Non-invasive ventilation 1

Beyond the guidelines for non-invasive ventilation in acute respiratory failure: implications for practice

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Non-invasive ventilation is standard therapy in the management of both hypoxaemic and hypercapnic respiratory failure of various causes. The evidence base for its use and when and how it should be used has been reviewed in two recent guidelines. In this Series paper, we look beyond the guidelines to what is happening in everyday clinical practice in the real world, how patient selection can be refined to maximise the chances of a successful outcome, and emerging alternative therapies. Real-world application of non-invasive ventilation diverges from guideline recommendations, particularly with regard to patient selection and timing of initiation. To improve patient outcomes education programmes need to stress these issues and the effectiveness of non-invasive ventilation that is delivered needs to be monitored by regular audit.

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This is the first in a Series of two papers about non-invasive ventilation

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Introduction

Recent guidelines have addressed the issue of the use of non-invasive ventilation (NIV): the 2017 European Respiratory Society and American Thoracic Society recommendations for the clinical application of NIV in acute respiratory failure,[1] and more specifically the 2017 British Thoracic Society (BTS) and Intensive Care Society guidelines for use of NIV in acute hypercapnic respiratory failure.[2] They make recommendations about when NIV should—and should not—be used, offer practical advice on the technical aspects of service delivery and care planning, and cover other aspects of the management of respiratory failure.[2] In this Series paper, we look beyond these guidelines to their implications for clinical practice in the real world.

Hypercapnic respiratory failure

NIV is part of the standard treatment for patients with acute hypercapnic respiratory failure (respiratory acidaemia) caused by exacerbation of chronic obstructive pulmonary disease (COPD), with guidelines[1,2] recommending NIV for those with hypercapnia (arterial partial pressure of carbon dioxide [$PaCO_2$] >6 kPa [45 mm Hg]) and a pH of less than 7·35. No lower limit of pH exists below which a trial of NIV is contraindicated, but the more acidotic the patient the more likely they are to fail with NIV (ie, die or require intubation).[3,4] NIV is also suggested as first-line treatment for patients with acute hypercapnic respiratory failure due to obesity, neuromuscular disease, and chest wall deformity.[1,2] This recommendation does not have the same evidence base, but because the clinical trials have not been done rather than because NIV has been shown to be inferior to standard therapy. Similar indications and absolute contraindications are used to indicate the need for acute NIV in these conditions as in COPD exacerbation, but with exceptions, including that hypercapnia in the absence of acidosis might be sufficient reason to recommend starting NIV.

What is happening in everyday clinical practice?

Although NIV shows substantial benefit in mortality and need for intubation in randomised controlled trials (RCTs), benefit is not always seen in clinical practice. Exclusion of high-risk patients in most RCTs probably explains a substantial part of this discrepancy, as well as NIV being offered to or requested by patients with end-stage disease with little chance of survival. Common exclusion criteria applied in clinical trials that would not preclude NIV in routine practice include pH less than 7·25, Glasgow Coma Scale less than 8, respiratory rate less than 12, systolic blood pressure less than 90 mm Hg, serious comorbidities (particularly cardiac), complicating

Key messages

- Guidelines for the use of non-invasive ventilation (NIV) in acute or chronic hypercapnic respiratory failure and acute hypoxaemic respiratory failure are evidence based and should be followed
- The right patient
  - The cause of respiratory failure is important in determining the likelihood of a successful outcome with NIV
  - NIV should not be used when it is very unlikely to succeed or when a purely palliative approach would be more appropriate—prediction tools should inform decision making
- The right time
  - Physiological criteria should be used to determine the timing of NIV
  - NIV should be discontinued in a timely manner if the patient is deteriorating on the basis of worsening pH and respiratory rate (for acute hypercapnic respiratory failure) or exhaled tidal volume >9·5 mL/kg and heart rate, acidosis, consciousness, oxygenation, respiratory rate score >5 after 1 h (for hypoxaemic respiratory failure)
- The right equipment
  - The correct interface should be used and should fit well
  - Condition-specific settings should be used, and adjusted according to response
- The right environment
  - The unit or ward should be properly staffed and resourced
  - Staff should be NIV trained and competency assessed
  - Training should be updated regularly
- Ongoing audits and quality assurance should be done

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pneumonia, older age, and late development of respiratory acidaemia after admission.[2] The fact that units involved in RCTs are usually, though not always,[5,6] expert in use of NIV will be a further factor.

Concerns have been raised about the way that NIV is delivered in everyday practice. In 2008, the UK Royal College of Physicians, BTS, and the British Lung Foundation nationally audited the acute care of patients admitted to hospital with COPD exacerbation—the National COPD Resources and Outcomes Project.[7] A total of 232 hospital units collected data on 9716 patients. All acidotic patients receiving NIV had a worse survival than acidotic patients treated without NIV. Contrary to contemporaneous and current guidelines, 42% of patients with progressive or new respiratory acidaemia did not receive NIV, while 11% of those with pure metabolic acidosis did. Use of oxygen with an unrestricted fractional concentration of oxygen in inspired air (FiO_2) was common and associated with increased need for ventilation (22·2% for unrestricted oxygen strategy *vs* 9·4% for restricted oxygen strategy) and mortality (11·1% *vs* 7·2%). Only 3·3% of the patients who received NIV and who died received invasive mechanical ventilation. This audit was repeated in consecutive years from 2010 to 2013.[8] The key outcomes (table) have shown an increase in mortality, although this increase might relate to increasingly severely unwell patients being treated with NIV, as shown by the progressive annual reduction in baseline pH. A notable finding across the three BTS audits was improvement in blood gases, with the median $PaCO_2$ falling consistently from the start of NIV. For example, in the 2012 audit, median $PaCO_2$ fell from 10·2 kPa to 8·9 kPa at 1–2 h and 8·3 kPa at 4–6 h. Median pH also improved from 7·25 at the onset of NIV to 7·3 after 1 h and 7·33 after 4–6 h. The hours of use in the first 24 h were consistent across the four audits (15–16 h) and compared very favourably with the RCTs. These data suggest that, when applied, NIV is being delivered effectively on average. However, the most common reason for NIV failure (pH <7·3 and $PaCO_2$ reduction <0·5 kPa) was a worsening $PaCO_2$ or deteriorating level of consciousness in 45% of patients with NIV failure. Although these findings might suggest a role for aggressive early optimisation of ventilation, they might also indicate a subgroup of patients who are very difficult to ventilate. Another striking finding from the UK audits was the high proportion of patients receiving NIV who also had pneumonia (table). Owing to uncertainty regarding the evidence, no recommendation was made in the European Respiratory Society and American Thoracic Society guidelines[1] about the use of NIV for acute respiratory failure, including cases caused by pneumonia. However, it is important to differentiate cases in which pneumonia complicates another condition associated with a favourable response—eg, COPD exacerbation. A small RCT in pneumonia (n=56) showed that NIV reduced the need for intubation and improved 2-month survival only if coexistent COPD was present.[9]

Results from the BTS audits suggest that poor patient selection, rather than inappropriate technical application of NIV, explains the worse outcomes in practice compared with RCTs. Patients with severe respiratory disease might not look particularly unwell, and failure to appreciate the severity of illness is an important factor explaining poor outcomes in other respiratory conditions, including pneumonia[10] and asthma.[11] Clinicians appear not to be basing decisions to start NIV on the objective criteria suggested by contemporaneous guidelines, but rather on the clinical perception that the patient needs ventilatory support, thus delaying the start of NIV. The guidelines are evidence based and their objective criteria should be followed.

Real-world data from large databases in the USA, collected for the purposes of billing or quality improvement, suggest much better outcomes from acute NIV in hospitals in the USA compared with the UK.[12–15] The BTS audits defined NIV failure based on pH and $PaCO_2$ reduction, whereas the US studies defined it as death or need for endotracheal intubation. Stefan and colleagues[13] reported NIV failure in 89 (13·7%) of 974 patients with COPD exacerbation, with hospital mortality of 7·4% for those treated with NIV and 22·5% for those who experienced failure of NIV. Lindenauer and colleagues[12] stratified 386 US hospitals into quartiles on the basis of NIV mortality (overall 15 448 patients received NIV); NIV failure occurred in 32·5% of patients in the worst quartile compared with 12·8% in the best quartile. In another

	Number of hospitals	Number of patients	Mean age	Consolidation on radiograph	Median initial $PaCO_2$	Median Initial pH	NIV unsuccessful	IMV	Died		Proportion discharged from hospital
									All causes	Respiratory	
2010	61	925	71	30%	10·2	7·30	27%	2·3%	29%	22%	67%
2011	122	2187	71	38%	10·1	7·26	33%	3·8%	30%	25%	66%
2012	130	2490	72	40%	10·2	7·25	31%	2·7%	31%	26%	65%
2013	148	2693	72	40%	10·2	7·24	33%	3·0%	34%	27%	66%

Table shows data for adult patients admitted to hospital with COPD exacerbation receiving NIV. NIV=non-invasive ventilation. $PaCO_2$=arterial partial pressure of carbon dioxide. IMV=invasive mechanical ventilation. COPD=chronic obstructive pulmonary disease.

Table: **British Thoracic Society national audits of NIV, 2010–13**

study,[15] 17 978 patients (70%) with COPD exacerbation only requiring assisted ventilation were initially treated with NIV on hospital day 1 or 2. Compared with those initially treated with invasive mechanical ventilation, NIV-treated patients were older, had fewer comorbidities, and were less likely to have concomitant pneumonia on admission. However, more than 40 000 patients were excluded from the analysis because they did not receive initial steroids or bronchodilators. In another study reporting NIV outcomes in COPD exacerbation across 252 Canadian hospitals,[14] NIV failure occurred in a median of 8·5% of patients (IQR 3·7–31·3%) and mortality for patients treated with invasive mechanical ventilation was 4·5–5·8%. However, only one of the studies[13] provided physiological data, making it difficult to gauge the severity of patients being treated; its findings suggested that both patients receiving NIV (median pH 7·34, $PaCO_2$ 8·3 kPa [62 mm Hg]) and those receiving invasive mechanical ventilation (pH 7·36, $PaCO_2$ 6·9 kPa [52 mm Hg]) had substantially less severe blood gas derangement than did patients in the UK audits (table). Indeed, many patients did not meet guideline criteria for needing any form of ventilatory support.[13] Patients with less severe acidosis have a much better prognosis, which might, in part, explain their better outcomes. Additionally, although the data show that many patients survive the hospital episode, a surprisingly high number do not return home (about 40% of patients receiving NIV or invasive mechanical ventilation discharged to a nursing home or long-term care facility: 27% of those receiving initial NIV, 31% of those receiving initial invasive mechanical ventilation, and 41% with NIV failure).[13] Death is usually regarded as a poor outcome in any study, but this might not always be the case in patients with a chronic progressive condition, such as COPD, because many will die of respiratory failure, despite optimal management.

NIV is sometimes used at the end of life when palliation, not survival, is the primary goal or when the patient who has refused intubation still desires active treatment.[16] It can be used to control breathlessness if well tolerated (allowing decreased opiate doses and, thereby, preserving the ability to communicate)[17] and its occasional use can buy time for family members to travel to reach the patient and for the patient to put their affairs in order. The goal of treatment must be clear, and caution taken not to unnecessarily prolong suffering and death. NIV, by contrast with both invasive mechanical ventilation and conventional treatment, provides both potentially lifesaving treatment and the possibility to transition seamlessly to a more palliative approach (panel 1).[18]

Analyses to explain differences in outcomes with NIV between different hospitals in the USA suggest that respiratory therapist autonomy (facilitating timely initiation of NIV, frequent reassessment, and attention to patient comfort) as well as adequate equipment and staffing numbers are key factors in high performing hospitals.[19] Lindenauer and colleagues[12] found that institutions with greater use of NIV had reduced use of invasive mechanical ventilation and better patient outcomes, suggesting that use of NIV improves outcomes overall and that its increased use improves effectiveness of delivery. However, Mehta and colleagues[14] found no mortality benefit and more frequent NIV failure in hospitals with high NIV case volumes compared with others, although these findings probably relate to patients with less chance of a successful outcome being offered a trial of NIV. In France, Dres and colleagues[20] showed a small but significant volume–outcome effect for the treatment of COPD exacerbation. A study from Australia[21] that compared outcomes in COPD exacerbation when NIV was delivered in an intensive care unit (ICU), a high dependency unit, or a general ward (one nurse to four patients [one to eight at night], daily registrar rounds, and a respiratory nurse specialist with a background in ICU) showed non-inferiority of the ward model for clinical outcomes, which were broadly similar to data from RCTs. The ward model was more cost-effective and treated more patients than ICUs and high dependency units; however, the ward model included regular involvement of highly trained and experienced staff and did not function in isolation from the ICU. Well trained staff are key to the success of NIV.

Determining prognosis in acute hypercapnic respiratory failure

Decisions on whether or not to provide NIV or invasive mechanical ventilation are strongly influenced by the clinician's estimates of acute and medium-term outcomes (panel 2). At least in COPD, these estimates are unduly

Panel 1: **An example of a good death**

Mr A has been admitted with his third exacerbation of chronic obstructive pulmonary disease in 3 months. He tolerates non-invasive ventilation (NIV) well, albeit reluctantly, when acutely unwell and has declined domiciliary NIV. He has an FEV_1 of 17% predicted and is housebound because of breathlessness. He has tolerated NIV well during this admission, with good mask fit and patient ventilator synchrony; however, his blood gas tensions have not improved and he remains acidotic with a pH of 7·30 and a $PaCO_2$ of 10 kPa on day 3. No evidence exists of any other potentially reversible factor. The question of invasive ventilation was discussed at the onset of NIV and, although he had initially indicated that he would consider invasive mechanical ventilation, it has now been agreed by the clinical team, patient, and his family that intubation would be unlikely to increase his chances of returning to live in his own home, even if he survived the acute episode. Mr A says he is getting fed up with the mask and would rather not use it. It is suggested by the doctor that rather than the nursing team encouraging him to use the NIV as much as possible it will be left to him to say when he wants it (eg, if he finds that breathlessness is getting too much), but that in this situation he will also be offered a small dose of morphine. 24 h later he has not asked for the ventilator and has had a couple of doses of morphine. With his agreement the ventilator is removed from the bedside and monitoring discontinued. He dies peacefully 12 h later with his family by his side. They express gratitude that he had been given the chance of lifesaving treatment and, when it had become apparent that it was highly unlikely to work, that he was able to die peacefully, unencumbered by medical equipment, and able to communicate with his family until the final few hours.

Panel 2: **Prognostic indices to be considered prior to initiation of acute non-invasive ventilation in acute hypercapnic respiratory failure**

Cause of acute hypercapnic respiratory failure

- Favourable: chronic obstructive pulmonary disease, extra-pulmonary restriction, and cardiogenic pulmonary oedema
- Adverse: pulmonary fibrosis and isolated pneumonia

Stable state

- Poor performance status
  - Unable to leave home unassisted
  - Requires help washing and dressing
- High comorbidity burden
- Low body-mass index

Severity of acute illness

- Blood gas abnormalities
  - Late development of acute hypercapnic respiratory failure after admission
  - Coexistent metabolic acidaemia or low base excess
  - Severe acidaemia (pH <7·25)
- Other organ failure or impairment
- Consolidation
- Observations including: respiratory rate >30, hypotension (particularly if unresponsive to fluid resuscitation), and low Glasgow Coma Scale (<11)
- Blood results including: eosinopenia (<50 cells per µL), raised urea, and hypoalbuminaemia
- Inability to clear secretions

Indices listed are associated with worse outcome unless otherwise stated. No single index in isolation should preclude a trial of non-invasive ventilation.

pessimistic in most patients and the lowest estimates of survival are mostly inaccurate,[22] which might lead to patients with a reasonable chance of survival not being ventilated. Conversely, NIV is sometimes used as a default ceiling of care when little chance of benefit exists, potentially causing avoidable distress. These factors emphasise the importance of basing such decisions on objective prognostic criteria and, when possible, supporting the patient to make a truly informed decision.

The Dyspnoea, Eosinopenia, Consolidation, Acidaemia and atrial Fibrillation (DECAF) prognostic score offers strong performance in the general population of patients with COPD exacerbation[23] and mortality remains low in low-risk COPD exacerbation even when acute hypercapnic respiratory failure is present. General severity scores, such as the Acute Physiology And Chronic Health Evaluation II (APACHE II), or scores specific to patients with acute hypercapnic respiratory failure, including the COPD and Asthma Physiology Score[24] and Confalonieri Risk Chart,[4] were mainly derived from physiological indices, are complex to administer, and offer only modest performance.[4,24–26] The limited performance of these risk scores is of concern. Important indices not assessed during development of the scores, but strongly associated with increased mortality, include poor recent stable-state performance status (particularly requiring help washing and dressing)[23,27] and development of acute hypercapnic respiratory failure after admission despite primary therapy.[7,28] Other indices associated with increased mortality include: coexistent pneumonia,[7,23] low body-mass index,[29] eosinopenia,[23] coexistent metabolic acidaemia,[7] respiratory rate greater than 30,[7] other organ dysfunction or failure (notably hypotension unresponsive to fluid resuscitation and impaired renal or liver function),[30] and inability to clear secretions.[30]

Incorrect or excessively adverse prognostic weighting placed on other indices could lead to NIV being inappropriately withheld. Previous receipt of NIV is sometimes assumed to confer a worse outcome; however, the converse is true.[31] Age is not consistently associated with a worse outcome after adjustment for other covariates[4] and NIV has been shown to improve survival in patients older than 75 years.[32] A consistent association with FEV_1 has not been shown, although the range is narrow in this population. Long-term oxygen therapy is associated with other adverse predictors but its use alone should not preclude a trial of NIV. Low Glasgow Coma Scale and severe acidaemia (pH <7·25 commonly cited) are associated with mortality.[7,33] However, a large observational study[25] showed that survival was similar in patients with and without hypercapnic coma managed in critical care, and favourable outcomes have been confirmed in patients with pH <7·25.[34] In common with coexistent pneumonia, hypercapnic coma and severe acidaemia should be regarded as indications for close monitoring, not as contraindications to NIV. Decisions regarding provision of ventilation are often difficult in patients with complex multimorbidity. A UK ten-centre prospective study of a novel prognostic scoring tool (ISRCTN22921168) will provide robust data to guide clinicians and support discussions with patients and their families. Indices captured during provision of NIV can help the decision to initiate treatment and might inform subsequent care. Early improvement in pH is strongly associated with survival,[33] whereas late failure (deterioration after 24 h of normalisation of pH with recurrent respiratory acidaemia) is associated with frailty[27] and poor survival.[8,27]

The low use of intubation in the UK audits compared with the USA data is striking and concerning, particularly as escalation to invasive mechanical ventilation was considered appropriate in 16–22% of cases in the four audits.[8] Inappropriate prognostic pessimism with regard to invasive mechanical ventilation in the UK has been confirmed in other studies.[22] However, several studies have shown that invasive ventilation of patients after failed NIV results in a poor prognosis.[13–15,35] Although this poor prognosis might relate to delays in intubation in some cases, in others it could be that a population with a poor prognosis no matter what was done was selected out by the initial use of NIV.[36] Because guidelines mandate a trial of NIV in all but a very small number of patients with a COPD exacerbation, decisions regarding use of invasive mechanical ventilation should usually be made after a failed trial of NIV.

When NIV is failing

A distinction needs to be made regarding the reasons for NIV failure. Failure of the non invasive part of NIV tends to occur early and is usually due to poor tolerance of the mask. Replacement of an interface which is not working well with a different type of interface (ie, an endotracheal tube), might result in a better outcome. Of note, failure to tolerate a non-invasive interface might be because the wrong size interface or one that has been incorrectly positioned is being used; it should not always be attributed to the patient and considered as patient failure. In the same way, if incorrect ventilator settings are chosen, the patient might be right to reject the ventilator. The way that a patient interacts with the ventilator requires an understanding of the physiology of respiratory failure and how mechanical ventilation changes, and responds to, the abnormal physiology. An understanding of how hyperinflation might worsen with ventilation and affect triggering function and synchrony between patient and ventilator is key.

Failure of the ventilation part of NIV tends to occur later. A patient who experiences failure of NIV despite good mask fit and careful selection and optimisation of ventilation settings might have very severe underlying disease, making continuation of ventilation difficult, even with a different interface. In such cases, a poor outcome from invasive mechanical ventilation would be expected. There are no further options available for medical therapy and late failure carries a poor prognosis (figure). Additionally, patients who do not initially need NIV but become acidotic (or more acidotic) in hospital have a worse prognosis than patients who are acidotic from the outset. In the National COPD Resources and Outcomes Project audit, 20% of individuals whose gases were recorded on admission were acidotic, and another 6% became acidotic later.[7] Patients with COPD exacerbation who either developed acidosis de novo during the admission or became more acidotic had a significantly worse prognosis than those whose lowest pH was recorded on admission (for all patients not receiving NIV, 27% *vs* 21% *vs* 9%, p<0·001).

The other key factor that should affect escalation to invasive mechanical ventilation is the presence of potentially reversible factors. Decisions regarding the appropriateness of escalation to invasive ventilation made at admission might not be appropriate subsequently; it is very important that plans are reviewed and changed if necessary (panel 3). An acute event in a patient with any chronic respiratory disease should trigger a review of all aspects of their care, ensuring optimal pharmacological treatment, pulmonary rehabilitation, and long-term oxygen and advanced care planning.[2] Any episode of acute-on-chronic hypercapnic respiratory failure requiring ventilatory support, whatever the cause, should prompt consideration of starting domiciliary NIV. For patients with COPD, good evidence now exists that NIV should not be started in patients who remain hypercapnic immediately after the acute episode has resolved,[37] but, for those remaining hypercapnic at least 2 weeks after a first COPD exacerbation requiring NIV, evidence suggests that domiciliary NIV improves outcomes.[38] The patient's experience of acute NIV will be an important factor in its success at home; those who have used NIV in hospital only with considerable encouragement are unlikely to continue it at home. For patients with obesity hypoventilation syndrome, continuous positive airway pressure is as effective as NIV in terms of improving $PaCO_2$ at 3 months, except in those with the most severe hypercapnia.[39] Patients with other conditions (eg, neuromuscular disease or chest wall deformity) will usually require domiciliary NIV. Patients considered for long-term ventilation should be managed in a specialist centre.

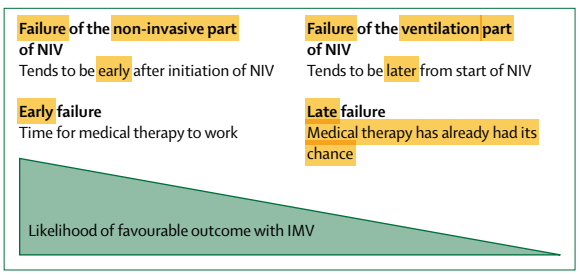

Figure: **The effects of NIV failure on the likelihood of a successful outcome with IMV over time**
NIV=non-invasive ventilation. IMV=invasive mechanical ventilation.

Alternatives to endotracheal intubation when NIV is failing

If a patient is tolerating NIV poorly, analgesia or sedation might be used, but no RCT with sufficient numbers of patients has been published to guide practice definitively.[40] According to an observational study,[41] only a minority of patients (<20%) receive analgesic or sedative drugs during NIV. Additionally, only a few institutions use a sedation protocol for NIV, and intermittent intravenous bolus rather than continuous infusion is the most commonly used method for drug delivery.[42] However, pilot studies,[43–46] mostly in patients with hypoxaemic respiratory failure, suggest that continuous infusion of a single sedative agent (either remifentanil,[43,44] dexmedetomidine,[45] or propofol[46]) is effective and safe in selected patients at risk of NIV failure due to mask discomfort and agitation. In contrast with other sedatives, dexmedetomidine causes minimal respiratory depression, making its use very attractive during NIV. Two RCTs[47,48] that compared dexmedetomidine with midazolam showed similar levels of sedation and safety profiles in patients with COPD exacerbation or those with acute cardiogenic pulmonary oedema who refused NIV. However, despite this encouraging preliminary data, Devlin and colleagues[49] showed that intravenous administration of dexmedetomidine immediately after NIV initiation in patients with acute respiratory failure did not improve NIV tolerance or maintain a desired target level of sedation, and was much more expensive to acquire than the alternatives.

Panel 3: **Questions to determine whether escalation to invasive mechanical ventilation is appropriate if non-invasive ventilation is failing**

- Has non-invasive ventilation been delivered optimally (in terms of quality of mask fit, patient–ventilator synchrony, and appropriate escalation of pressures)?
  - If not, adjust or change interface and make appropriate changes to ventilator settings
- How long has the patient been in hospital?
  - The longer the patient has been in hospital, the less likely a favourable outcome with non-invasive ventilation
- Are any factors still potentially reversible?
  - If not, there is a risk of prolonging the dying process
- What was the patient's functional status before admission?
  - A poor functional status is associated with a worse outcome

Patient cooperation during mechanical ventilation is crucial in determining NIV success or failure. Sedation can be part of a strategy designed to reduce discomfort and to improve the patient's adaptation to ventilation. However, a pharmacological approach is not routinely required and should be attempted only after specific aspects, such as the choice of appropriate interface or ventilator setting, have been considered, as well as all other causes of patient-related NIV failure. The choice between opioids and hypnotic agents should consider their pharmacokinetic and pharmacodynamic properties, the patient's age, and comorbidities. If sedation is used, it should only be in a well monitored environment.

Extracorporeal carbon dioxide removal ($ECCO_2R$) refers to a partial extracorporeal support able to selectively extract carbon dioxide (CO_2) from the blood and is emerging as a possible alternative to endotracheal intubation and invasive mechanical ventilation for patients failing NIV (reviewed elsewhere[50]). Although several pilot studies[51–59] have been conducted with the aim of assessing the efficacy and safety of $ECCO_2R$, no RCTs have been published on its role in patients with COPD exacerbation. A systematic review[60] showed that the evidence available to date is still scarce and of poor quality and the results heterogeneous. Del Sorbo and colleagues[61] compared 25 patients at risk for NIV failure treated with NIV plus venovenous $ECCO_2R$ with a well matched control group of 21 patients treated with NIV only. The primary endpoint, cumulative prevalence of endotracheal intubation, was 12% in the NIV plus $ECCO_2R$ group, whereas in the NIV only group it was 33%. They also showed a significant improvement in blood gases and respiratory rate after 1 h of treatment in patients treated with NIV plus $ECCO_2R$, but not in the historical controls who received NIV only. Braune and colleagues[62] conducted a similar clinical study in which the intervention group was given NIV plus venovenous $ECCO_2R$. Invasive mechanical ventilation was avoided in 14 (56%) of 25 patients with acute hypercapnic respiratory failure refractory to NIV receiving $ECCO_2R$. Although less invasive than extracorporeal membrane oxygenation, $ECCO_2R$-related complications remain an issue. All of these studies reported an important number of well known adverse events, including mechanical or patient-associated complications.[60,62] Similar to trials of acute NIV, a study of the real-life application of extracorporeal systems to facilitate treatment of acute respiratory failure showed worse prognosis compared with data from prospective clinical trials in experienced centres.[63] In conclusion, higher-quality studies are needed to evaluate the risk–benefit balance of $ECCO_2R$ and its effects on long-term outcomes in patients with COPD exacerbation admitted to the ICU, who have poor prognosis and high mortality.

Heated high-flow nasal therapy (HFNT) might also have a role in patients with hypercapnic respiratory failure. Its use could avoid the need for NIV in some patients with mild acidosis, during NIV breaks, and in patients intolerant of NIV. One study[64] showed non-inferiority of HFNT compared with NIV as initial treatment for patients presenting to the emergency room with a clinical diagnosis of respiratory failure. Based on discharge diagnosis, only 20% had hypercapnic respiratory failure and more patients crossed over from HFNT to NIV than vice versa. HFNT should therefore not be regarded as a simpler form of NIV for acidaemic patients with COPD exacerbation. Further research is required.

Next steps and quality assurance

As a result of the apparent poor outcomes in UK hospitals, the National Confidential Enquiry into Patient Outcome and Death (NCEPOD) reviewed the delivery of acute NIV in COPD exacerbation.[31] The methods are detailed in the report, but in brief involved completion of a questionnaire relating to the provision of the NIV service and review of cases selected at random from a sample generated from hospital coding data. This report raises major concerns about delivery of NIV in the real world. Most NIV for COPD was delivered outside critical care, and the decision to start NIV was made by a non-specialist in 65% of 361 cases (respiratory physician in 23% of cases and intensivist in 12%), although this question was not answered in 20% of cases. Respiratory physicians were least likely to initiate NIV inappropriately (four of 49 *vs* 15 of 40 intensivists) but were involved in less than a quarter of decisions. In 18% of cases the use of NIV was considered inappropriate, and a delay in starting NIV was identified in 27% of cases. The quality of NIV was considered good in 27% of cases, adequate in 49%, poor in 20%, and unacceptable in 4%. In 33% of cases monitoring was considered to be not frequent enough. The overall quality of care was good in 19% of cases, in 34% clinical care needed improvement, in 12% organisation needed improvement, and in 27% improvement was needed in both clinical and organisational aspects. Initiation of NIV following transfer from the emergency department to the ward was a common cause of delayed treatment, whereas initiation in the

emergency department was associated with better survival. Both inappropriate use of NIV and delays in recognising the need for NIV were common, highlighting the importance of basing patient selection on objective criteria.

Other national or local audits of NIV delivery in COPD and detailed structured case reviews are rare or non-existent. If the evidence from the UK were to be generalised internationally, it would represent a major failure to deliver an intervention that has been conclusively shown to be both effective and cost-effective.[65,66] The reasons for poor NIV-related care are complex and include inadequate staffing, poor training, failure to update training and confirm competence, poor decision making by clinicians (in terms of patient selection, non-ventilatory management, and appropriate escalation to invasive ventilation), inappropriate environment, inadequate equipment, and a failure to learn from mistakes and clinical incidents. The answers are equally complex, but a good place to start would be the NCEPOD self-assessment checklist, the BTS quality standards for acute NIV,[67] and regular audits), ideally national, with the opportunity to compare practice against a benchmark. Prediction tools might improve prognostication and allow some adjustment of achieved outcomes for severity and likelihood of a successful outcome. The single most important recommendation, however, is that clinicians and organisations should follow the guidelines.

Hypoxaemic respiratory failure

The use of NIV in the treatment of acute hypoxaemic respiratory failure has been an area of interest for many years but also a source of considerable controversy. From an initial enthusiasm about the possibility of avoiding endotracheal intubation, the use of this technique in hypoxaemic patients has been followed by doubts regarding the ability of NIV to change outcome and by concerns about a potential for harm. Several factors might explain the discrepant results found in the published literature. These factors include the relatively small time and severity windows for when to start and to stop NIV and move to invasive mechanical ventilation, the necessary skills and workforce to deliver and monitor NIV correctly, and specific technical aspects, such as selection of optimal settings and interface, which have varied across studies.

Following early studies suggesting a role for NIV in patients with COPD exacerbation, its potential in the management of acute respiratory failure without COPD started to be evaluated. In 1995, Wysocki and colleagues[68] conducted a single-centre RCT of NIV plus conventional therapy or conventional therapy alone in patients presenting with acute hypoxaemic respiratory failure without hypercapnia ($PaCO_2$ ≥7kPa [50 mm Hg]) or COPD. They found no difference in the number of patients requiring endotracheal intubation or in hospital mortality. Antonelli and colleagues[69] then published a study showing that NIV could replace intubation in acute hypoxaemic respiratory failure with fewer complications. This study used NIV as an alternative to endotracheal intubation; however, it has not been replicated, because all other studies have mostly used NIV as a preventive tool.

In a systematic review, Keenan and colleagues[70] concluded that, although the evidence appeared to support a reduction in the need for endotracheal intubation when NIV was used, the mortality benefit was unclear. Additionally, on the basis of the substantial (p=0·05) heterogeneity between the RCTs regarding the need for endotracheal intubation, when patients with COPD and cardiogenic pulmonary oedema were excluded, the general use of NIV in patients with de-novo hypoxaemic failure was not recommended and required further study. The differences in the cause of hypoxaemia appeared to have an important role in deciding whether NIV should be used. For example, they found that the subgroup of patients with immunosuppression and patients after lung resection might benefit from NIV, but these observations were based on small studies.[71–73] Several RCTs have convincingly documented a benefit of continuous positive pressure or NIV in reducing reintubation and pulmonary or infectious complications after abdominal surgery.[74,75] The different results according to specific indications were highlighted in the Canadian Critical Care Trials Group recommendations for NIV in the acute care setting.[76] Although recommendations were made for the use of NIV in acute respiratory failure due to several causes, they did not provide a recommendation for generalised acute lung injury.

More recent studies have focused on the effectiveness of NIV in cohort studies for de-novo acute hypoxaemic respiratory failure in the absence of underlying chronic respiratory disease or pulmonary oedema. In 2006, Demoule and colleagues[77] used a large prospective cohort to assess the benefits and risks of NIV, comparing patients with known acute-on-chronic hypercapnic failure or cardiogenic pulmonary oedema versus patients with de-novo acute hypoxaemic respiratory failure. The data were collected in clinical practice and not as part of a RCT. They found that, although successful application of NIV was independently associated with survival in all indications of NIV, failure of NIV was independently associated with ICU mortality in patients with de-novo respiratory failure (odds ratio 3·24, 95% CI 1·61–6·53). This association of NIV failure with mortality was not found for patients with acute-on-chronic lung or heart diseases. Several reports suggested that delaying intubation could be a reason for worsened outcomes in this situation.[78–80] In a follow-up study reporting data on the use of NIV in France over 15 years, Demoule and colleagues[78] showed that the use of NIV in COPD or pulmonary oedema was stable but had significantly decreased in acute hypoxaemic respiratory failure. The benefits of NIV in immunosuppressed patients were initially thought to be indisputable,[71,81] but have now also been questioned, in part because of the improved prognosis of these patients in the ICU over the years,

For the **NCEPOD self-assessment checklist** see http://www.ncepod.org.uk/2017niv.html

For the **NCEPOD audit toolkit** see http://www.ncepod.org.uk/2017nivtoolkit.html

even when invasively ventilated. NIV now seems to be of reduced benefit when compared with initial descriptions, although adequately powered studies are scarce.[82]

In 2001, Antonelli and colleagues[83] reported key predictors of NIV failure in patients with acute hypoxaemic respiratory failure. As expected, a higher severity score, older age, and the presence of acute respiratory distress syndrome (ARDS) were all risk factors for failure. Additionally, no improvement after 1 h of NIV predicted treatment failure. These results suggest, at best, a limited opportunity to deliver NIV and the need for careful selection of patients and for close monitoring in appropriate settings, to detect when patients should be switched to invasive mechanical ventilation.[84] The 1 h time frame for predicting failure was the subject of a recent single centre study,[85] in which the authors developed and validated a scoring system using readily available clinical variables to predict NIV failure in hypoxaemic patients (heart rate, acidosis, consciousness, oxygenation, respiratory rate—the HACOR score). At 1 h after starting NIV, a score greater than 5 predicted NIV failure with a sensitivity of 73% and a specificity of 90%. They found that patients with a 1 h score greater than 5 who were intubated within 12 h had a significantly lower mortality (66%) than those who were intubated after 12 h (79%, p=0·03). Although the data are consistent in showing a delay in intubation can be harmful, further external validation for the HACOR score is needed.

The importance of monitoring spontaneous effort and tidal volume generation during NIV has been explored, with the idea that some patients might develop a self-inflicted lung injury[86] because of excessive respiratory drive. Carteaux and colleagues[87] investigated the role of monitoring exhaled tidal volume in patients with de-novo acute hypoxaemic respiratory failure receiving NIV and made two important findings. First, controlling tidal volume in this patient population was extremely difficult, indicating that their respiratory drive might sometimes be very high and poorly sensitive to ventilatory management. If we consider the role of lung-protective ventilation commencing at the onset of positive pressure delivery, maintaining safe limits of tidal volume might not be feasible in many patients. Second, an exhaled tidal volume greater than 9·5 mL/kg of predicted body weight was highly predictive of NIV failure, suggesting that close monitoring of these patients is essential to ensure timely intubation. The threshold of 9 mL/kg as a predictor of NIV failure was supported by a post-hoc analysis of an RCT that compared NIV to high-flow therapy.[88] The potential risk of providing NIV in patients with de-novo acute hypoxaemic respiratory failure and the importance of close monitoring has resulted in NIV not being recommended for use in this population in the recent guidelines.[1]

Acute respiratory distress syndrome

The role of NIV in the treatment of acute lung injury and ARDS (according to the American-European Consensus Conference[89]) has been assessed in at least two meta-analyses.[90,91] Agarwal and colleagues[91] published a meta-analysis of RCTs that included only patients with ARDS with arterial partial pressure of oxygen [PaO_2]/FiO_2 less than or equal to 200 mm Hg. Owing to the fact that none of the RCTs specifically enrolled this group of patients, only 111 patients in the meta-analysis met the ARDS criteria, and they had diverse underlying pathologies. The authors concluded that NIV did not significantly reduce endotracheal intubation or improve ICU survival in patients with ARDS, and that use of NIV in these patients should only be done in the context of a clinical trial. Furthermore, recognition of NIV failure is required to ensure that care is escalated, when necessary, without delay. Due to the paucity of data regarding use of NIV in patients with ARDS, the same group published another meta-analysis in 2010 that included observational studies and RCTs for patients with PaO_2/FiO_2 less than 300 mm Hg.[90] The analysis included 540 patients, and the ranges of patients requiring intubation (30–85%) and mortality (15–71%) were large, with significant clinical and statistical heterogeneity. They concluded that NIV should be used cautiously in these patients, and that monitoring is extremely important. Xu and colleagues[92] published a systematic review and meta-analysis of RCTs comparing NIV with conventional oxygen therapy for acute hypoxaemic respiratory failure. Although they did not specifically analyse patients meeting criteria for acute lung injury or ARDS, they analysed patients with different levels of PaO_2/FiO_2. They found an overall reduction in intubation, but not in ICU mortality. A subgroup analysis found that bilevel positive airway pressure, but not continuous positive airway pressure, resulted in lower ICU mortality compared with conventional oxygen therapy. Hospital mortality was significantly lower with NIV only in patients with PaO_2/FiO_2 200–300 mm Hg treated with a helmet interface (not with oral-nasal mask). They concluded that insufficient evidence exists to recommend NIV in patients with acute hypoxaemic respiratory failure.

Although NIV is not recommended for the management of ARDS, it is frequently used to try to prevent intubation. Data regarding NIV use in patients with ARDS analysed from the Large Observational Study to Understand the Global Impact of Severe Acute Respiratory Failure study showed NIV use to be similar among the different ARDS severities (mild, moderate, and severe, as per the Berlin Definition).[93] Of the 2813 patients analysed, 436 (16%) were managed with NIV for day 1 and day 2 of meeting ARDS criteria. In the mild ARDS group, 78% of patients were successfully managed with NIV. However, proportions of patients successfully managed were much smaller for those with moderate (58%) and severe (53%) ARDS. In a propensity score-matched group of patients with PaO_2/FiO_2 less than 150 mm Hg managed with NIV versus invasive mechanical ventilation, mortality was higher in patients

managed with NIV (36·2% *vs* 24·7%, p=0·033). A decline in PaO_2/FiO_2 between day 1 and day 2 of NIV treatment and a $PaCO_2$ increase over the first 2 days were associated with failure of NIV. These results suggest that NIV should not be considered as a first-line therapy in patients with severe (PaO_2/FiO_2 <150 mm Hg) hypoxaemia that potentially meet criteria for ARDS.

Cardiogenic pulmonary oedema

Cardiogenic pulmonary oedema is a frequent reason for admission to the emergency department.[94] Pulmonary congestion reduces lung compliance and increases the work of breathing, causing hypoxaemia, respiratory distress, and sometimes hypercapnia with respiratory or mixed acidosis. Although most patients improve rapidly with medical therapy, a few develop severe respiratory distress and require some form of ventilatory support. For many years[95] it has been known that positive pressure applied at the mouth can relieve respiratory distress and slightly improve cardiac function.[96] Numerous studies have shown a rapid physiological improvement using either continuous positive airway pressure alone or bilevel NIV, and a meta-analysis suggested improved mortality compared with medical treatment alone.[97] However, the largest study[98] (n=1069) did not find any benefit on mortality when comparing medical treatment and oxygen with the two positive pressure techniques, despite a more rapid physiological improvement with the latter. In the standard oxygen group, however, 15% of patients were switched to receive positive pressure through a face mask (ie, crossed over), so the possibility that these patients would have otherwise required endotracheal intubation (with a higher mortality) cannot be excluded. These results suggest that patients improve faster with NIV than without it, but we do not know the exact proportion who really need this technique to avoid intubation and improve survival. The effects of this technique on long-term mortality, especially in older patients, is unclear. The mid-term to long-term prognosis of older patients admitted for acute pulmonary oedema is often poor, with a high hospital mortality.[99,100] NIV is often used as a ceiling technique for these patients without offering intubation. For those discharged alive after treatment with NIV as a ceiling of therapy, however, quality of life is similar to patients without limitation in the intensity of therapy, suggesting that NIV can prolong life, as opposed to merely prolonging the dying process.[100]

Interface and settings

In 2016, Patel and colleagues[101] planned a study that compared helmet NIV with face mask NIV for 206 patients to show a 20% absolute reduction in the primary outcome of endotracheal intubation, but they stopped enrolment after 83 patients when the interim analysis found an absolute difference in intubation use of 43% in favour of the helmet device (p<0·001). Ventilator-free days were higher in the helmet group (p<0·001) and 90-day mortality (p=0·04) and hospital mortality (p=0·02) were also significantly improved in the helmet group. The helmet interface seemed to make a huge difference; however, the settings in the two groups were not identical. Although this interface is not new in some centres, it is not widely used and requires additional training to use properly.[102,103] Further prospective studies should be done to confirm these dramatic improvements in patient outcomes.

Ventilator settings are important in acute hypoxaemic respiratory failure and can considerably modify the effects of the technique. A low positive end-expiratory pressure has been shown to be inefficient for oxygenation or to improve the work of breathing,[104] but, paradoxically, a positive end-expiratory pressure of only around 5 cm H_2O has been used in many studies, probably as a means to limit peak pressures and leaks. Pressure support is necessary to reduce the work of breathing,[104] but it might be harmful by inappropriately increasing tidal volume when the respiratory drive is already high. Additionally, high pressure might result in increased leaks and poor tolerance. Individual titration of ventilatory settings, particularly positive end-expiratory pressure, is important but complex in acute hypoxaemic respiratory failure and can considerably modify the effects of the technique.[87] The same, non-individualised, settings seem to be applied across many studies or centres, which might contribute to some negative results.

High-flow nasal therapy

Over the past few years evaluation of HFNT in patients with acute hypoxaemic respiratory failure has rapidly increased. In 2015, the Clinical Effect of the Association of Non-invasive Ventilation and High Flow Nasal Oxygen Therapy in Resuscitation of Patients with Acute Lung Injury study was published and quickly became a landmark paper supporting the role of HFNT in the management of acute hypoxaemic respiratory failure.[105] In this study, no difference in the number of patients requiring intubation existed among patients with PaO_2/FiO_2 less than 300 mm Hg between the three groups (HFNT, NIV, or oxygen alone) but the large subgroup of patients with PaO_2/FiO_2 less than 200 experienced significantly less (p=0·01) endotracheal intubation with HFNT (35%) compared with oxygen (53%) and NIV (58%). Importantly, the 90-day mortality was significantly lower (p=0·02) for patients treated with HFNT (12%) compared with those treated with oxygen (23%) or NIV (28%). In this study, no benefit was observed with NIV compared with oxygen alone. The introduction of this new technique has also been an opportunity to re-explore the results of NIV in immunosuppressed patients and compare the respective benefits of HFNT and NIV,[106,107] but more studies are needed that explore their relative efficacy. The good tolerance of this technique is an advantage over NIV given the non-inferiority of the two approaches.

Panel 4: **Prognostic factors for successful non-invasive ventilation in acute hypoxaemic respiratory failure**

Cause of acute hypoxaemic respiratory failure

- Favourable: cardiogenic pulmonary oedema, post-operative, and PaO_2/FiO_2 >200 mm Hg
- Adverse: PaO_2/FiO_2 <200 or 150 mm Hg

Predictors of failure

- PaO_2/FiO_2 <150 mm Hg
- Tidal volume (exhaled) under non-invasive ventilation (NIV) ≥9·0 or 9·5 mL/kg
- High severity score (eg, Acute Physiology And Chronic Health Evaluation II or Sequential Organ Failure Assessment)
- Heart rate, acidosis, consciousness, oxygenation, respiratory rate score >5 after 1 h of NIV

Considerations

- Trial of high-flow nasal cannula for PaO_2/FiO_2 <200 mm Hg
- Avoid delaying intubation

Search strategy and selection criteria

References were identified through searches of MEDLINE, PubMed, Embase, and the Cochrane Database of Systematic Reviews for articles published in English up until March 1, 2018. The following keywords were used: "non invasive ventilation", "noninvasive ventilation", "NIV", "NIPPV", "acute hypercapnic respiratory failure", "acute hypoxemic respiratory failure", "COPD", "ARDS", "mortality", "survival", "prognostic tools", "ROC curve", "receiver operating curve", "c statistic", "sedation", "analgosedation", "extracorporeal CO_2 removal", "CO_2 removal", and "$ECCO_2R$".

To summarise, NIV has the potential to prevent endotracheal intubation in patients with acute hypoxaemic respiratory failure, but it does not appear to improve other important clinical outcomes, such as mortality, for different reasons. Patients with acute hypoxaemic respiratory failure treated with NIV who experience failure of therapy might have an increased risk of mortality, particularly in ARDS, and determining when to stop NIV if it is not helping is essential. In addition to delaying intubation, one further risk with NIV is the development of self-inflicted lung injury in patients with high respiratory drive. This potential for harm highlights the importance of close monitoring of these patients (panel 4). Further prospective studies to assess the efficacy of helmet interfaces for NIV and of HFNT are required to understand their role better in the management of acute hypoxaemic respiratory failure.

Conclusions

A much clearer understanding and evidence base now exists for the role of NIV in both acute hypercapnic and hypoxaemic respiratory failure. Failure of NIV in both clearly confers a worsened prognosis, especially in hypoxaemic patients, but although in some patients NIV failure indicates the need to change the focus of care to symptom control and palliation, in others timely endotracheal intubation and invasive mechanical ventilation are required. Careful monitoring of readily available physiological parameters and use of prognostic tools help in this decision making process. Inappropriate patient selection, timing of initiation, or settings can all lead to worsened outcomes for NIV and need to be addressed by education programmes and monitoring of effectiveness by regular audit. The recent guidelines provide clear recommendations, and should be followed.

Contributors

SCB, LP, and MWE wrote the section on hypercapnic respiratory failure. TP and LB wrote the section on hypoxaemic respiratory failure. All authors revised the final draft.

Declaration of interests

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