Long-Term Oxygen Therapy: Comparison of the German and British Guidelines

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Key Words

Blood gas analysis · Chronic obstructive pulmonary disease · Guidelines · Oxygen therapy · Respiratory insufficiency

Abstract

Background: The German guideline on long-term oxygen therapy (LTOT) was published in 2008 by the German Respiratory Society (DGP), while the British Thoracic Society (BTS) published their most recent guideline in 2015. **Objectives:** The aim of the present article was to highlight the major areas of consensus and disagreement in the recently published BTS and DGP guidelines on LTOT. **Methods:** The BTS and DGP guidelines were directly compared in terms of congruencies and differences. A critical appraisal was then performed and authors' suggestions were provided. **Results:** The 2 guidelines are almost congruent in 2 major areas, namely, (1) the indication criteria for LTOT in chronic obstructive pulmonary disease (COPD) patients at rest and (2) the recommended duration of LTOT over a 24-h period. However, 8 major areas in which the guidelines differ considerably were identified: (1) techniques for blood gas analysis; (2) timing of LTOT in stable patients; (3) LTOT in post-exacerbation COPD patients; (4) ambulatory oxygen therapy;

(5) nocturnal oxygen therapy; (6) titration of oxygen flow rates; (7) follow-up visits; and (8) LTOT for patients who still smoke. Furthermore, the BTS guideline is much more detailed, includes more references (161 vs. 71) and is more up to date than the DGP guideline. **Conclusion:** There are major differences between the 2 guidelines. Many of the aspects raised by the BTS guideline appear to be reasonable with regard to the current literature, clinical experience and prescription practices. However, an international consensus on LTOT is lacking.

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Introduction

Long-term oxygen therapy (LTOT) is a widely and increasingly used treatment option for chronic respiratory failure [1]. LTOT was first described in 1967 by Petty and colleagues [2] after 6 patients had received supplemental oxygen during a rehabilitation programme. Numerous studies followed and subsequently led to the publication of landmark trials in the early 1980s, which showed improved survival rates in chronic obstructive pulmonary disease (COPD) patients who received oxygen for at least

15 h per day [3, 4]. However, 2 subsequent trials did not show survival benefits for LTOT in COPD patients with moderate hypoxaemia [5] and sleep-related oxygen desaturation (nocturnal oxygen therapy [NOT] only) [6], although these trials were underpowered to assess mortality.

LTOT is also prescribed today for many conditions beyond COPD, even though there are no clearly established survival benefits associated with LTOT in non-COPD patient groups [7]. Specifically, suggestions for usage of LTOT in other diseases than COPD as well as general aspects regarding LTOT prescription are mainly extrapolated from evidence gained from studies on COPD patients.

Although improvements in dyspnoea and exercise tolerance have been demonstrated in many disease groups [7], LTOT remains an expensive and elaborate treatment modality with potential side effects. Furthermore, LTOT can promote psychosocial side effects, such as stigma, social isolation, lack of self-confidence, depression and fear of dependence [8–10]. Therefore, a set of comprehensive guidelines with clear indication criteria for LTOT are urgently needed. Indeed, increases in experience, knowledge and evidence have led to the publication of national guidelines; however, many aspects of LTOT still remain scientifically unclear. Of note, the German guideline on LTOT was published in 2008 by the German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V., DGP), but it has not been updated since then [11].

Importantly, the German guideline is classified according to criteria provided by the Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V., AWMF) and includes the stages S1 (developed by an expert group in informal consensus), S2 (formal consensus or formal evidence-based research) and S3 (guideline with all elements of systematic development including logic, decision and outcome analyses). Accordingly, S3 guidelines have the most evidence-based impact. The German DGP guideline on LTOT was developed as a S2 guideline [11].

Although there has been the intention to update the DGP guideline for a long time, it was also deemed sensible to wait for the outcome of a large US-based trial that started in 2009 and has just been published [12], since this trial was expected to have the potential to elicit fundamental changes in prescription practices in oxygen therapy [1, 12, 13]. To this end, the trial was designed to answer an essential question that has not been adequately

addressed so far: does LTOT improve survival rates in COPD patients with either moderate resting desaturation or moderate exercise-induced desaturation [1]? In the US multi-centre study, 738 patients with moderate resting hypoxaemia (SpO_2 89–93%) and/or moderate exercise-induced desaturation ($\text{SpO}_2 \geq 80\%$ for ≥ 5 min and $<90\%$ for ≥ 10 s during a 6-minute walking test, 6MWT) were randomly assigned to treatment with or without supplemental oxygen. The primary outcome was the composite of death or first hospitalisation. The main result was that neither the primary outcome nor the overall hospitalisation rates, COPD-related hospitalisations or COPD exacerbations were significantly different between the 2 groups. Furthermore, no consistent changes in quality of life, 6MWT distance or lung function were found in both groups [12]. Unfortunately, however, systematic arterial blood gas (ABG) analyses had not been performed in this trial.

However, in order to address the need for updating the DGP guideline, the DGP authors published a position paper [13], in which they confirmed the 2008 recommendations (based on the current literature) and emphasised the importance of the current US trial [12].

Interestingly, the new British guideline on LTOT was published by the British Thoracic Society (BTS) in 2015 [7]. It was written according to criteria set by the AGREE collaboration and the BTS Standards of Care Committee guideline production manual, which can be found online (<http://www.agreetrust.org/resource-centre/agree-ii/> and <http://www.brit-thoracic.org.uk/guidelines-and-quality-standards/>). The BTS guideline was still published despite the fact that the results of the above-mentioned US trial [12] were pending. Nevertheless, there are some important differences between the DGP and BTS guidelines (Table 1). Therefore, the aim of the present investigation was to first highlight the major areas of consensus and disagreement in the recently published BTS and DGP guidelines on LTOT. Additionally, the identified differences were evaluated in view of the existing evidence.

Methods

A direct comparison of the 2015 BTS guideline [7] with the most recent DGP guideline (published in 2008) [11] was performed. For this purpose, the position paper published by the DGP in 2014 was also included in the comparison [13]. A strong focus was placed on identifying the areas of consensus and disagreement in each guideline's recommendation for LTOT. The differences between the 2 guidelines were then described in terms of the main

Table 1. Basic characteristics of the BTS and DGP guidelines

	British guideline (BTS)	German guideline (DGP)
Publication date	2015	2008 and position paper 2014
Pages, <i>n</i>	49 ^a	9 ^a
Language	English	German
Scientific references, <i>n</i>	161	71
Underlying criteria	AGREE collaboration, BTS Standards of Care Committee guideline production manual	AWMF (S2)
<i>Specifically addressed diseases</i>		
COPD	+	+
Interstitial lung disease	+	+
Cystic fibrosis	+	+
Pulmonary hypertension/pulmonary vascular disease	+	± ^e
Neuromuscular diseases	+	+
Chest wall diseases	+	+
Cluster headache	+	–
Cardiac disease ^b	+	± ^e
Obstructive sleep apnoea	+(NOT) ^c	–
OHS/overlap syndrome	+(NOT) ^c	–
Pulmonary malignancy	± ^d	± ^e
<i>Specifically addressed types of oxygen therapy</i>		
LTOT	+	+
Ambulatory oxygen therapy	+	+
Nocturnal oxygen therapy	+	+
Palliative oxygen therapy	+	–
Short-burst oxygen therapy	+	–

AWMF, Association of the Scientific Medical Societies in Germany (Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften e.V.); BTS, British Thoracic Society; COPD, chronic obstructive pulmonary disease; DGP, German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V.); LTOT, long-term oxygen therapy; NOT, nocturnal oxygen therapy; OHS, obesity hypoventilation syndrome; +, specifically covered; –, not specifically covered; ±, mentioned, but not specifically covered. ^a The British guideline is more detailed and also provides extensive practical advice. ^b Including congestive cardiac failure and adult congenital heart disease. ^c Recommendation only regarding NOT. ^d Recommendation regarding palliative oxygen therapy. ^e Global statement that other diseases leading to chronic respiratory failure type 1 should receive LTOT if PaO₂ is <55 mm Hg (<7.3 kPa).

issues with regard to prescription and application practices. A Critical Appraisal section is provided for each topic with reference to the current literature, and this information is then summarised in the section Authors' Suggestions for future recommendations.

Results

Major Areas of Consensus

In both the DGP and BTS guidelines, the evidence-based indication for LTOT mainly arises from the Nocturnal Oxygen Therapy (NOT) and Medical Research

Council (MRC) trials, which both evaluated COPD patients only (see below) [3, 4].

1. Indication for LTOT

The DGP and BTS guidelines are almost congruent regarding the indication for LTOT at rest (classical criteria):

- Arterial partial pressure of oxygen (PaO₂) ≤55 mm Hg (≤7.3 kPa).

There are only minor differences regarding secondary indication parameters (milder hypoxaemia):

- BTS guideline: PaO₂ ≤60 mm Hg (≤8.0 kPa) in the presence of peripheral oedema, polycythaemia (hae-

matocrit $\geq 55\%$) or with evidence of pulmonary hypertension.

- DGP guideline: PaO₂ 55–60 mm Hg (7.3–8.0 kPa) in the presence of secondary polycythaemia (not further quantified) and/or cor pulmonale with or without right heart insufficiency.

Critical Appraisal. The 2 landmark randomised-controlled trials (RCTs) in the early 1980s laid the foundation for LTOT in COPD [3, 4]. The NOT trial was published in 1980 as the first RCT evaluating LTOT in COPD patients. Patients ($n = 203$) were included in the study if PaO₂ was ≤ 55 mm Hg (≤ 7.3 kPa) or ≤ 59 mm Hg (≤ 7.87 kPa) accompanied by either oedema, P pulmonale (electrocardiogram) or raised haematocrit ($\geq 55\%$). The trial compared the use of 24 h of continuous oxygen to the use of 12 h of nocturnal oxygen, and patients were followed up for at least 12 months (mean 19.3 months). Overall mortality was 1.94 times higher in the nocturnal than in the continuous oxygen group ($p = 0.01$) [3]. The MRC trial from 1981 studied 87 COPD patients with chronic bronchitis or emphysema with irreversible airways obstruction (forced expiratory volume in one second < 1.2 L), 1 or more recorded episodes of heart failure with ankle oedema and a PaO₂ between 40 and 60 mm Hg (5.3–8 kPa) whilst breathing room air at rest. Patients were assigned to supplemental oxygen treatment for at least 15 h/day or no supplemental oxygen treatment. After 5 years, 19 of the 42 patients in the oxygen group had died compared to 30 out of the 45 controls [4]. The survival benefit of LTOT in COPD patients was confirmed by subsequent trials when LTOT was given for at least 15 h/day in the presence of chronic hypoxaemia (irrespective of previous episodes of oedema or pulmonary hypertension or chronic hypercapnia) [14–16]. In contrast, no survival benefits of LTOT were found in COPD patients with moderate hypoxaemia (PaO₂ 56–65 mm Hg, 7.4–8.7 kPa) [5] compared to those with moderate hypoxaemia (PaO₂ 56–69 mm Hg, 7.4–9.2 kPa) and sleep-related oxygen desaturation who received NOT only [6]. It should be noted, however, that both trials were too underpowered to assess mortality.

Authors' Suggestions. The results of the above-mentioned trials showed that LTOT prolongs life in COPD patients with significant hypoxaemia. However, both initial trials (NOT and MRC) were performed in the late 1970s, where both COPD and related co-morbidities were treated differently from current approaches [3, 4]. Similarly, the subsequent studies that confirmed the survival benefits of LTOT were not performed as RCTs but rather as observational studies or registries, and most

were also performed at a time when treatment approaches were different [14–16]. In addition, there is increasing evidence from previous trials [5, 6], and particularly from the current US trial [12], to suggest that LTOT has no beneficial effects, at least in patients with mild to moderate hypoxaemia. Therefore, it could be argued that the older studies showing an improved survival rate are not applicable to current practices.

2. Hours of Use

LTOT should be ordered for a minimum of 15 h per day according to the BTS guideline and for ≥ 16 h per day according to the DGP guideline. Up to 24 h of use are of additional benefit according to the BTS guideline and are recommended by the DGP guideline, respectively.

Major Differences (Table 2)

1. Techniques for Blood Gas Analysis

The DGP guideline suggests that the assessment for LTOT eligibility can be satisfactorily performed using capillary blood gas (CBG) analysis in the non-intensive care unit setting.

In contrast, the BTS guideline recommends ABG analysis as the first-line diagnostic tool, since CBG analysis alone can lead to a false indication for LTOT in some patients. However, the BTS guideline acknowledges that performing ABG assessments is not always practical, especially in an ambulatory setting, and that a combination of CBG analysis and oximetry can be used under these circumstances.

Critical Appraisal. The DGP guideline justifies their approach by referring to 1 trial by Pitkin et al. [17], which reported a sufficient correlation between CBG and ABG. The authors of the BTS guideline reviewed the current literature on CBG versus ABG and also refer to the trial by Pitkin et al. [17]. It is interesting that this trial was interpreted differently by the 2 societies: while the BTS guideline also acknowledges that the correlation between CBG and ABG was extremely good (where CBG underestimates PaO₂ by a mean of just 1.28 mm Hg [0.17 kPa]), it also refers to the 95% confidence interval, which was -8.18 to 5.62 mm Hg (-1.09 to 0.75 kPa), and therefore suggests that individual values for ABG and CBG can substantially differ. It should also be taken into account that even though the trial by Pitkin et al. [17] is regarded as an important study by both guidelines, only 40 patients were included in this trial.

Furthermore, as discussed in the BTS guideline, a meta-analysis by Zavorsky et al. [18] showed that CBG underestimated PaO₂ by 2.4 mm Hg (0.32 kPa), with a stan-

Table 2. Overview of the major differences between the BTS and DGP guidelines for LTOT

	British guideline (BTS)	German guideline (DGP)
1. Blood gas analysis technique	ABG	CBG
2. Criteria for initiation of LTOT in stable patients	2 ABG analyses at least 3 weeks apart	3 CBG analyses in a 4-week period
3. Initiation of LTOT in COPD patients after exacerbation	Discharge with oxygen only if patients cannot manage without oxygen, are breathless and with SpO ₂ ≤92% on room air, assessment for LTOT after 8 weeks	Direct, with later follow-up to re-evaluate indication
4. AOT for patients without classic indication criteria	Only during rehabilitation program	Indicated if resting PaO ₂ is ≤60 mm Hg, plus drop in PaO ₂ , or improvement with AOT in 6MWT; not indicated if resting PaO ₂ is >55 mm Hg without increasing dyspnoea during exercise
5. NOT	Only in severe CHF, used in combination with NIV in other diseases	No clear statement, sleep laboratory assessment recommended
6. Titration of flow rates	Based on SpO ₂ (followed by ABG)	Based on CBG
7. Follow-up	One visit at home within 4 weeks, following re-assessment initially after 3 months, and every 6–12 months thereafter	Every 3 months (outpatient setting)
8. Smoking patients	No contraindication	Conflicting information: LTOT is indicated after avoidance of all inhalative noxae; table states “no contraindications”

ABG, arterial blood gas; AOT, ambulatory oxygen therapy; BTS, British Thoracic Society; CBG, capillary blood gas; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DGP, German Respiratory Society (Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V.); LTOT, long-term oxygen therapy; NOT, nocturnal oxygen therapy; NIV, non-invasive ventilation; PaO₂, arterial partial pressure of oxygen; 6MWT, 6-minute walking test.

dard error of 6 mm Hg (0.8 kPa). Another trial from 2001 also demonstrated that using CBG alone would have resulted in 16% of the patients receiving LTOT inappropriately, whereas no patient would have been denied LTOT inappropriately [19].

In contrast to the DGP guideline, the BTS guideline also provides a section on the evidence of LTOT assessment using pulse oximetry and concludes that SpO₂ levels of ≤92% can be safely used for screening patients for LTOT assessment (≤94% with clinical evidence of peripheral oedema, polycythaemia or pulmonary hypertension), but that oximetry cannot be used alone for formal assessment without a blood gas analysis [7].

Authors' Suggestions. In view of the given arguments, we suggest that indicating LTOT based on CBG alone leads to a relevant number of unnecessary prescriptions. Interestingly, a recently published trial also showed that an ABG analysis is less painful than a CBG analysis if a very fine needle (26 G) is used, which further favours the use of ABG [20]. However, in general, an ABG analysis is not more painful than a CBG analysis, as frequently suggested. It should also be noted that LTOT is an expensive treatment option and has just been shown to provide no survival benefits in patients with moderate desaturations [12]. Apart from this important argument, LTOT may also have a bad influence on patients' psychosocial func-

tioning [8–10]. Therefore, it is fundamentally important not to oversupply patients with LTOT and to guarantee that only patients with severe hypoxaemia receive LTOT. In light of this evidence, we would recommend performing an ABG analysis for LTOT prescription, even if this approach may seem to be less practical under certain circumstances.

2. Timing of LTOT Initiation in Stable Patients

The DGP guideline recommends the initiation of LTOT if the above-mentioned indication criteria are met in a stable phase of the disease for about 4 weeks and if PaO₂ is measured for at least 3 times during this period.

The BTS guideline states that patients should undergo 2 blood gas analyses at least 3 weeks apart during a period of apparent clinical stability.

Critical Appraisal. There are no RCTs to date that have evaluated the best time points at which to perform blood gas analyses for estimating whether there is an indication for LTOT. The BTS recommendation is based on the MRC trial [4], while the German recommendation does not have a clearly stated scientific background. Of note, patients in the NOT trial were screened via 2 ABG analyses more than 1 week apart during a 3-week observation period [3].

Authors' Suggestions. In the authors' experience, both the BTS and DGP recommendations for the timing of blood gas analyses are not reliably fulfilled in the clinical setting. Instead, LTOT is frequently prescribed following hospitalisation, with no time period between hospital discharge and LTOT initiation. Therefore, this issue needs to be addressed by future guidelines and should also be more strictly followed in daily practice in order not to oversupply patients with LTOT. This seems to be especially important for COPD patients discharged following hospitalisation due to exacerbation (next issue).

3. LTOT in Post-Exacerbation COPD Patients

The BTS guideline promotes an assessment for LTOT in COPD patients after at least 8 weeks of stability since their last exacerbation. It is advised that post-exacerbation patients should not be discharged from hospital with LTOT, unless they cannot manage without oxygen, are breathless and SpO₂ is ≤92% during spontaneous breathing of room air.

According to the DGP guideline, initiation of LTOT is promoted after an exacerbation if the patient is still hypoxaemic, but re-checking the indication for LTOT is recommended after the exacerbation has been successfully treated. However, the extent of hypoxaemia and the time for re-evaluation are not specified.

Critical Appraisal. Studies have demonstrated that COPD patients who become hypoxaemic due to an exacerbation can show significant improvements in gas exchange after 8 weeks [19, 21–24]. However, re-evaluating the indication for LTOT after an acute exacerbation in COPD patients is not standard clinical practice in Germany. This means that some patients might stay on LTOT even if they no longer meet the indication criteria after stabilisation. In addition, whether rehabilitation plays a role in preventing patients from meeting LTOT prescription criteria still needs to be elucidated.

Authors' Suggestions. To avoid unnecessary LTOT usage, patients should be routinely re-evaluated 8 weeks after a COPD exacerbation.

4. Ambulatory Oxygen Therapy (AOT)

The DGP guideline recommends that AOT should be prescribed to LTOT patients with classic indication parameters and who are mobile outdoors. An exercise test should be performed to evaluate the necessary flow rate for supplemental oxygen during exercise. In addition, the DGP guideline also recommends AOT for patients who do not meet the classic indication criteria if PaO₂ is ≤60 mm Hg (≤8 kPa) at rest and drops by more than 5 mm Hg (0.7 kPa) to less than 55 mm Hg (7.3 kPa) during ergometric assessment, or if AOT substantially improves exercise performance. A sufficient oxygen flow rate (usually 5–6 L/min) should be used for testing. If the patient is only hypoxaemic during exercise without increased dyspnoea, and if the resting PaO₂ is >55 mm Hg (>7.3 kPa), AOT should not be prescribed. Finally, the DGP guideline also mentions that further research is required for a more conclusive recommendation for patients who primarily have exercise-induced hypoxaemia.

The BTS guideline states that AOT should not be routinely prescribed in patients who are not eligible for LTOT based on their classic indication criteria at rest. In general, AOT should only be offered to patients already on LTOT if they are mobile outdoors. It may also be offered to patients who otherwise cannot manage 15 h per day of oxygen use, or who are too symptomatic to leave their house without AOT. AOT should be offered during exercise to patients undergoing a pulmonary rehabilitation programme, or during an exercise programme if formal assessment demonstrates an improvement in exercise capacity. The guideline provides a protocol for AOT assessment, which is based on SpO₂ rather than on PaO₂ measurements during the 6MWT or the incremental and endurance shuttle walking test.

Critical Appraisal. Trials have shown that AOT acutely increases exercise tolerance in patients who are ineligible for LTOT but desaturate during exercise [25–29]. In contrast, long-term use of AOT is not associated with sustained benefits in clinical or outcome parameters in patients ineligible for LTOT [30–35]. This is in line with the aforementioned US trial, which reported no benefits of AOT on mortality or walking distance in the 6MWT in patients with moderate exercise-induced desaturation [12].

Authors' Suggestions. The current US trial shows that COPD patients with moderate desaturation during physical activity who do not meet the classic indication parameters should not receive AOT [12]. According to the BTS guideline, in patients who are ineligible for LTOT at rest, AOT should only be administered in the course of a rehabilitation programme, which seems feasible.

5. Nocturnal Oxygen Therapy

The BTS guideline does not recommend NOT for COPD patients who only have nocturnal hypoxaemia but do not meet the classic criteria for LTOT at rest. As an exception, NOT can be prescribed to severe heart failure patients who are under optimal medical treatment and show daytime symptoms related to sleep-disordered breathing (determined by first ruling out other causes of nocturnal desaturation, such as obstructive sleep apnoea and obesity hypoventilation syndrome). It should not be given to patients with cystic fibrosis, neuromuscular weakness and interstitial lung disease or to patients with obstructive sleep apnoea, obesity hypoventilation syndrome or overlap syndrome with exclusively nocturnal hypoxaemia if these patients do not fulfil the classic LTOT criteria. NOT can also be considered for hypoxaemic patients with cystic fibrosis, neuromuscular weakness as well as those with obstructive sleep apnoea, obesity hypoventilation syndrome or overlap syndrome who also receive long-term non-invasive ventilation (NIV) for the treatment of hypercapnic respiratory failure.

In contrast, there is no clear statement in the DGP guideline about NOT in patients who have nocturnal hypoxaemia only and do not meet the classic indication criteria for LTOT at rest. It is stated that hypoxaemia which is purely sleep related should be further assessed in a sleep laboratory.

Critical Appraisal. With regard to COPD patients who have sole nocturnal hypoxaemia, the BTS guideline discusses trials which showed that NOT alone does not lead to consistent improvements in pulmonary haemodynamics, survival or sleep quality [3, 6, 36–38]. The DGP

guideline states that NOT likely has no effect on morbidity, health-related quality of life (HRQL) and mortality [6, 38]. One trial showed that patients on NOT had a slight decrease in mean pulmonary artery pressure (Δ PAP = 3.7 mm Hg [0.49 kPa]), although there was no mortality benefit [38]. The other trial was larger and showed no differences in pulmonary haemodynamics and survival [6]. The BTS guideline additionally discusses trials reporting that NOT reduces symptomatic sleep-disordered breathing in heart failure patients [39–42]. Furthermore, exercise capacity (in the 6MWT) in symptomatic severe heart failure patients was shown to improve if patients received NOT for 4 weeks or 3 months, respectively [43, 44]. In contrast, improvements in HRQL, cognitive function and cardiac function – including ventricular arrhythmias – were not established [39, 40, 43, 45, 46]. In addition, there is no evidence for long-term benefits of NOT regarding survival and sleep quality in cystic fibrosis and interstitial lung disease patients [47–50]. In patients with neuromuscular weakness, NOT may even lead to a worsening of central sleep apnoea [51]. Finally, there are no trials on supplemental home oxygen therapy alone (without NIV) in obesity hypoventilation syndrome or overlap syndrome.

Authors' Suggestions. There is insufficient evidence to promote the use of NOT in patients with COPD, cystic fibrosis, interstitial lung disease, obstructive sleep apnoea, obesity hypoventilation syndrome, overlap syndrome or those with neuromuscular weakness who do not qualify for LTOT according to classic indication criteria. However, based on the evidence described above, the use of NOT in heart failure patients should be further addressed by future guidelines. It also remains completely unclear how to handle LTOT in patients receiving long-term NIV. Importantly, whether patients with persistent nocturnal hypoxaemia under optimal overnight NIV should receive additional oxygen, and the extent of hypoxaemia for which oxygen should be given, is scientifically ambiguous. This issue should be addressed by further investigations.

6. Titration of Oxygen Flow Rates

The DGP guideline provides the following instructions for the titration of oxygen flow rates: assessment should be performed after a resting time of ≥ 15 min. If PaO_2 is ≤ 55 mm Hg (≤ 7.3 kPa), 2 L O_2 /min should be administered via a nasal cannula. PaO_2 should be re-evaluated after ≥ 5 min and should be ≥ 60 mm Hg (≥ 8 kPa) or more than 10 mm Hg (1.33 kPa) higher than without supplemental oxygen. The guideline provides no infor-

mation on how nocturnal flow rates should be evaluated in patients on LTOT.

The BTS guideline recommends performing a SpO₂-based titration after the eligibility for LTOT at rest has been confirmed via ABG. The guideline advises starting with a flow rate of 1 L/min and increasing the flow rate by 1 L/min every 20 min until SpO₂ is >90%. Afterwards, an ABG test should confirm a PaO₂ ≥60 mm Hg (≥8 kPa). Of note, in non-hypercapnic patients, oxygen flow rates during sleep should always be increased by 1 L/min in the absence of any contraindications without further testing. Thus, nocturnal oxygen flow rates are typically 1 L/min higher than diurnal oxygen flow rates.

Critical Appraisal. The recommendation for titrating oxygen flow rates in the BTS guideline arises from the NOT study protocol but has been expanded by the SpO₂-titration [3]. Furthermore, the BTS guideline emphasises that different flow rates during sleep compared to exercise lead to survival benefits. In contrast, the German approach seems to arise from the MRC trial, although this is not mentioned in the guideline [4].

Authors' Suggestions. In clinical practice, there are some patients who only require 1 L of oxygen per minute. Therefore, a stepwise approach to oxygen titration with steps of 1 L/min is reasonable. In addition, titrating flow rates by SpO₂ is suggested to be sufficient if a final ABG test provides evidence for a sufficient increase in PaO₂ after oxygen titration. Future guidelines should also provide a recommendation on how to choose nocturnal oxygen flow rates, even though RCTs are lacking.

7. Follow-Up Visits

According to the DGP guideline, patients should be followed up every 3 months by their pulmonologist during a stable phase and in an outpatient setting. It advises documenting the clinical state of the patient as well as adverse events, correcting misconduct (i.e., smoking) and checking the hours of usage of LTOT at every visit. More frequent check-ups are recommended during unstable phases of the disease.

The BTS guideline precisely advises follow-up visits for patients on LTOT. Accordingly, patients should be reassessed 3 months after initiation of LTOT with tests that include blood gas analyses and re-evaluation of oxygen flow rates. Further follow-ups should be performed at 6–12 months or sooner if the patient's clinical condition changes. If AOT was started during an unstable phase (e.g., exacerbation), patients should be reviewed after 4–6 weeks to check if AOT is still indicated. Remarkably, even a visit at home by a specialist nurse or health-

care professional with experience in domiciliary oxygen therapy is advised within 4 weeks of the first prescription of LTOT. This provides an opportunity to uncover potential risks and further educate the patient, as well as to check compliance, smoking status, symptoms of hypercapnia and to measure SpO₂ on oxygen to ascertain proper oxygenation.

Critical Appraisal. The BTS guideline emphasises the importance of follow-up visits. A follow-up 3 months after starting LTOT can ensure that the flow rate is adequate and that LTOT is still required [3, 4]. It is remarkable that a home visit is recommended within 4 weeks after the first prescription of LTOT. This is based on studies showing that home follow-ups (either alone or in combination with hospital follow-ups) were more effective than hospital follow-ups and that a home visit with education improves compliance with LTOT [52–57]. The BTS guideline also provides a suggested protocol for the withdrawal of home oxygen therapy if the patient no longer requires LTOT or if the patient is non-compliant with LTOT use according to the guideline (i.e., usage <15 h/day, inconsistent usage of AOT). However, it can be assumed that the withdrawal of LTOT can be distressing for patients and challenging for the caregiver, thus requiring a significant amount of resources. In the case of non-compliance with LTOT, patients should be emphatically advised that this is a waste of National Health Service resources (BTS guideline).

Authors' Suggestions. Although the BTS approach to LTOT non-compliance is not evidence based, it is suggested to be reasonable; however, it remains unclear if such an approach would be feasible in other countries. Nevertheless, this issue should be addressed by future guidelines, with particular emphasis on the following 2 points: (1) avoiding unnecessary LTOT prescriptions and (2) guaranteeing optimal LTOT application in the home environment.

8. LTOT for Patients Who Still Smoke

The DGP guideline states that LTOT is indicated in cases of chronic hypoxaemia after adequate treatment of the underlying disease and avoidance of all inhalation noxae. On the other hand, it is stated that there are no contraindications for LTOT (Table 2).

In contrast, the BTS guideline does not explicitly name smoking as an exclusion criterion for the prescription of LTOT. However, the potential of a more limited clinical benefit in the case of ongoing smoking should be discussed with patients after detailed informed consent about the potential risks of burns/explosions (see below).

Critical Appraisal. The BTS guideline also addresses evidence on smoking patients on LTOT. All available data are derived from COPD patients [58]. There are no RCTs that have specifically evaluated actively smoking patients on LTOT, but the large outcome trials did not exclude active smokers. For example, in the MRC study ($n = 87$), 52% of the patients in the LTOT group were active smokers at the time of randomisation (44% by the end of the study). There were no adverse events attributed to smoking. A subgroup analysis of non-smokers versus smokers was not performed [4]. Interestingly, smoking is not specifically addressed in the DGP guideline, but there are conflicting statements regarding this issue. On the one hand, the requirement for avoiding all inhalative noxae prior to LTOT prescription might be interpreted as smoking serving as a contraindication for LTOT. However, since the handling of smoking patients is not specifically mentioned, the DGP guideline also does not mention the length of time for which patients need to have stopped smoking before the initiation of LTOT. In addition, it remains unclear whether LTOT should be withdrawn if patients start smoking again. This has important implications, given that smoking substantially increases the probability of burns and explosions if a cigarette is lit or smoked whilst using oxygen via a nasal cannula [59, 60]. It should also be noted that burns and explosions can also be triggered by other sources, such as spark occurrence or lighting a candle/stove [59]. On the other hand, the statement that there are no contraindications for this treatment might indicate that the prescription for LTOT in smoking patients is feasible.

Authors' Suggestions. The question of whether active smokers can either be prescribed or can continue on LTOT has at least 3 different aspects that need to be considered: (1) scientific evidence and clinically established benefits; (2) ethical issues; and (3) potential complications. The current authors suggest that LTOT should neither be wholly denied nor recommended to active smokers. Rather, the decision of whether or not to prescribe LTOT should be assessed on an individual basis by taking the 3 above-mentioned aspects into account. This, however, should be more precisely addressed by future guidelines on LTOT.

Conclusion

The DGP and the BTS guidelines are almost congruent in 2 major issues, namely, the classic indication criteria for LTOT in COPD patients at rest and the recommenda-

tion for the daytime duration of LTOT use. However, there are 8 major topics on which the guidelines differ considerably:

- Optimal technique for blood gas analysis sampling
- Timing of LTOT initiation in stable patients
- LTOT in COPD patients after exacerbation
- AOT
- NOT
- Titration of oxygen flow rates
- Follow-up visits
- LTOT for patients who still smoke

Importantly, the BTS guideline was published in 2015, while the DGP guideline was published in 2008. In addition, the 2 guidelines also differ with regard to literature search and evaluation. As a consequence, the BTS guideline includes more recently published research papers. The BTS guideline is also more detailed and specific with regard to most of the topics listed above. Furthermore, in contrast to the DGP guideline, many aspects of the BTS guideline are suggested to be reasonable according to the current literature, clinical experience and prescription practices. Finally, it needs to be clearly stated that there is no evidence-based international consensus on when and how to start LTOT in many diseases. Certainly, most of the existing evidence is derived from studies on COPD patients. However, the scientific background for LTOT in non-COPD patients is sparse. Therefore, the international research community is advised to agree on recommendations for LTOT in COPD and non-COPD patients.

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