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Management of infants with chronic lung disease of prematurity in Australasia

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Abstract Chronic lung disease is common in extremely preterm infants born in Australasia. In 2002, 53% of surviving infants born before 28 weeks' gestation remained either oxygen-dependent or on other respiratory support at 36 weeks' postmenstrual age.

In the first weeks of life oxygenation should be kept generally 'lower', although what is the most appropriate level remains uncertain. During the mid-phase of the neonatal course, functional oxygen saturation levels around 90—95% probably confer the best benefit/risk balance. The most appropriate target saturation range for infants on home oxygen also remains uncertain.

Definitive data to guide clinical practice is lacking regarding the use of postnatal corticosteroids, bronchodilators, and diuretics for either the treatment or prevention of chronic lung disease.

Home oxygen programmes are effective in avoiding prolonged hospitalisation for infants with chronic lung disease, but require the coordination of a large, multidisciplinary team.

1. Introduction

1.1. Definition of CLD

Chronic lung disease of prematurity (CLD) was originally defined as oxygen dependency and abnormal chest X-ray changes at 28 postnatal days [1] and was known as bronchopulmonary dysplasia (BPD). More recently, chronic lung disease has been defined as continued oxygen dependency and/or

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ventilatory support at 36 weeks postmenstrual age (pma) [2]. The pathophysiology of the disease in today's more extremely preterm infants differs from the original histopathological changes described by Northway in 1967. This so-called "new BPD" results in more distal lung injury, characterised by derangements in elastic fibre architecture, airway muscle thickening, alveolar hypoplasia and saccular wall fibrosis, but with minimal bronchial changes [3]. The histopathology of the "new" BPD indicates an interference with the normal anatomical development of the lung, which may prevent subsequent lung growth and development.

1.2. Risk factors for CLD

The major risk factor for prolonged oxygen need is extreme prematurity (gestational age at birth less than 28 completed weeks). [4] Additional risk factors for chronic lung disease include male sex [4,5], a long duration of assisted ventilation [6], and other antenatal risk factors such as intrauterine growth restriction [5], maternal *Ureaplasma urealyticum* [7], and other infections [8].

1.3. Prevention of CLD

The prevention of chronic lung disease remains elusive, ultimately depending on avoiding or delaying preterm birth whenever possible [9]. Strategies to prevent oxygen toxicity and barotrauma have included the use of treatments such as endogenous surfactant, high-frequency ventilation, and the early use of nasal CPAP [3], as well as nutritional supplementation [10], postnatal steroids, diuretics, and bronchodilators (see Section 3), respiratory syncytial virus prophylaxis [11], and avoiding excessive fluid intake [12]. Although many of these treatments have short-term benefits, none have been shown to significantly alter the natural history of the condition.

1.4. Incidence of CLD in Australasia

Chronic lung disease is common in extremely preterm infants born in Australasia (Australia and New Zealand). In 2002, there were 1112 infants born at less than 28 weeks and admitted to neonatal intensive care in Australia and New Zealand. At 28 days of age, 78% of the 874 survivors were receiving supplemental oxygen. At 36 weeks postmenstrual age (pma), 53% of the 849 survivors remained either on oxygen or on other respiratory support [13].

2. The use of oxygen in extremely preterm infants (less than 28 weeks' gestation)

2.1. During the early weeks of life (birth to 2 weeks)

The use of supplemental oxygen therapy is extremely common for infants born at less than 28 weeks' gestation in Australasia. In 2002, 96% of these infants received supplemental oxygen during their neonatal course, with the median duration of oxygen therapy for infants born between 24 and 27 weeks' gestation being 53 days (interquartile range: 12—95 days) [13].

Despite supplemental oxygen being probably the most common therapy given to preterm infants in the newborn period, uncertainty remains as to the most appropriate oxygenation target ranges, and the most appropriate forms of oxygen monitoring for these infants, in order to maximise benefits whilst minimising harms [14]. This uncertainty has led to wide practice variation in this area in Australasian neonatal units. A recent review of nationwide practice within the Australia New Zealand Neonatal Network (ANZNN) indicated that whilst several units now target very preterm infants at a functional oxygen saturation (SpO_2) range of 85—92% or an equivalent PaO_2 range of about 6.5—9.0 kPa during the first 2—4 weeks of life [15], others prefer a higher target range of around SpO_2 90—95% (or equivalent PaO_2 8.0—10.0 kPa or 60—80 mmHg) [16]. Generally, units in Australasia aim to avoid significant or prolonged hyperoxia during the first weeks of life for extremely preterm infants.

Whilst the association between unrestricted, high levels of oxygen has long been associated with the development of retinopathy of prematurity (ROP) [17], there have been no randomised trials conducted in the modern NICU era (and thus including infants born extremely preterm who undergo continuous oxygen monitoring) that have demonstrated whether the *potential* benefits of lower oxygen levels in the early neonatal period—such as less ROP, shorter duration of ventilation and oxygenation—occur at the expense of higher rates of important long-term outcomes such as death and major disability. Several recent observational studies have suggested the potential benefit of lower oxygen targeting in the early neonatal phase [18,19], but only a large, definitive randomised trial (or series of trials) will be able to rule out the possibility that adopting such a policy worldwide would not result in small, but significant changes to