*Topic Expert Group:* **Medical care and clinical practice**

**Prevention of Bronchopulmonary Dysplasia (BPD)**

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## *Target group*
Very preterm and particularly extremely preterm infants, intrauterine growth restricted (IUGR) and small-for-gestational-age (SGA) infants, and parents

## *User group*
Healthcare professionals, neonatal units, hospitals, and health services

## *Statement of standard*
Bronchopulmonary Dysplasia (BPD) is best prevented using evidence-based strategies, including continuous distending pressure or non-invasive ventilation to maintain patency of airways and avoiding invasive mechanical ventilation and intermittent hypoxemia when possible, minimally invasive early administration of exogenous surfactant, aiming at volume targeted ventilation and early caffeine, administration of systemic steroids in infants still requiring mechanical ventilation during their 2nd postnatal week, and supporting parental involvement in preterm infant care starting shortly after birth.

## *Rationale*
Bronchopulmonary Dysplasia BPD results from the effects of non-physiologic stimuli (e.g. inflammation, ventilator induced lung injury, high supplemental oxygen levels) in an infant with underdeveloped lungs and defence mechanisms (e.g. anti-oxidant capacity). (1) Interventions that reduce inflammation (e.g. steroids) or any of these non-physiologic stimuli (e.g. mechanical ventilation) are likely to reduce BPD rates. Improving patient comfort through the early involvement of parents and/or family-centred care is also associated with a reduction in BPD rates. (2–4) Some of these interventions may additionally promote the survival of the target group; none decreases the chances of survival. (5)

BPD is defined as supplemental oxygen or ventilator requirement at 36 weeks post-menstrual age (PMA). According to one proposal these requirements last for ≥3 consecutive days to maintain arterial oxygen saturation in the 90-95% range plus the presence of persistent parenchymal lung disease. (6) There are proposals for defining the grade of BPD at 36 weeks PMA which differ in their predictive power. (7) BPD is a risk factor for later respiratory hospitalisation in infancy, compromised lung function in childhood, neurodevelopmental impairment, and a potential risk factor for chronic obstructive pulmonary disease in later life. (1,8) However, the risk of BPD has not decreased in population-based studies of extremely preterm infants (9), suggesting that more innovative research is needed to enhance the benefits.

## *Benefits*

### *Short-term benefits*
- Reduced risk of BPD by avoiding invasive mechanical ventilation (risk ratio (RR), 0.91; 95% Confidence Interval 0.84-0.99) (5)
- Reduced risk of BPD by use of minimally invasive surfactant administration (RR 0.75; 0.59-0.94) (10,11)

- Reduced risk of BPD by use of volume targeted ventilation (as opposed to pressure targeting) (RR 0.61; 0.46-0.82) (12)
- Reduced risk of BPD by starting caffeine on postnatal day one or two instead of later (RR 0.51; 0.40-0.64) (13,14)
- Reduced risk of BPD by administration of vitamin A intramuscularly for the first four postnatal weeks (RR 0.87; 0.77-0.98) (15)
- Reduced risk of BPD by involving parents early in their infants' care and/or by applying NIDCAP (OR 0.42; 0.18-0.95). (3,4)
- Reduced rate of death or BPD by administration of systemic steroids to respirator-dependent infants after the first postnatal week (RR 0.75; 0.67-0.84) without increasing the risks of cerebral palsy (16)
- Reduced risk of BPD by avoiding intermittent hypoxemia (IH) in extremely low gestational age infants, e.g. through closed-loop oxygen control (9,17)
- Reduced risk of BPD by feeding breast milk (particularly if given as raw milk) (18)

*Long-term benefits*

- Reduced adverse neurodevelopmental outcome if BPD can be prevented (8)
- Reduced risk of pulmonary arterial hypertension through reduced numbers BPD (consensus)
- Reduced risk of chronic obstructive lung disease in adulthood (consensus)

*Components of the standard*

| **Component** | **Grading of evidence** | **Indicator of meeting the standard** |
|---|---|---|
| For parents and family | | |
| 1. Parents are informed by healthcare professionals about Bronchopulmonary Dysplasia (BPD) and strategies to minimise its risk. (1) | A (High quality) | Patient information sheet |
| 2. Parents are closely involved in their baby's care, e.g. through family-integration or NIDCAP. (2–4) | A (Moderate quality) | Parent feedback |
| For healthcare professionals | | |
| 3. A unit guideline on the management and prevention of BPD is adhered to by all healthcare professionals, and includes the following advice: | A (Moderate quality) | Guideline |
| • Surfactant is administered via a thin intra-tracheal catheter if FiO2 is >0.30 or using INSURE (intubation surfactant and extubation). (19) Some extremely immature infants still require early intubation, ventilation and surfactant. | A (High quality) | Guideline |
| • Volume targeted ventilation (at 5-7 ml/kg) is used plus adequate PEEP level, if intubation cannot be avoided. (12) | A (High quality) | Guideline |

| | | |
|---|---|---|
| • Infants on n-CPAP are switched to synchronised nasal ventilation if respiratory distress visible while on CPAP. (20) | A (High quality) | Guideline |
| • Caffeine is administered from day 1-2 after birth (10 mg/kg loading, 5 mg/kg/d maintenance for caffeine base). (13,14) | A (High quality) | Guideline |
| • Vitamin A is considered (5000 IE i.m. three times/week for week 1-4 after birth). (15) | A (High quality) | Guideline |
| • If mechanical ventilation is still necessary during postnatal week 2, postnatal steroid use is considered (dexamethasone at the lowest effective dose possible). (21,22) | A (High quality) | Guideline |
| • In infants receiving additional inspired oxygen, avoiding IH is considered, e.g. through closed-loop oxygen control. (9,17) | A (Moderate quality) | Guideline |
| • Breast milk is the preferred nutrient. (18) | A (Moderate quality) | Guideline |
| • Efforts to reduce rates of infection, as a risk factor for BPD, are made. (23) | A (Moderate quality) | Guideline |
| 4. Training on the management and prevention of BPD is attended by all responsible healthcare professionals. | B (High quality) | Training documentation |
| For neonatal unit | | |
| 5. A unit guideline on prevention and management of BPD is available and regularly updated. | B (High quality) | Guideline |
| 6. A protocol is in place for how to involve parents early on in their baby's care. | A (Moderate quality) | Clinical records |
| For hospital | | |
| 7. Training on management and prevention of BPD is ensured. | B (High quality) | Training documentation |
| 8. Institutional BPD rates are monitored together with length of hospital stay and use of supplemental oxygen. | B (High quality) | Audit report |
| For health service | | |
| 9. A national guideline on management and prevention of BPD is available and regularly updated. | B (High quality) | Guideline |

*Where to go – further development of care*

| Further development | Grading of evidence |
|---|---|
| For parents and family | |
| N/A | |
| For healthcare professionals | |
| • Investigate in larger numbers whether using synchronised nasal ventilation rather than n-CPAP is the preferred mode of nasal respiratory support. (12) | A (Moderate quality) |
| • Evaluate alternative anti-inflammatory strategies, e.g. hydrocortisone, inhaled budesonide, or tracheal instillation of budesonide together with exogenous surfactant to generate more data on their long-term effectiveness and safety. (16,24,25) | A (High quality) |
| • Investigate the benefits of high frequency oscillatory ventilation for preventing BPD, particularly in infants with significant oxygen requirement and low lung compliance despite surfactant treatment and mechanical ventilation. (12) | A (Moderate quality) |
| • Investigate whether high-flow nasal cannula, compared to n-CPAP, can reduce the risk of developing BPD. (26,27) | A (Moderate quality) |
| • Investigate the role of eradicating Ureaplasma urealyticum shortly after birth. (28) | A (Moderate quality) |
| • Investigate oral Vitamin A administration as well as the role of other nutrients. (15,29) | A (High quality) |
| • Find the optimal drug and dose for postnatal steroid treatment. (15) | A (High quality) |
| • Investigate the potential of mesenchymal stem cells in repairing the injured immature lung. (30,31) | A (Moderate quality) |
| • Investigate the effect of various delivery-room practices and of early enteral feeding on the prevention of BPD. (22) | A (High quality) |
| • Investigate the role of inhaled nitric oxide (NO) in preventing BPD, and of vasodilators, particularly inhaled NO, in the early persistence of pulmonary hypertension, for possible prevention of BPD. (32) | A (Moderate quality) |
| • Investigate the role of serum markers (e.g. Clara cell secretory protein 16 (CC16), KL-6 and end-tidal carbon monoxide) and develop advanced prediction models for the early identification of infants at increased risk of BPD. (33) | A (Moderate quality) |
| • Investigate new management practices during very high-risk perinatal transition; among them antenatal N-acetylcysteine, prophylactic acetaminophen to extremely preterm infants for prevention of BPD. (34,35) | A (Moderate quality) |
| • Investigate towards improving the anti-inflammatory properties of surfactant drugs (36) and the use of surfactant as carrier of other drugs. | A (Moderate quality) |
| • Investigate methods for advancing the perinatal transition of high-risk extremely preterm infants. | A (Moderate quality) |
| For neonatal unit | |
| • Identify further synergies between family-oriented care and advanced neonatal management practices | A (Moderate quality) |
| For hospital | |
| • Encourage multidisciplinary collaboration between perinatal and neonatal teams, as well as neonatal and paediatric teams. | A (Moderate quality) |

For health service

- Promote research on medicines for very high-risk neonates through legislation similar to medicines for children. B (Moderate quality)

## *Getting started*

**Initial steps**

For parents and family

- Parents are verbally informed by healthcare professionals about BPD and strategies to minimise its risk. (1)
- Parents are educated by healthcare professionals about the particular need of a smoke-free environment.

For healthcare professionals

- Attend training on management and prevention of BPD.
- Apply exogenous surfactant via less/minimally invasive administration via a thin catheter, i.e. without using an endotracheal tube (LISA or MIST), or via the INSURE method (intubation, surfactant, extubation); under investigation: nebulisation, pharyngeal instillation and laryngeal mask airway (LMA) surfactant administration.
- Use nasal continuous positive airway pressure (n-CPAP) instead of intubation and mechanical ventilation. (37)
- Start caffeine on postnatal day 1 or 2 instead of later.

For neonatal unit

- Develop and implement a unit guideline on management and prevention of BPD.
- Develop information material about BPD for parents.

For hospital

- Support healthcare professionals to participate in training on management and prevention of BPD.

For health service

- Develop and implement a national guideline on management and prevention of BPD.

## *Source*


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