


## The Danish respiratory society guideline for long-term high flow nasal cannula treatment, with or without supplementary oxygen

Ulla Møller Weinreich <sup>a,b</sup>, Kasper Svendsen Juhl<sup>a</sup>, Malene Søby Christophersen<sup>c</sup>, Svend Gundestrup<sup>d</sup>, Munsoor Ali Hanifa<sup>e</sup>, Kristine Jensen<sup>f</sup>, Frank Dyekjær Andersen<sup>g</sup>, Ole Hilberg<sup>h</sup> and Line Hust Storgaard<sup>a</sup>

<sup>a</sup>Department of Respiratory Diseases, Aalborg University Hospital, Aalborg, Denmark; <sup>b</sup>The Clinical Department, Aalborg University, Aalborg, Denmark; <sup>c</sup>Department of Emergency Medicine, Horsens Regional Hospital, Horsens, Denmark; <sup>d</sup>Department of Internal Medicine, Rigshospitalet Glostrup, Glostrup, Denmark; <sup>e</sup>Department of Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, Aalborg, Denmark; <sup>f</sup>Department of Cardiology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; <sup>g</sup>The Diagnostics Center, Silkeborg Regional Hospital, Silkeborg, Denmark; <sup>h</sup>Department of Medicine, Vejle Hospital, Southern Danish University Hospital, Vejle, Denmark

### ABSTRACT

**Introduction:** Long-term High Flow Nasal Cannula (LT-HFNC), defined as High Flow Nasal Cannula treatment provided to patients with chronic pulmonary conditions during stable phases, has emerged as a home treatment in different categories of patients with chronic lung diseases in recent years.

**Methods:** This paper summarizes the physiological effects of LT-HFNC and evaluates the clinical knowledge to date about treatment in patients with chronic obstructive lung disease, interstitial lung disease and bronchiectasis. The guideline is translated and summarized in this paper and presented unabridged as an appendix to the paper.

**Results:** The paper describes the working process behind the Danish Respiratory Society's National guideline for treatment of stable disease, which has been written to support clinicians in both evidence-based decision making and practical issues concerning the treatment.

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## Background

Over the past two decades, the literature on long-term High Flow Nasal Cannula (LT-HFNC), defined as High Flow Nasal Cannula treatment provided to patients with chronic pulmonary conditions during stable phases, has increased considerably [1–3]. Most studies have been conducted in the treatment of patients with Chronic obstructive pulmonary disease (COPD), but studies have also investigated the effect of long-term home treatment in patients with interstitial lung disease and bronchiectasis. In COPD and interstitial lung disease, the target populations have been patients with persistent respiratory failure.

In the paper below, the authors summarize the literature that, after thorough review of the existing literature on physiological and clinical effects in stable chronic respiratory disease, was chosen as the background for the Danish National Guideline for LT-HFNC treatment.

### Physiological effects



The physiological effects of High Flow Nasal Cannula have primarily been studied during short-term use of


the device, however, the physiological effects of LT-HFNC are expected to be similar, although in some instances with varying importance, to those seen in acute use [4]. The most important are mentioned below.

### Mucociliary clearance

Humidification of the airways is essential for a number of reasons. Firstly, patients using long-term oxygen therapy frequently experience dryness of the airways and congestion [5], which has been found to increase airway resistance and increase the work of breathing [6]. Humidification of the airway is also important for airway resistance to inflammation and infection [7,8], and improves the velocity of mucociliary transport [9]. This, alongside the ventilatory mechanisms described below, leads to improved alveolar recruitment [10].

By delivering humidified and heated air, High Flow Nasal Cannula has been shown to improve the mucociliary clearance [11–13]. A temperature and humidity matching human physiology (100%/37°Celsius) will provide the best conditions for mucociliary clearance [14], as ciliary beating has optimal performance at full

**CONTACT** Ulla Møller Weinreich  [ulw@rn.dk](mailto:ulw@rn.dk)  Department of Respiratory Diseases, Aalborg University Hospital, Mølleparkvej 4, DK-9000 Aalborg Denmark.

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humidification [15,16], which should therefore be the target for LT-HFNC treatment.

### **Anatomical dead space wash-out**

High Flow Nasal Cannula treatment increases the wash-out of carbon dioxide (CO<sub>2</sub>) from the anatomical dead space [17]. The effect is proportional to the flow, and thereby the decrease in reduction of CO<sub>2</sub> rebreathing [18]. Although the physiological effect on acute hypercapnic failure in COPD is much debated, recent papers do indicate that this may be of use to chronic hypercapnic patients, as short-term use led to reduction, and long-term use to stabilization, of PaCO<sub>2</sub> in COPD [19,20]. In addition, the oxygen deposited in the anatomical dead space may also contribute to stabilize oxygen saturation in these respiratorily challenged patient groups [21]. It has been speculated, based on the lack of effect on work of breathing in patients who are treated with High Flow through tracheostomies, that the effect on the work of breathing is mediated through changes in the upper airways [22]. However, this needs further investigation.

### **Work of breathing**

High Flow Nasal Cannula treatment has been shown to reduce the trans-diaphragmatic pressure, the measure of inspiratory effort and the work load of breathing [23,24]. Although the positive end-expiratory pressure effect of High Flow Nasal Cannula is minimal [25], it adequately counteracts hyperinflation in patients with COPD and thereby also decreases the expiratory work load [4,24]. Additionally, the improved ventilation also adds to the stabilization of oxygenation [23], driven by changes in anatomical dead space and alveolar recruitment, described above [10,21]. The optimal flow in the individual patient is closely related to the patients' work of breathing, which has been primarily investigated in patients who are not spontaneously breathing [26]. Whereas the optimal wash out of the anatomical dead space in patients with acute respiratory failure is best obtained with high flows, studies suggest that due to the lower work of breathing, it is better obtained with lower flows in patients with chronic respiratory failure [27–29]. Although not fully understood, this is, through technical models, explained by more optimal conditions for exhalation at lower flows [30].

### **Domiciliary high flow nasal cannula – current knowledge**

Only in recent years has High Flow Nasal Cannula moved out of the hospital and into patients' homes. Most studies have been conducted in patients with

COPD; studies in patients with bronchiectasis and interstitial lung disease are sparse.

### **Long term high flow nasal cannula in COPD**

Most studies of the effect of LT-HFNC have been conducted in patients with COPD with persistent hypoxic failure. A study by Nagata et al found improved health-related quality of life in a 6-week cross-over study [25]. A recent feasibility study also showed improved health-related quality of life in patients with COPD treated with High Flow Nasal Cannula after COPD exacerbations requiring hospitalization [31]. D'Cruz et al found reduced symptoms, judged by the COPD assessment test, and a significantly lower 30-day readmission rate in a similar feasibility study [3]. A qualitative study by Storgaard et al found patient-perceived reductions in symptoms [32]. In a 12-month observational study by Rea et al, in a mixed population of patients with respiratory diseases, half with COPD, patients had a prolonged time to first acute exacerbation of COPD, a shorter duration of exacerbations, as well as a significant improvement in forced expiratory volume in the first second (FEV1), despite usage of less than two hours per day [33]. In a 12-month randomized controlled trial, including 200 patients with stable COPD and persistent respiratory failure (randomized equally to recommended therapy or recommended therapy plus LT-HFNC), Storgaard et al found several significant differences compared to a control group: a reduction in acute exacerbations of COPD; reduction in hospitalizations, when corrected for time of use; reduced dyspnea; and preserved walking distance, FEV1 and health-related quality of life [34]. A later sub-study revealed the effect on exacerbations and hospitalizations to be primarily for patients with frequent acute exacerbations of COPD (≥2 per 12 months) [35]. A number of studies have shown improved exercise performance [33,36,37]. In a qualitative study from Storgaard et al, a reduction in night-time symptoms was a very consistent finding from all participating patients [32]. Although LT-HFNC has primarily been targeted to persistent hypoxic failure, a number of studies have also reported an effect on persistent hypercapnia. Both Pisani et al and Bräunlich et al found, in a comparison between non-invasive ventilation (NIV) and High Flow Nasal Cannula on PaCO<sub>2</sub>-levels, that there were no significant differences in PaCO<sub>2</sub> levels following NIV or LT-HFNC treatment [19,38]. Both Nagata et al and Storgaard et al found that PaCO<sub>2</sub> remained stable in patients treated with

LT-HFNC, which was significantly different from controls, whose PaCO<sub>2</sub> increased. Furthermore, both studies found a significant reduction in exacerbations in the HFNC treated group [39,40]. Three studies have indicated that LT-HFNC treatment is cost-effective [41–43].

In study settings, treatment has been well tolerated; however, D’Cruz et al found that 83% completed the first month [3], and Storgaard et al also found drop-out to be most pronounced in the first month [44]. The drop out is comparable to that seen in patients treated with LT-NIV [45]. Furthermore, an abstract on a post-trial analysis of the Danish cohort showed that most patients used LT-HFNC until time of death [44]. Lastly, higher flows have been associated with lower adherence [46]. In summary, a number of authors have found that LT-HFNC reduces number- and increase time to next exacerbation; reduces dyspnea, and there are indications of a stabilizing effect for patients with COPD and stable hypercapnic failure on PaCO<sub>2</sub>-levels and number of exacerbations.

### **Long term high flow nasal cannula in bronchiectasis**

Literature on LT- HFNC treatment in patients with bronchiectasis is sparse. More than a decade ago, Hasani et al showed that mucociliary clearance improved in patients with bronchiectasis after only seven-days treatment [8]. Recently, a subgroup analysis was published on the 12-month randomized controlled trial by Rea et al [33], investigating the 45 patients with bronchiectasis from the original cohort of patients with obstructive lung diseases. The study found that patients had a reduction in acute exacerbations of bronchiectasis and improved health-related quality of life [47]. One large randomized controlled trial is ongoing, investigating the effect of High Flow Nasal Cannula on health-related quality of life in bronchiectasis (ClinicalTrials.gov NCT04142827); recruitment status is unknown. Otherwise, literature consists of case reports at present [48].

In summary, literature is sparse in LT-HFNC treatment of patients with bronchiectasis, but there are indications of a reduction in number of exacerbations.

### **Long term high flow nasal cannula in interstitial lung disease**

As in bronchiectasis, the literature on LT-HFNC use in interstitial lung disease is sparse. Bräunlich et al have shown that LT-HFNC reduced respiratory rate in patients with interstitial lung disease [49]. Chikhanie

et al found LT-HFNC to increase both endurance and exercise tolerance in interstitial lung disease, and to reduce leg fatigue, which was consistent with the findings of Suzuki et al, who also found LT-HFNC to improve endurance [50]. Huremovic et al found improved walking distance and reduced time to oxygen saturation recovery [51]. All aforementioned studies found the effect of LT-HFNC to be highly variable in between individual patients. A single abstract suggests improved recovery, in terms of endurance, after an acute exacerbation of interstitial lung disease [52].

In summary, studies on LT-HFNC treatment in patients with interstitial lung disease are few, but there are indications of an effect on exercise tolerance.

Based on the clinical and physiological evidence available for LT-HFNC, the Danish Respiratory Society decided to make a clinical guideline for the use of LT-HFNC treatment in stable phase in 2019. The guideline has been updated in 2022 [53].

## **Methods**

The Danish Respiratory Society guidelines are short and operational clinical guidelines based on the principles of the National Institute for Health and Care Excellence [54].

A background literature search was performed in PubMed, Embase and on Google Scholar; as there are no established Mesh- and Emtree terms for HFNC, the searches were performed as free text searches. Three literature searches were performed, utilizing ‘High Flow’ OR ‘High Flow Nasal Cannula’ OR ‘HFNC’ OR ‘High Flow nasal oxygen’ OR ‘HFNO’ OR ‘Nasal High Flow’ OR ‘NHF’ OR ‘High Flow Oxygen Therapy’ OR ‘HFOT’ in connection with the specific lung diseases: ‘COPD’ OR ‘Chronic Obstructive Lung Disease’ OR ‘Chronic Obstructive Pulmonary Disease’; ‘Interstitial lung disease’ OR ‘ILD’; and ‘Bronchiectasis’, respectively.

The initial guideline was based on a workshop, where the authors of the guideline discussed the available literature and knowledge of LT-HFNC use, to set the outline of the guideline. The revision was based on the literature published since 2019, on the physiological knowledge about High Flow Nasal Cannula and LT-HFNC clinical outcomes. Furthermore, the group behind the guideline had made themselves available to the Danish Respiratory Community for questions about the guideline and LT-HFNC in general, and the reflections on implementation were recorded and used in the revision of the guideline.

The Danish Guideline was translated from Danish to English by forth-back translation: two of the participating authors of the Danish version translated the

guideline to English, compared translations and agreed on a proposed English version. Hereafter, the guideline was back-translated by a bilingual third person not affiliated to the work, and the original Danish version and the back-translation were compared. Minor changes to the original English translation were made, based on this.

## Results

The Danish Respiratory Society guideline recommends use of LT-HFNC in patients with COPD with frequent acute exacerbations of COPD ( $\geq$ two severe acute exacerbations of COPD per year) and persistent hypoxic respiratory failure, defined according to Danish Respiratory Society guidelines as  $\text{PaO}_2$  (without supplementary oxygen treatment)  $\leq 7.3$  kPa in clinically stable conditions, including optimized COPD treatment regimens, or  $\text{PaO}_2$  (without supplementary oxygen treatment)  $\leq 8.0$  kPa in case of concomitant right sided heart failure or haematocrit  $> 55\%$  [55]. Furthermore, LT-HFNC is recommended for patients with COPD who are difficult to wean from High Flow Nasal Cannula treatment after an acute exacerbation of COPD. In addition to this, LT-HFNC may be considered for the treatment of patients with interstitial lung disease and persistent hypoxic failure, and patients with severe bronchiectasis, both with- and without persistent hypoxic failure, with frequent acute exacerbations of bronchiectasis. Lastly, LT-HFNC may be considered for patients with COPD with persistent hypercapnic failure, to whom long term NIV is recommended, according to Danish Respiratory Society guidelines (persistent stable hypercapnia,  $\text{paCO}_2 \geq 7$  kPa, 2–4 weeks after NIV-treated acute exacerbation of COPD and  $>$  three NIV treated acute exacerbations of COPD, in addition to patients who cannot be weaned after NIV treated acute exacerbation of COPD) [56], but who do not tolerate long term NIV.

It is recommended to treat patients with a flow of 15–35 L/min, depending on the patients' respiratory work. Higher flows of up to 40 L/min should only be considered for patients with a high respiratory rate or a large respiratory workload, based on clinical evaluation. Hereafter, a target saturation is set, and based on this, the  $\text{FiO}_2$  is titrated in order to reach the target saturation. A daily use of 6–8 hours is recommended, and in order to keep patients as physically active as possible, the guideline suggests night-time use. A temperature of 37°Celsius is recommended. Both flow and temperature may be titrated towards the target over a longer period of time.

The full version of the translated guideline is available in Supplementary material.

## Discussion

The Danish Respiratory Society Guideline for LT-HFNC is the first guideline in this area in the world.

Although guidelines and reviews have recommended the use of High Flow Nasal Cannula in an acute setting [57,58], previous reviews have concluded that more evidence was needed before LT-HFNC could be incorporated into clinical practice in the treatment of patients with chronic lung disease in stable phases [46,59]. LT-HFNC has been evaluated in different institutions. Although not recommended for patients with COPD and persistent hypoxic failure by the German Institute for Quality and Efficiency in Health Care [59], German insurance companies do re-imburse LT-HFNC costs to patients who do not tolerate long-term NIV, despite the lack of literature on the area [60]. Therefore, there may be those who question why the Danish Respiratory Society chose to make a national guideline. There are several reasons why we chose to make this guideline. Firstly, the treatment is used throughout the country for treatment of persistent hypoxic failure, with no real contraindications apart from poor adherence to therapy, and it is desirable that health care professionals are aware of the level of evidence on which they base their clinical choices. Secondly, to give clinicians who wish to use LT-HFNC a clear understanding of the fact that acute- and long-term use of High Flow Nasal Cannula are not the same. Thirdly, when used, it is important that the treatment is used correctly for patients to get optimal treatment, and for clinicians to evaluate the effect of LT-HFNC on a sound basis. And lastly, by aligning treatment throughout the country, we hope to improve the validity of real-life data, which could be used for quality control and scientific purposes in the future.

The guideline recommends treatment for patients with COPD and bronchiectasis with exacerbations, although evidence is limited. The post hoc analysis by Weinreich of the Danish randomized controlled trial of patients with COPD indicates that the effect of LT-HFNC on exacerbations is primarily seen in patients with previous exacerbations [35]. Similarly, the post hoc analysis of the study by Rea et al also indicates that the effect is primarily seen in patients with exacerbations. Recently, studies by Nagata and Crimi et al, not published when the Danish guideline was reviewed, support the use of LT-HFNC in COPD and bronchiectasis with exacerbations [39,40]. Despite this, it is important to remember that the effect on dyspnea has

been convincing in both COPD, bronchiectasis, and interstitial lung diseases. Therefore, dyspnea could also be an indication for LT-HFNC treatment.

The Danish Respiratory Society guideline is, of course, targeted to Danish respiratory physicians. There may be numerous differences in practical and logistical matters that make the guideline not directly applicable for colleagues in other countries. Furthermore, the guideline refers to other Danish guidelines, which may not apply to other countries' settings. When we choose to publish the guideline in an English version, as a direct translation of the Danish version, it is to offer inspiration to colleagues around the world, and to offer a guide to the hands-on use of LT-HFNC.

Do we need more data on LT-HFNC? Of that there is no doubt. In both interstitial lung disease and bronchiectasis, data are limited, and studies are needed in every aspect of LT-HFNC treatment, be it target population, treatment effect or health-economic evaluation. In COPD, confirmatory studies are needed to further establish the target population for LT-HFNC treatment, and to investigate the role and the effect of LT-HFNC in persistent hypercapnic failure. The optimal flow is not established; lower flows will probably improve adherence and mechanical models suggest better airway clearance at lower flows – however, no studies on higher flows in stable conditions exist. The optimal duration of use has not been investigated in any of the chronic diseases, and it is therefore not known whether it differs between diseases; the most common recommended time of use in the different studies has therefore been applied in the guideline. Therefore, the Danish Respiratory Society guideline will also need frequent updates in years to come, and there is a hypothetical risk that conclusions may change considerably over time.

In conclusion, evidence about the use of LT-HFNC treatment in stable chronic respiratory disease is emerging, and there are strong indications of the treatment being useful in patients with COPD and bronchiectasis with recurrent exacerbations, as well as in patients with interstitial lung diseases for improving physical performance. The Danish Respiratory Society guideline for LT-HFNC treatment is a proposal to help clinicians make evidence-based decisions regarding treatment; to give the users hands-on guidance in the use of the device; to ensure that patients treated with LT-HFNC are treated correctly, based on current knowledge; and to build a platform for national evaluation of treatment.

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## ORCID

Ulla Møller Weinreich  <http://orcid.org/0000-0003-1975-3654>

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