# Management of infants with chronic lung disease of prematurity in Chile

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**Abstract** Despite advances in the prevention and management of respiratory distress syndrome, chronic lung disease of prematurity (CLD) remains a major cause of morbidity and mortality in preterm babies in Chile. Its incidence varies from 10% to 60% in different regions of Chile. Since 1998, the management of CLD after discharge from neonatal unit follows national guidelines. Target oxygen saturation is 85% to 91% in the first week of life, 91% to 94% from 1 to 2 weeks and over 95% after 44 weeks postconceptional age. National home oxygen program has improved outcome in infants with CLD. Other specific treatments are used with caution. Diuretics are used for pulmonary oedema. The adverse neurological outcome in infants treated with postnatal steroids restricts its use to infants who cannot be weaned from mechanical ventilation. Inhaled steroids and bronchodilators may reduce asthma-like symptoms in established CLD. Prevention of RSV infection in CLD babies is paramount. The preterm infant population has been maintained under surveillance nationally since 1998.

## 1. Introduction

Chile is a country of over 15 million, of which 25% are less than 15 years old. Forty percent of the population lives in the capital, Santiago. Its economic status is that of a developing country with an annual income of US Dollars $4937 per capita. The National Ministry of Health (MINSAL) in

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Chile has a long-standing tradition in health organisation. Thus the country exhibits good health development: overall mortality rate of 5.4 per 1000 inhabitants, hospital deliveries of 99.6%, paediatric immunization rates of 95%, tap water available to 99.3% of the population, sewer system to 91%, scholarships to 97.5% and life expectancy of 75.2 years [1,2]. Health is provided by a mixed public and private system. The public health system cares for 70% of the population and dictates health policies. Private health accounts for the 30% and is through an insurance system. Mortality from pneumonia in infants has decreased from 221.2 per 100,000 in 1990 to 38.8 per 100,000 infants in 2000 [3,4]. Infant mortality rate is less than 8 per 1000 live births and more than 50% occur in the neonatal period. Fifty percent is due to prematurity and most of the rest due to congenital malformations. Incidence of newborn born at less than 32 weeks of gestation was 0.9% in Chile in 2000. Survival varied from 8% in babies with less than 600 g at birth to 90% in babies with birth weight of between 1250 and 1500 g. Forty three percent of deaths occur during the first day of life. Late mortality, beyond 28 days, was 12% [5,6].

Collection of statistics of very low birth weight babies (VLBW) in our country has not been accurate because of lack of a national register. Since 1998 there has been a national working group led by neonatologists, with assistance of other paediatric specialists, to unify and provide common criteria for diagnosis and management of VLBW infants. The aim of the group was to improve coordination at different levels within the 28 Health Regional Areas in Chile in order to obtain information concerning the health status of VLBW babies at discharge from Neonatal Intensive Care Unit (NICU) and on their follow-up. Chronic lung disease of prematurity (CLD) or bronchopulmonary dysplasia (BPD) has been one area of focus. Special follow-up of preterm and CLD infants started in 1995 as a pilot program, focusing on babies born in the North Area of Santiago. This pilot scheme has evolved into a national program.

## 2. Incidence

The incidence of CLD in Chile varies geographically (Fig. 1). Changing epidemiology and definitions of the disease complicate analysis. In our country, as with others, the increased survival of VLBW can be attributed to the introduction and subsequent widespread use of antenatal steroids as well as the introduction of exogenous surfactant replacement therapy in 1998 [2,6]. Newer modes of mechanical ventilation that reduce barotrauma, improved nutritional interventions and, accurate and continuous monitoring of oxygen therapy were introduced. During 1995 to 1997, pre-surfactant era in the North Area of Santiago, the incidence of CLD/BPD was 16% using the more useful definition of oxygen requirement at 36 weeks postconceptional age, rather than at 28 days postnatal age, where a 21% incidence was found (Palomino MA, Morgues M, Valdes I, Vernal P. unpublished data). The national survey in 2000 of 1477 newborn less

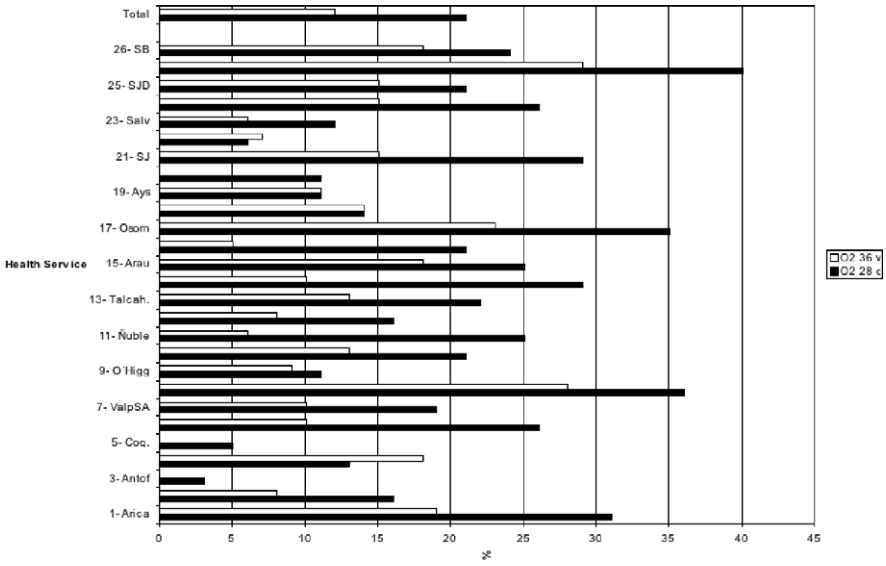


**Figure 1** Regional and national incidence of Chronic Lung Disease of Prematurity. Chile 2000.

**Table 1** Incidence of CLD at 28 days and 36 weeks postconceptional age and birth weight

| Birth weight (g) | <750 | 750—999 | 1000—1249 | 1250—1500 |
|---|---|---|---|---|
| BPD O2 36 weeks[a] | 47% | 34% | 15% | 7% |
| BPD O2 28 days | 69% | 50% | 28% | 10% |

Chile 2000.
[a] At risk of home oxygen.

than 32 weeks, with a working definition of BPD based on oxygen requirement beyond 28 days of age and at 36 weeks postconceptional age, showed an incidence varying from 10% to 40% in children less than 1500 g and 60% in less than 1000 g (Table 1).

## 3. Prevention and management of evolving and established CLD

As mentioned above, there is a widespread use of antenatal steroids in our country, stimulated by national guidelines [2,6]. The initial management of respiratory distress syndrome includes early surfactant replacement before 2 h in the extremely low birth weight infants (ELBW), because it has demonstrated an increase in survival and lower incidence of severe CLD. Continuous nasal positive airway pressure (nCPAP) is preferred and if mechanical ventilation is required, this must be with short inspiratory times, minimal inspiratory pressures, optimal positive end expiratory pressure (PEEP), minimal oxygen and permissive hypercapnia, because oxygen toxicity and barotrauma are considered to be major contributors to CLD. Precaution in prevention and early treatment of nosocomial infection are effected [6—9]. Many studies have demonstrated an association between patent ductus arteriosus (PDA) and CLD in preterm infants. Furthermore, late episodes of PDA in association with nosocomial infection may be important in the development of CLD in infants who initially have no or mild respiratory distress [8,9]. Thus, indomethacin is available at the 28 centres in our country since 2001, again through the national program. Its use has decreased the need for ductal ligation which is only performed in 5 referral centres [6].

Infants who have pulmonary insufficiency in early life may benefit from special nutritional management both for the prevention of and recovery from CLD. Infants with CLD are at great risk for delayed skeletal mineralization and osteopenia of prematurity [6,8,9]. Special milk formulas include vitamin A, calcium, phosphorus, unsaturated lipids, other antioxidants and elements like copper, zinc, selenium and manganese.

### 3.1. Discharge planning and outpatient management of CLD

The spectrum of CLD varies from minimal disease, with some signs of respiratory insufficiency to a more severe form that may require home oxygen. Discharging an infant with CLD to their home on oxygen is a complex process. It requires an interdisciplinary team, with clear discharge criteria and coordinated management [10]. Parent education with an outline of the comprehensive discharge teaching, home care and multi-specialty follow-up is provided. The aim is to avoid unnecessary visits to hospital and to improve outcomes. Since 1998, our management of the child with CLD after discharge from the NICU follows MINSAL guidelines based on the best evidence available [6].

### 3.2. The use of oxygen in extremely preterm infants

There is a potential injury associated with oxygen therapy in preterm babies, but it is known to be beneficial in management of RDS and in children with CLD. The goal of oxygen therapy in established CLD is to promote growth and therefore repair of the developing lung and to diminish pulmonary artery hypertension. There is controversy surrounding target saturations in CLD patients [11]. The STOP-ROP trial randomized 649 VLBW babies to 2 weeks of higher oxygen saturation (96—99%) versus lower saturation (89—94%). They found no difference in retinopathy progression, but a higher risk of exacerbations of CLD in the high saturation group [12]. A review of five units in England showed no difference in outcome regardless of target oxygen saturation levels, even in the unit where saturation was allowed to fall to 70% [13]. The BOOST trial randomized 358 babies at 32 weeks postconceptional age to standard (91—94%) and high (95—98%) oxygen saturation. They showed that targeting a higher oxygen saturation range in CLD babies dependent on supplemental oxygen conferred no significant benefit with respect to growth and development and resulted in an increased burden on health services [14]. In our experience, oxygen saturation level is maintained between 85% and 91% during the first 2

weeks, with the lower values in the first 4 days of life. Beyond 1—2 weeks postnatal age to 44 weeks postconceptional age, oxygen saturation is maintained between 91% and 94% due to incomplete retinal vascularization. After 44 weeks, beyond the age of oxygen-induced retinopathy, we recommend the provision of supplemental oxygen sufficient to achieve a saturation of 95% or more including sleeping and feeding.

The best way to assess oxygen requirements is with an oxygen saturation monitor. Continuous monitoring is performed weekly until the patient is ready to go home on oxygen. Criteria used for home oxygen therapy vary widely [13]. Home oxygen program in Chile started in the mid 1990s initially in non-CLD/BPD patients, adenovirus sequelae, in an effort to discharge patients home rather than to a chronic care facility. Initially, oxygen was provided by some hospitals thus was limited to their referral area. This system changed in 2003, when a National Home Oxygen program was started. The new program is funded by MINSAL and coordinated at each hospital level [2]. Oxygen is provided nationwide through a private company. They also instruct families on its use and do periodical home visits. For discharge home, preterm babies with CLD must be thriving with at least 2 kg weight and feeding orally by bottle or breast. Oxygen requirements need to be less than 0.5 l/min through a nasal cannula placed on the nostril and stable for the last 15 days. Delivering oxygen via a nasal cannula especially during feeding, sleeping and handling provides more consistent oxygenation. Oxygen saturation levels are maintained over 95% after 44 weeks postconceptional age. Multiple determinations are made in various states including rest, sleep, feeds, activity and in various positions. Continuous oximetry is becoming standard, and it must have an average over 95% saturation. Less than 10% of the time saturation under 93% and no episodes under 85% are allowed. Families should be willing and capable of looking after a child on oxygen. Social service assessment is done before the home oxygen program is instituted. Families must have financial support, educational level sufficient to understand written instructions and family support network. A suitable house for this purpose is one with a solid structure, with cement or wooden floor, enough space for the installation of oxygen cylinders and adequate basic service conditions (water, electricity and gas). A specialist nurse instructs parents in the use of equipment and does home visits with a social worker. Low flow regulators valve and a portable cylinder (300 l) are needed. Oxygen concentrators are used in patients with requirements more than 1 l/min and liquid oxygen is only provided for school age children who usually have non-CLD/BPD diseases. The first respiratory clinic visit is scheduled within 10 days of discharge. In the first visit, a cardiology evaluation and a chest X-ray is requested, and a pulse oximetry is performed awake and asleep. Parents are instructed on what to do in case of worsening respiratory status. They can attend the respiratory clinic without a previous appointment; beyond clinics hours they may visit either the primary care emergency clinic or the Hospital Emergency Room. Emergency ambulance transport is also available. The following visits are scheduled at least monthly during the first 12 months, according to the patient status. After 12 month follow-up, a 6 monthly appointment is given. During and after viral infections, children are closely monitored. The decision to begin weaning from oxygen is done based on clinical assessment and continuous pulse oximetry during visits. We try not to wean a child off oxygen during wintertime, since exacerbations due to viral infections are likely. Weaning is carried out gradually and stopped only when saturation is more than 95% during feeding, activity and sleeping. Prolonged use of nighttime oxygen is often necessary after daytime use has been discontinued. Infants on home oxygen are seen in a separate clinic in order to reduce exposure to other children who may be suffering from respiratory infections. Families are instructed that respiratory infections often result in the infant being administered supplemental oxygen once again.

### 3.3. Prevention of respiratory morbidity

Medical fragility persists in infants with BPD, placing additional stress on families. One of the aims of follow-up is to prevent readmission to hospital and death due to respiratory exacerbations with viruses. The more severe cases have very limited respiratory reserve. Education starts early in the NICU and continues at follow-up. Parents are strongly discouraged from smoking and in using non-contaminant heating. They are also advised in strict hand washing, avoidance of over-crowding and of day care facilities. Oxygen dependence at 28 days remained a useful definition predicting subsequent respiratory morbidity in our patients. In fact, in our experience in the North Area of Santiago, CLD babies born between 1995 and 2001 and discharged home without supplementary oxygen were more frequently readmitted to hospital due to lower respiratory

tract infections (LRI) than babies who were not (45% versus 34%). Thirteen percent of CLD patients died during the first 2 years of life, mainly due to LRI.

Immunizations are given according to the national vaccine program, including Triple, oral Polio and *Haemophilus influenzae* type B. Vaccines against influenza viruses are given every year to infants older than 6 month and their families. Every 2 or 3 years, an influenza epidemic occurs in late April for 6 weeks. The use of RSV monoclonal antibodies has been suggested in the MINSAL guidelines, to be given between May and September each year. Its use is currently limited to private hospitals as there is no national budget for it. RSV LRI occurs every year and accounts for more than 50% of hospitalizations during winter. The average length of the RSV epidemic is between 3.5 to 5.5 months. Two epidemic patterns of RSV infections have been described in our country every other year; one starts earlier and lasts 3 months and the other one starts later and lasts 5.5 months [15]. Admissions to hospital due to an RSV infection in our CLD patients born between 1995 and 2001 and followed for 2 years was 21% (Palomino MA, Morgues M. unpublished data). Based on the hypothetical use of palivizumab in this cohort of patients, we could have decreased hospitalization rate to 10% according to the results of the IMpact study [16]. CLD patients are also at risk of acquired nosocomial infections due to adenovirus that are more severe and fatal. Pneumococcal vaccines are recommended, but not always given, as it has not yet been included in a national program.

## 3.4. Nutrition

Nutritional support after hospital discharge should be assessed with a goal of promoting catch-up growth. Chile has a national program since 2003 that allows continuation of nutrient-enriched feeding formulas for at least 1 year corrected age in order to provide 120 to 170 Kcal/kg/day [2,5].

## 3.5. Gastroesophageal reflux

Infants with CLD are prone to gastroesophageal reflux, which, on occasion, may worsen an already compromised respiratory system by causing asymptomatic aspiration or triggering bronchospasm. Some medications, increased work of breathing and cough may also contribute. It should be suspected and treated aggressively. When diagnosed, medical management with H-2 receptor antagonists and prokinetic agents is often useful. When symptoms are life threatening or persistent, a fundoplication may be indicated [8].

## 3.6. The use of drugs on NICU and after discharge

### 3.6.1. Corticosteroids

Evidence has shown that corticosteroids administered systemically in the first weeks of life to infants at risk of CLD improve respiratory status. Administration of steroids within the first 96 h of life or between 7 and 14 days of age facilitates weaning from the ventilator, can decrease death or CLD and a later need for rescue steroids [17,18]. Steroids have been associated with an increased incidence of hyperglycemia, hypertension, gastrointestinal bleeding, intestinal perforation, decreased growth and nosocomial infection [17,18]. Treatment after 3 weeks of age facilitates extubation but this is associated with hypertension and poor growth [19]. Data suggest that early and moderate early treatment with steroids is associated with adverse neurological outcome and may result in decreased alveolar number. Cardiomyopathy and interventricular septal hypertrophy have also been described [17,18]. In view of the adverse side effects and lack of clear long-term benefit, routine use of early or moderately early oral corticosteroids is discouraged in our country. We would use steroids for weaning from mechanical ventilation, with parent informed consent as recommended by American Academy of Pediatric [20]. Inhaled steroids that started before 2 weeks of age and given for 4 weeks to ventilator-dependent preterm infants may reduce the need for mechanical ventilation and rescue systemic steroids, but do not reduce the incidence of CLD [9,21]. Inhaled steroids given for 1 to 4 weeks facilitate extubation in infants with CLD [21]. As the evidence for inhaled corticosteroids is not convincing and as it is difficult to know how much steroids is deposited in the lungs with inhaler devices particularly in ventilated infants, routine use of inhaled steroids is not recommended in our country. In established CLD, oral corticosteroids may be used during respiratory exacerbations to reduce asthma-like symptoms. There are few studies documenting that corticosteroids, given via a metered-dose inhalers (MDI) and spacer, can reduce symptoms, improve lung function and lessen the need for bronchodilator therapy. We start on a trial of small dose of inhaled budesonide or fluticasone if they have persistent wheezing, particularly with a family history of asthma.

### 3.7. Diuretics

These are often used to treat infants with CLD. Furosemide or hydrochlorothiazide and spironolactone have been shown to improve pulmonary function by increasing dynamic pulmonary compliance, increasing specific airway conductance and decreasing airway resistance. There is a short-term effect on respiratory mechanics due to direct and indirect action. Side effects of furosemide include hypercalciuria, and this has led to nephrocalcinosis. It is common practice to use oral hydroclorotiazide and spironolactone to decrease the adverse effects of furosemide. Its uses in our patients has diminished, because there is little demonstrated effect of its long-term use in infants with developing or established CLD with regard to survival, duration of ventilatory support or oxygen administration, potential complications and long-term outcome [22]. Furosemide is used when there is evidence of pulmonary edema. We do not use inhaled diuretics in our practice [23].

### 3.8. Bronchodilators

Bronchodilators have the potential effect of dilating small airways with muscle hypertrophy. They have demonstrated an improvement in pulmonary function by reducing bronchospasm, increasing dynamic compliance, increasing specific airway conductance, increasing forced vital capacity and decreasing in airway resistance. Anticholinergic agents (e.g., ipratroprium) may produce bronchodilation in this population, perhaps with synergism with salbutamol. Bronchodilator responsiveness, however, is patient-dependent. In ventilated infants regular bronchodilator therapy does not improve long-term outcome [8]. Bronchodilator therapy is restricted to those with obvious bronchospasm. The method of administration is an important consideration. There is a low deposition of bronchodilators regardless of whether this is given via a nebulizer or MDI and spacer with a mask. MDI has advantages: it has rapid onset and achieves similar levels of bronchodilation after 15 min to nebulizers [8,24]. At follow-up, in our practice, salbutamol is given if the child is wheezing and bronchodilation occurs after its use.

## 4. Complications

Children with CLD are developmentally vulnerable due to preterm birth, infections, poor growth and brain injury. Visual impairment or blindness due to retinopathy of prematurity (ROP) and hearing abnormalities is common. The incidence of ROP was 16%, with 25% requiring surgery and 4.2% developed blindness [5]. Regular neurological, ophthalmologic and hearing assessment are required for early detection and prompt rehabilitation. Respiratory status in CLD may also be complicated by other conditions such as gastroesophageal reflux, aspiration, cardiovascular abnormalities and immunodeficiencies. Upper airway abnormalities like subglottic stenosis must be ruled out if there is a weak cry, stridor or history of difficulty with extubation, or multiple/difficult intubations. Tracheomalacia is suspected when cyanosis is present with crying or persistent wheezing, particularly if it worsens with bronchodilators [8]. Direct visualization with flexible bronchoscopy may be necessary.

Follow-up of CLD babies for 2 years showed at least one episode of wheezing in 53% and chronic atelectasis in 22%. Atelectasis is a frequent complication that is decreased with physiotherapy and bronchoscopy in our patients. Airway obstruction and hyper-reactivity with response to bronchodilators and inhaled steroids has been the most common finding at 7 years old.

## 5. Key guidelines

- Prevention and management of RDS with a widespread use of antenatal steroids, early surfactant therapy, careful oxygen monitoring and optimal nutrition.
- Home oxygen program and prevention of RSV infection are highly important.
- Specific treatments like diuretics, steroids and bronchodilators must be used individually in each case with precaution.
- Early diagnosis and treatment of gastroesophageal reflux, aspiration, cardiovascular and upper airway abnormalities that may worsen the respiratory status.

## 6. Research directions

- Improvement of objective and accurately diagnostic criteria in Chile.
- Continuous surveillance of incidence and follow-up of CLD patients.
- Controlled trials of the best target ranges of oxygen saturation at different periods.

- Evaluation of the cost-benefit of palivizumab in CLD in Chile.
- Evaluation of therapies to assess health policies and clinical guidelines.

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