Official ERS/ATS clinical practice guidelines: noninvasive ventilation for acute respiratory failure

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ABSTRACT Noninvasive mechanical ventilation (NIV) is widely used in the acute care setting for acute respiratory failure (ARF) across a variety of aetiologies. This document provides European Respiratory Society/American Thoracic Society recommendations for the clinical application of NIV based on the most current literature.

The guideline committee was composed of clinicians, methodologists and experts in the field of NIV. The committee developed recommendations based on the GRADE (Grading, Recommendation, Assessment, Development and Evaluation) methodology for each actionable question. The GRADE Evidence to Decision framework in the guideline development tool was used to generate recommendations. A number of topics were addressed using technical summaries without recommendations and these are discussed in the supplementary material.

This guideline committee developed recommendations for 11 actionable questions in a PICO (population–intervention–comparison–outcome) format, all addressing the use of NIV for various aetiologies of ARF. The specific conditions where recommendations were made include exacerbation of chronic obstructive pulmonary disease, cardiogenic pulmonary oedema, *de novo* hypoxaemic respiratory failure, immunocompromised patients, chest trauma, palliation, post-operative care, weaning and post-extubation.

This document summarises the current state of knowledge regarding the role of NIV in ARF. Evidence-based recommendations provide guidance to relevant stakeholders.

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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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Introduction

The purpose of the current European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines is to provide evidence-based recommendations on the application of noninvasive ventilation (NIV) in acute respiratory failure (ARF). We also address some practical issues relating to NIV application and maintenance. As much as possible, we pose questions in a PICO (population–intervention–comparison–outcome) format and use the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) methodology to assess the certainty of the evidence. However, some of the questions were best addressed with technical summaries without formal recommendations. These summaries and a brief narrative literature review are provided in the supplementary material. In this document, NIV includes noninvasive variable positive airway pressure (most commonly "bilevel") devices consisting of a higher inspiratory positive airway pressure and a lower expiratory pressure as well as continuous positive airway pressure (CPAP) delivered using various nasal, oronasal and facial interfaces.

Methods

Committee composition

The guideline committee was composed of clinicians and experts in the field of NIV. Members were either physicians (pulmonologists or intensivists) or respiratory therapists. Two clinician-methodologists with expertise in evidence synthesis and the guideline development process provided GRADE support. Committee members signed a confidentiality agreement and disclosed all potential conflicts of interest according to the policies of the ERS and ATS.

Evidence review and development of clinical recommendations

The committee developed recommendations based on the GRADE methodology for each actionable question [1]. The committee chose the clinical questions based on perceived clinical importance and prioritisation based on sampling of the committee members. The methodologists performed pragmatic literature searches, screening of potential studies for inclusion, pooling of outcome data when appropriate and evidence summary/analysis. The methodologists designed a search strategy for each question using medical subject heading keywords and text words limited to human studies or nonindexed citations and articles in English or in any language with English abstracts. The Ovid platform was used to search MEDLINE and the Cochrane Registry of Controlled Trials (CENTRAL). A single reviewer screened all potential references for inclusion. The last update of the search was performed in November 2016.

The committee selected outcomes of interest for each question and these were explicitly rated for their relative importance (from the perspective of a patient with respiratory failure) from "not important" to "critical" [2]. Ranking outcomes by their relative clinical importance helps to focus on those that are most relevant to patients and may lead to improved clarification during potential disagreements in decision making. Rankings of all outcomes were agreed upon through consensus of the committee. The critical outcomes prioritised for this guideline effort were: mortality, need for intubation and nosocomial pneumonia. These prioritised outcomes applied to all actionable questions except the one pertaining to palliation (Question 7), for which the panel prioritised patient-reported dyspnoea as the critical outcome

of interest. For questions where critical outcome data was unavailable, other important outcomes are presented as part of the evidence synthesis.

The certainty in effect estimates for each outcome were then categorised as high, moderate, low or very low according to the GRADE process. The GRADE Evidence to Decision framework in the guideline development tool was used to help facilitate discussion around each recommendation [3, 4]. The Evidence to Decision framework ensures each of the following factors are considered in recommendation development: quality of the evidence, balance of desirable and undesirable consequences of compared management options, assumptions about the values and preferences associated with the decision, implications for resource use and health equity, acceptability of intervention to stakeholders, and feasibility of implementation. Recommendations and their strength were decided by consensus. The entire committee agreed on the final wording of each recommendation and rationale with further qualifications for each recommendation (*e.g.* subgroup considerations, justification and implementation considerations).

Each recommendation was designated as "strong" or "conditional" [5]. As outlined by GRADE, we used the phrasing "we recommend" for strong recommendations and "we suggest" for conditional recommendations. Table 1 provides an interpretation of these recommendations by stakeholders (patients, clinicians and healthcare policy makers). Further description and details of the methodology used to compose these guidelines can be found in the supplementary material.

Manuscript preparation

For each of the recommendations, a narrative summary was provided for contextualisation and then a justification section, which summarised pooled estimates of effect, certainty of evidence and relevant Evidence to Decision framework factors. The committee was divided into pairs or groups of three who were responsible for composing individual components of the guidelines (organised by recommendation). Articles cited in the narrative reviews were selected by the authors to highlight the evidence relied upon to arrive at the recommendation (usually the largest, most significant or most directly relevant to our PICO question). These manuscript components were then collated by the executive to ensure cohesiveness and distributed to the entire committee for vetting and review. Feedback was provided by electronic communication. The final approved version was submitted to each co-sponsoring professional society for peer review.

Confidentiality agreement and conflict of interest management

Committee members signed a confidentiality agreement and disclosed all potential conflicts of interest according to the ERS policies. The co-chairs were responsible for reviewing all potential conflicts of interest of committee members with the staff of the ERS. After review, there was no limitation of committee member's involvement in the recommendation formulation process. The methodologists participated in discussions, but were nonvoting participants.

How to use these guidelines

These ERS/ATS evidence-based guidelines for the use of NIV in critically ill patients provide the basis for stakeholders to make rational, informed decisions. Clinicians, patients, third-party payers, institutional

TABLE 1 Interpretation of strong and conditional recommendations for stakeholders (patients, clinicians and healthcare policy makers)

	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 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 debates and 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.

review committees, other stakeholders or the courts should never view these recommendations as dictates. No recommendation can take into account all of the often-compelling unique individual clinical circumstances. Therefore, no one charged with evaluating a healthcare professional's actions should view these recommendations as absolute. Statements regarding the underlying values and preferences as well as qualifying remarks accompanying each recommendation are integral to the recommendations and serve to facilitate more accurate interpretation; they should be included when quoting recommendations from these guidelines.

PICO questions and recommendations

Question 1: Should NIV be used in COPD exacerbation?

Chronic obstructive pulmonary disease (COPD) exacerbations are a very common reason for admission to hospital. Approximately 20% of patients hospitalised for COPD present with [6] or develop hypercapnic respiratory failure [7], which is an indicator of an increased risk of death [6–8]. ARF leading to acute or acute-on-chronic respiratory acidosis, later referred to in this guideline as acute respiratory acidosis, develops when the respiratory muscles fail to achieve adequate alveolar ventilation despite high levels of diaphragmatic activity [9]. It is likely that hyperinflation during exacerbation also contributes to respiratory muscle compromise. When faced with a load that exceeds the capacity of the respiratory muscle pump, a rapid shallow breathing pattern develops which is characterised by an increased respiratory rate with small tidal volumes. Although this is not always beneficial in terms of respiratory muscle energy expenditure, this pattern seems to have a complex pathophysiological mechanism and occurs at the expense of adequate alveolar ventilation. As a consequence, the level of arterial carbon dioxide (CO_2) rises and respiratory acidosis ensues. Measuring respiratory rate, observing chest and abdominal wall movement, and obtaining a sample of arterial blood are therefore key in the initial assessment of the patient at risk of acute respiratory acidosis (pH $\leqslant$7.35). Many patients with COPD are hypercapnic at baseline and the development of acidosis indicates acute-on-chronic hypercapnic respiratory failure.

Bilevel NIV may be considered in COPD patients with an acute exacerbation in three clinical settings [10]:

1) To prevent acute respiratory acidosis, *i.e.* when the arterial CO_2 tension (P_aCO_2) is normal or elevated but pH is normal (see Question 1a).
2) To prevent endotracheal intubation and invasive mechanical ventilation in patients with mild to moderate acidosis and respiratory distress, with the aim of preventing deterioration to a point when invasive ventilation would be considered (see Question 1b).
3) As an alternative to invasive ventilation in patients with severe acidosis and more severe respiratory distress (see Question 1b).

Bilevel NIV may also be used as the only method for providing ventilatory support in patients who are not candidates for or decline invasive mechanical ventilation.

Question 1a: Should NIV be used in ARF due to a COPD exacerbation to prevent the development of respiratory acidosis?

One randomised study [11] of 52 patients with COPD comparing bilevel NIV to standard oxygen therapy used inclusion criteria of recent onset of shortness of breath and a pH >7.30 (average pH of randomised patients was within the normal range), suggesting that most enrolled patients had not developed acute respiratory acidosis. NIV was poorly tolerated and there was no effect of NIV on intubation rate (8% in NIV arm and 7% in control arm) or mortality (4% in NIV arm and 7% in control arm). However, there was a decrease in Borg dyspnoea score with NIV compared with standard oxygen therapy at 1 h and on day 2. When one outlier was removed from the analysis, there was a statistically significant reduction in hospital length of stay with bilevel NIV compared with the control group (5 *versus* 7 days).

In three other studies (two randomised controlled trials (RCTs) and one prospective observational study [12–14]) the mean pH was only very mildly acidotic, suggesting again that patients without acute respiratory acidosis were included; none of these studies showed an advantage to bilevel NIV. In a large study (n=342) in which bilevel NIV was started within 24–48 h of admission compared with standard oxygen therapy, in patients with a mean pH at randomisation of 7.35, there was a decrease in patients meeting criteria for intubation with NIV (1.4% *versus* 4.6%; p=0.002), but no difference in mortality [15]. Subgroup analysis of patients with a pH >7.35 (n=151) showed a beneficial effect of NIV for patients meeting clinical criteria for intubation *versus* those that did not (9 out of 80 *versus* 2 out of 71; p=0.045) but not for mortality. However, NIV was started much later than in other studies (24–48 h after admission) and the number of patients deteriorating to the point at which endotracheal intubation was considered necessary was surprisingly high, considering the mild acidosis. The main focus in hypercapnic patients with COPD who are not acidotic should be medical therapy and, most importantly, oxygen

targeted to a saturation of 88–92% [16]. Austin *et al.* [17] showed a better survival in COPD patients being transferred to hospital when oxygen was delivered to achieve this range of saturation.

Recommendation

We suggest NIV not be used in patients with hypercapnia who are not acidotic in the setting of a COPD exacerbation. (Conditional recommendation, low certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis was very imprecise but demonstrated that bilevel NIV does not reduce mortality (RR 1.46, 95% CI 0.64–3.35) and decrease the need for intubation (RR 0.41, 95% CI 0.18–0.72). Given the lack of consistent evidence demonstrating benefit in those without acidosis and the potential for harm, the committee decided on a conditional recommendation against bilevel NIV in this setting.

Question 1b: Should NIV be used in established acute hypercapnic respiratory failure due to a COPD exacerbation?

Bilevel NIV to prevent intubation

Patients with a pH of 7.25–7.35, in the absence of a metabolic cause for the acidosis, would normally not be deemed to require intubation and mechanical ventilation. It is in this group that there is the strongest evidence base to support the use of bilevel NIV [11–34]. An improvement in either pH or respiratory rate, or ideally both, is a good predictor of a successful outcome with NIV; in those that will respond, response is almost universally seen within the first 1–4 h after NIV initiation [35]. Bilevel NIV reduces the sensation of dyspnoea, the need for immediate intubation, and intensive care unit (ICU) and probably hospital length of stay, and improves survival. There is a reduction in both respiratory and nonrespiratory infectious complications [36, 37]. No clinical trials have shown a worse outcome with bilevel NIV compared with standard nonventilatory management, although there was a trend towards increased mortality with NIV in one study that included some patients with COPD, which was attributed to a delay in escalation to invasive mechanical ventilation [14]. Bilevel NIV has been shown to be cost-effective in this patient group [38].

Bilevel NIV as an alternative to first-line endotracheal intubation

Two studies have compared bilevel NIV directly with invasive ventilation [24, 27]. The mean pH was 7.20, significantly lower than in the studies discussed earlier. In the study of Conti *et al.* [24], survival was similar in both groups, but in patients in whom NIV was successful the advantages included shorter duration of ICU and hospital stay, fewer complications, reduced need for *de novo* oxygen supplementation, and fewer hospital readmissions in the subsequent year. There were important exclusions: the need for urgent intubation due to respiratory arrest, apnoeic episodes, psychomotor agitation requiring sedation, heart rate <60 beats·min^{-1} and systolic arterial pressure <80 mmHg. The study of Jurjevic *et al.* [27] enrolled patients similar to those in the Conti *et al.* [24] study, but inclusion criteria and primary end-points were not clearly defined. The authors found that invasive ventilation was associated with more rapid improvement in physiological abnormalities in the first few hours, but was also associated with a longer total duration of ventilation and ICU stay. Mortality was similar in the two groups. Patients receiving bilevel NIV had fewer episodes of ventilator-associated pneumonia and less requirement for tracheostomy. Coma has been described as a contraindication to NIV, but in a large case series Diaz *et al.* [39] showed no difference in outcome between patients with and without hypercapnic coma. Bilevel NIV in the ICU for COPD exacerbation is also cost-effective, with one Canadian study showing a cost savings of CAD3442 per patient admission [40].

Recommendations

We recommend bilevel NIV for patients with ARF leading to acute or acute-on-chronic respiratory acidosis (pH ⩽7.35) due to COPD exacerbation. (Strong recommendation, high certainty of evidence.)

We recommend a trial of bilevel NIV in patients considered to require endotracheal intubation and mechanical ventilation, unless the patient is immediately deteriorating. (Strong recommendation, moderate certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that bilevel NIV decreased mortality (relative risk (RR) 0.63, 95% CI 0.46–0.87; high certainty) and decreased the need for intubation (RR 0.41, 95% CI 0.33–0.52; moderate certainty) in this population. There was also a decrease in nosocomial pneumonia with bilevel NIV (OR 0.26, 95% CI 0.08–0.81; low certainty).

Based on this evidence review, the committee felt the anticipated desirable effects of bilevel NIV in patients with acute hypercapnic respiratory failure due to a COPD exacerbation definitely outweighed the anticipated undesirable effects. This is true across the severity spectrum, but increasing caution must be used towards the more severe end.

Implementation considerations

1) Bilevel NIV should be considered when the pH is ⩽7.35, P_{aCO_2} is >45 mmHg and the respiratory rate is >20–24 breaths·min^{-1} despite standard medical therapy.
2) Bilevel NIV remains the preferred choice for patients with COPD who develop acute respiratory acidosis during hospital admission. There is no lower limit of pH below which a trial of NIV is inappropriate; however, the lower the pH, the greater risk of failure, and patients must be very closely monitored with rapid access to endotracheal intubation and invasive ventilation if not improving.

Question 2a: Should NIV be used in ARF due to cardiogenic pulmonary oedema?

Over 30 trials have been published on the use of CPAP and/or NIV compared with standard therapy or each other for patients with acute cardiogenic pulmonary oedema. The majority are small single-centre trials that span a period of 30 years, during which cardiogenic pulmonary oedema management, particularly in the setting of acute coronary syndrome, has evolved along with trial inclusion and exclusion criteria. Patients in cardiogenic shock have been almost universally excluded from trials and thus are not included in our NIV recommendations. Many trials have also excluded patients requiring acute revascularisation and some have excluded patients with acute coronary syndrome.

The pathophysiology of respiratory failure during cardiogenic pulmonary oedema includes decreased respiratory system compliance and alveolar flooding due to high capillary pressure associated or not with left ventricular systolic dysfunction [41]. NIV (including both bilevel and CPAP) in this context has the ability to improve respiratory mechanics and facilitate left ventricular work by decreasing left ventricular afterload [42]. This is facilitated by the decrease in negative pressure swings generated by the respiratory muscles.

In 2008, Gray *et al.* [43] published the largest multicentre trial from 26 emergency departments, in which 1069 patients were randomised to CPAP, bilevel NIV or standard oxygen therapy. This trial found physiological improvement in the CPAP and bilevel NIV groups compared with the standard group, but no difference in intubation rate or mortality at 7 and 30 days. However, interpretation of the results is limited by the high crossover rate (56 out of 367 patients (15%) in the oxygen group crossed over to bilevel NIV). Subsequently, five systematic reviews [44–48] that have incorporated the data from Gray *et al.* [43], as well as other new trials, have been published. They consistently conclude that: 1) NIV decreases the need for intubation, 2) NIV is associated with a reduction in hospital mortality, 3) NIV is not associated with increased myocardial infarction (a concern raised by the first study comparing NIV and CPAP [49]), and 4) CPAP and NIV have similar effects on these outcomes.

Recommendation

We recommend either bilevel NIV or CPAP for patients with ARF due to cardiogenic pulmonary oedema. (Strong recommendation, moderate certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV decreased mortality (RR 0.80, 95% CI 0.66–0.96; moderate certainty) and decreased the need for intubation (RR 0.60, 95% CI 0.44–0.80; low certainty) in this population. An increase in myocardial infarction was seen in the NIV group although this was based on a very low certainty of evidence (OR 1.18, 95% CI 0.95–1.48). Based on this evidence review, the committee felt the anticipated desirable effects of NIV patients with ARF due to cardiogenic pulmonary oedema definitely outweighed the anticipated undesirable effects. Given the justifiable reluctance to include patients with acute coronary syndrome or cardiogenic shock in studies evaluating NIV for cardiogenic pulmonary oedema, the above recommendation does not apply to these subgroups. The recommendation is inclusive of both bilevel NIV and CPAP, as the current evidence summary demonstrates significant benefit of both interventions compared with standard care, and insufficient evidence to recommend one modality over the other. CPAP has advantages over bilevel NIV of simpler technology, easier synchronisation and potentially less expensive equipment, but the importance of these has not been adequately assessed.

Question 2b: Should a trial of CPAP prior to hospitalisation be used to prevent deterioration in patients with ARF due to cardiogenic pulmonary oedema?

Six single-centre RCTs have evaluated the use of CPAP or bilevel NIV to treat cardiogenic pulmonary oedema in the pre-hospital setting. Four trials focused on acute cardiogenic pulmonary oedema and two

included a subset of cardiogenic pulmonary oedema patients within a general population of patients with ARF (Thompson *et al.* [50]: 44 out of 69 cardiogenic pulmonary oedema; Roessler *et al.* [51]: 25 out of 49 cardiogenic pulmonary oedema). The studies were heterogeneous, with four using CPAP and two using bilevel NIV, and they were conducted in different settings. Five studies were conducted in Europe with a physician supporting the ambulance staff; one study was conducted in Canada, with pre-hospital care and study procedures managed by ambulance staff alone. The intubation rates varied among studies, suggesting potential differences in severity of illness or experience of the ambulance attendants. One study compared early *versus* delayed NIV [52], while the rest used a control arm of usual medical therapy.

Recommendation

We suggest that CPAP or bilevel NIV be used for patients with ARF due to cardiogenic pulmonary oedema in the pre-hospital setting. (Conditional recommendation, low certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV decreased mortality (RR 0.88, 95% CI 0.45–1.70; moderate certainty) and decreased the need for intubation (RR 0.31, 95% CI 0.17–0.55; low certainty) in this population. In general, oxygenation and patients' dyspnoea scores improved more rapidly with CPAP or bilevel NIV compared with control. Some studies showed a reduction in mortality associated with use of bilevel NIV [50], but this effect was inconsistent.

Heterogeneity in trial design, support personnel and patient selection prevent a firm recommendation regarding the use of NIV for cardiogenic pulmonary oedema in the pre-hospital setting. Overall, the results are favourable, but we emphasise the need for appropriate training and adequate infrastructure, including coordination with emergency departments before initiating a programme. More research is needed, including pre-hospital use of bilevel NIV *versus* CPAP, selection of patients, personnel on ambulances and role of communication with emergency departments.

Question 3: Should NIV be used in ARF due to acute asthma?

The main feature of acute asthma is a sudden and reversible episode of bronchoconstriction, leading to an increase in airways resistance that varies in severity. The acute change in mechanical load (mainly resistive) generates hyperinflation, increased respiratory muscle effort and dyspnoea. Hyperinflation also reduces respiratory muscle efficiency and thus the respiratory muscle pump may ultimately become exhausted, leading to hypercapnia [53].

NIV is used, together with conventional pharmacological treatment, with the aim to decrease the respiratory muscle work that is much increased during the episodes of acute bronchoconstriction, to improve ventilation, decrease the sensation of dyspnoea, and ultimately avoid intubation and invasive mechanical ventilation.

Possibly because the magnitude of the problem is small (*i.e.* episodes of acute asthma requiring ICU admission are uncommon), there is not much published research in this field. One physiological study gives some support to the use of CPAP. This study [54] showed that in asthmatic individuals subjected to histamine challenge causing acute bronchoconstriction, the use of CPAP (average 12 cmH_2O), compared with spontaneous breathing, substantially decreased the pressure–time product of the respiratory muscles (an index of energy utilisation), which was explained by a change in mechanics and breathing pattern.

A few uncontrolled studies and RCTs have compared NIV *versus* routine care in patients with acute asthma [55, 56]. Uncontrolled studies have shown physiological improvements in selected patients, whereas the RCTs and a meta-analysis have not shown differences in clinically relevant outcomes when comparing NIV with usual care [57]. A retrospective observational study by Fernandez *et al.* [58] described three types of patients admitted in the ICU for acute asthma: those with acute severe near-fatal asthma requiring emergency intubation, those responding well to medical therapy (the majority) and a small subgroup not responding well to medical therapy, who in this study were treated with NIV, mostly with success. RCTs in asthma mostly considered physiological end-points such as improvement in peak flows and suggested some beneficial effects.

In a recent retrospective cohort study [59] conducted in 97 US hospitals during a 4-year period, the use of NIV in patients with acute asthma was 4% (556 out of 13 930) and the use of invasive ventilation was 5% (668 out of 13 930). Failure rate (defined as intubation) of NIV was 4.7% (26 patients). Hospital mortality rates in those who received invasive mechanical ventilation without a previous trial of NIV, those who failed a NIV attempt and those who succeeded on NIV were 14.5%, 15.4% and 2.3%, respectively.

Recommendation

Given the uncertainty of evidence we are unable to offer a recommendation on the use of NIV for ARF due to asthma.

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV has an unclear effect on mortality, intubation (RR 4.48, 95% CI 0.23–89.23; very low certainty) or ICU length of stay (mean difference 0.3 higher, 95% CI 0.63 lower to 1.23 higher) in this population. NIV does appear to improve forced expiratory volume in 1 s (mean difference 14.02 higher, 95% CI 7.73–20.32 higher; low certainty) and peak expiratory flow (mean difference 19.97 higher, 95% CI 15.01–24.93 higher; low certainty). The lack of evidence precludes making a recommendation regarding the use of NIV for acute asthma. Studies have demonstrated a more rapid reversal of airway obstruction and a reduced need for hospitalisation compared with standard therapy that could reflect a bronchodilator effect of positive airway pressure, but in the absence of any evidence to show a beneficial effect of NIV on intubation rate or survival, the committee considered that the potential desirable effects have not been shown to outweigh the risks of adverse effects. However, given the possibility of overlap between asthma and COPD, bilevel NIV may be considered in a subgroup of patients diagnosed with asthma who are behaving more like patients with COPD (*i.e.* fixed airway obstruction).

Question 4: Should NIV be used for ARF in immunocompromised patients?

ARF is the main indication for ICU admission in immunocompromised patients. Currently available literature supports the use of NIV as a first-line approach for managing mild to moderate ARF in selected patients with immunosuppression of various aetiologies. Several studies have reported clinical benefits of NIV, although strict monitoring in the ICU and prompt availability of invasive mechanical ventilation are mandatory [60–62]. A large observational multicentre Italian survey investigated the clinical impact of NIV use in 1302 haematological patients admitted to the ICU with ARF [63]. The authors, after a propensity score analysis, confirmed the role of NIV as an independent predictor of survival. Similarly, early CPAP has been reported as a practical, simple and inexpensive method to prevent deterioration of respiratory function and complications in such patients [64]. However, in a recent multicentre randomised trial of 374 immunocompromised subjects, early NIV, compared with standard oxygen, was not associated with clinical benefits in mortality, ICU-acquired infections, duration of mechanical ventilation or length of ICU stay [65].

In addition, a more recent *post hoc* analysis of immunosuppressed patients enrolled in a larger trial of patients with ARF suggested no benefit of NIV, either for intubation or survival [66].

Recommendation

We suggest early NIV for immunocompromised patients with ARF. (Conditional recommendation, moderate certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV use led to a decrease in mortality (RR 0.68, 95% CI 0.53–0.88; moderate certainty), the need for intubation (RR 0.71, 95% CI 0.58–0.87; moderate certainty) and the rates of nosocomial pneumonia (RR 0.39, 95% CI 0.20–0.76; low certainty) in this population. Based on this evidence review, the anticipated desirable effects of NIV in immunocompromised patients with ARF outweigh undesirable consequences in most settings. The recommendation is inclusive both of bilevel NIV and early CPAP as the current evidence demonstrates the benefit of both interventions compared with standard care. In addition, one recent RCT [67] showed benefits of high-flow nasal cannula oxygen therapy over bilevel NIV with regard to intubation and mortality, and more study is required to determine whether this modality has advantages over NIV in immunocompromised patients with ARF.

Question 5: Should NIV be used in de novo *ARF?*

De novo respiratory failure refers to respiratory failure occurring without prior chronic respiratory disease. Most patients in this category have hypoxaemic respiratory failure, usually defined as significant hypoxaemia (arterial oxygen tension/inspiratory oxygen fraction ratio (P_{aO_2}/F_{IO_2}) $\leqslant$200), tachypnoea (respiratory rate >30–35 breaths·min^{-1}) and a non-COPD diagnosis (*e.g.* pneumonia and/or acute respiratory distress syndrome (ARDS)). Although included in some of the studies, patients with cardiogenic pulmonary oedema or with post-operative respiratory distress are not considered here because their pathophysiology is different and the indications and outcomes for NIV differ.

Defining whether a patient has all the features of ARDS [68] may be difficult or impossible in nonintubated patients because precise measurement of the actual inspired fraction of oxygen is unavailable and positive end-expiratory pressure is not used or its level is uncertain (*e.g.* with high-flow oxygen). Therefore, we considered studies on patients with hypoxaemic respiratory failure, community-acquired pneumonia and ARDS in the same category. NIV is used in these patients with the aims of improving oxygenation, facilitating ventilation, decreasing the work of breathing and dyspnoea, avoiding intubation, and reducing the complications associated with invasive mechanical ventilation.

Limitations of NIV in achieving some of these aims relative to invasive ventilation in patients with *de novo* ARF include its lack of efficacy in reducing work of breathing, in contrast to hypercapnic respiratory failure where its ability to reduce work of breathing has been clearly demonstrated. In ARDS patients, it has been shown that the use of noninvasive inspiratory pressure support can decrease the inspiratory effort compared with no inspiratory assistance only if sufficient pressure support is added [69]. Of concern, the tidal volume can also be significantly higher during NIV, especially when substantial inspiratory pressure is delivered, and further exacerbated by the high inspiratory demand seen in patients with acute hypoxic respiratory failure [70]. Therefore, the total pressure dissipated to inflate the lungs can be excessive during NIV. Such large transpulmonary pressures and the resulting large tidal volumes may exacerbate lung injury if prolonged over time. It is possible, although not proven, that NIV is especially useful in patients who do not substantially increase their tidal volume, but further work is needed in this area [71].

Invasive ventilation for hypoxaemic respiratory failure clearly reduces work of breathing and permits paralysis if total control of breathing is desired, effects that can redistribute blood flow from the respiratory muscles to other organs in patients with shock and hence help to treat shock itself [72]. The ability of NIV to achieve optimal pressures to reduce the work of breathing reliably in acute hypoxaemic respiratory failure is challenging because the high pressures often required increase air leaks, gastric insufflation and patient intolerance [69]. Thus, the ability to use lung protective ventilator strategies (such as maintaining a low tidal volume of 6 $mL \cdot kg^{-1}$ of predicted body weight) may be more difficult with NIV than with invasive ventilation [73, 74]. Some evidence even supports the idea that spontaneous ventilation can induce harm similar to ventilator-induced lung injury in situations of severe lung injury [75–77], which raises a note of caution when using NIV that combines spontaneous effort with ventilator support.

Hypoxaemia and high work of breathing return immediately when NIV is removed, explaining the risk associated with NIV interruptions. This may be ameliorated, as suggested by some recent trials, by the use of high-flow nasal cannula therapy (using a specialised nasal cannula to deliver heated and humidified oxygenated gas at flows between 30 and 60 $L \cdot min^{-1}$) during breaks or using longer sessions of NIV [78]. Also, the duration of NIV and its tolerance may depend on the type of interface used; recent evidence suggests that the use of a helmet may offer better tolerance over prolonged periods [79–82].

Potential uses of NIV for *de novo* ARF include as a preventive strategy for avoiding intubation. One pilot study on patients with "early" ARDS (P_{aO_2}/F_{IO_2} >200 and ⩽300) showed avoidance of intubation and reduced cytokine levels as favourable outcomes [83]. However, this study has not been replicated. NIV has also been studied as an alternative to intubation, with occasional reports showing benefit [84]. Positive studies on hypoxaemic, nonhypercapnic respiratory failure, mainly caused by community- or hospital-acquired pneumonia, have enrolled carefully selected patients who are cooperative with no associated major organ dysfunction, cardiac ischaemia or arrhythmias, and with no limitations in clearing secretions [29, 60, 85–87], which may explain the benefits seen.

Until recently, almost all studies on NIV for *de novo* ARF compared it with oxygen delivered with standard air entrainment (Venturi masks) or reservoir masks. Recently, high-flow nasal cannula therapy has been shown to offer several advantages compared with NIV, including better tolerance and dead space reduction [88]. One recent RCT reported a survival benefit of high-flow nasal cannula over standard oxygen therapy and bilevel NIV, although the primary end-point of intubation was not significantly different [67]. Although high-flow nasal cannula therapy is not specifically addressed in these recommendations, it may assume an important role in the therapy of *de novo* respiratory failure in the future.

The main risk of NIV for the indication of *de novo* ARF is to delay a needed intubation [86]. Early predictors of NIV failure include higher severity score, older age, ARDS or pneumonia as the aetiology for respiratory failure, or a failure to improve after 1 h of treatment [89]. Although the reasons for a poorer outcome are not completely understood, patients with NIV failure have higher tidal volumes before intubation [71] and develop more complications after intubation [90]. Studies have shown that NIV failure is an independent risk factor for mortality specifically in this population, although careful patient selection seems to reduce this risk [91, 92].

Recommendation

Given the uncertainty of evidence we are unable to offer a recommendation on the use of NIV for *de novo* ARF.

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV use led to a decrease in mortality (RR 0.83, 95% CI 0.65–1.05) and the need for intubation (RR 0.75, 95% CI 0.63–0.89), although these were both based on a low certainty of evidence. In highly selected cooperative patients with isolated respiratory failure, NIV has been shown in experienced hands to prevent intubation [85]. The overall effect in the studies is positive on this end-point, but not for other end-points such as mortality. Specific risks have been described with NIV and there is not enough evidence to recommend its use. Further research is needed and this question requires re-appraisal in the future. Considering that some studies have identified populations likely to succeed with NIV, a trial of NIV might be offered to a patient with hypoxaemic respiratory failure, community-acquired pneumonia or early ARDS if they are being managed by an experienced clinical team, are carefully selected (no contraindications such as abnormal mental status, shock or multiorgan system failure), are closely monitored in the ICU, reassessed early after starting NIV and intubated promptly if they are not improving.

Question 6: Should NIV be used in ARF in the post-operative setting?

Surgery, particularly that approaching the diaphragm, anaesthesia and post-operative pain may all have deleterious effects on the respiratory system, causing hypoxaemia, a decrease in lung volume and atelectasis due to diaphragm dysfunction [93]. These modifications of respiratory function occur early after surgery and diaphragm dysfunction may last up to 7 days, leading to an important deterioration in arterial oxygenation [94]. Maintenance of adequate oxygenation and avoidance of symptoms of respiratory distress in the post-operative period are of major importance, especially when pulmonary complications such as ARF occur [95, 96].

Both bilevel NIV and CPAP are frequently used in these clinical situations. Imaging studies have shown that the use of NIV may increase lung aeration and decrease the amount of atelectasis during the post-operative period of patients undergoing major abdominal surgery [93]. Physiological studies have shown that CPAP and bilevel NIV are effective at improving lung aeration and arterial oxygenation and decreasing the amount of atelectasis without adverse haemodynamic effects during the post-operative period after extubation [93, 97].

Supra-diaphragmatic surgery

One RCT demonstrated that in patients who developed respiratory failure during the post-operative period of lung cancer resection, NIV decreased the need for re-intubation and reduced hospital mortality [98]. Stephan *et al.* [96] reported that, in 830 patients following cardiothoracic surgery with or at risk for respiratory failure, the use of high-flow nasal cannula therapy compared with intermittent NIV did not result in a worse rate of treatment failure defined as need for re-intubation.

Abdominal and/or pelvic surgery

In a prospective observational study in patients who had respiratory failure after abdominal surgery, Jaber *et al.* [99] reported that the use of NIV resulted in avoidance of intubation in 67% cases, and a reduction in the hospital length of stay and mortality, compared with intubated patients. In a randomised trial on 40 patients undergoing solid organ transplantation (mainly liver transplantation) and developing post-operative respiratory failure, Antonelli *et al.* [60] found that NIV improved oxygenation and decreased the need for tracheal intubation compared with conventional therapy. Squadrone *et al.* [100] evaluated the use of helmet-CPAP after abdominal surgery in 209 patients who developed hypoxaemia without respiratory symptoms immediately after extubation. Their early use of CPAP significantly decreased the incidence of re-intubation from 10% to 1% (p=0.005). Jaber *et al.* [95] recently reported the results of a multicentre RCT including 298 patients with hypoxaemic ARF following abdominal surgery. The use of NIV compared with standard oxygen therapy reduced the risk of tracheal re-intubation within 7 days (46% *versus* 33%; p=0.03) and the incidence of healthcare-associated infections (31% *versus* 49%; p=0.003).

Recommendation

We suggest NIV for patients with post-operative ARF. (Conditional recommendation, moderate certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV use led to a decrease in mortality (RR 0.28, 95% CI 0.09–0.84; moderate certainty), the need for intubation (RR 0.27, 95% CI 0.12–0.61; low certainty) and the incidence of nosocomial pneumonia (RR 0.20, 95% CI 0.04–0.88; very low certainty) in this post-operative population. Both CPAP and bilevel NIV counter the pathophysiological mechanisms predisposing to post-operative respiratory failure. The evidence suggests that both are effective to improve clinical outcomes in patients with post-operative ARF, particularly those with abdominal and thoracic surgery, but also after cardiac surgery. NIV reduces intubation rates, nosocomial infections, lengths of stay, morbidity and mortality. Before initiating NIV in post-operative patients with ARF, surgical complications such as anastomotic leak or intra-abdominal sepsis should be addressed first. Then, if the patient is cooperative and able to protect the airway, NIV can be initiated safely.

Question 7: Should NIV be used in patients with ARF receiving palliative care?

In palliative care, the intensity of breathlessness frequently worsens as death approaches. Patients and their families expect symptomatic relief of this devastating symptom. Clinicians often respond by providing opioids, a highly effective treatment for this symptom but with a number of potentially undesirable side-effects, including excessive sedation.

The Society of Critical Care Medicine charged a Task Force to provide guidance for the use of NIV in palliative care settings [101]. Apart from type 1 patients in whom NIV is a life support with no limitation of therapy, the authors identified distinct goals for patients in palliative settings; identifying a "type 2" scenario in which a patient has decided to forego intubation, but still wants to receive salvage NIV therapy with the goal of surviving the hospitalisation. "Type 3" patients seek symptom alleviation, mainly dyspnoea, and survival is not a goal for these patients. Most of these type 3 patients, with the support of their families, are interested in ensuring comfort while dying, but some may also be interested in prolonging their lives for a few hours while maintaining cognition and the ability to communicate as they await relatives or to finalise their affairs. In this context, NIV would be considered effective if it improves breathlessness and respiratory distress without causing other troubling consequences, such as mask discomfort or unduly prolonging life. One large observational study on patients using NIV in ICUs found that those in whom NIV was a ceiling for therapy had the same quality of life as patients with no treatment limitations if they survived to day 90 [102].

Two RCTs in patients with advanced cancer have evaluated the efficacy of NIV in reducing dyspnoea. Hui *et al.* [103] showed a similar improvement in dyspnoea scores between NIV and high-flow oxygen, while a larger multicentre study [104] demonstrated a significantly greater reduction in breathlessness using NIV, especially in the hypercapnic subgroup of patients. Interestingly, the latter investigation showed that NIV might reduce the dose of morphine necessary to palliate dyspnoea, maintaining better cognitive function. Overall, NIV had a similar rate of acceptance by patients compared with oxygen therapy (~60%).

Recommendation

We suggest offering NIV to dyspnoeic patients for palliation in the setting of terminal cancer or other terminal conditions. (Conditional recommendation, moderate certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV improved patient dyspnoea as assessed by the Borg scale (mean difference 0.89 lower, 95% CI 0.79–0.99 lower; moderate certainty) and led to decreased morphine requirements (mean difference 32.4 mg lower, 95% CI 17.4–47.4 lower; low certainty). The effect on respiratory rate and oxygenation was less clear due to significant imprecision (both very low certainty in evidence). The small number of studies, heterogeneity in trial design and the relatively low acceptance rate of this technique in this scenario prevent a firm recommendation regarding the use of NIV as a palliative tool. Overall, the results are favourable, but we emphasise the need for appropriate patient selection and staff training, especially where the use of NIV is not usual practice (*i.e.* palliative care unit).

No recommendation was made for type 2 patients, lacking RCT evidence; however, in the observational studies, the use of NIV in "do not intubate" patients was associated, at least in some subsets of patients (COPD and congestive heart failure), with a surprisingly high (>30–60%) hospital survival and a 3-month quality of life equivalent to patients treated with NIV and having no limitation placed on support.

Question 8: Should NIV be used in ARF due to chest trauma?

The utility of bilevel NIV or CPAP for treatment of respiratory failure in chest trauma patients has been investigated in three RCTs [105–107] and in a small subgroup of patients enrolled in a fourth trial [85].

Two of these studies compared NIV *versus* supplemental oxygen [85, 107], while the other two used invasive mechanical ventilation as control [105, 106].

A single-centre RCT randomised 69 trauma patients with at least four unilateral rib fractures to receive either CPAP or invasive mechanical ventilation [105]. Two out of 33 patients in the CPAP group died in hospital compared with none of the invasively ventilated patients ($p>0.05$). Patients randomised to CPAP had a significantly shorter ICU length of stay and less nosocomial pneumonia. A second RCT randomised 52 patients with multiple rib fractures and hypoxia to either CPAP or invasive ventilation [106], but no statistical difference was observed in any of the outcomes considered.

A third study randomised chest trauma patients with any injury and respiratory failure to NIV or high-flow oxygen therapy (>10 $L \cdot min^{-1}$) [107]. The study was stopped early after a second interim analysis after 50 patients had been included. Patients enrolled in this study were significantly more hypoxaemic (mean P_{aO_2}/F_{IO_2} 100±34.5) than those in other studies. Significantly fewer intubations were performed in patients randomised to receive NIV (RR 0.20, 95% CI 0.05–0.87), resulting in a significant decrease in ICU length of stay with NIV.

The last study was a multicentre RCT that randomised patients with respiratory failure from multiple aetiologies to receive NIV *versus* standard oxygen therapy [85]. 17 out of 105 hypoxaemic patients (16%) that were enrolled had a presenting diagnosis of chest trauma. Outcome data for mortality and intubation was presented for the chest trauma subgroup, but no significant difference between groups was seen for either of these outcomes.

Recommendation

We suggest NIV for chest trauma patients with ARF. (Conditional recommendation, moderate certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV use led to a decrease in mortality (RR 0.55, 95% CI 0.22–1.41; moderate certainty), the need for intubation (OR 0.21, 95% CI 0.06–0.74; moderate certainty) and the incidence of nosocomial pneumonia (OR 0.29, 95% CI 0.13–0.64; low certainty) in this population. There was also a decrease in ICU length of stay (mean difference 2.47 lower, 95% CI 1.5–3.45 lower). The dearth of studies, heterogeneity in trial design, different comparators (*i.e.* oxygen or invasive ventilation), different severities of patients at enrolment and different causes of ARF (*i.e.* rib fracture or flail chest) prevent us from making a definitive recommendation. However, given the positive overall results, we suggest a cautious NIV trial in these patients when pain is controlled and hypoxaemia not severe.

Question 9: Should NIV be used in ARF due to pandemic viral illness?

The use of NIV for severe acute respiratory syndrome and other airborne diseases has been assessed in several observational studies and remains controversial. These studies reported NIV failure rates of 30% and 33% [108, 109], with no evidence of viral spread to caregivers who took appropriate precautions. More recently, NIV was also used in patients with ARF due to influenza A H1N1 infection, with failure rates ranging between 13% and 77% [110–112]. However, no randomised clinical trial has assessed the efficacy of NIV in such pandemics.

Recommendation

Given the uncertainty of evidence we are unable to offer a recommendation for this question.

Justification

Despite the lack of any RCTs, the positive data from most of the observational studies and the controversial issue of possible increased risk of passing infection on to caregivers, we consider the prior recommendations against the use of NIV for pandemics as unsupportable. Although a cautious NIV trial in carefully selected patients at experienced centres, in a protected environment (*i.e.* negative pressure rooms), may be reasonable, further research is needed before a recommendation is possible.

Question 10: Should NIV be used in ARF following extubation from invasive mechanical ventilation?

Re-intubation following extubation failure is a major clinical problem. Rates of extubation failure as high as 23.5% have been reported [113]. In contrast to patients who are successfully extubated, those who are re-intubated because of post-extubation respiratory failure are characterised as having a worse prognosis,

even after controlling for level of severity, which suggests a direct adverse effect of re-intubation itself on patient outcomes [114].

As re-intubation is associated with increased mortality, any strategy aimed at reducing the rate of post-extubation respiratory failure and avoiding re-intubation deserves consideration. NIV might be a means to avoid re-intubation either by treating post-extubation respiratory failure when it develops or preventing it from developing at all by instituting NIV immediately after extubation. As these are different questions, they are best considered and discussed separately. For the sake of clarity, post-operative patients are not considered in this section.

Question 10a: Should NIV be used to prevent respiratory failure post-extubation?

The benefits of early application of NIV soon after extubation have been assessed in unselected patients (*i.e.* any patients after planned extubation) and in at-risk patients. For most included studies, at-risk included patients >65 years or those with underlying cardiac or respiratory disease.

Unselected patients

In 1999, Jiang *et al.* [115] enrolled 93 consecutive patients following planned (60.2%) or unplanned (39.8%) extubation, who were randomised either to preventive NIV (treatment group) or standard treatment (control group). They found no difference in the rate of re-intubation between the two groups. In the 37 patients in whom extubation was unplanned, the re-intubation rate was 38% compared with 11% in the 56 patients undergoing planned extubation [115]. More recently, Su *et al.* [116] enrolled 406 unselected patients extubated after passing a spontaneous breathing trial (SBT). Consistent with the previous study [115], compared with standard treatment, NIV did not decrease the rate of re-intubation. ICU mortality also was not significantly different [116]. Overall, in unselected patients post-extubation, NIV provides no benefit compared with standard oxygen therapy.

At-risk patients

Two multicentre RCTs evaluated whether NIV could prevent re-intubation when applied immediately after planned extubation to selected patients at high risk of post-extubation respiratory failure [117, 118]. Nava *et al.* [117] enrolled 97 patients who were randomised 1 h after extubation, following a successful SBT, to receive either NIV (minimum 8 $h \cdot day^{-1}$ for 2 days) or standard treatment (oxygen therapy). NIV reduced the rate of re-intubation, which resulted in a reduced ICU mortality. Ferrer *et al.* [118] randomised 162 patients considered to be at risk for extubation failure to either NIV (near-continuously for 24 h) or oxygen therapy only. NIV decreased the number of patients developing post-extubation respiratory failure and ICU mortality; however, the rate of re-intubation, ICU and hospital length of stay, and hospital mortality were not significantly different between the two groups. A *post hoc* analysis showed that NIV improved hospital and 90-day survival in the subgroup of patients who developed hypercapnia during the SBT prior to extubation [118]. Subsequent to these observations, the same authors enrolled a select group of 106 patients with chronic respiratory disorders developing hypercapnia during the SBT to investigate the benefits of NIV, as opposed to oxygen therapy alone, after extubation [119]. The rate of respiratory failure after extubation was lower in the NIV group than in the controls. While ICU and hospital mortality were not different between the treatment and control groups, the 90-day survival rate was significantly improved in the NIV group, as opposed to controls.

Two small single-centre trials (40 patients each) also randomised patients to NIV or standard treatment after planned extubation [120, 121]. Kihlnani *et al.* [120] enrolled COPD patients and found no differences in intubation rate or ICU and hospital lengths of stay. In a small group of patients for whom the only inclusion criterion was mechanical ventilation for >72 h because of ARF, predominantly secondary to COPD exacerbations, Ornico *et al.* [121] found a reduction in re-intubation and death in the NIV group.

Recommendations

We suggest that NIV be used to prevent post-extubation respiratory failure in high-risk patients post-extubation. (Conditional recommendation, low certainty of evidence.)

We suggest that NIV should not be used to prevent post-extubation respiratory failure in non-high-risk patients. (Conditional recommendation, very low certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV use led to a decrease in mortality (RR 0.41, 95% CI 0.21–0.82; moderate certainty) and the need for intubation (RR 0.75, 95% CI 0.49–1.15; low certainty). There are

some inconsistencies regarding the criteria for considering patients at high risk of extubation failure. Recent work reports that patients >65 years and with underlying cardiac or respiratory disease are at high risk for extubation failure with a re-intubation rate >30% if both comorbidities are present and >20% if one of the two is present [122]. Early NIV after planned extubation decreases both intubation rate and mortality in patients at high risk of extubation failure. Patients with an unplanned extubation are a higher risk group and further studies should specifically address the use of NIV in this group.

Question 10b: Should NIV be used in the treatment of respiratory failure that develops post-extubation?

Following the positive findings of case series and case–control studies, two RCTs compared NIV with conventional treatment (oxygen therapy) in patients who developed respiratory failure after planned extubation [123, 124].

Keenan *et al.* [123] investigated the role of NIV, compared with standard treatment, to avert re-intubation in 78 patients who developed respiratory distress, defined as tachypnoea and use of respiratory accessory muscles, within 48 h of extubation. This single-centre RCT did not find any beneficial effect of NIV on re-intubation, ICU and hospital mortality or length of ICU and hospital stay. In a multicentre RCT, Esteban *et al.* [124] enrolled 221 patients with respiratory failure defined by at least two of the following: hypoxaemia, respiratory acidosis, tachypnoea or respiratory distress within 48 h of extubation; patients were randomised to NIV or standard treatment. The trial showed no benefit from NIV on re-intubation and ICU length of stay. ICU mortality was higher in the NIV group, suggesting that it was harmful, probably by delaying intubation. A meta-analysis performed by Lin *et al.* [125] in 2014 on these two studies indicates no benefit of NIV compared with standard treatment with respect to re-intubation rate and mortality.

Recommendation

We suggest that NIV should not be used in the treatment of patients with established post-extubation respiratory failure. (Conditional recommendation, low certainty of evidence.)

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV use led to an increase in mortality (RR 1.33, 95% CI 0.83–2.13, low certainty), with an uncertain effect on intubation (RR 1.02, 95% CI 0.83–1.25, low certainty). The use of NIV to avoid re-intubation in patients with overt respiratory distress and/or respiratory failure consequent to failed planned extubation is not advisable. However, because of some limitations in the trials this statement is not definitive. In particular, in the study by Esteban *et al.* [124], the use of NIV as rescue therapy had a much higher success rate than in those who received it as initial treatment, there was a lack of experience of NIV in some participating centres and there was very limited enrolment rate at some sites. In addition, both the Keenan *et al.* [123] and Esteban *et al.* [124] studies had few COPD patients (~10%), so this recommendation may not apply to post-extubation COPD patients with respiratory failure. Further studies are needed.

Question 11: Should NIV be used to facilitate weaning patients from invasive mechanical ventilation?

NIV has been shown to be as effective as invasive mechanical ventilation in improving breathing pattern, reducing inspiratory effort and maintaining adequate gas exchange during the weaning phase in selected patients intubated and ventilated for hypercapnic ARF [126]. Based on this physiological rationale, NIV has been utilised in these patients as a means to speed up the weaning process, while avoiding the side-effects and complications of invasive ventilation.

Burns *et al.* [127] identified 16 RCTs enrolling a total of 994 participants, mostly with COPD. Of the 16 studies, nine included only patients with COPD [128–136], six included mixed populations (predominantly hypercapnic) [137–142] and one small pilot study included only hypoxaemic patients [143]. Compared with conventional weaning using either a progressive reduction of inspiratory support or SBTs, NIV was associated with a significant decrease in mortality (RR 0.53, 95% CI 0.36–0.80; 994 patients). The pooled data showed a significant reduction in the proportion of weaning failures with NIV (RR 0.63, 95% CI 0.42–0.96). There were also significant reductions in ventilator-associated pneumonia (RR 0.25, 95% CI 0.15–0.43; 953 patients), ICU (mean difference −5.59 days, 95% CI −7.90 to −3.28) and hospital (mean difference −6.04 days, 95% CI −9.22 to −2.87) length of stay, total duration of mechanical ventilation (mean difference −5.64 days, 95% CI −9.50 to −1.77), and duration of invasive ventilation (mean difference −7.44 days, 95% CI −10.34 to −4.55). Weaning time and weaning failure were no different between NIV and conventional weaning (mean difference −0.25 days, 95% CI −2.06 to 1.56).

TABLE 2 Recommendations for actionable PICO questions

Clinical indication[#]	Certainty of evidence[¶]	Recommendation
Prevention of hypercapnia in COPD exacerbation	⊕⊕	Conditional recommendation against
Hypercapnia with COPD exacerbation	⊕⊕⊕⊕	Strong recommendation for
Cardiogenic pulmonary oedema	⊕⊕⊕	Strong recommendation for
Acute asthma exacerbation		No recommendation made
Immunocompromised	⊕⊕⊕	Conditional recommendation for
***De novo* respiratory failure**		No recommendation made
Post-operative patients	⊕⊕⊕	Conditional recommendation for
Palliative care	⊕⊕⊕	Conditional recommendation for
Trauma	⊕⊕⊕	Conditional recommendation for
Pandemic viral illness		No recommendation made
Post-extubation in high-risk patients (prophylaxis)	⊕⊕	Conditional recommendation for
Post-extubation respiratory failure	⊕⊕	Conditional recommendation against
Weaning in hypercapnic patients	⊕⊕⊕	Conditional recommendation for

[#]: all in the setting of acute respiratory failure; [¶]: certainty of effect estimates: ⊕⊕⊕⊕, high; ⊕⊕⊕, moderate; ⊕⊕, low; ⊕, very low.

Of the 16 studies, the largest multicentre RCT (including 208 patients randomised to three groups receiving either conventional weaning through the endotracheal tube, early extubation followed by NIV or early extubation followed by oxygen therapy) resulted in similar rates of re-intubation in all three groups (30%, 32%, and 37%, respectively; p-value nonsignificant) [138]. However, the cumulative rates of weaning success were significantly better in patients randomised to the NIV group. The reason for this discrepancy in re-intubation *versus* weaning success was related to the use of NIV as a rescue treatment for patients who failed conventional weaning and oxygen therapy.

Recommendations

We suggest NIV be used to facilitate weaning from mechanical ventilation in patients with hypercapnic respiratory failure. (Conditional recommendation, moderate certainty of evidence.)

We do not make any recommendation for hypoxaemic patients.

Justification

See forest plots and the evidence profile in the supplementary material for further details regarding included evidence. Pooled analysis demonstrated that NIV use led to a decrease in mortality (RR 0.54, 95% CI 0.41–0.70; moderate certainty), weaning failure (RR 0.61, 95% CI 0.48–0.79; low certainty) and the incidence of ventilator-associated pneumonia (RR 0.22, 95% CI 0.15–0.32; low certainty) in this population. Based on this evidence review, the committee felt the anticipated desirable effects of NIV applied immediately following extubation in patients with an acute COPD exacerbation who fail the SBT outweigh the anticipated undesirable effects. The intricacies of using NIV for weaning are more difficult (compared with other indications) and therefore the committee felt more comfortable with a conditional, rather than a strong, recommendation. Centres must have adequate experience using NIV in this setting before considering use.

Conclusions

Based on a systematic review of the literature, and building upon previous meta-analyses and guidelines, we make recommendations regarding the current use of NIV for various forms of respiratory failure encountered in acute care settings (table 2). Our recommendations are largely in line with guidelines published within the past 15 years, but there have been incremental alterations as new studies and information have become available. We anticipate that some of these recommendations will change in the future as new studies are completed, especially regarding the use of NIV as opposed to other emerging technologies such as high-flow nasal cannula therapy and extracorporeal CO_2 removal. We emphasise that these guidelines should not be interpreted as absolute and should be implemented based on patient factors, including individual values and preferences, only in combination with clinical judgement. We also refer readers to the supplementary material in which we address a number of issues related to practical application of NIV that have not been subject to the GRADE process.

References

1 Guyatt G, Oxman AD, Akl EA, *et al.* GRADE guidelines: 1. Introduction – GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol* 2011; 64: 383–394.

2 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.
3 GRADE Working Group. Guideline Development Tool. 2014. http://gdt.guidelinedevelopment.org/app/handbook/handbook.html Date last accessed: January 17, 2017.
4 Alonso-Coello P, Oxman AD, Moberg J, *et al.* GRADE Evidence to Decision (EtD) frameworks: a systematic and transparent approach to making well informed healthcare choices. 2: Clinical practice guidelines. *BMJ* 2016; 353: i2089.
5 Andrews JC, Schunemann 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.
6 Plant PK, Owen J, Elliott MW. One year period prevalence study of respiratory acidosis in acute exacerbation of COPD; implications for the provision of non-invasive ventilation and oxygen administration. *Thorax* 2000; 55: 550–554.
7 Roberts CM, Stone RA, Buckingham RJ, *et al.* Acidosis, non-invasive ventilation and mortality in hospitalised COPD exacerbations. *Thorax* 2011; 66: 43–48.
8 Jeffrey AA, Warren PM, Flenley DC. Acute hypercapnic respiratory failure in patients with chronic obstructive lung disease: risk factors and use of guidelines for management. *Thorax* 1992; 47: 34–40.
9 Brochard L, Isabey D, Piquet J, *et al.* Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *N Engl J Med* 1990; 323: 1523–1530.
10 Nava S, Navalesi P, Conti G. Time of non-invasive ventilation. *Intensive Care Med* 2006; 32: 361–370.
11 Keenan SP, Powers CE, McCormack DG. Noninvasive positive-pressure ventilation in patients with milder chronic obstructive pulmonary disease exacerbations: a randomized controlled trial. *Respir Care* 2005; 50: 610–616.
12 Barbe F, Togores B, Rubi M, *et al.* Noninvasive ventilatory support does not facilitate recovery from acute respiratory failure in chronic obstructive pulmonary disease. *Eur Respir J* 1996; 9: 1240–1245.
13 Bardi G, Pierotello R, Desideri M, *et al.* Nasal ventilation in COPD exacerbations: early and late results of a prospective, controlled study. *Eur Respir J* 2000; 15: 98–104.
14 Wood KA, Lewis L, Von Harz B, *et al.* The use of noninvasive positive pressure ventilation in the emergency department. *Chest* 1998; 113: 1339–1346.
15 Collaborative Research Group of Noninvasive Mechanical Ventilation for Chronic Obstructive Pulmonary Disease. Early use of non-invasive positive pressure ventilation for acute exacerbations of chronic obstructive pulmonary disease: a multicentre randomized controlled trial. *Chin Med J* 2005; 118: 2034–2040.
16 O'Driscoll BR, Howard LS, Davison AG. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008; 63: Suppl. 6, vi1–vi68.
17 Austin MA, Wills KE, Blizzard L, *et al.* Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ* 2010; 341: c5462.
18 Angus RM, Ahmed AA, Fenwick LJ, *et al.* Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. *Thorax* 1996; 51: 1048–1050.
19 Avdeev SN, Tretyakov AV, Grigoryants RA, *et al.* Issledovanie primeneniia neinvazivnoi ventiliatsii legkikh pri ostroi dykhatel'noi nedostatochnosti na fone obostreniia khronicheskogo obstruktivnogo zabolevaniia legkik. [Study of the use of noninvasive ventilation of the lungs in acute respiratory insufficiency due exacerbation of chronic obstructive pulmonary disease.] *Anesteziol Reanimatol* 1998; 3: 45–51.
20 Bott J, Carroll MP, Conway JH, *et al.* Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet* 1993; 341: 1555–1557.
21 Brochard L, Mancebo J, Wysocki M, *et al.* Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med* 1995; 333: 817–822.
22 Carrera M, Marin JM, Anton A, *et al.* A controlled trial of noninvasive ventilation for chronic obstructive pulmonary disease exacerbations. *J Crit Care* 2009; 24: 473–414.
23 Celikel T, Sungur M, Ceyhan B, *et al.* Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. *Chest* 1998; 114: 1636–1642.
24 Conti G, Antonelli M, Navalesi P, *et al.* Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. *Intensive Care Med* 2002; 28: 1701–1707.
25 del Castillo D, Barrot E, Laserna E, *et al.* Ventilacion no invasiva por soporte de presion en pacientes con enfermedad pulmonar obstructiva cronica en insuficiencia respiratoria aguda hipercapnica ingresados en una unidad de hospitalizacion convencional de neumologia. [Noninvasive positive pressure ventilation for acute respiratory failure in chronic obstructive pulmonary disease in a general respiratory ward.] *Med Clin* 2003; 120: 647–651.
26 Dikensoy O, Ikidag B, Filiz A, *et al.* Comparison of non-invasive ventilation and standard medical therapy in acute hypercapnic respiratory failure: a randomised controlled study at a tertiary health centre in SE Turkey. *Int J Clin Pract* 2002; 56: 85–88.
27 Jurjevic M, Matic I, Sakic-Zdravcevic K, *et al.* Mechanical ventilation in chronic obstructive pulmonary disease patients, noninvasive vs. invasive method (randomized prospective study). *Coll Antropol* 2009; 33: 791–797.
28 Khilnani GC, Saikia N, Banga A, *et al.* Non-invasive ventilation for acute exacerbation of COPD with very high $PaCO_2$: a randomized controlled trial. *Lung India* 2010; 27: 125–130.
29 Kramer N, Meyer TJ, Meharg J, *et al.* Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med* 1995; 151: 1799–1806.
30 Martin TJ, Hovis JD, Costantino JP, *et al.* A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. *Am J Respir Crit Care Med* 2000; 161: 807–813.
31 Nava S, Grassi M, Fanfulla F, *et al.* Non-invasive ventilation in elderly patients with acute hypercapnic respiratory failure: a randomised controlled trial. *Age Ageing* 2011; 40: 444–450.
32 Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet* 2000; 355: 1931–1935.

33 Schmidbauer W, Ahlers O, Spies C, *et al.* Early prehospital use of non-invasive ventilation improves acute respiratory failure in acute exacerbation of chronic obstructive pulmonary disease. *Emerg Med J* 2011; 28: 626–627.
34 Thys F, Roeseler J, Reynaert M, *et al.* Noninvasive ventilation for acute respiratory failure: a prospective randomised placebo-controlled trial. *Eur Respir J* 2002; 20: 545–555.
35 Plant PK, Owen JL, Elliott MW. Non-invasive ventilation in acute exacerbations of chronic obstructive pulmonary disease: long term survival and predictors of in-hospital outcome. *Thorax* 2001; 56: 708–712.
36 Girou E, Brun-Buisson C, Taille S, *et al.* Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. *JAMA* 2003; 290: 2985–2991.
37 Girou E, Schortgen F, Delclaux C, *et al.* Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA* 2000; 284: 2361–2367.
38 Plant PK, Owen JL, Parrott S, *et al.* Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: economic analysis of randomised controlled trial. *BMJ* 2003; 326: 956–961.
39 Diaz GG, Alcaraz AC, Talavera JCP, *et al.* Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. *Chest* 2005; 127: 952–960.
40 Keenan SP, Gregor J, Sibbald WJ, *et al.* Noninvasive positive pressure ventilation in the setting of severe, acute exacerbations of chronic obstructive pulmonary disease: more effective and less expensive. *Crit Care Med* 2000; 28: 2094–2102.
41 Lenique F, Habis M, Lofaso F, *et al.* Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. *Am J Respir Crit Care Med* 1997; 155: 500–505.
42 D'Andrea A, Martone F, Liccardo B, *et al.* Acute and chronic effects of noninvasive ventilation on left and right myocardial function in patients with obstructive sleep apnea syndrome: a speckle tracking echocardiographic study. *Echocardiography* 2016; 33: 1144–1155.
43 Gray A, Goodacre S, Newby DE, *et al.* Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med* 2008; 359: 142–151.
44 Potts JM. Noninvasive positive pressure ventilation: effect on mortality in acute cardiogenic pulmonary edema: a pragmatic meta-analysis. *Pol Arch Med Wewn* 2009; 119: 349–353.
45 Weng CL, Zhao YT, Liu QH, *et al.* Meta-analysis: noninvasive ventilation in acute cardiogenic pulmonary edema. *Ann Intern Med* 2010; 152: 590–600.
46 Mariani J, Macchia A, Belziti C, *et al.* Noninvasive ventilation in acute cardiogenic pulmonary edema: a meta-analysis of randomized controlled trials. *J Card Fail* 2011; 17: 850–859.
47 Vital FM, Ladeira MT, Atallah AN. Non-invasive positive pressure ventilation (CPAP or bilevel NPPV) for cardiogenic pulmonary oedema. *Cochrane Database Syst Rev* 2013; 5: CD005351.
48 Cabrini L, Landoni G, Oriani A, *et al.* Noninvasive ventilation and survival in acute care settings: a comprehensive systematic review and metaanalysis of randomized controlled trials. *Crit Care Med* 2015; 43: 880–888.
49 Mehta S, Al-Hashim AH, Keenan SP. Noninvasive ventilation in patients with acute cardiogenic pulmonary edema. *Respir Care* 2009; 54: 186–195.
50 Thompson J, Petrie DA, Ackroyd-Stolarz S, *et al.* Out-of-hospital continuous positive airway pressure ventilation *versus* usual care in acute respiratory failure: a randomized controlled trial. *Ann Emerg Med* 2008; 52: 232–241.
51 Roessler MS, Schmid DS, Michels P, *et al.* Early out-of-hospital non-invasive ventilation is superior to standard medical treatment in patients with acute respiratory failure: a pilot study. *Emerg Med J* 2012; 29: 409–414.
52 Plaisance P, Pirracchio R, Berton C, *et al.* A randomized study of out-of-hospital continuous positive airway pressure for acute cardiogenic pulmonary oedema: physiological and clinical effects. *Eur Heart J* 2007; 28: 2895–2901.
53 Leatherman J. Mechanical ventilation for severe asthma. *Chest* 2015; 147: 1671–1680.
54 Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am Rev Respir Dis* 1982; 126: 812–817.
55 Murase K, Tomii K, Chin K, *et al.* The use of non-invasive ventilation for life-threatening asthma attacks: changes in the need for intubation. *Respirology* 2010; 15: 714–720.
56 Ganesh A, Shenoy S, Doshi V, *et al.* Use of noninvasive ventilation in adult patients with acute asthma exacerbation. *Am J Ther* 2015; 22: 431–434.
57 Lim WJ, Mohammed Akram R, Carson KV, *et al.* Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev* 2012; 12: CD004360.
58 Fernandez MM, Villagra A, Blanch L, *et al.* Non-invasive mechanical ventilation in status asthmaticus. *Intensive Care Med* 2001; 27: 486–492.
59 Stefan MS, Nathanson BH, Lagu T, *et al.* Outcomes of noninvasive and invasive ventilation in patients hospitalized with asthma exacerbation. *Ann Am Thorac Soc* 2016; 13: 1096–1104.
60 Antonelli M, Conti G, Bufi M, *et al.* Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA* 2000; 283: 235–241.
61 Elliott MW, Steven MH, Phillips GD, *et al.* Non-invasive mechanical ventilation for acute respiratory failure. *BMJ* 1990; 300: 358–360.
62 Adda M, Coquet I, Darmon M, *et al.* Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Crit Care Med* 2008; 36: 2766–2772.
63 Gristina GR, Antonelli M, Conti G, *et al.* Noninvasive *versus* invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. *Crit Care Med* 2011; 39: 2232–2239.
64 Squadrone V, Massaia M, Bruno B, *et al.* Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive Care Med* 2010; 36: 1666–1674.
65 Lemiale V, Mokart D, Resche-Rigon M, *et al.* Effect of noninvasive ventilation vs oxygen therapy on mortality among immunocompromised patients with acute respiratory failure: a randomized clinical trial. *JAMA* 2015; 314: 1711–1719.
66 Frat JP, Ragot S, Girault C, *et al.* Effect of non-invasive oxygenation strategies in immunocompromised patients with severe acute respiratory failure: post-hoc analysis of a randomized trial. *Lancet Respir Med* 2016; 4: 646–652.

67 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.
68 Ranieri VM, Rubenfeld GD, Thompson BT, *et al.* Acute respiratory distress syndrome: the Berlin Definition. *JAMA* 2012; 307: 2526–2533.
69 L'Her E, Deye N, Lellouche F, *et al.* Physiologic effects of noninvasive ventilation during acute lung injury. *Am J Respir Crit Care Med* 2005; 172: 1112–1118.
70 Kallet RH, Diaz JV. The physiologic effects of noninvasive ventilation. *Respir Care* 2009; 54: 102–115.
71 Carteaux G, Millan-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.
72 Viires N, Silly G, Aubier M, *et al.* Regional blood flow distribution in dog during induced hypotension and low cardiac put out. *J Clin Invest* 1983; 72: 935–947.
73 The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med* 2000; 342: 1301–1308.
74 Bellani G, Laffey JG, Pham T, *et al.* Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. *JAMA* 2016; 315: 788–800.
75 Mascheroni D, Kolobow T, Fumagalli R, *et al.* Acute respiratory failure following pharmacologically induced hyperventilation: an experimental animal study. *Intensive Care Med* 1988; 15: 8–14.
76 Yoshida T, Torsani V, Gomes S, *et al.* Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med* 2013; 188: 1420–1427.
77 Yoshida T, Uchiyama A, Matsuura N, *et al.* Spontaneous breathing during lung-protective ventilation in an experimental acute lung injury model: high transpulmonary pressure associated with strong spontaneous breathing effort may worsen lung injury. *Crit Care Med* 2012; 40: 1578–1585.
78 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.
79 Antonelli M, Conti G, Pelosi P, *et al.* New treatment of acute hypoxemic respiratory failure: noninvasive pressure support ventilation delivered by helmet – a pilot controlled trial. *Crit Care Med* 2002; 30: 602–608.
80 Esquinas Rodriguez AM, Papadakos PJ, Carron M, *et al.* Clinical review: helmet and non-invasive mechanical ventilation in critically ill patients. *Crit Care* 2013; 17: 223.
81 Vargas F, Thille A, Lyazidi A, *et al.* Helmet with specific settings *versus* facemask for noninvasive ventilation. *Crit Care Med* 2009; 37: 1921–1928.
82 Brambilla AM, Aliberti S, Prina E, *et al.* Helmet CPAP vs. oxygen therapy in severe hypoxemic respiratory failure due to pneumonia. *Intensive Care Med* 2014; 40: 942–949.
83 Zhan Q, Sun B, Liang L, *et al.* Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. *Crit Care Med* 2012; 40: 455–460.
84 Antonelli M, Conti G, Rocco M, *et al.* A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med* 1998; 339: 429–435.
85 Ferrer M, Esquinas A, Leon M, *et al.* Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med* 2003; 168: 1438–1444.
86 Brochard L, Lefebvre JC, Cordioli RL, *et al.* Noninvasive ventilation for patients with hypoxemic acute respiratory failure. *Semin Respir Crit Care Med* 2014; 35: 492–500.
87 Keenan SP, Sinuff T, Burns KE, *et al.* Clinical practice guidelines for the use of noninvasive positive-pressure ventilation and noninvasive continuous positive airway pressure in the acute care setting. *CMAJ* 2011; 183: E195–E214.
88 Dysart K, Miller TL, Wolfson MR, *et al.* Research in high flow therapy: mechanisms of action. *Respir Med* 2009; 103: 1400–1405.
89 Antonelli M, Conti G, Moro ML, *et al.* Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med* 2001; 27: 1718–1728.
90 Mosier JM, Sakles JC, Whitmore SP, *et al.* Failed noninvasive positive-pressure ventilation is associated with an increased risk of intubation-related complications. *Ann Intensive Care* 2015; 5: 4.
91 Demoule A, Chevret S, Carlucci A, *et al.* Changing use of noninvasive ventilation in critically ill patients: trends over 15 years in francophone countries. *Intensive Care Med* 2016; 42: 82–92.
92 Demoule A, Girou E, Richard JC, *et al.* Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med* 2006; 32: 1756–1765.
93 Jaber S, Chanques G, Jung B. Postoperative noninvasive ventilation. *Anesthesiology* 2010; 112: 453–461.
94 Warner M. Preventing postoperative pulmonary complications. the role of the anesthesiologist. *Anesthesiology* 2000; 92: 1467–1472.
95 Jaber S, Lescot T, Futier E, *et al.* Effect of noninvasive ventilation on tracheal reintubation among patients with hypoxemic respiratory failure following abdominal surgery: a randomized clinical trial. *JAMA* 2016; 315: 1345–1353.
96 Stephan 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.
97 Chiumello D, Chevallard G, Gregoretti C. Non-invasive ventilation in postoperative patients: a systematic review. *Intensive Care Med* 2013; 37: 918–929.
98 Auriant I, Jallot A, Herve P, *et al.* Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. *Am J Respir Crit Care Med* 2001; 164: 1231–1235.
99 Jaber S, Delay J, Sebbane M, *et al.* Outcomes of patients with acute respiratory failure after abdominal surgery treated with noninvasive positive-pressure ventilation. *Chest* 2005; 128: 2688–2695.
100 Squadrone V, Coha M, Cerutti E, *et al.* Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. *JAMA* 2005; 293: 589–595.
101 Curtis JR, Cook DJ, Sinuff T, *et al.* Noninvasive positive pressure ventilation in critical and palliative care settings: understanding the goals of therapy. *Crit Care Med* 2007; 35: 932–939.
102 Azoulay E, Kouatchet A, Jaber S, *et al.* Noninvasive mechanical ventilation in patients having declined tracheal intubation. *Intensive Care Med* 2013; 39: 292–301.

103 Hui D, Morgado M, Chisholm G, *et al.* High-flow oxygen and bilevel positive airway pressure for persistent dyspnea in patients with advanced cancer: a phase II randomized trial. *J Pain Symptom Manage* 2013; 46: 463–473.
104 Nava S, Ferrer M, Esquinas A, *et al.* Palliative use of non-invasive ventilation in end-of-life patients with solid tumours: a randomised feasibility trial. *Lancet Oncol* 2013; 14: 219–227.
105 Bolliger CT, Van Eeden SF. Treatment of multiple rib fractures. Randomized controlled trial comparing ventilatory with nonventilatory management. *Chest* 1990; 97: 943–948.
106 Gunduz M, Unlugenc H, Ozalevli M, *et al.* A comparative study of continuous positive airway pressure (CPAP) and intermittent positive pressure ventilation (IPPV) in patients with flail chest. *Emerg Med J* 2005; 22: 325–329.
107 Hernandez G, Fernandez R, Lopez-Reina P, *et al.* Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia: a randomized clinical trial. *Chest* 2010; 137: 74–80.
108 Cheung TM, Yam LY, So LK, *et al.* Effectiveness of noninvasive positive pressure ventilation in the treatment of acute respiratory failure in severe acute respiratory syndrome. *Chest* 2004; 126: 845–850.
109 Han F, Jiang YY, Zheng JH, *et al.* [Acute respiratory failure and noninvasive positive pressure ventilation treatment in patients with severe acute respiratory syndrome.] *Zhonghua Jie He He Hu Xi Za Zhi* 2004; 27: 593–597.
110 Belenguer-Muncharaz A, Reig-Valero R, Altaba-Tena S, *et al.* Utilizacion de la ventilacion mecanica no invasiva en neumonia grave por virus H1N1. [Noninvasive mechanical ventilation in severe pneumonia due to H1N1 virus.] *Med Intensiva* 2011; 35: 470–477.
111 Estenssoro E, Rios FG, Apezteguia C, *et al.* Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med* 2010; 182: 41–48.
112 Masclans JR, Perez M, Almirall J, *et al.* Early non-invasive ventilation treatment for severe influenza pneumonia. *Clin Microbiol Infect* 2013; 19: 249–256.
113 Boles JM, Bion J, Connors A, *et al.* Weaning from mechanical ventilation. *Eur Respir J* 2007; 29: 1033–1056.
114 Thille AW, Harrois A, Schortgen F, *et al.* Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med* 2011; 39: 2612–2618.
115 Jiang JS, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. *Respirology* 1999; 4: 161–165.
116 Su CL, Chiang LL, Yang SH, *et al.* Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. *Respir Care* 2012; 57: 204–210.
117 Nava S, Gregoretti C, Fanfulla F, *et al.* Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med* 2005; 33: 2465–2470.
118 Ferrer M, Valencia M, Nicolas JM, *et al.* Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med* 2006; 173: 164–170.
119 Ferrer M, Sellares J, Valencia M, *et al.* Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet* 2009; 374: 1082–1088.
120 Khilnani GC, Galle AD, Hadda V, *et al.* Non-invasive ventilation after extubation in patients with chronic obstructive airways disease: a randomised controlled trial. *Anaesth Intensive Care* 2011; 39: 217–223.
121 Ornico SR, Lobo SM, Sanches HS, *et al.* Noninvasive ventilation immediately after extubation improves weaning outcome after acute respiratory failure: a randomized controlled trial. *Crit Care* 2013; 17: R39.
122 Thille AW, Boissier F, Ben-Ghezala H, *et al.* Easily identified at-risk patients for extubation failure may benefit from noninvasive ventilation: a prospective before–after study. *Crit Care* 2016; 20: 48.
123 Keenan SP, Powers C, McCormack DG, *et al.* Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. *JAMA* 2002; 287: 3238–3244.
124 Esteban A, Frutos-Vivar F, Ferguson ND, *et al.* Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med* 2004; 350: 2452–2460.
125 Lin C, Yu H, Fan H, *et al.* The efficacy of noninvasive ventilation in managing postextubation respiratory failure: a meta-analysis. *Heart Lung* 2014; 43: 99–104.
126 Vitacca M, Ambrosino N, Clini E, *et al.* Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. *Am J Respir Crit Care Med* 2001; 164: 638–641.
127 Burns KE, Meade MO, Premji A, *et al.* Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. *CMAJ* 2014; 186: E112–E122.
128 Zheng R, Liu L, Yang Y. Prospective randomized controlled clinical study of sequential non-invasive following invasive mechanical ventilation in patients with acute respiratory failure induced COPD. *Chin J Emerg Med* 2005; 14: 21–25.
129 Chen J, Qiu D, Tao D. [Time for extubation and sequential noninvasive mechanical ventilation in COPD patients with exacerbated respiratory failure who received invasive ventilation.] *Zhonghua Jie He He Hu Xi Za Zhi* 2001; 24: 99–100.
130 Nava S, Ambrosino N, Clini E, *et al.* Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med* 1998; 128: 721–728.
131 Prasad SB, Chaudhry D, Khanna R. Role of noninvasive ventilation in weaning from mechanical ventilation in patients of chronic obstructive pulmonary disease: an Indian experience. *Indian J Crit Care Med* 2009; 13: 207–212.
132 Collaborating Research Group for Noninvasive Mechanical Ventilation of Chinese Respiratory Society. Pulmonary infection control window in treatment of severe respiratory failure of chronic obstructive pulmonary diseases: a prospective, randomized controlled, multi-centred study. *Chin Med J* 2005; 118: 1589–1594.
133 Zou SH, Zhou R, Chen P, *et al.* [Application of sequential noninvasive following invasive mechanical ventilation in COPD patients with severe respiratory failure by investigating the appearance of pulmonary-infection-control-window.] *Zhong Nan Da Xue Xue Bao Yi Xue Ban* 2006; 31: 120–124.
134 Gamal MR, Ashraf ZM, Rania NM. Noninvasive ventilation in the weaning of patients with acute-on-chronic respiratory failure due to COPD. *Chest* 2004; 126: Suppl. 4, 755S.

135 Wang X, Du X, Zhang W. Observation of the results and discussion on the timing of transition from invasive mechanical ventilation to noninvasive ventilation in COPD patients with concomitant acute respiratory failure. *Shandong Med J* 2004; 44: 4–6.

136 Agmy GM, Metwally MM. Noninvasive ventilation in the weaning of patients with acute-on-chronic respiratory failure due to COPD. *Egyptian J Chest Dis Tuberculosis* 2012; 61: 84–91.

137 Tawfeek MM, Ali-Elnabtity AM. Noninvasive proportional assist ventilation may be useful in weaning patients who failed a spontaneous breathing trial. *Egyptian J Anaesthes* 2012; 28: 89–94.

138 Girault C, Bubenheim M, Abroug F, *et al.* Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. *Am J Respir Crit Care Med* 2011; 184: 672–679.

139 Ferrer M, Esquinas A, Arancibia F, *et al.* Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. *Am J Respir Crit Care Med* 2003; 168: 70–76.

140 Trevisan CE, Vieira SR. Noninvasive mechanical ventilation may be useful in treating patients who fail weaning from invasive mechanical ventilation: a randomized clinical trial. *Crit Care* 2008; 12: R51.

141 Hill NS, Lin D, Levy M. Noninvasive positive pressure ventilation (NPPV) to facilitate extubation after acute respiratory failure: a feasibility study. *Am J Respir Crit Care Med* 2000; 161: B18.

142 Girault C, Daudenthun I, Chevron V, *et al.* Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. *Am J Respir Crit Care Med* 1999; 160: 86–92.

143 Vaschetto R, Turucz E, Dellapiazza F, *et al.* Noninvasive ventilation after early extubation in patients recovering from hypoxemic acute respiratory failure: a single-centre feasibility study. *Intensive Care Med* 2012; 38: 1599–1606