benefit of HFNC, but NIV had short therapeutic time (8 h·day$^{-1}$) and lower levels of PEEP than those commonly prescribed (especially with helmet interface) and possibly no humidification used in the NIV arm. Additionally, the included studies generally used facemask ventilation, which may not be as well tolerated [67]. Therefore, the task force rates down all outcomes for indirectness, resulting in very low certainty for critical outcomes. Reassuringly, for almost every outcome (other than dyspnoea), HFNC appeared to be beneficial or at least neutral compared to NIV.

The task force acknowledges uncertainty regarding which patients are most likely to benefit from each device. Individual patient factors and clinical decision-making play an important role in choosing which respiratory support should be adopted. While NIV may be relatively contraindicated in some patients (e.g. excessive secretions, facial hair/structure resulting in air leaks, poor compliance), and HFNC the clearly superior option, there may be a subset of patients for whom NIV may be preferable. These may be patients with increased work of breathing, respiratory muscle fatigue and congestive heart failure, in which the positive pressure of NIV may positively impact haemodynamics. A trial of NIV might be considered for select patients with AHRF, pneumonia or early ARDS if there are no contraindications and close monitoring by an experienced clinical team who can intubate patients promptly if they deteriorate [20]. In such cases, individual clinician judgement is key to choose NIV, interface and settings.

The task force does not identify any major trade-offs where patient values may play a role in deciding between HFNC and NIV; almost all outcomes favoured HFNC. Overall, the task force’s considerations for resource use are similar to those in recommendation 1, although it is noted that the actual device and setup for NIV require more resources than COT, making the difference between the two alternatives less pronounced. Resource considerations and cost-effectiveness of HFNC versus NIV may vary between regions.

Benefits of HFNC may be greater in immunocompromised patients. However, these results are entirely derived from one study and remain imprecise, and judged insufficient for a strong recommendation. The task force chose to make only a single recommendation.

No RCTs comparing HFNC to NIV in COVID-19 were available, and the panel choose not to make a separate recommendation. Subsequent to the task force voting, an RCT comparing HFNC to helmet NIV in COVID was published: it found no differences in respiratory support-free days or mortality at 30 or 60 days, but a reduction in intubation at 28 days (OR 0.37; 95% CI 0.17 to 0.82; risk difference $-23\%$, 95% CI $-39\%$ to $-5\%$) [68]. While suggesting that helmet NIV may reduce intubation compared to HFNC in COVID-19, it is interesting that mortality between the groups is unchanged. While this study demonstrates the viability of both devices in COVID-19, further research is needed before a definitive recommendation can be issued, especially as helmet NIV is not available in all centres and such a recommendation would require substantial change in practice for many hospitals.

PICO question 3: Should HFNC or COT be used during breaks from NIV in patients with acute hypoxaemic respiratory failure?

**Recommendation 3**

We suggest use of HFNC over COT during breaks from NIV in patients with acute hypoxaemic respiratory failure (conditional recommendation, low certainty of evidence).

**Background**

While NIV is frequently used to treat ARF, breaks from NIV are necessary for practical reasons (feeding, speaking), patient’s tolerance (relief from mask pressure), and to ascertain readiness for weaning from NIV. COT is used during these breaks; however, HFNC may be a more effective alternative. Sequential alternating protocols (e.g. sessions of 2 h HFNC followed by 1 h NIV) may limit the need for prolonged NIV by maintaining adequate oxygenation. In a small ($n=28$) prospective single-centre observational study, it was shown that HFNC was better tolerated than NIV and allowed for significant improvement in oxygenation and tachypnoea compared with COT [69]. Thus, for patients treated with NIV, the question of whether COT or HFNC should be prescribed during breaks remains open.
Evidence summary

One RCT evaluated 47 patients receiving humidified facemask NIV for ≥24 h [70]. Half had AHNF, the majority of whom showing a $P_{aO2}/F_iO2$ ratio <300 mmHg. The study was prematurely terminated for slow recruitment rate. Although underpowered to determine differences in intubation rate (two out of 28 versus 0 out of 26, p-value 0.49; very low certainty) the total time spent on NIV between the HFNC and COT groups was similar (1315 (225) min versus 1441 (220) min, p-value 0.07). However, HFNC resulted in better comfort measured with mean±SD visual analogue scores (8.3±2.7 versus 6.9±2.3), and, during breaks, mean±SD respiratory rate (20.1±4.1 breaths·min$^{-1}$ versus 21.8±5.2 breaths·min$^{-1}$) and mean±SD perceived dyspnoea (2.1±2.8 versus 2.4±2.2) were reduced. The frequency of adverse events (e.g. eye irritation, 8% versus 21.6%) and of difficulty in eating (13.3% versus 36.2%) were lower with HFNC during breaks compared to COT.

Justification

Given that the direct evidence consisted of a single study, the task force considered indirect evidence from recommendation 1. Both direct and indirect evidence suggest a small benefit from HFNC over COT during breaks off NIV, with few undesirable effects. The impact upon critical outcomes (e.g. mortality, intubation) is unclear, but likely to be small. Thus, the task force suggests that in the subset of patients with AHNF HFNC may be preferred over COT during breaks. As the potential benefits are small and there is a likely wide variation in resources, these should be the primary factor in deciding whether to prescribe HFNC over COT during breaks from NIV. As the major benefits appear to be linked to patient comfort, rather than to reduction in intubation requirement, the cost-effectiveness is likely to be low.

HFNC in post-operative patients

Background

Post-operative pulmonary complications (PPCs) play a significant role in determining patient morbidity, mortality and length of hospital stay [71–73]. Most frequent during the first 7 days after an operation, PPCs range from atelectasis to ARDS. The risk of ARF, probably the most important PPC, is dependent upon many factors including the surgery (e.g. duration of surgery or type of surgical procedure leading to increased post-operative pain or respiratory muscle dysfunction), anaesthesia (e.g. general anaesthesia), mechanical ventilation (e.g. intra-operative high tidal volume ventilation) and patient (e.g. age, comorbidities and lifestyle factors). The choice of post-operative respiratory supportive strategies may affect the risk of PPCs. COT is the first-line post-operative respiratory therapy, but it does not provide a reliable $F_iO2$ or real support for work of breathing. NIV and continuous positive airway pressure (CPAP) are second-line respiratory support when COT fails, leading to airway splinting and reduced work of breathing through better respiratory compliance and inspiratory effort [20]. Both NIV and CPAP appear to be effective in patients with post-operative ARF, especially after abdominal and thoracic surgery. NIV was shown to reduce intubation rate, incidence of nosocomial infections, length of stay and mortality rates; therefore, official ERS/ATS clinical practice guidelines suggest NIV for patients with post-operative ARF [20]. Other pre-operative guidelines suggest that NIV should be performed by physicians with skill in airway management and ventilation of patients with lung injury [74]. HFNC should be prescribed in hypoxaemic patients with poor tolerance of noninvasive respiratory support.

Drawbacks of post-operative NIV/CPAP are related to a monitored setting and to the risk of failure due to poor patient tolerance of the positive pressure or interface, or skin breakdown. HFNC may overcome these limitations [75, 76]. These findings are particularly relevant in surgical hypoxaemic patients, given the potential for anastomotic leakage and delayed wound healing when positive pressure NIV or mechanical ventilation are applied [77, 78]. COT shows several drawbacks, including insufficient warming and humidification. Because of increased mucociliary clearance [1], augmented dead space washout and improved pulmonary mechanics, HFNC may be an effective alternative alongside COT and NIV/CPAP in post-operative patients whose hypoxaemia is often highly dependent on alveolar collapse [79].

According to the PPO risk profile (low versus high), two recommendations have been produced comparing HFNC to COT and NIV in post-operative patients.

PICO question 4: Should HFNC or COT be used in post-operative patients after extubation?

Recommendation 4

We suggest the use of either COT or HFNC in post-operative patients at low risk of respiratory complications (conditional recommendation, low certainty of evidence).
Evidence summary

The task force identified 14 RTCs evaluating HFNC in comparison with COT in post-operative patients [77, 80–92]. HFNC probably has little to no effect upon mortality (risk ratio 0.64, 95% CI 0.19 to 2.14; risk difference –0.5%, 95% CI –1.1% to 1.5%; moderate certainty). It may result in small reduction in risk of reintubation (risk ratio 0.66, 95% CI 0.23 to 1.91; risk difference –1.2, 95% CI –2.8 to 3.3; low certainty) and uncertain reduction in risk of escalation to NIV (risk ratio 0.77, 95% CI 0.42 to 1.40; risk difference –2.6, –6.8 to 4.7; very low certainty). Length of stay in hospital and ICU is reported in 10 and 11 RTCs, respectively, demonstrating that HFNC has little effect on ICU length of stay (MD 0.02 days, 95% CI –0.09 days to 0.13 days; high certainty) and on hospital stay (MD –0.47 days, 95% CI –0.83 days to –0.11 days; high certainty).

HFNC has little effect on discomfort (SMD 0.54 lower, 95% CI –1.12 to 0.05; low certainty), but may result in higher $P_{aO2}/FiO2$ ratio (MD 34.89 mmHg, 95% CI –15.19 mmHg to 84.96 mmHg; moderate certainty) and $P_{aO2}$ values (MD 6.2 mmHg, 95% CI 3.58 mmHg to 8.28 mmHg; high certainty); with no significant effect on $P_{aCO2}$ values (MD –1.9 mmHg, 95% CI –4.81 mmHg to 0.38 mmHg; high certainty) or respiratory rate (MD 0.14 breaths·min$^{-1}$, 95% CI –0.83 breaths·min$^{-1}$ to 0.54 breaths·min$^{-1}$; moderate certainty).

Justification

As the evidence was unclear regarding whether the balance of effects favours the routine use of HFNC versus COT post-operatively, the task force decided on a conditional recommendation for either HFNC or COT in post-operative patients. While point estimates for mortality, reintubation, hospital length of stay and physiological variables potentially favour HFNC, the certainty of evidence for critical outcomes (mortality, reintubation, escalation to NIV) is low, limited by imprecision.

The following limitations were found: heterogeneity and low event rates, higher prevalence of patients undergoing cardiac and thoracic surgery, different ways of COT application (e.g. low- versus high-flow facemask delivery system). As the panel does not identify any significant undesirable clinical effects with HFNC, either would be reasonable; however, in most centres, it is likely that HFNC will cost more and COT would be the preferred respiratory support. The task force did not identify any major trade-offs where variability of patient values and preferences would impact the use of HFNC.

Even though costs and cost-effectiveness of HFNC and COT will vary between centres, COT may be favoured over HFNC in low-income countries in terms of limited resource utilisation. The panel did not identify any significant elements regarding the acceptability of HFNC. HFNC is likely to be a feasible supportive option in patients after surgery, especially those already planned for admission to a monitored setting.

Clinicians and patients may choose to use HFNC over COT in specific circumstances, based upon patient comfort, perceived risk of pulmonary complications and resources/availability of devices. Key issues to consider if HFNC is to be chosen over COT are related to patient characteristics (e.g. comorbidities), surgical variables (i.e. risk of complications), resource considerations (e.g. availability of devices, monitoring, staffing, oxygen) and patient preferences (e.g. comfort, dyspnoea, etc.).

PICO question 5: Should HFNC or NIV be used in post-operative patients after extubation?

Recommendation 5

We suggest either HFNC or NIV in post-operative patients at high risk of respiratory complications (conditional recommendation, low certainty of evidence).
Justification

The evidence comes from a single trial of patients with or at risk of respiratory failure after cardiothoracic surgery, and patients with other types of surgery are described. While HFNC appears to be similar to NIV, data are limited by imprecision. Point estimate for mortality favours NIV over HFNC, but this is limited by very serious imprecision, which does not exclude clinically meaningful benefit nor harm from the use of HFNC. As the desirable and undesirable effects appear to be closely balanced between HFNC and NIV, the task force choose to make a conditional recommendation suggesting that either HFNC or NIV could reasonably be used, based upon individual patient, surgical and resource considerations. A subgroup analysis of this trial demonstrated similar effects in obese subjects (body mass index >30 kg·m$^{-2}$) (n=231) [93].

The task force does not identify any major instances where variation in patient values, acceptability, or feasibility would be likely to impact the use of HFNC versus NIV for patients planned for admission to a monitored setting. Resources and cost-effectiveness are expected to vary.

HFNC to prevent extubation failure in nonsurgical patients

**PICO question 6: Should HFNC or COT be used in nonsurgical patients after extubation?**

**Recommendation 6**

We suggest HFNC over COT in nonsurgical patients after extubation at low or moderate risk of extubation failure (conditional recommendation, low certainty of evidence).

**Background**

Extubation remains a challenge in some patients (e.g. presence of weak cough, poor neurological status, older patients with severe cardiac or respiratory disease) and 10–20% of attempts at extubation will fail [94, 95]. Re-intubation may lead to prolonged mechanical ventilation and longer ICU stay, increased hospital morbidity and mortality. Sufficient oxygen delivery after extubation is critical to maintain adequate oxygenation. Exubated patients often require elevated inspiratory flow and adequate oxygen administration. HFNC may prevent hypoxaemic episodes after extubation, decrease respiratory rate, facilitate removal of secretions, reduce atelectasis and lead to a higher probability of extubation success when compared to COT. The question is based on the assessment of HFNC as a first-line therapy for ICU patients after extubation.

**Evidence summary**

Pooled analysis of RCTs [96–107] shows that HFNC when compared to COT probably reduces the rate of reintubation (risk ratio 0.62, 95% CI 0.38 to 1.01; risk difference −5.1%, 95% CI −8.2% to 0.1%; moderate certainty) and the need for escalation to NIV (risk ratio 0.38, 95% CI 0.17 to 0.85; risk difference −9.4%, 95% CI −12.5% to −2.3%; moderate certainty) for ICU patients at risk of respiratory failure after extubation. There is probably no effect on mortality (risk ratio 1.01, 95% CI 0.68 to 1.52; risk difference −0.1%, 95% CI −3.7% to 4.3%; moderate certainty). Lengths of ICU (MD 0.29 days, 95% CI −0.27 to 0.85 days; high certainty) and hospital stay (MD −1.08 days, 95% CI −4.83 days to 2.66; low certainty) are similar for HFNC and COT. HFNC is associated with small improvement in comfort (SMD 0.77SD, 95% CI 0.03 SD to 1.5 SD; high certainty) and reduction of respiratory rate (MD −1.98 breaths·min$^{-1}$, 95% CI −3.9 breaths·min$^{-1}$ to −0.06 breaths·min$^{-1}$; high certainty). Gas exchange is not significantly different exposed to HFNC or COT ($P_{aO2}$ MD 7.57 mmHg, 95% CI 2.68 mmHg to 12.46 mmHg; high certainty; $P_{aCO2}$ MD 0.15 mmHg, 95% CI −1.89 mmHg to 1.58 mmHg; high certainty).

**Justification**

HFNC after extubation in nonsurgical patients may reduce reintubation rate and escalation to NIV with no major undesirable side-effects. There is no effect on mortality, with moderate certainty, limited by imprecision. The task force does not identify any trade-offs where patient values and preferences would be likely to vary; almost all patients would prefer to avoid re-intubation. The major limitation for widespread use of HFNC is accessibility of HFNC and available resources. A UK cost-effectiveness analysis suggested that HFNC is likely to be cost-effective even in patients at low risk of reintubation [108]. Cost-effectiveness regionally varies, and is probably less for patients at low risk of complications.

**PICO question 7: Should HFNC or NIV be used in nonsurgical patients after extubation?**

**Recommendation 7**

We suggest the use of NIV over HFNC after extubation for patients at high risk of extubation failure unless there are relative or absolute contraindications to NIV (conditional recommendation, moderate certainty of evidence).
Background
NIV has been proposed as a method to prevent post-extubation respiratory failure and need for reintubation, especially in patients at high risk of extubation failure. Patients at high risk are those who can develop hypercapnia during the spontaneous breathing trial, those with chronic cardiac and respiratory disorders, with advanced age and with airway patency problems [109]. Official ERS/ATS clinical practice guidelines for NIV in ARF suggested NIV to prevent post-extubation respiratory failure in patients at high risk of extubation failure (conditional recommendation, low certainty of evidence) [20]. Indeed, early NIV administration after planned extubation decreases both rate of reintubation and mortality. Compared to NIV, HFNC improves patient comfort and limits the risk of NIV-related adverse events and may be better tolerated alternative to NIV.

Evidence summary
Seven RCTs [13–19] which compared HFNC to NIV in patients at high risk of reintubation were found [76, 110–115]. Two studies reported few outcomes of interest [111, 114], and one study compared HFNC with CPAP (5 cmH2O through a mechanical valve) and was not included in the comparison [110]. Out of the remaining four studies, two enrolled only patients with COPD [112, 115] and one compared NIV interspaced with HFNC between NIV sessions versus HFNC alone [113].

Compared to NIV, HFNC increases the rate of reintubation (risk ratio 1.31, 95% CI 1.04 to 1.64; risk difference 4.4%, 95% CI 0.6% to 9.2%; high certainty), with little effect on mortality (risk ratio 1.07, 95% CI 0.84 to 1.36; risk difference 1.0%, 95% CI −2.3% to 5.1%; moderate certainty). HFNC results in slightly longer length of stay in ICU (MD 1.0 day lower, 95% CI 1.52 days to 0.47 days lower; high certainty) and hospital (MD 1.44 days lower, 95% CI 2.63 day to 0.25 days lower; high certainty). Compared to NIV, HFNC provides a small increase in patient comfort (SMD 0.73SD lower, 95% CI 0.98 to 0.49 SD lower, high certainty). There is no difference with respect to respiratory rate (MD 0.59 breaths·min\(^{-1}\) lower, 95% CI −2.48 breaths·min\(^{-1}\) to 1.29 breaths·min\(^{-1}\); high certainty) and gas exchange (\(P_{aO2}/FiO2\) MD 3.86 mmHg, 95% CI 0.39 mmHg to 7.34 mmHg; high certainty; \(P_{aCO2}\) MD 1.01 mmHg lower; 95% CI −1.47 mmHg to −0.55 mmHg; high certainty).

Justification
HFNC appears to result in small, but probably clinically important increased risk of reintubation (~4%) compared to NIV in nonsurgical patients at high risk of extubation failure. However, compared to NIV, HFNC slightly improves patient comfort. Therefore, in patients who are intolerant or have contraindications to NIV, HFNC may be an alternative to NIV for preventing post-extubation respiratory failure. NIV interspaced with HFNC breaks between NIV sessions is a strategy that may be effective to further improve oxygenation and reduce post-extubation respiratory failure by gaining the benefits of NIV, with increased comfort from HFNC [113]. The task force judges that the large majority of the patients would value avoiding reintubation over the increased comfort of HFNC, and, thus, in patients without any contraindications, NIV would generally be preferred. There is limited evidence related to costs for both NIV and HFNC, and these are likely to vary between centres.

HFNC in hypercapnic respiratory failure

PICO question 8: Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?

Recommendation 8
We suggest a trial of NIV prior to use of HFNC in patients with COPD and acute hypercapnic respiratory failure (conditional recommendation, low certainty of evidence).

Background
COPD is the fourth leading cause of chronic morbidity in the world [116]. COPD can result in acute exacerbations, characterised by worsening of respiratory symptoms and hypercapnic acute-on-chronic respiratory failure [117]. While other conditions, such as neuromuscular disease, may be characterised by acute episodes of ARF, the mechanism for the increase in carbon dioxide is distinct from COPD [118]. Official ERS/ATS guidelines recommend NIV for patients with COPD and acute hypercapnic acidotic respiratory failure (pH ≤7.35), including those requiring endotracheal intubation and mechanical ventilation, unless the patient is immediately deteriorating [20]. HFNC has physiological rationale (i.e. oxygenation, positive pressure, reduced dead space) for use in hypercapnic exacerbation of COPD, which, along with its ease of use and patient comfort, make it an alternative to NIV for acute-on-chronic hypercapnic respiratory failure of mild to moderate severity degree of respiratory acidosis [3, 25, 119]. However, its role in COPD and other diseases presenting with acute hypercapnic respiratory failure is not yet well established.
Evidence summary

Five parallel-group RCTs [120–124] and one crossover RCT [125] comparing HFNC to NIV in hypercapnic respiratory failure, in which most patients had COPD, were found. Mean baseline $P_{aCO_2}$ ranged from 56 to 73.7 mmHg, and pH ranged between 7.26 and 7.4, indicating mild to moderate hypercapnic decompensated respiratory failure.

HFNC may not reduce mortality (risk ratio 0.82, 95% CI 0.46 to 1.47; risk difference $-3.1\%$, 95% CI $-9.2\%$ to $8.0\%$; low certainty) or intubation rate (risk ratio 0.79, 95% CI 0.46 to 1.35; risk difference $-3.6\%$, 95% CI $-9.3\%$ to $6.0\%$; low certainty); both measures are limited by very serious imprecision. Length of stay in ICU (MD 0.1, 95% CI $-0.73$ to $0.94$; moderate certainty) and hospital (MD $-0.82$, 95% CI $-1.83$ to $0.20$) are similar between HFNC and NIV. HFNC may be more comfortable compared to NIV (MD $-0.57$, 95% CI $-0.98$ to $-0.16$; low certainty), although dyspnoea is similar (MD $-0.31$, 95% CI $-0.94$ to $0.33$; moderate certainty). Gas exchange, including $P_{aCO_2}$, and respiratory rate were similar between HFNC and NIV.

Justification

Overall, the evidence for mortality and intubation is of low certainty, primarily due to imprecision, which does not rule out a clinically significant benefit or harm of HFNC versus NIV. This is insufficient to make a recommendation in favour of HFNC, given the high-certainty evidence for the use of NIV in COPD, and that more evidence would be required before HFNC could be considered equivalent or superior to NIV [20]. Hence, the panel chose to make a weak/conditional recommendation, suggesting a trial of NIV prior to use

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Key research recommendations</th>
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<tbody>
<tr>
<td>1. Should HFNC or COT be used in patients with acute hypoxaemic respiratory failure?</td>
<td>More evidence is needed to identify patients at high risk of deterioration and therefore more likely to benefit from HFNC. Which treatment (HFNC or COT) results in aerosolisation of infectious particles in COVID-19, and what are the clinical implications of this?</td>
</tr>
<tr>
<td>2. Should HFNC or NIV be used in patients with acute hypoxaemic respiratory failure?</td>
<td>More evidence is needed to assess the impact of HFNC versus NIV in COVID-19 and other viral illnesses, as well as in patients at different risk of induced lung injury and different $P_{aO_2}/F_{iO_2}$ ratio severity. More evidence is needed regarding effectiveness of HFNC versus NIV in both helmet and facemask forms. Which treatment (HFNC or COT) results in aerosolisation of infectious particles in COVID-19, and what are the clinical implications of this?</td>
</tr>
<tr>
<td>3. Should HFNC or COT be used during breaks from NIV in patients with acute hypoxaemic respiratory failure?</td>
<td>More evidence is needed to identify patients who are likely to benefit from HFNC during breaks from NIV (hypoxic and hypercapnic populations).</td>
</tr>
<tr>
<td>4. Should HFNC or COT be used in post-operative patients after extubation?</td>
<td>More evidence is needed to identify which patients (type of surgery, comorbidities, $P_{aO_2}/F_{iO_2}$ level) are most likely to benefit from HFNC over COT when used post-operatively according to different settings (high- versus low-intensity monitoring); however, it is likely that any such effects in low-risk groups will be small.</td>
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<tr>
<td>5. Should HFNC or NIV be used in post-operative patients after extubation?</td>
<td>Further large RCTs are needed to compare NIV and HFNC in different subgroups of surgical patients according to different settings (high- versus low-intensity monitoring). Additional research is needed to identify the subgroups of post-operative patients at high risk of respiratory failure most likely to benefit from use of combination treatment (NIV plus HFNC) versus NIV alone.</td>
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<tr>
<td>6. Should HFNC or COT be used in nonsurgical patients after extubation?</td>
<td>More evidence is needed to identify which patients (underlying disease, comorbidities, $P_{aO_2}/F_{iO_2}$ level) according to different settings (high- versus low-intensity monitoring) are most likely to benefit from post extubation HFNC over COT.</td>
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<tr>
<td>7. Should HFNC or NIV be used in nonsurgical patients after extubation?</td>
<td>More evidence is needed to identify which patients (underlying disease, comorbidities, $P_{aO_2}/F_{iO_2}$ level) according to different settings (high- versus low-intensity monitoring) are most likely to benefit from post extubation HFNC over COT are most likely to benefit from NIV over HFNC.</td>
</tr>
<tr>
<td>8. Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?</td>
<td>More randomised data are required to determine populations where HFNC can be a first-line alternative to NIV (e.g. severity of COPD; patients with hypercapnic failure from causes other than COPD; hypersecretion, poor mask tolerance, agitation). More evidence needed to predict which patients are likely to successfully transition to HFNC from NIV.</td>
</tr>
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</table>

HFNC: high-flow nasal cannula; COT: conventional oxygen therapy; NIV: noninvasive ventilation; COVID-19: coronavirus disease 2019; $P_{aO_2}$: arterial oxygen partial pressure; $F_{iO_2}$: inspiratory oxygen fraction; RCT: randomised controlled trial.
of HFNC. While NIV has high evidence for hypercapnic acidic respiratory failure, it cannot be tolerated by some patients, who may prefer HFNC, being more comfortable, and allowing easier communication, feeding and oral care. A trial of NIV allows clinicians to determine the severity of respiratory failure, the response to treatment and whether a patient can have a transition to HFNC. HFNC should be preferred over COT during breaks off NIV, but also in exacerbated COPD patients, as HFNC significantly reduces the activation of the diaphragm and improves comfort, without affecting gas exchange [126].

HFNC settings were heterogeneous. The flow was set in a range between 35 and 60 L·min\(^{-1}\) and titrated as much as tolerated by the patients. The temperature was set at 34°C or 37°C according to patient’s preference, whereas \(F_{\text{CO}_2}\) was adjusted to achieve arterial oxygen saturation by pulse oximetry (\(S_{\text{PO}_2}\)) between 88% and 92%.

There is poor evidence on resource requirements. The cost of one HFNC device (e.g. interface, circuit, humidity) may be similar to that of a ventilator for NIV, although other resources (e.g. staffing and monitoring), and some ICU ventilators have integrated both HFNC and NIV software, making the interface the only substantive cost difference. In addition, the prescription of HFNC requires fewer resources than NIV, even in terms of healthcare workload. Acceptability and feasibility of HFNC in COPD is probably high, as clinicians are increasingly comfortable with using HFNC.

**Discussion**

The task force developed eight evidence-based, actionable recommendations, along with implementation considerations to assist patients, clinicians, policy-makers and other healthcare stakeholders to make rational and evidence-based decisions for using HFNC in the acute care setting. The task force identified key areas where further research is necessary to guide practice (table 3).

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The guidelines published by the European Respiratory Society (ERS) incorporate data obtained from a comprehensive and systematic literature review of the most recent studies available at the time. Health professionals are encouraged to take the guidelines into account in their clinical practice. However, the recommendations issued by this guideline may not be appropriate for use in all situations. It is the individual responsibility of health professionals to consult other sources of relevant information, to make appropriate and accurate decisions in consideration of each patient’s health condition and in consultation with that patient and the patient’s caregiver where appropriate and/or necessary, and to verify rules and regulations applicable to drugs and devices at the time of prescription.

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