Management of Bronchopulmonary Dysplasia / Chronic lung disease

Introduction: Bronchopulmonary Dysplasia (BPD) is a chronic respiratory disease of preterms; caused by abnormal healing following lung injury and impaired lung growth and development. Despite advances in neonatal care, BPD remains a major morbidity, with increased risks of mortality, long-term pulmonary sequelae, and neurodevelopmental implications. The incidence of BPD in VLBW infants varies between 4-42% and is inversely proportional to the birth weight.

BPD is divided into old and new. 'Old' BPD occurred in more mature preterm infants with severe RDS requiring aggressive ventilatory support and high oxygen concentration with radiological and pathological changes of atelectasis, cystic changes, inflammation and fibrosis. 'New' BPD is encountered in extreme preterm infants exposed to antenatal steroids and surfactant with mild RDS but needing prolonged ventilation; pathology showing impaired alveolarisation, dysregulated angiogenesis but less fibrosis. Since its first description by Northway et al in 1967, the definition of BPD has evolved. Currently, the most widely used definition (Shennam’s since 1988) is ‘treatment with supplemental oxygen at 36 weeks post menstrual age’.

The pathophysiology of BPD is complex and multifactorial. The various factors involved in the development of BPD are lung immaturity, ventilator induced lung injury, oxygen toxicity, immature antioxidant defences, infection, inflammation and pulmonary oedema. Hence there is no single ‘magic-bullet’ to prevent or manage it. Several management strategies have been tried with the aim to prevent BPD or to mitigate the course of established condition. Though there is strong evidence to support the use of some therapies, many are used only based on short term benefits with limited or no evidence in their role in long term prevention or management of BPD.

Prevention and Management of BPD

Antenatal: Prevention of premature birth is the single most effective preventive measure. Good quality antenatal care with strategies to prevent preterm labour and appropriate use of tocolysis, erythromycin and prenatal corticosteroid in case of threatened preterm labour are vital.

Postnatal: A comprehensive approach based on ventilatory and non-ventilatory measures is required. 

Respiratory management:
- Follow current resuscitation/stabilisation guidelines for preterm infants and individualise initial respiratory management of RDS (invasive vs. non-invasive respiratory support), appropriate use of surfactant.
- Ventilatory goals should be: gentle ventilation, permissive hypercapnia and adequate oxygenation avoiding frequent and large swings in oxygenation (please refer to unit guideline for neonatal oxygen saturation).

Fluid and nutrition:
- Judicious fluid management, avoiding fluid overload is important.
- Nutritional management to promote optimum growth, with weekly monitoring of weight and head circumference. Aim for caloric intake of 120-150 kcal/kg/day. Growth failure in infants with BPD is predominantly due to under nutrition which exacerbates BPD by compromising lung growth and any potential repair of on-going lung injury.
- Manage gastro oesophageal reflux.

Caffeine: In a large multicentre RCT (CAP trial), Caffeine initiated within first 10 days of life in preterm VLBW infants, significantly reduced the rate of BPD (36% caffeine group vs. 47% placebo group). Infants on respiratory support (mechanical ventilation, CPAP) appear to derive more benefit from caffeine especially when started early within first 3 days of life. The neurodevelopmental benefit of Caffeine therapy on survival without disability seen at 18 months of age was attenuated at 5 years follow up. Though not statistically significant, at 5 years the combined outcome of death or disability was still lower in caffeine group and gross motor impairment was less severe.
- All preterm VLBW infants especially those on mechanical ventilation and non-invasive respiratory support should be started on Caffeine within first three days of life and continued until 34 to 36 weeks PMA unless contraindicated.
- Dose: Caffeine citrate 20 mg/kg loading followed by 5 to 10 mg/kg/day

Diuretics: Both loop diuretics (furosemide) and those acting on distal renal tubules (thiazide, spironolactone) aid lung fluid reabsorption and improve pulmonary mechanics. They have short term benefits; improved lung compliance, transient improvement in airway resistance and decreased oxygen requirement. However, these are not translated into any meaningful long term clinical benefits and there are risks of fluid and electrolyte disturbances, nephrocalcinosis, bone demineralisation, nephrotoxicity and ototoxicity.
- Diuretics may be considered; if there are signs of fluid overload; in ventilator dependent infants with developing or established BPD and non-ventilated BPD infants with high oxygen requirement
- Review on going requirement regularly and monitor electrolytes, renal function and bone profile.

PDA: Although there is an association between persistent PDA and BPD, neither its prophylactic treatment nor treatment of echocardiographically and/or clinically significant PDA has been shown to reduce BPD. Whether to treat a significant PDA in a ventilator dependent infant would be an individualised consultant decision.

Corticosteroids: Postnatal systemic corticosteroids modulate lung inflammation and have been used to prevent and treat BPD for the past 30 years. Steroids decrease recruitment of polymorphonuclear leucocytes to the lungs, reduce the production
of prostaglandins and other inflammatory mediators, decrease vascular permeability and pulmonary oedema and modulate repair by reducing fibrosis. Metanalysis of RCTs of systemic steroids (mainly Dex) have shown that though they facilitate extubation, decrease BPD and decrease the need for home oxygen, they do not reduce mortality and short term side effects like hyperglycaemia, hypertension, hypertrophic cardiomyopathy, growth failure, GI bleeding, intestinal perforation are increased. More worrying the risk of Cerebral Palsy and neurodevelopmental impairment is increased.

**Dexamethasone** has a long half-life (36-72 h), high glucocorticoid (anti-inflammatory) activity and insignificant mineralocorticoid activity. Adverse neurodevelopmental effects of Dexamethasone are due to its preferential binding to glucocorticoid receptors and ‘chemical adrenalectomy’ resulting in apoptosis in the hippocampus and degeneration of neurons. Quantitative MRI has shown significant reduction of cerebral cortical grey matter volume in preterms post Dex. Sulphite preservative used in some Dex preparations has a neurotoxic effect. Alternative regimes using low dose dexamethasone over shorter duration (DART, MiniDex) have been shown to facilitate extubation without short term adverse effects. However, BPD is not reduced and the effect on long term neurodevelopmental outcome has not been adequately studied.

**Hydrocortisone** has moderate anti-inflammatory activity, high mineralocorticoid activity and a shorter half-life (8-12 h). Animal studies suggest that hydrocortisone has no detrimental effect on the brain. In a retrospective study, hydrocortisone was as potent as dexamethasone in reducing oxygen requirement and ventilator dependency with less short term side effects. Retrospective cohort studies evaluating long term neurodevelopmental effects, found no difference in the incidence of CP, neurocognitive outcomes and neurostructural brain development on MRI at 8 years between hydrocortisone treated and controls. There is an on-going multicentre RCT (SToP-BPD) to determine the efficacy and safety of moderately early postnatal hydrocortisone administration in ventilator dependent preterm infants.

On balance, Hydrocortisone may be safer due to its preferential binding to mineralocorticoid receptors which may be protective against apoptosis, absence of neurotoxic sulphite preservative and modulation of immune response. Also, due to shorter half-life there is lower risk of accumulation with hydrocortisone.

- Systemic corticosteroids should be considered after the 2nd week of life in ventilator dependent preterm infants to facilitate extubation and to reduce risk/severity of BPD after other potentially less harmful strategies have been tried.
- The decision to treat will be on a case by case basis, usually after a discussion in grand round. The decision should be discussed clearly with the parents and documented in the notes.
- Based on current evidence hydrocortisone is our first line systemic corticosteroid to use in ventilator dependent infants.

**DOSE Hydrocortisone regime:** 5 mg/kg/day in four divided doses for 7 days followed by 3.75 mg/kg/day for 5 days, 2.5 mg/kg/day for 5 days and 1.25 mg/kg/day for 5 days; total dose of 72.5 mg/kg over 22 days.

- Monitor progress and side effects closely and aim to extubate as soon as possible.
- Only add in Dexamethasone as a “rescue”

**DOSE for Dexamethasone DART regime:** 150 mcg/kg/day in two divided doses for 3 days followed by 100 mcg/kg/day for 3 days, 50 mcg/kg/day for 2 days and 20 mcg/kg/day for 2 days; total dose of 0.89 mg/kg over 10 days

- There is no evidence to support inhaled corticosteroids.

**Multidisciplinary discharge planning**

- Clear feeding regime with input from SALT and dietetic teams if necessary
- Home oxygen: please refer to separate guidelines, parental health education and CPR training
- Immunisations: routine and influenza vaccination at appropriate age, RSV protection with Palivizumab
- Community support by neonatal outreach team and rapid access arrangement for emergencies
- Outpatient follow up with mandatory neurodevelopmental assessment

**References:**

6. Halliday HL, Ehrenkranz RA, Doyle LW. Late (>7 days) postnatal corticosteroids for chronic lung disease in preterm infants. *Cochrane Database of Systematic Reviews* 2009, Issue 1. Art. No.: CD001145

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