Infants with chronic neonatal lung disease: recommendations for the use of home oxygen therapy.

**Position statement from the Thoracic Society of Australia and New Zealand.**


On behalf of the Paediatric Medical Respiratory Group and the Thoracic Society of Australia and New Zealand.

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Abstract

• Chronic neonatal lung disease [CNLD] is defined as a supplemental oxygen requirement beyond 36 weeks post-menstrual age, with more severely affected infants requiring oxygen beyond a term equivalent age.

• Low flow supplemental oxygen facilitates the discharge from hospital of infants with CNLD who are hypoxic in air.

• There is a lack of data on the most appropriate minimum mean target oxygen saturations. Reflecting a variety of clinical practices and infant co-morbidities [frequency of oxygen desaturation, presence of pulmonary hypertension, retinopathy of prematurity and adequacy of growth], the minimum mean target range for SpO2 during overnight oximetry should be 93% to 95%.

• Consideration of the effect of supplemental oxygen upon CO\textsubscript{2} retention is indicated before deciding upon an oxygen flow.

• The majority of infants with CNLD are not ready for discharge until their supplemental oxygen requirement is \leq 0.5 litres per minute delivered via nasal cannulae.

• The safety of short-term disconnection from supplemental oxygen should be assessed before discharge.

• Assessment of oxygenation while asleep with continuous overnight oximetry or polysomnography is recommended when weaning supplemental oxygen.

• Discontinuation of oxygen therapy is based upon clinical assessments and documentation of adequate oxygenation in room air.
Development of the document

This is a position paper developed by the working party (named authors, chaired by Dominic Fitzgerald) of the Australasian Paediatric Respiratory Group (APRG) consisting of all the paediatric respiratory physicians within the Thoracic Society of Australia and New Zealand [TSANZ]. The recommendations were developed after examining evidence from English language publications obtained by searching MEDLINE with the key words “bronchopulmonary dysplasia”, “chronic neonatal lung disease” and “home oxygen” (1966 to July 2007). A total of 62 articles were identified with 23 publications of relevance considered dating back to 1976. Levels of evidence[Levels I-IV] were derived from The National Health and Medical Research Council’s recommended guidelines [designated E1-E4] [Table 1]. The position paper was presented in a workshop to the annual meeting of the APRG. All co-authors provided additional comments from their respective centres. A revised manuscript was circulated to the entire group for final comment before submission to the Clinical Care and Resources subcommittee of the TSANZ.
Introduction

The development of home oxygen programmes for infants born prematurely who have chronic neonatal lung disease [CNLD] followed the successful introduction of such schemes for adults with chronic obstructive pulmonary disease (COPD). Home oxygen therapy was first introduced for adults with COPD in the 1960’s with continuous or nocturnal oxygen treatment showing benefit for mortality and quality of life [1,2].

Previous work has suggested that home oxygen therapy provides symptomatic relief of breathlessness in adults with chronic lung disease, although more recently considerable debate about the validity of this observation has emerged. As a result, in adults with chronic lung disease, long term home oxygen therapy is generally prescribed for the relief of breathlessness only in the presence of hypoxia, defined by a PaO2 < 55 mmHg [SpO2 ≤ 88%] [3]. In contrast, the assessment of home oxygen requirements for infants involves a combination of clinical assessment, oximetry and intermittent blood gas analyses. Consequently, tachypnoea, poor growth and mildly reduced oxygen saturation [SpO2 88%-93%] in an infant with CNLD would prompt consideration for supplemental oxygen therapy [4,5] [E3,E4].

The first significant publication on the utility of home oxygen for children was provided by Pinney & Cotton in 1976 who reported on the use of home oxygen in children with chronic neonatal lung disease [CNLD] allowing earlier discharge from hospital [4] [E3].

Over the last 30 years, centres all over the world have established small-scale home oxygen programmes based upon local experience. Home oxygen programmes are recognized as an effective way of reducing the length of initial hospitalization and reducing health care costs for young infants with CNLD [5] [E3]. In Australasia, the
process has evolved similarly, with neonatal intensive care units discharging small numbers of infants with CNLD home in supplemental oxygen each year. Recent figures data from the Australian and New Zealand Neonatal network reported that 214 babies were discharged on home oxygen in 2004 which represented 6.1% of survivors born < 32 weeks gestation [personal communication, Dr Robert Halliday].

**CNLD occurs predominantly as a consequence of preterm birth.**
The vast majority of the infants with CNLD are born prematurely [< 28 weeks gestation] of extremely low birth weight [<1000g] [6]. The aetiology of CNLD is multifactorial. It is believed to result from a combination of arrested pulmonary development occurring as a consequence of antenatal factors, preterm delivery coupled with ventilator induced barotrauma, volutrauma, oxygen toxicity and complications of persistent patent ductus arteriosus, lower respiratory tract infections and possibly undetermined genetic susceptibilities to chronic lung disease [6-9]. These factors typically contribute to prolonged ventilator dependency, oxygen requirement beyond a post-menstrual age of 36 weeks and abnormalities on the chest radiograph culminating in a diagnosis of CNLD.

**Can CNLD occur in a term infant?**
CNLD is a descriptive term and does not require a histopathological diagnosis [6]. The end result of high-pressure positive pressure ventilation and a high concentration of inspired oxygen used in term infants may also result in chronic oxygen requirements [10,11] . Conditions that may require home oxygen therapy in near term or term infants include structural lung disease, meconium aspiration syndrome with pulmonary hypertension or severe cyanotic congenital heart disease and respiratory compromise.
These cases are less common, but functionally there are similar considerations when titrating supplemental oxygen.

**CNLD phenotype and pathophysiology**

The predominant clinical findings in infants with CNLD are tachypnoea, wheeze, cough, chest wall retractions and paradoxical respirations [6,8-18]. The clinical features are a consequence of small airways disease [airflow obstruction, hyperplasia of bronchial epithelium, increased mucus production from glandular hyperplasia, decreased mucociliary clearance and bronchial hyper-reactivity] [6,8-11]. Additional complications may include dynamic obstruction from degrees of bronchomalacia and fixed obstruction from sub-glottic narrowing related to damage from endotracheal tube positioning and frequent suctioning [6,8]. Additionally, there is significant parenchymal and interstitial lung damage [6,8]. Other abnormalities include: increased dead space ventilation, decreased lung compliance, maldistribution of ventilation and increased work of breathing and ventilation-perfusion mismatching [6,8,13]. The specific findings in individual patients vary, reflecting the timing and degree of lung injury superimposed upon the stage of lung development [6,10,11].

**Definition of CNLD**

There is agreement within the neonatal literature, for the purposes of statistical reporting and research, that an infant [born at less than 32 weeks gestation] who has a supplemental oxygen requirement at the arbitrary age of 36 weeks post-menstrual age has CNLD [9,11,14-17]. However, most clinicians recognize a clinical spectrum of CNLD such that infants born preterm who are weaned from ventilation and supplemental
oxygen by 36 weeks have mild CNLD, those weaned by term have moderate CNLD and those requiring home oxygen therapy beyond a term equivalent age have severe CNLD [6].

There is some debate about the optimal target oxygen saturations at which to wean supplemental oxygen which will influence the diagnosis of CNLD. Nonetheless, a definition of CNLD based on whether supplemental oxygen is required fails to consider the underlying pathophysiology. Similarly, an infant can have an abnormal chest radiograph and be classified as not having CNLD if supplemental oxygen is not necessary. In clinical practice, there is no way to estimate reduced lung function in infants to predict the need for supplemental oxygen. In contrast, a persistent supplemental oxygen requirement in adult chronic lung disease generally, not withstanding other co-morbidities, may not occur until lung function is less than 35% of predicted values [3].

**Demographics of CNLD**
CNLD is the commonest form of chronic lung disease of infancy, occurring in up to 20% of infants with respiratory distress syndrome [RDS] [11] and approximately 40% to 50% of infants born < 28 weeks gestation [12]. The risk of CNLD increases with decreasing gestational age and birthweight [8,10]. CNLD has been reported in up to 85% of infants with birthweights between 501 and 750 grams, up to 45% in infants with birthweights 751-1000 g but decreasing to 5% in infants with birthweights > 1500g [4,8,10,11]. Thus, CNLD is seen predominantly in infants born prior to 28 weeks gestation with birthweights < 1000g [6,10-14].
Estimated size of the CNLD population in Australasia

Supplemental oxygen is used in the neonatal intensive care unit for over 95% of infants born prior to 28 weeks gestation in Australia and New Zealand [12]. The supplemental oxygen requirement declines such that approximately 75% require supplemental oxygen at 28 days of life and 50% at 36 weeks post-menstrual age. The median [inter-quartile range] duration of supplemental oxygen therapy in infants born below 28 weeks gestation is 53 days [12-95 days] [12]. The survival rate to discharge from hospital for infants born at 27 weeks gestation or later is at least 90% [12].

The proportion of preterm infants being discharged on home oxygen therapy varies widely between neonatal units and is largely dependent upon target oxygenation strategies [6,7,15,16]. Discharge strategies may be influenced by the health and wellbeing of the infant, degree of tachypnoea in relation to the ability to take oral feeds, the amount of supplemental oxygen requirement, social factors within the infant’s family and the location of the infant’s home [urban versus regional] together with the extent of outreach support [nursing, allied health and medical] [13, 14, 16-18].

Determination of Adequate Oxygenation

Intermittent oximetry is unreliable and should not be used as the basis for determining adequate oxygenation. Continuous oximetry provides better screening information but does not assess the impact of the SpO₂ upon the CO₂ profile [6]. More information can be determined from polysomnography, which may provide an objective physiologic measure of the impact of different oxygen levels upon sleep quality [6]. However, from
a practical viewpoint, the limited availability of polysomnography makes this challenging, despite evidence of improved sleep quality while on higher levels of oxygen [17,18].

As well as the threshold for provision of home oxygen, the indications for home oxygen therapy vary, but commonly include lung disease, pulmonary hypertension and retinopathy of prematurity [6,8,19,20]. It is unclear is whether recommendations based on evidence acquired from the Benefits Of Oxygen Saturation Targeting ["BOOST"] study of preterm infants[15] should be extrapolated to a term equivalent age and beyond. In particular, the available data is limited to growth and developmental assessment at 12 months corrected age rather than to cognitive outcome at school-age[6,14]. Thus, despite the existence of home oxygen programmes in Australia, New Zealand and overseas, there has been limited consensus on:

1. Indications for supplemental oxygen,
2. Target oxygen saturations,
3. Duration of supplemental oxygen therapy,
4. Logistics and ongoing care,
5. Indications for weaning supplemental oxygen,

Consequently, this paper will consider these shortcomings, drawing upon the limited evidence available together with the combined views of paediatric respiratory physicians experienced in the care of infants with chronic neonatal lung disease and suggest a practical approach to the provision of home oxygen therapy for infants with chronic neonatal lung disease [E4].
1. INDICATIONS FOR SUPPLEMENTAL OXYGEN THERAPY

The rationale for the prolonged use of supplemental oxygen in infants with CNLD.

The goal of home oxygen therapy is to prevent the effects of chronic hypoxaemia which include pulmonary vasoconstriction leading to pulmonary hypertension, bronchial constriction leading to airway obstruction and changes in growth of pulmonary, ocular and systemic vasculature [6,8,11]. Improved oxygenation may result in improved lung growth and repair [6,16]. In addition, there is evidence to support improved nutrition and somatic growth occurring in response to improved oxygenation [6,16,23]. However, the long-term implications of mild hypoxaemia, either persistent or intermittent, upon cognitive development have not been adequately studied in preterm infants with CNLD.

The duration of supplemental oxygen therapy varies primarily with the severity of lung injury and with the target oxygen saturations desired [14, 15].

It is important to ascertain the effect of supplemental oxygen upon carbon dioxide levels, particularly if the lung disease is severe. In contrast to adults with lung disease, where arterial blood gas analyses are obligatory for defining hypoxia, documentation in infants usually includes a combination of transcutaneous CO₂ monitoring with venous or capillary blood gas analyses. Arterial blood gas analyses are rarely used after the initial weeks in the neonatal intensive care unit because of the risks of trauma to the smaller calibre vessels, embolic phenomena and arterial occlusion. Furthermore, when crying results from holding the infant tightly in order to obtain the blood gas, the PaO₂ readings may give an inaccurate guide to the adequacy of oxygenation. Thus, continuous
oximetry and intermittent measures of venous or capillary pCO₂ remains the mainstay of titrating supplemental oxygen prior to hospital discharge [E4].

As a safety measure, some physicians will conduct an air challenge for infants immediately prior to discharge with supplemental oxygen [E4]. The purpose of this is to see the nadir of SpO₂ reached in room air should oxygen become disconnected [6]. Protocols for these air challenges vary between neonatal intensive care units, both in the duration of the challenge and the acceptable nadir of SpO₂. Once discharged, the tools used to assess readiness for withdrawal of supplemental oxygen include clinical assessment (work of breathing, growth) combined with continuous overnight oximetry (or polysomnography where available) [E4].

2. TARGET OXYGEN SATURATIONS

Evidence for higher and lower target oxygen saturations in CNLD

There are only two randomised controlled trials of supplemental oxygen for infants with CNLD to guide clinicians in setting target SpO₂. [15,20]. The BOOST trial randomised infants born < 30 weeks with CNLD to target oxygen saturation levels at 32 weeks post-menstrual age, either 91-94% or 95-98% [15]. Higher oxygen targets (95-98%) increased the median length of oxygen therapy [72 vs 56 days, p< 0.0001], the diagnosis of CNLD [64% vs 46%, p=0.0006] and home oxygen rates [30% vs 17%, p=0.004]. Higher oxygenation did not afford any benefits in terms of growth or neuro-developmental assessment up to 12 months corrected age [15]. However, there was no assessment of pulmonary hypertension nor was there assessment of the relative
proportions of adult versus foetal haemoglobin values and the relationship to oxygen carrying capacity and the oxygenation profiles of the infants.

The only advantage for those infants who received higher target levels of oxygenation in the BOOST trial [15] was in those with significant retinopathy of prematurity [ROP] who required less ablative retinal surgery. This may have occurred because the higher target oxygen zone minimised the frequency and extent of swings in oxygenation, which has been shown in an animal model to contribute to ROP [19]. This protective finding was consistent with the other trial of supplemental oxygen for premature infants, the “Supplemental therapeutic oxygen for pre-threshold retinopathy of prematurity” [STOP-ROP] trial [20]. In this study the effect of a SpO$_2$ range of 89%-94% was compared to a range of 96%-99% in preterm infants with pre-threshold ROP for a minimum of 2 weeks to see whether this influenced the progress of retinopathy. It did not, with the exception of a post-hoc analysis which suggested some benefit of higher oxygen for infants without plus disease [tortuous and dilated vessels in at least two quadrants of the posterior pole] with a 30% lower rate of progression. However, it was noted that the respiratory morbidity [rates of pneumonia or exacerbations of chronic neonatal lung disease] of these infants in the higher target oxygen range was 50% higher [8.5% vs 13.2%]. In addition, infants in the higher target oxygen band at 50 weeks post menstrual age [approx 8 months corrected age] were more likely to remain hospitalised [6.8% vs 12.7%], on oxygen [46.8% vs 37.0%] and on diuretics [35.8% vs 24.4%] [20]. Thus, the STOP-ROP trial [20] infants in higher supplemental oxygen had a greater incidence of chest infections, raising the possibility that even low flow nasal oxygen may be toxic to respiratory epithelium. Questions not addressed by any studies of infants...
with CNLD receiving supplemental oxygen at higher versus lower levels include the effects on cardiovascular development, pulmonary hypertension and more subtle neuro-developmental outcomes [eg learning difficulties at school-age].

Based on this information our recommendation is to target a minimum mean SpO₂ of 93-95% as measured by continuous overnight oximetry in infants with CNLD. Despite this minimum target SpO₂, some infants may have persistent tachypnoea, increased work of breathing, frequent oxygen desaturations in sleep, pulmonary hypertension and poor growth which may require a higher target SpO₂. [4-6,16-18,21] [E3,E4].

3. DURATION OF OXYGEN THERAPY

As infants are more vulnerable to hypoxaemia at times of feeding, sleeping and bathing [6,8,14-16], most clinicians would continue supplemental oxygen 24 hours a day until ready for weaning [E4]. However, if the infant is older [i.e. closer to 12 months corrected age] and more ambulant, restricting nasal catheter oxygen to sleep times may be practical [5] [E4]. This is not a common issue as the majority of infants with CNLD in Australia and New Zealand are weaned from supplemental oxygen by 6 months corrected age.

4. LOGISTICS AND ONGOING CARE

Delivery of supplemental oxygen

Hospital discharge is rarely considered in most parts of Australasia until the infant has an oxygen requirement of ≤ 0.5 L/min [14]. Supplemental oxygen is delivered via nasal cannulae attached to oxygen cylinders or oxygen concentrator for those receiving
oxygen usually at flow rates \( \leq 0.5 \text{ L/min} \), but can be increased up to 2 L/min if needed such as in the setting of a lower respiratory tract infection [E4]. At oxygen flows \( \leq 0.5\text{L/min} \) humidification is rarely required. However, delivery of oxygen by nasal cannula may lead to nasal inflammation and trauma, especially in the presence of an intercurrent viral upper respiratory tract infection [6,11,13]. Higher flow rates of supplemental oxygen are seldom sustainable at home because of the high number of portable oxygen cylinders required and thus the limitations upon travel. A fixed oxygen concentrator may be viewed as a cheaper [by the provider] and reliable alternative for delivering oxygen in the child’s bedroom [E4]. However, they are noisy and the direct cost to the family for the electricity required should be considered. Portable oxygen cylinders are needed in addition to allow outings from the house [8, 13, 14] and for power failures. State funded programmes generally meet the cost of supplemental oxygen therapy in Australia and New Zealand. Most programmes require a small financial contribution by families for consumables such as nasal catheters and disposable tubing. There is no funding for home oximeters.

**Team approach to the care of infants in a home oxygen programme**

Many infants with CNLD being discharged on home oxygen will have other complications of their preterm birth and will need ongoing supervision of a well-resourced multi-disciplinary team [14]. However, the availability of multi-disciplinary teams to support home oxygen programmes for infants with CNLD in Australasia is inconsistent, primarily due to funding constraints.
Monitoring of home oxygen therapy

Measuring “spot oximetry” in the outpatient setting has considerable limitations when estimating the adequacy of oxygenation [17, 18, 24] [E4]. Such times will not include when the infant is most vulnerable to hypoxia, specifically during bathing, feeding and rapid eye movement [REM] sleep [17].

When prolonged periods of oximetry recording are used, the averaging time [16-20 seconds] used in older oximeters [pre 2000] tends to smooth out results, underestimating true dips in oxygenation. This has been overcome with newer oximeters which have improved algorithms and software that use a shorter averaging time, typically less than 4 seconds. A continuous recording of SpO₂ values overnight in the home setting, preferably for periods of 6 hours or more, taken periodically affords more clinically useful information than spot checks and should be used for decision making in back-titration of supplemental oxygen flow [E4].

More detailed physiologic information on control of breathing, respiratory and heart rates, oximetry and transcutaneous CO₂ profiles and sleep architecture can be obtained through the use of overnight polysomnography [17,18,24]. Polysomnography is available through many paediatric teaching hospitals in Australasia, although there is variation in the access to this resource.

Fitness to fly: Is supplemental oxygen needed in an infant with recent oxygen dependency?
Air travel results in exposure to a mildly hypoxic environment where cabin pressure equivalent to 1500 to 2500 metres results in an equivalent FiO\(_2\) of approximately 15\% to 17\% at sea level [25]. This can be simulated in a respiratory laboratory with the infant and parent seated in a body plethysmograph where inspired oxygen is diluted with nitrogen to give a FiO\(_2\) of approximately 15\% while oximetry is measured continuously over a period of 20 minutes [25,26]. Nasal prong oxygen can be introduced (or titrated) to achieve satisfactory oxygen saturations. If such a test is not readily accessible and the infant is flying for longer than one hour, supplemental oxygen could be increased by 0.25 L/min or provided at 0.25 L/min for the flight if the infant has ceased supplemental oxygen in the last 3 months [E4].

5. INDICATIONS FOR WEANING SUPPLEMENTAL OXYGEN

When could oxygen therapy be discontinued?

There is no data on the best way to wean supplemental oxygen and hence there is a range of clinical practices [5, 6, 14]. The following is our recommendation for weaning an infant with CNLD from supplemental oxygen [E4]. The infant should remain in continuous (24 hour) supplemental oxygen and achieve adequate growth and have no evidence of pulmonary hypertension while maintaining a minimum mean target oxygen SpO\(_2\) of 93-95\% as estimated by continuous overnight oximetry or documented by polysomnography [E4]. Target oxygen saturation may be set higher for some infants. Once these criteria are met, the supplementary oxygen can be reduced and the assessment repeated. In most cases it is recommended to clinically review the infant on a monthly basis [E4].
6. LONG TERM OUTCOMES OF OXYGEN STRATEGIES APPLIED IN INFANCY

Future Directions: Australasian register of infants with CNLD on home oxygen

It is apparent that infants with CNLD who require home oxygen have increased healthcare utilisation and delayed developmental progress in the preschool years compared to infants with CNLD who did not require home oxygen [27-29]. There is a need to establish an Australasian register of infants with CNLD to document baseline practice and subsequently study proposed parameters for home oxygen therapy and outcome measures to school age. Ideally, this would incorporate the expertise of neonatologists, respiratory and general paediatricians and allied health with a co-operative approach in designing appropriate studies to assess short term and long terms outcomes.
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Legend

Table 1: NH&MRC level of evidence ratings [30]
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References


