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

Simon Oczkowski[1,2,26], Begüm Ergan[3,26], Lieuwe Bos[4,5], Michelle Chatwin[6], Miguel Ferrer[7], Cesare Gregoretti[8,9], Leo Heunks[10], Jean-Pierre Frat[11,12], Federico Longhini[13], Stefano Nava[14,15], Paolo Navalesi[16,17], Aylin Ozsancak Uğurlu[18], Lara Pisani[14,15], Teresa Renda[19], Arnaud W. Thille[11,12], João Carlos Winck[20], Wolfram Windisch[21], Thomy Tonia[22], Jeanette Boyd[23], Giovanni Sotgiu[24] and Raffaele Scala[25]

[1]Dept of Medicine, Division of Critical Care, McMaster University, Hamilton, ON, Canada. [2]Dept of Health Research Methods, Evidence, and Impact, McMaster University, Hamilton, ON, Canada. [3]Dept of Pulmonary and Critical Care, Dokuz Eylul University School of Medicine, Izmir, Turkey. [4]Dept of Intensive Care and Laboratory of Experimental Intensive Care and Anesthesiology (LEICA), Amsterdam UMC, location Academic Medical Center, Amsterdam, The Netherlands. [5]Respiratory Medicine, Amsterdam UMC, location Academic Medical Center, Amsterdam, The Netherlands. [6]Academic and Clinical Department of Sleep and Breathing and NIHR Respiratory Biomedical Research Unit, Royal Brompton and Harefield NHS Foundation Trust, London, UK. [7]Dept of Pneumology, Respiratory Institute, Hospital Clinic, IDIBAPS, University of Barcelona and CIBERES, Barcelona, Spain. [8]Dept of Surgical, Oncological and Oral Science, University of Palermo, Palermo, Italy. [9]G. Giglio Institute, Cefalù, Italy. [10]Dept of Intensive Care Medicine, Amsterdam UMC, Location VUmc, Amsterdam, The Netherlands. [11]Centre Hospitalier Universitaire de Poitiers, Médecine Intensive Réanimation, Poitiers, France. [12]INSERM Centre d'Investigation Clinique 1402 ALIVE, Université de Poitiers, Poitiers, France. [13]Anesthesia and Intensive Care Unit, Dept of Medical and Surgical Sciences, Magna Graecia University, Catanzaro, Italy. [14]Dept of Clinical, Integrated and Experimental Medicine (DIMES), Alma Mater Studiorum University of Bologna, Bologna, Italy. [15]IRCCS Azienda Ospedaliero-Universitaria di Bologna, Respiratory and Critical Care Unit, Bologna, Italy. [16]Department of Medicine – DIMED, University of Padua, Padua, Italy. [17]Anesthesia and Intensive Care, Padua University Hospital, Padua, Italy. [18]Dept of Pulmonary Medicine, Baskent University, Istanbul, Turkey. [19]Cardiothoracic and Vascular Department, Respiratory and Critical Care Unit, Careggi University Hospital, Florence, Italy. [20]Faculdade de Medicina da Universidade do Porto, Porto, Portugal. [21]Dept of Pneumology, Cologne Merheim Hospital, Kliniken der Stadt Köln, gGmbH, Witten/Herdecke University, Faculty of Health/School of Medicine, Köln, Germany. [22]Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland. [23]European Lung Foundation (ELF), Sheffield, UK. [24]Clinical Epidemiology and Medical Statistics Unit, Dept of Medical, Surgical, Experimental Sciences, University of Sassari, Sassari, Italy. [25]Pulmonology and Respiratory Intensive Care Unit, Cardio-Thoraco-Neuro-Vascular Dept, Usl Toscana Sudest, S Donato Hospital, Arezzo, Italy. [26]Co-first authors.

Corresponding author: Raffaele Scala (raffaele_scala@hotmail.com)

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

Cite this article as: Oczkowski S, Ergan B, Bos L, *et al*. ERS clinical practice guidelines: high-flow nasal cannula in acute respiratory failure. *Eur Respir J* 2022; 59: 2101574 [DOI: 10.1183/13993003.01574-2021].

Received: 3 June 2021
Accepted: 13 Aug 2021

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

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 1 Interpretation of strong and conditional recommendations

	Strong recommendation	Weak recommendation
For patients	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	The majority of individuals in this situation would want the suggested course of action, but many would not.
For clinicians	Most individuals should receive the recommended course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.	Different choices are likely to be appropriate for different patients and therapy should be tailored to the individual patient's circumstances. Those circumstances may include the patient's or family's values and preferences.
For policy-makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debate and the involvement of many stakeholders. Policies are also more likely to vary between regions. Performance indicators would have to focus on the fact that adequate deliberation about the management options has taken place.

Reproduced and modified from [6] with permission.

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 2 Population, intervention, comparison, outcomes (PICO) questions and recommendations

1. Should HFNC or COT be used in patients with acute hypoxaemic respiratory failure?	The ERS task force suggests the use of HFNC over COT in patients with acute hypoxaemic respiratory failure (conditional recommendation, moderate certainty of evidence)
2. Should HFNC or NIV be used in patients with acute hypoxaemic respiratory failure?	The ERS task force suggests the use of HFNC over NIV in acute hypoxaemic respiratory failure (conditional recommendation, very low certainty of evidence)
3. Should HFNC or COT be used during breaks from NIV in patients with acute hypoxaemic respiratory failure?	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)
4. Should HFNC or COT be used in post-operative patients after extubation?	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)
5. Should HFNC or NIV be used in post-operative patients after extubation?	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)
6. Should HFNC or COT be used in nonsurgical patients after extubation?	The ERS task force suggests the use of HFNC over COT in nonsurgical patients after extubation (conditional recommendation, low certainty of evidence)
7. Should HFNC or NIV be used in nonsurgical patients after extubation?	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)
8. Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?	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)

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 (www.gradepro.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 (F_{iO_2}), 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 F_{iO_2} 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 airflows as high as 50–60 $L \cdot min^{-1}$, HFNC closely matches the inspiratory demands of dyspnoeic patients with AHRF, and reliably achieves an F_{iO_2} 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_{aO_2}) values (MD 16.72 mmHg, 95% CI 5.74 mmHg higher to 27.71 mmHg higher; high certainty) and, possibly, the P_{aO_2}/F_{iO_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_{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 heterogenous: 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_{aO_2}/F_{iO_2} ⩽200 mmHg), when the risks of intubation and death are higher [20, 21]. In more severe AHRF (P_{aO_2}/F_{iO_2} <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_{aO_2}/F_{iO_2} <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_{aO_2}/F_{iO_2} <175 mmHg after 1 h of NIV is associated with need for intubation [20]. Finally, expired tidal volume exceeding 9–9.5 $mL \cdot kg^{-1}$ 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_2O) 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 $h \cdot day^{-1}$), 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_{aO_2} values (MD −19.98 mmHg, 95% CI −11.97 mmHg to −28.0 mmHg; moderate certainty) and P_{aO_2}/F_{iO_2} ratio (MD −43.26, 95% CI −29.48 to −57.04; moderate certainty), respectively, with little difference in P_{aCO_2} values (MD 0.45 mmHg, 95% CI 1.94 mmHg lower to 1.05 mmHg higher; low certainty) or respiratory rate (MD 0.83 $breaths \cdot min^{-1}$, 95% CI −1.04 $breaths \cdot min^{-1}$ to 2.7 $breaths \cdot min^{-1}$; low certainty).

Justification

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 $h \cdot day^{-1}$) 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.

Subgroup considerations

Benefits of HNFC 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 AHRF, the majority of whom showing a P_{aO_2}/F_{iO_2} 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 AHRF for whom clinicians and patients choose NIV 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_{iO_2} 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 RCTs, 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_{aO_2}/F_{iO_2} ratio (MD 34.89 mmHg, 95% CI −15.19 mmHg to 84.96 mmHg; moderate certainty) and P_{aO_2} values (MD 6.2 mmHg, 95% CI 3.58 mmHg to 8.28 mmHg; high certainty); with no significant effect on P_{aCO_2} 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).

Evidence summary

One trial compared HFNC to NIV in 830 patients with or at high risk of ARF after cardiothoracic surgery [75]. When compared to NIV (⩾4 h·day^{-1}, pressure support level at 8 cmH_2O, PEEP level at 4 cmH_2O, F_{iO_2} 50%), HFNC (continuous, flow 50 L·min^{-1}, F_{iO_2} 50%) may result in a small increase in mortality (risk ratio 1.22, 95% CI 0.72 to 2.09; risk difference 1.2%, 95% CI −1.5% to 6.0%; low certainty), with probably little to no difference in reintubation (risk ratio 1.02, 95% CI 0.73 to 1.44; risk difference 0.3%, 95% CI −3.7% to 6.0%; moderate certainty). HFNC results in little to no difference in length of stay in ICU (MD 0 days, 95% CI −0.6 days to 0.6 days; moderate certainty) or hospital (MD −1 day, 95% CI −2.21 days to 0.21 days; moderate certainty). HFNC has little to no effect upon P_{aCO_2} values and respiratory rate, but results in a slightly lower P_{aO_2}/F_{iO_2} ratio (MD −63, 95% CI −80 to −46; high certainty). Skin breakdown is significantly more prevalent with NIV than HFNC after 24 h.

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 $kg \cdot m^{-2}$) (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. Extubated 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 0.77 SD, 95% CI 0.03 SD to 1.5 SD; high certainty) and reduction of respiratory rate (MD -1.98 breaths$\cdot min^{-1}$, 95% CI -3.9 breaths$\cdot min^{-1}$ to -0.06 breaths$\cdot min^{-1}$; high certainty). Gas exchange is not significantly different exposed to HFNC or COT (P_{aO_2} MD 7.57 mmHg, 95% CI 2.68 mmHg to 12.46 mmHg; high certainty; P_{aCO_2} 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 cmH_2O 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 lower 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 0.73 SD 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_{aO_2}/F_{iO_2} MD 3.86 mmHg, 95% CI 0.39 mmHg to 7.34 mmHg; high certainty; P_{aCO_2} 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 3 Key research recommendations

1. Should HFNC or COT be used in patients with acute hypoxaemic respiratory failure?	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?
2. Should HFNC or NIV be used in patients with acute hypoxaemic respiratory failure?	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?
3. Should HFNC or COT be used during breaks from NIV in patients with acute hypoxaemic respiratory failure?	More evidence is needed to identify patients who are likely to benefit from HFNC during breaks from NIV (hypoxic and hypercapnic populations).
4. Should HFNC or COT be used in post-operative patients after extubation?	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.
5. Should HFNC or NIV be used in post-operative patients after extubation?	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.
6. Should HFNC or COT be used in nonsurgical patients after extubation?	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.
7. Should HFNC or NIV be used in nonsurgical patients after extubation?	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.
8. Should HFNC or NIV be used in patients with acute hypercapnic respiratory failure?	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.

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 acidotic 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 $L \cdot min^{-1}$ 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_{iO_2} was adjusted to achieve arterial oxygen saturation by pulse oximetry (S_{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).

Acknowledgements: Thank you to Kaitryn Campbell for developing and running the database searches and Elaine Ho for her contributions to screening and data abstraction (McMaster University, Hamilton, ON, Canada), and Andrea Cortegiani for input and advice (University of Palermo, Palermo, Italy).

This document was endorsed by the ERS executive committee on 10 September 2021.

Conflict of interest: S. Oczkowski reports support for the current manuscript from librarian support services; support for attending meetings and/or travel from ERS, European Society of Intensive Care Medicine and Society of Critical Care Medicine, outside the submitted work. B. Ergan has nothing to disclose. L. Bos reports grants from the Dutch Lung Foundation (young investigator grant), the Dutch Lung Foundation and Health Holland (public-private partnership grant), the Dutch Lung Foundation (Dirkje Postma Award), IMI COVID19 initiative and Amsterdam UMC fellowship, outside the submitted work. M. Chatwin reports lecture fees from ResMed UK, Breas Medical UK, MPR Italy; and since December 2020 has worked part time for Breas Medical as their global clinical specialist, including CAB membership and support for attending meetings and/or travel. M. Ferrer has nothing to disclose. C. Gregoretti reports consulting fees from Mindray and Air Liquide; lecture fees from Vivisol, Philips and Air Liquide; support for attending meetings and/or travel from Fisher & Paykel; outside the submitted work. L. Heunks reports grants from InflaRx; consulting fees from Liberate Medical, USA; speaker fees from Fisher & Paykel and Maquet; outside the submitted work. J-P. Frat reports funding, provision of study materials, personal fees for lectures, travels and accommodations expenses reimbursement from Fisher and Paykel Healthcare; personal fees as a member of a scientific board from SOS Oxygene; grants from French Ministry of health; outside the submitted work. F. Longhini reports honoraria for a lecture from Draeger; issued patent for a new device for noninvasive ventilation (European patent number 3320941) from Intersurgical SPA; outside the submitted work. S. Nava has nothing to disclose. P. Navalesi has nothing to disclose. A. Ozsancak Uğurlu has nothing to disclose. L. Pisani has nothing to disclose. T. Renda has nothing to disclose. A.W. Thille reports payments for lectures and support for attending meetings and/or travel from Fisher & Paykel; Fisher & Paykel provided the high-flow nasal oxygen equipment and masks for NIV in several randomised clinical trials coordinated by our center. J.C. Winck

reports webinar fees from Armstrong Medical, Breas, Philips and Nippon Gases; outside the submitted work. W. Windisch reports grants from Philips/Respironics/USA, Löwenstein Medical/Germany, VitalAire/Germany and Vivisol/Germany; speaking fees from Philips/Respironics/USA, Löwenstein Medical/Germany and VitalAire/Germany; outside the submitted work. T. Tonia acts as ERS Methodologist. J. Boyd is an employee of the European Lung Foundation. G. Sotgiu has nothing to disclose. R. Scala has nothing to disclose.

References

1 Chidekel A, Zhu Y, Wang J, *et al.* The effects of gas humidification with high-flow nasal cannula on cultured human airway epithelial cells. *Pulm Med* 2012; 2012: 380686.
2 Renda T, Corrado A, Iskandar G, *et al.* High-flow nasal oxygen therapy in intensive care and anaesthesia. *Br J Anaesth* 2018; 120: 18–27.
3 Pisani L, Astuto M, Prediletto I, *et al.* High flow through nasal cannula in exacerbated COPD patients: a systematic review. *Pulmonology* 2019; 25: 348–354.
4 Ricard J-D, Roca O, Lemiale V, *et al.* Use of nasal high flow oxygen during acute respiratory failure. *Intensive Care Med* 2020; 46: 2238–2247.
5 Kang BJ, Koh Y, Lim C-M, *et al.* Failure of high-flow nasal cannula therapy may delay intubation and increase mortality. *Intensive Care Med* 2015; 41: 623–632.
6 Schünemann H, Brożek J, Guyatt G, *et al.* GRADE Handbook. Version 3.2. 2008. https://gdt.gradepro.org/app/handbook/handbook.html Date last updated: October 2013.
7 Guyatt GH, Oxman AD, Santesso N, *et al.* GRADE guidelines: 12. Preparing summary of findings tables – binary outcomes. *J Clin Epidemiol* 2013; 66: 158–172.
8 Guyatt GH, Thorlund K, Oxman AD, *et al.* GRADE guidelines: 13. Preparing summary of findings tables and evidence profiles – continuous outcomes. *J Clin Epidemiol* 2013; 66: 173–183.
9 Balshem H, Helfand M, Schünemann HJ, *et al.* GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol* 2011; 64: 401–406.
10 Guyatt GH, Oxman AD, Vist G, *et al.* GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). *J Clin Epidemiol* 2011; 64: 407–415.
11 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 7. Rating the quality of evidence – inconsistency. *J Clin Epidemiol* 2011; 64: 1294–1302.
12 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 8. Rating the quality of evidence – indirectness. *J Clin Epidemiol* 2011; 64: 1303–1310.
13 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines 6. Rating the quality of evidence – imprecision. *J Clin Epidemiol* 2011; 64: 1283–1293.
14 Guyatt GH, Oxman AD, Montori V, *et al.* GRADE guidelines: 5. Rating the quality of evidence – publication bias. *J Clin Epidemiol* 2011; 64: 1277–1282.
15 Guyatt GH, Oxman AD, Kunz R, *et al.* GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol* 2011; 64: 395–400.
16 Andrews JC, Schünemann HJ, Oxman AD, *et al.* GRADE guidelines: 15. Going from evidence to recommendation – determinants of a recommendation's direction and strength. *J Clin Epidemiol* 2013; 66: 726–735.
17 Andrews J, Guyatt G, Oxman AD, *et al.* GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. *J Clin Epidemiol* 2013; 66: 719–725.
18 Matthay MA, Thompson BT, Ware LB. The Berlin definition of acute respiratory distress syndrome: should patients receiving high-flow nasal oxygen be included? *Lancet Respir Med* 2021; 9: 933–936.
19 Scala R, Heunks L. Highlights in acute respiratory failure. *Eur Respir Rev* 2018; 27: 180008.
20 Rochwerg B, Brochard L, Elliott MW, *et al.* Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure. *Eur Respir J* 2017; 50: 1602426.
21 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2017; 195: 438–442.
22 Yoshida T, Grieco DL, Brochard L, *et al.* Patient self-inflicted lung injury and positive end-expiratory pressure for safe spontaneous breathing. *Curr Opin Crit Care* 2020; 26: 59–65.
23 Papazian L, Corley A, Hess D, *et al.* Use of high-flow nasal cannula oxygenation in ICU adults: a narrative review. *Intensive Care Med* 2016; 42: 1336–1349.
24 Mauri T, Turrini C, Eronia N, *et al.* Physiologic effects of high-flow nasal cannula in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2017; 195: 1207–1215.
25 Cortegiani A, Crimi C, Noto A, *et al.* Effect of high-flow nasal therapy on dyspnea, comfort, and respiratory rate. *Crit Care* 2019; 23: 201.
26 Azoulay E, Pickkers P, Soares M, *et al.* Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study. *Intensive Care Med* 2017; 43: 1808–1819.
27 Frat J-P, Coudroy R, Marjanovic N, *et al.* High-flow nasal oxygen therapy and noninvasive ventilation in the management of acute hypoxemic respiratory failure. *Ann Transl Med* 2017; 5: 297.

28 Parke RL, McGuinness SP, Eccleston ML. A preliminary randomized controlled trial to assess effectiveness of nasal high-flow oxygen in intensive care patients. *Respir Care* 2011; 56: 265–270.
29 Bell N, Hutchinson CL, Green TC, *et al.* Randomised control trial of humidified high flow nasal cannulae *versus* standard oxygen in the emergency department. *Emerg Med Australas* 2015; 27: 537–541.
30 Frat JP, Thille AW, Mercat A, *et al.* High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med* 2015; 372: 2185–2196.
31 Lemiale V, Mokart D, Mayaux J, *et al.* The effects of a 2-h trial of high-flow oxygen by nasal cannula *versus* Venturi mask in immunocompromised patients with hypoxemic acute respiratory failure: a multicenter randomized trial. *Crit Care* 2015; 19: 380.
32 Rittayamai N, Tscheikuna J, Praphruetkit N, *et al.* Use of high-flow nasal cannula for acute dyspnea and hypoxemia in the emergency department. *Respir Care* 2015; 60: 1377–1382.
33 Jones PG, Kamona S, Doran O, *et al.* Randomized controlled trial of humidified high-flow nasal oxygen for acute respiratory distress in the emergency department: the HOT-ER Study. *Respir Care* 2016; 61: 291–299.
34 Makdee O, Monsomboon A, Surabenjawong U, *et al.* High-flow nasal cannula *versus* conventional oxygen therapy in emergency department patients with cardiogenic pulmonary edema: a randomized controlled trial. *Ann Emerg Med* 2017; 70: 465–472.
35 Azoulay E, Lemiale V, Mokart D, *et al.* Effect of high-flow nasal oxygen *vs* standard oxygen on 28-day mortality in immunocompromised patients with acute respiratory failure: the HIGH randomized clinical trial. *JAMA* 2018; 320: 2099–2107.
36 Raeisi S, Fakharian A, Ghorbani F, *et al.* Value and safety of high flow oxygenation in the treatment of inpatient asthma: a randomized, double-blind, pilot study. *Iran J Allergy Asthma Immunol* 2019; 18: 615–623.
37 Geng W, Batu W, You S, *et al.* High-flow nasal cannula: a promising oxygen therapy for patients with severe bronchial asthma complicated with respiratory failure. *Can Respir J* 2020; 2020: 2301712.
38 Ko DR, Beom J, Lee HS, *et al.* Benefits of high-flow nasal cannula therapy for acute pulmonary edema in patients with heart failure in the emergency department: a prospective multi-center randomized controlled trial. *J Clin Med* 2020; 9: 1937.
39 Nö AM, Temel Ş, Yüksel R, *et al.* The use of high-flow nasal oxygen *vs*. standard oxygen therapy in hematological malignancy patients with acute respiratory failure in hematology wards. *Turkish J Med Sci* 2021; 51: 1756–1763.
40 Cuquemelle E, Pham T, Louis B, *et al.* Heated and humidified high flow oxygen therapy reduces discomfort during hypoxemic respiratory failure. *Intensive Care Med* 2011; 37: S190.
41 Schwabbauer N, Berg B, Blumenstock G, *et al.* Nasal high-flow oxygen therapy in patients with hypoxic respiratory failure: effect on functional and subjective respiratory parameters compared to conventional oxygen therapy and non-invasive ventilation (NIV). *BMC Anesthesiol* 2014; 14: 66.
42 Ruangsomboon O, Dorongthom T, Chakorn T, *et al.* High-flow nasal cannula *versus* conventional oxygen therapy in relieving dyspnea in emergency palliative patients with do-not-intubate status: a randomized crossover study. *Ann Emerg Med* 2019; 75: 615–626.
43 Bos LD, Artigas A, Constantin J-M, *et al.* Precision medicine in acute respiratory distress syndrome: workshop report and recommendations for future research. *Eur Respir Rev* 2021; 30: 200317.
44 Renda T, Scala R, Corrado A, *et al.* Adult pulmonary intensive and intermediate care units: the Italian Thoracic Society (ITS-AIPO) position paper. *Respiration* 2021; 100: 1027–1037.
45 Jahagirdar D, Picheca L. Heated Humidified High Flow Oxygen for Respiratory Support: a Review of Clinical Effectiveness, Cost-Effectiveness, and Guidelines. 2019. https://www.ncbi.nlm.nih.gov/books/NBK544686/
46 Attaway AH, Scheraga RG, Bhimraj A, *et al.* Severe covid-19 pneumonia: pathogenesis and clinical management. *BMJ* 2021; 372: n436.
47 Agarwal A, Basmaji J, Muttalib F, *et al.* High-flow nasal cannula for acute hypoxemic respiratory failure in patients with COVID-19: systematic reviews of effectiveness and its risks of aerosolization, dispersion, and infection transmission. *Can J Aneasth* 2020; 67: 1217–1248.
48 Ferioli M, Cisternino C, Leo V, *et al.* Protecting healthcare workers from SARS-CoV-2 infection: practical indications. *Eur Respir Rev* 2020; 29: 200068.
49 Franco C, Facciolongo N, Tonelli R, *et al.* Feasibility and clinical impact of out-of-ICU noninvasive respiratory support in patients with COVID-19-related pneumonia. *Eur Respir J* 2020; 56: 2002130.
50 Winck J, Scala R. Non-invasive respiratory support paths in hospitalized patients with COVID-19: proposal of an algorithm. *Pulmonology* 2021; 27: 305–312.
51 Ding L, Wang L, Ma W, *et al.* Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. *Crit Care* 2020; 24: 28.
52 Ibarra-Estrada MÁ, Marín-Rosales M, García-Salcido R, *et al.* Prone positioning in non-intubated patients with COVID-19 associated acute respiratory failure, the PRO-CARF trial: a structured summary of a study protocol for a randomised controlled trial. *Trials* 2020; 21: 940.
53 Al-Hazzani W. Awake prone position in hypoxemic patients with coronavirus disease 19 (COVI-PRONE): a randomized clinical trial (COVI-PRONE). 2021. ClinicalTrials.Gov identifier NCT04350723.

54 Garcia MA, Rampon GL, Doros G, *et al.* Rationale and design of the awake prone position for early hypoxemia in COVID-19 study protocol: a clinical trial. *Ann Am Thorac Soc* 2021; 18: 1560–1566.

55 Grieco DL, Menga LS, Eleuteri D, *et al.* Patient self-inflicted lung injury: implications for acute hypoxemic respiratory failure and ARDS patients on non-invasive support. *Minerva Anestesiol* 2019; 85: 1014–1023.

56 Bellani G, Laffey JG, Pham T, *et al.* Noninvasive ventilation of patients with acute respiratory distress syndrome. Insights from the LUNG SAFE study. *Am J Respir Crit Care Med* 2017; 195: 67–77.

57 Carteaux G, Millán-Guilarte T, De Prost N, *et al.* Failure of noninvasive ventilation for *de novo* acute hypoxemic respiratory failure: role of tidal volume. *Crit Care Med* 2016; 44: 282–290.

58 Frat JP, Ragot S, Coudroy R, *et al.* Predictors of intubation in patients with acute hypoxemic respiratory failure treated with a noninvasive oxygenation strategy. *Crit Care Med* 2018; 46: 208–215.

59 Patel BK, Kress JP. The changing landscape of noninvasive ventilation in the intensive care unit. *JAMA* 2015; 314: 1697–1699.

60 Ferreyro BL, Angriman F, Munshi L, *et al.* Association of noninvasive oxygenation strategies with all-cause mortality in adults with acute hypoxemic respiratory failure: a systematic review and meta-analysis. *JAMA* 2020; 324: 57–67.

61 Azevedo JR, Montenegro WS, Leitao AL, *et al.* High flow nasal cannula oxygen (HFNC) *versus* non-invasive positive pressure ventilation (NIPPV) in acute hypoxemic respiratory failure. A pilot randomized controlled trial. *Intensive Care Med Exp* 2015; 3: Suppl. 1, A166.

62 Doshi P, Whittle JS, Bublewicz M, *et al.* High-velocity nasal insufflation in the treatment of respiratory failure: a randomized clinical trial. *Ann Emerg Med* 2018; 72: 73–83.

63 Shebl E, Embarak S. High-flow nasal oxygen therapy *versus* noninvasive ventilation in chronic interstitial lung disease patients with acute respiratory failure. *Egypt J Chest Dis Tuberculosis* 2018; 67: 270–275.

64 Adi O, Kai Fei S, Azma Haryaty A, *et al.* Preliminary report: a randomized controlled trial comparing helmet continuous positive airway pressure (CPAP) *vs* high flow nasal cannula (HFNC) for treatment of acute cardiogenic pulmonary oedema in the emergency department. *Critical Care* 2019; 23: Suppl. 2, P340.

65 Artaud-Macari E, Bubenheim M, Le Bouar G, *et al.* High-flow oxygen therapy *vs* non invasive ventilation – a prospective cross-over physiological study of alveolar recruitment in acute respiratory failure. *Ann Intensive Care* 2019; 9: Suppl. 1, CO-27.

66 Grieco DL, Menga LS, Raggi V, *et al.* Physiological comparison of high-flow nasal cannula and helmet noninvasive ventilation in acute hypoxemic respiratory failure. *Am J Respir Crit Care Med* 2020; 201: 303–312.

67 Patel BK, Wolfe KS, Pohlman AS, *et al.* Effect of noninvasive ventilation delivered by helmet *vs* face mask on the rate of endotracheal intubation in patients with acute respiratory distress syndrome: a randomized clinical trial. *JAMA* 2016; 315: 2435–2441.

68 Grieco DL, Menga LS, Cesarano M, *et al.* Effect of helmet noninvasive ventilation *vs* high-flow nasal oxygen on days free of respiratory support in patients with COVID-19 and moderate to severe hypoxemic respiratory failure: the HENIVOT randomized clinical trial. *JAMA* 2021; 325: 1731–1743.

69 Frat JP, Brugiere B, Ragot S, *et al.* Sequential application of oxygen therapy *via* high-flow nasal cannula and noninvasive ventilation in acute respiratory failure: an observational pilot study. *Respir Care* 2015; 60: 170–178.

70 Spoletini G, Mega C, Pisani L, *et al.* High-flow nasal therapy *vs* standard oxygen during breaks off noninvasive ventilation for acute respiratory failure: a pilot randomized controlled trial. *J Crit Care* 2018; 48: 418–425.

71 Jammer I, Wickboldt N, Sander M, *et al.* Standards for definitions and use of outcome measures for clinical effectiveness research in perioperative medicine: European Perioperative Clinical Outcome (EPCO) definitions: a statement from the ESA-ESICM joint taskforce on perioperative outcome measures. *Eur J Anaesthesiol* 2015; 32: 88–105.

72 O'Gara B, Talmor D. Perioperative lung protective ventilation. *BMJ* 2018; 362: k3030.

73 Odor PM, Bampoe S, Gilhooly D, *et al.* Perioperative interventions for prevention of postoperative pulmonary complications: systematic review and meta-analysis. *BMJ* 2020; 368: m540.

74 Leone M, Einav S, Chiumello D, *et al.* Noninvasive respiratory support in the hypoxaemic peri-operative/periprocedural patient: a joint ESA/ESICM guideline. *Intensive Care Med* 2020; 46: 697–713.

75 Stéphan F, Barrucand B, Petit P, *et al.* High-flow nasal oxygen *vs* noninvasive positive airway pressure in hypoxemic patients after cardiothoracic surgery: a randomized clinical trial. *JAMA* 2015; 313: 2331–2339.

76 Hernández G, Vaquero C, Colinas L, *et al.* Effect of postextubation high-flow nasal cannula *vs* noninvasive ventilation on reintubation and postextubation respiratory failure in high-risk patients: a randomized clinical trial. *JAMA* 2016; 316: 1565–1574.

77 Yu Y, Qian X, Liu C, *et al.* Effect of high-flow nasal cannula *versus* conventional oxygen therapy for patients with thoracoscopic lobectomy after extubation. *Can Respir J* 2017; 2017: 7894631.

78 Xia M, Li W, Yao J, *et al.* A postoperative comparison of high-flow nasal cannula therapy and conventional oxygen therapy for esophageal cancer patients. *Ann Palliat Med* 2021; 10: 2530–2539.

79 D'Cruz RF, Hart N, Kaltsakas G. High-flow therapy: physiological effects and clinical applications. *Breathe* 2020; 16: 200224.

80 Parke R, McGuinness S, Dixon R, *et al.* Open-label, phase II study of routine high-flow nasal oxygen therapy in cardiac surgical patients. *Br J Anaesth* 2013; 111: 925–931.

81 Corley A, Bull T, Spooner AJ, *et al.* Direct extubation onto high-flow nasal cannulae post-cardiac surgery *versus* standard treatment in patients with a BMI ⩾30: a randomised controlled trial. *Intensive Care Med* 2015; 41: 887–894.

82 Ansari BM, Hogan MP, Collier TJ, *et al.* A randomized controlled trial of high-flow nasal oxygen (Optiflow) as part of an enhanced recovery program after lung resection surgery. *Ann Thorac Surg* 2016; 101: 459–464.

83 Futier E, Paugam-Burtz C, Godet T, *et al.* Effect of early postextubation high-flow nasal cannula *vs* conventional oxygen therapy on hypoxaemia in patients after major abdominal surgery: a French multicentre randomised controlled trial (OPERA). *Intensive Care Med* 2016; 42: 1888–1898.

84 Blaudszun G, Zochios V, Butchart A, *et al.* A randomised controlled trial of high-flow nasal oxygen (OptiflowTM) in high-risk cardiac surgical patients. *Anaesthesia* 2017; 72: Suppl. 4, 15.

85 Brainard J, Scott BK, Sullivan BL, *et al.* Heated humidified high-flow nasal cannula oxygen after thoracic surgery – a randomized prospective clinical pilot trial. *J Crit Care* 2017; 40: 225–228.

86 Sahin M, El H, Akkoç I. Comparison of mask oxygen therapy and high-flow oxygen therapy after cardiopulmonary bypass in obese patients. *Can Respir J* 2018; 2018: 1039635.

87 Zochios V, Collier T, Blaudszun G, *et al.* The effect of high-flow nasal oxygen on hospital length of stay in cardiac surgical patients at high risk for respiratory complications: a randomised controlled trial. *Anaesthesia* 2018; 73: 1478–1488.

88 Ferrando C, Puig J, Serralta F, *et al.* High-flow nasal cannula oxygenation reduces postoperative hypoxemia in morbidly obese patients: a randomized controlled trial. *Minerva Anestesiol* 2019; 85: 1062–1070.

89 Pennisi MA, Bello G, Congedo MT, *et al.* Early nasal high-flow *versus* Venturi mask oxygen therapy after lung resection: a randomized trial. *Crit Care* 2019; 23: 68.

90 Twose P, Thomas C, Morgan M, *et al.* Comparison of high-flow oxygen therapy with standard oxygen therapy for prevention of postoperative pulmonary complications after major head and neck surgery involving insertion of a tracheostomy: a feasibility study. *Br J Oral Maxillofac Surg* 2019; 57: 1014–1018.

91 Tatsuishi W, Sato T, Kataoka G, *et al.* High-flow nasal cannula therapy with early extubation for subjects undergoing off-pump coronary artery bypass graft surgery. *Respir Care* 2020; 65: 183–190.

92 Vourc'h M, Nicolet J, Volteau C, *et al.* High-flow therapy by nasal cannulae *versus* high-flow face mask in severe hypoxemia after cardiac surgery: a single-center randomized controlled study – the HEART FLOW study. *J Cardiothorac Vasc Anesth* 2020; 34: 157–165.

93 Stéphan F, Bérard L, Rézaiguia-Delclaux S, *et al.* High-flow nasal cannula therapy *versus* intermittent noninvasive ventilation in obese subjects after cardiothoracic surgery. *Respir Care* 2017; 62: 1193–1202.

94 Esteban A, Frutos-Vivar F, Muriel A, *et al.* Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med* 2013; 188: 220–230.

95 Miu T, Joffe AM, Yanez ND, *et al.* Predictors of reintubation in critically ill patients. *Respir Care* 2014; 59: 178–185.

96 Tiruvoipati R, Lewis D, Haji K, *et al.* High-flow nasal oxygen *vs* high-flow face mask: a randomized crossover trial in extubated patients. *J Crit Care* 2010; 25: 463–468.

97 Maggiore SM, Idone FA, Vaschetto R, *et al.* Nasal high-flow *versus* Venturi mask oxygen therapy after extubation. Effects on oxygenation, comfort, and clinical outcome. *Am J Respir Crit Care Med* 2014; 190: 282–288.

98 Perbet S, Gerst A, Chabanne R, *et al.* High-flow nasal oxygen cannula *versus* conventional oxygen therapy to prevent postextubation lung aeration loss: a multicentric randomized control lung ultrasound study. *Intensive Care Med* 2014; 40: S128.

99 Rittayamai N, Tscheikuna J, Rujiwit P. High-flow nasal cannula *versus* conventional oxygen therapy after endotracheal extubation: a randomized crossover physiologic study. *Respir Care* 2014; 59: 485–490.

100 Hernández G, Vaquero C, González P, *et al.* Effect of postextubation high-flow nasal cannula *vs* conventional oxygen therapy on reintubation in low-risk patients: a randomized clinical trial. *JAMA* 2016; 315: 1354–1361.

101 Arman PD, Varn MN, Povian S, *et al.* Effects of direct extubation to high-flow nasal cannula compared to standard nasal cannula in patients in the intensive care unit. *Am J Respir Crit Care Med* 2017; 195: A1887.

102 Fernandez R, Subira C, Frutos-Vivar F, *et al.* High-flow nasal cannula to prevent postextubation respiratory failure in high-risk non-hypercapnic patients: a randomized multicenter trial. *Ann Intensive Care* 2017; 7: 47.

103 Song HZ, Gu JX, Xiu HQ, *et al.* The value of high-flow nasal cannula oxygen therapy after extubation in patients with acute respiratory failure. *Clinics* 2017; 72: 562–567.

104 Di Mussi R, Spadaro S, Stripoli T, *et al.* High-flow nasal cannula oxygen therapy decreases postextubation neuroventilatory drive and work of breathing in patients with chronic obstructive pulmonary disease. *Crit Care* 2018; 22: 180.

105 Cho JY, Kim H-S, Kang H, *et al.* Comparison of postextubation outcomes associated with high-flow nasal cannula *vs*. conventional oxygen therapy in patients at high risk of reintubation: a randomized clinical trial. *J Korean Med Sci* 2020; 35: e194.

106 Hu TY, Lee CH, Cheng KH, *et al.* Effect of high-flow nasal oxygen *vs*. conventional oxygen therapy on extubation outcomes and physiologic changes for patients with high risk of extubation failure in the medical ICU: a tertiary center, randomized, controlled trial. *Int J Gerontol* 2020; 14: 36–41.

107 Matsuda W, Hagiwara A, Uemura T, *et al.* High-flow nasal cannula may not reduce the re-intubation rate after extubation in respiratory failure compared with a large-volume nebulization-based humidifier. *Respir Care* 2020; 65: 610–617.

108 Eaton Turner E, Jenks M. Cost-effectiveness analysis of the use of high-flow oxygen through nasal cannula in intensive care units in NHS England. *Expert Rev Pharmacoecon Outcomes Res* 2018; 18: 331–337.

109 Maggiore SM, Battilana M, Serano L, *et al.* Ventilatory support after extubation in critically ill patients. *Lancet Respir Med* 2018; 6: 948–962.

110 Theerawit P, Natpobsuk N, Sutherasan Y. The efficacy of the Whispherflow CPAP system *versus* high flow nasal cannula in patients at high risk for postextubation failure. *Intens Care Med Exp* 2017; 5: Suppl. 2: 0407.

111 Zhang JC, Wu FX, Meng LL, *et al.* [A study on the effects and safety of sequential humidified high flow nasal cannula oxygenation therapy on the COPD patients after extubation]. *Zhonghua Yi Xue Za Zhi* 2018; 98: 109–112.

112 Jing G, Li J, Hao D, *et al.* Comparison of high flow nasal cannula with noninvasive ventilation in chronic obstructive pulmonary disease patients with hypercapnia in preventing postextubation respiratory failure: a pilot randomized controlled trial. *Res Nurs Health* 2019; 42: 217–225.

113 Thille AW, Muller G, Gacouin A, *et al.* Effect of postextubation high-flow nasal oxygen with noninvasive ventilation *vs* high-flow nasal oxygen alone on reintubation among patients at high risk of extubation failure: a randomized clinical trial. *JAMA* 2019; 322: 1465–1475.

114 Tseng CW, Chao KY, Chiang CE, *et al.* The efficacy of heated humidifier high-flow nasal cannula compared with noninvasive positive-pressure ventilation in prevention of reintubation in patients with prolonged mechanical ventilation. *Eur Respir J* 2019; 54: Suppl. 63, RCT5097.

115 Tan D, Walline JH, Ling B, *et al.* High-flow nasal cannula oxygen therapy *versus* non-invasive ventilation for chronic obstructive pulmonary disease patients after extubation: a multicenter, randomized controlled trial. *Crit Care* 2020; 24: 489.

116 Halbert R, Natoli J, Gano A, *et al.* Global burden of COPD: systematic review and meta-analysis. *Eur Respir J* 2006; 28: 523–532.

117 Vogelmeier CF, Criner GJ, Martinez FJ, *et al.* Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report. GOLD executive summary. *Am J Respir Crit Care Med* 2017; 195: 557–582.

118 Deenen JC, Horlings CG, Verschuuren JJ, *et al.* The epidemiology of neuromuscular disorders: a comprehensive overview of the literature. *J Neuromuscul Dis* 2015; 2: 73–85.

119 Bruni A, Garofalo E, Cammarota G, *et al.* High flow through nasal cannula in stable and exacerbated chronic obstructive pulmonary disease patients. *Rev Recent Clin Trials* 2019; 14: 247–260.

120 Papachatzakis I, Velentza L, Kontogiannis S, *et al.* High flow nasal cannula with warm humidified air *versus* non-invasive mechanical ventilation in respiratory failure type II. *Eur Respir J* 2017; 50: Suppl. 61, PA2182.

121 Cong L, Zhou L, Liu H, *et al.* Outcomes of high-flow nasal cannula *versus* non-invasive positive pressure ventilation for patients with acute exacerbations of chronic obstructive pulmonary disease. *Int J Clin Exp Med* 2019; 12: 10863–10867.

122 Wang JH, Li Q. Randomized controlled study of HFNC and NPPV in the treatment of AECOPD combined with type II respiratory failure. *Chin J Integr Med* 2019: 39: 945–948.

123 Cortegiani A, Longhini F, Madotto F, *et al.* High flow nasal therapy *versus* noninvasive ventilation as initial ventilatory strategy in COPD exacerbation: a multicenter non-inferiority randomized trial. *Crit Care* 2020; 24: 692.

124 Doshi PB, Whittle JS, Dungan G II, *et al.* The ventilatory effect of high velocity nasal insufflation compared to non-invasive positive-pressure ventilation in the treatment of hypercapneic respiratory failure: a subgroup analysis. *Heart Lung* 2020; 49: 610–615.

125 Sklar MC, Dres M, Ritayamai N, *et al.* A randomized cross-over physiological study of high flow nasal oxygen cannula versus non-invasive ventilation in adult patients with cystic fibrosis: The HIFEN study. *Int Care Med Exp* 2017; 5: Suppl. 2, 0674.

126 Longhini F, Pisani L, Lungu R, *et al.* High-flow oxygen therapy after noninvasive ventilation interruption in patients recovering from hypercapnic acute respiratory failure: a physiological crossover trial. *Crit Care Med* 2019; 47: e506–e511.