Long-term Non-invasive Ventilation in Chronic Stable Hypercapnic Chronic Obstructive Pulmonary Disease

A summary of an official American Thoracic Society Clinical Practice Guideline[1] from an expert panel comprising: Madalina Macrea (Burlington, VT, US), Simon Oczkowski (Hamilton, ON, Canada), Bram Rochwerg (Hamilton, ON, Canada), Richard D. Branson (Cincinnati, OH, US), Bartolome Celli (Boston, MA, US), John M. Coleman III (Chicago, IL, US), Dean R. Hess (Boston, MA, US), Shandra Lee Knight (Denver, CO, US), Jill A. Ohar (Winston-Salem, NC, US), Jeremy E. Orr (San Diego, CA, US), Amanda J. Piper (Sydney, NSW, Australia), Naresh M. Punjabi (Baltimore, MD, US), Shilpa Rahangdale (Boston, MA, US), Peter J. Wijkstra (Groningen, Netherlands), Susie Yim-Yeh (Anaheim, CA, US), M. Bradley Drummond (Chapel Hill, NC, US), and Robert L. Owens (Boston, MA, US).

Chronic obstructive pulmonary disease (COPD) exerts a heavy toll on populations worldwide being a major cause of morbidity and the 4th leading cause of death in the United States.[2,3] Effective treatments for COPD are currently limited but non-invasive ventilation (NIV) has been shown to be beneficial in acute exacerbations and to improve survival in patients with COPD and chronic stable hypercapnia.

The American Thoracic Society (ATS) Clinical Practice Guideline on long-term ventilation in stable hypercapnic chronic COPD is based on five key questions on NIV in this indication.[1] The answers to these and recommendations are drawn from a 19-member expert panel analysis of recent evidence obtained in a systematic literature search. The questions, recommendations, and levels of recommendation/evidence are summarised in Table 1.

Question 1: Should long-term nocturnal NIV versus usual care be used for chronic stable outpatients with hypercapnic COPD?

The panel identified 8 clinical studies[4-11] that addressed the effects of NIV compared with regular care including effects on mortality. In these studies, NIV reduced mortality risk by 14% with NIV (RR 0.86); reduced hospitalisation risk (mean difference [MD]: 1.26), improved quality of life (QoL) measures (standardised MD: 0.48) and improved dyspnoea (standardised MD: –0.51). NIV also reduced awake $PaCO_2$ (MD: 3.49 mm Hg lower) and increased awake PaO_2 (MD: 3.1 mm Hg). No significant difference was seen in lung function (FEV_1 and FVC) or sleep efficiency. The 6m walking distance (6MWD) was greater with NIV (MD: 32m). Four of the studies assessed adverse events and showed a 10-fold increase in risk of discomfort, skin breakdown and rash with NIV vs regular care, but there were no reports of hypotension or pneumothorax in any of the studies.

Overall, the panel considered that NIV produced more desirable than undesirable effects in this patient population.[1] They recognised

that NIV can be expensive to provide but that on balance, it is cost-effective in many settings.[10] The consequent recommendation is:[1]

'We suggest the use of nocturnal NIV in addition to usual care for patients with chronic stable hypercapnic COPD (conditional recommendation, moderate certainty).'

Question 2: Should patients with chronic stable hypercapnic COPD undergo assessment for sleep apnoea (i.e., overlap syndrome) before initiation of long-term NIV?

The rates of patients with both obstructive sleep apnoea with COPD (COPD-OSA) varies between populations; 0.5% in mild COPD to 65% in those with moderate COPD.[12-14] This combination or 'overlap syndrome' has a different presentation and results in more serious nocturnal oxygen desaturation and sleep disturbance than COPD or OSA alone.[13] It is therefore important to identify patients with COPD-OSA and asses the effects of NIV on them.

Some small non-randomised controlled studies have show benefits of NIV in COPD-OSA,[15-19] some randomised trials are ongoing (n=70,292), but evidence is currently limited. No trials assessing the

Table 1: American Thoracic Society recommendations for long-term non-invasive ventilation use[1]

Question	Recommendation	Level of recommendation/evidence
Should LT-NIV vs. usual care be used for stable outpatients with COPD?	Nocturnal NIV, in addition to usual care should be used for patients with chronic stable hypercapnic COPD	Conditional recommendation, moderate certainty
Should patients with stable COPD undergo assessment for sleep apnoea before initiating LT-NIV?	Patients with chronic stable hypercapnic COPD should undergo screening for OSA before initiation of long-term NIV	Conditional recommendation, very low certainty
Should LT-NIV be initiated in patients hospitalized with a COPD exacerbation associated with acute-on-chronic respiratory failure?	In-hospital initiation of long-term NIV should not be used after an episode of acute-on-chronic hypercapnic respiratory failure, favouring instead reassessment for NIV at 2–4 weeks after resolution	Conditional recommendation, low certainty
Should LT-NIV settings be determined by an in-laboratory overnight PSG in patients with stable COPD?	An in-laboratory overnight PSG should not be used to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV	Conditional recommendation, very low certainty
Should NIV with targeted normalization of $PaCO_2$ amounts vs NIV without targeting normal $PaCO_2$ amounts be used for LT-NIV in patients with COPD?	NIV with targeted normalization of $PaCO_2$ should be used in patients with hypercapnic COPD on long-term NIV	Conditional recommendation, low certainty

COPD = chronic obstructive pulmonary disease; LTH-NIV = long-term home non-invasive ventilation; OSA = obstructive sleep apnoea ; $PaCO_2$ = arterial partial pressure of carbon dioxide; PSG = polysomnography.

benefits of screening for OSA in COPD or in those who are already receiving NIV have been identified. Based on data from patients with OSA alone, the overall certainty of test accuracy for OSA with COPD was judged to be low.

Despite the lack of test accuracy, the panel believed that it is important to recognise patients with COPD-OSA; it helps clinicians choose between NIV and continuous positive airway pressure or and guides other interventions such as titration of expiratory positive airway pressure and discontinuation of inhalers. Their recommendation is:[1]

'We suggest that patients with chronic stable hypercapnic COPD undergo screening for OSA before initiation of long-term NIV (conditional recommendation, very low certainty).'

Question 3: Should long-term NIV be initiated in patients hospitalized with a COPD exacerbation associated with acute-on-chronic respiratory failure?

Patients who are admitted to hospital for an acute COPD exacerbation have a high risk of readmission (60–80%) or death (30–49%) within a year.[20] It is important to consider whether such patients should be given long-term NIV to improve outcomes. An assessment of 4 randomised controlled trials (RCTs) including the RESCUE (n=201)[21] and HOT-HMV (n=116)[22] studies showed no major difference for NIV initiation after hospitalisation in terms of: mortality (RR: 0.92), COPD exacerbations MD: 0.3 fewer), hospitalisation (RR: 0.61, very low certainty), changes in dyspnoea (MD 0.8 points lower), measures of QoL (MD 2.89 points lower) and 6MWD, (MD: 8.64 m). There was a significant reduction in $PaCO_2$ (MD 3.41 mm Hg lower, 95% CI: 4.09–2.73 mm lower) but no reduction in $PaCO_2$ or FEV_1.

In these studies, NIV did not particularly affect comorbidities or QoL and in the HOT-HMV study, hypercapnia resolved in some patients and NIV could be initiated unnecessarily. The panel recommendation is:[1]

'We suggest not using in-hospital initiation of long-term NIV after an episode of acute-on-chronic hypercapnic respiratory failure, favouring instead reassessment for NIV at 2–4 weeks after resolution (conditional recommendation, low certainty).'

Question 4: Should long-term NIV settings be determined by an in-laboratory overnight PSG in patients with chronic stable hypercapnic COPD?

Guidance for the initiation of NIV in COPD is mostly lacking. Polysomnography (PSG) and real-time $PaCO_2$ monitoring in sleep could have benefits but these facilities are not readily available at many treatment centres.[23] A study of 60 patients compared NIV titrated with PSG with therapy titrated during daytime alone. NIV titrated with PSG had no effect on mortality, NIV asynchrony, adverse events or QoL.[23] In both group arterial CO_2 tension, somnolence and sleep quality improved and there were no differences in nocturnal gas exchange or HRQoL measures. Pooled data from this study and a pilot study[24] showed no difference in NIV adherence, QoL or $PaCO_2$. In-laboratory overnight PSG has some benefits for optimising NIV but it has a high cost and there are few sleep laboratories are able to provide CO_2 monitoring. In-laboratory titration could therefore

be reserved for COPD patients having difficulty with therapy. Many issues remain to be addressed on the optimal mode and settings for NIV in COPD and in COPD-OSA, how they should be adjusted for optimal effectiveness and adherence and the best treatment time course. Based on this current lack of evidence the panel's advice is:[1]

'We suggest not using an in-laboratory overnight PSG to titrate NIV in patients with chronic stable hypercapnic COPD who are initiating NIV (conditional recommendation, very low certainty).'

Question 5: Should NIV with targeted normalization of $PaCO_2$ amounts versus NIV without targeting normal $PaCO_2$ amounts be used for long-term NIV in patients with COPD?

There have been no head-to-head comparisons of $PaCO_2$-targeted vs $PaCO_2$-non-targeted titration in NIV in chronic stable COPD. Only indirect comparisons from small studies[9,25,26] are currently possible to answer this question. Pooled data from these studies indicate greater $PaCO_2$ when NIV is used to target CO_2 clearance (MD: 4.9 mm Hg lower) and PaO_2 3.4 mm Hg higher) but no difference in measures of QoL). An analysis of some of the RCTs, discussed in question 1, that targeted normalization of $PaCO_2$ (high intensity) vs studies that did not specifically target $PaCO_2$ (low intensity) did not show any particular difference between these two approaches. This may have been due to only a small difference in $PaCO_2$ between high- and low-intensity treatments of 2.8 mm Hg but $PaCO_2$ was not always measured in these studies and might show a greater effect.

Due to the lack of evidence from any large trial, no comparative data and the failure to show any effect of targeted $PaCO_2$ on mortality, the panel recommends as follows:[1]

'We suggest NIV with targeted normalization of $PaCO_2$ in patients with hypercapnic COPD on long-term NIV (conditional recommendation, low certainty).'

Conclusions

For NIV in chronic stable hypercapnic COPD it is important to select suitable patients and overcome barriers to long-term NIV use such as physician awareness and education in the use of the technique. More studies are needed to increase evidence of the benefits of NIV in this indication, to better determine the goals of therapy and to optimise its use. In addition, regulatory bodies and payers need to qualify a patient for long-term NIV and reduce/simplify the criteria necessary to enable funding. The cost of this treatment and differing availability, however, could create inequalities in access to it. Overall, the panel believed that the evidence supports the use of long-term NIV in chronic stable hypercapnic COPD but more supporting evidence is needed and barriers to implementation need to be overcome.[1]

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