# Corticosteroids Therapy for Bronchopulmonary Dysplasia: Review Article

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**Abstract:**

Bronchopulmonary dysplasia (BPD) remains a major morbidity for infants born preterm. Postnatal corticosteroids might reduce the risk of developing BPD, or reduce its severity when it occurs, because of their powerful anti-inflammatory effects. However, corticosteroids have adverse effects, including on the developing brain. There have been numerous randomized clinical trials of corticosteroids given via various routes, of varying types, and started at different postnatal ages. There is some evidence that inhaled corticosteroids started earlier in the postnatal period may reduce BPD, but increase mortality. Inhaled corticosteroids started after the first week of age have little effect, but data are sparse. Systemic corticosteroids started in the first week after birth reduce BPD but increase cerebral palsy. Systemic corticosteroids started after the first week of age reduce both BPD and mortality, without evidence of long-term neurological harm.

**Keywords:** Corticosteroids, Bronchopulmonary Dysplasia, Intratracheal.

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## Introduction:

Corticosteroids are powerful anti-inflammatory agents and have been used to treat a wide range of inflammatory conditions**.** The initial enthusiasm following reports of efficacy to treat or prevent BPD in preterm newborns resulted in widespread rollout of systemic post- natal corticosteroids (PCS). However, over time important long-term complications of systemic PCS began to appear, particularly cerebral palsy, which led to warnings about their overuse **(1).**

## Post- natal corticosteroids (PCS):

### Pharmacological actions:

Synthetic corticosteroids mimic the action of endogenous corticosteroid hormones. Cortisol is the primary endogenous corticosteroid and has a wide range of actions including regulation of protein, carbohydrate, lipid, and nucleic acid metabolism, maintenance of cardiac and vascular responses to vasoconstrictors, regulation of extracellular water balance and water excretion, suppression of the inflammatory response, and modulation of central nervous system processing and behavior**.** The

commonest synthetic corticosteroids used in neonatology are dexamethasone, hydrocortisone, and more recently budesonide, which have different potencies and half-lives **(2).**

The two most widely used corticosteroids in newborns, dexamethasone and hydrocortisone, have different effects on the brain, in particular in the hippocampus. The hippocampus is rich in glucocorticoid and mineralocorticoid receptors**,** and is critical to learning, memory and spatial processing. Hydrocortisone binds to both glucocorticoid and mineralocorticoid receptors which is akin to endogenous cortisol. In contrast, dexamethasone predominantly binds to glucocorticoid receptors only, and consequent neuronal apoptosis in animal models has been described which may, in part, explain the associations between dexamethasone and adverse long-term neurodevelopment in preterm infants **(3, 4)**.

## History of Post- natal corticosteroids (PCS) in neonatology:

An appreciation of the history of PCS in neonatology is key to understanding why uncertainty exists today about their clinical application. PCS, in particular systemic dexamethasone, highlight several important lessons about evaluation of new therapies, and their adoption into widespread clinical practice. By the late 1980s, several trials had shown the efficacy of postnatal dexamethasone in facilitating extubating from mechanical ventilation in preterm infants **(5).**

This was followed by the widespread introduction of postnatal dexamethasone to treat or prevent BPD, without necessarily taking into account timing of commencement and the cumulative dosing that had been used in the randomized controlled trials (RCTs). At this time, there was a paucity of information on the long-term effects of PCS. Postnatal dexamethasone was introduced increasingly earlier (during the first week after birth) and in high doses, most commonly in a cumulative dose of approximately 8 mg/kg over 42 days **(6).** However, by the late 1990s, reports began to appear of potential long-term harms, such as an increased risk of cerebral palsy in children treated with dexamethasone **(7)**. Then followed widespread condemnation of the use of postnatal dexamethasone, leading to many influential bodies recommending against routine use of PCS to treat or prevent BPD in preterm newborns **(8).** Trials attempting to evaluate the efficacy of low dose dexamethasone (approximately one-tenth of the dose above, and for a shorter duration), starting after the first week of life in infants at high risk of developing BPD were not able to recruit adequately due to a lack of equipoise **(9).** Since then, a meta- regression by **Doyle et al. (10)** provided further insight into the pros and cons of dexamethasone to treat or prevent BPD.

In an assessment of the risk: benefit ratio of PCS for BPD, the combined outcome of death or cerebral palsy was related to the baseline risk of developing BPD. For infants with a high risk of developing BPD, postnatal corticosteroids reduced the chances of death or cerebral palsy. The converse was true for infants at low risk of developing BPD. An update of these data nine years later confirmed the relationships reported above (**10)**.

In the absence of RCTs after the swing against postnatal dexamethasone use in the early 2000s, data to assist clinical decision- making about PCS has come about from several cohort studies. These studies have reported similar rates of mortality, cerebral palsy or major neurosensory disability

despite lower rates of PCS use over time **(11).** As these are not RCTs, only associations can be inferred, rather than causation.

More RCTs using hydrocortisone **(5)**, which has theoretical advantages compared with dexamethasone for adverse effects on the brain, have shown promise. In addition, there is now renewed interest for inhaled and intratracheal corticosteroids to prevent or treat BPD **(12, 13).**

## Long-term benefits and risks of Post- natal corticosteroids (PCS):

The benefits and risks are considered according to type of corticosteroid, mode of administration, and also timing of use, i.e., 'early' (< 2 weeks after birth for inhaled corticosteroids, or < 8 days after birth for systemic corticosteroids) versus 'late' (≥7 days after birth for inhaled corticosteroids, or > 7 days after birth for systemic corticosteroids) administration, based on cut-offs reported in the Cochrane reviews on PCS **(14).**

## Inhaled corticosteroids:

### Early (< 2 weeks) inhaled corticosteroids:

Short-term benefits of early inhaled corticosteroids (administered within 2 weeks after birth) compared with placebo have been confirmed in the update of the Cochrane systematic review and meta-analyses, such as reduced BPD in survivors at 36 weeks (early inhaled corticosteroids 24% [131/544] vs placebo 31% [171/544], relative risk), and reduced death or BPD at 36 weeks in all randomized neonates (early inhaled corticosteroids 35% [227/649] vs placebo 40% [256/636],; 6 studies; 1285 participants). The results are dominated by the largest trial, the Neonatal European Study of Inhaled Steroids (NEuroSIS) trial **(15),** where 863 infants born 23–27 weeks' gestation who at < 12 h were receiving respiratory support were randomized to receive either inhaled budesonide or placebo. The intervention was commenced within 24 h of birth.

The primary outcome of death or BPD at 36 weeks was 40% [175/437] in the budesonide group compared with 46% [194/419] in the placebo group. The rate of BPD was lower, but there was a small increase in mortality in the budesonide group**(5)**.

Long-term outcome data are available from three published studies of early inhaled budesonide. The two smaller earlier trials did not report any differences in neurodevelopmental outcomes or hospitalizations between 18 months to three years of age. By two years' of age in the NEuroSIS trial, neurodevelopmental disability was similar between the groups (budesonide 48% vs placebo 51%)

Although there were no differences in the components of the composite outcome of death or neurodevelopmental disability between the groups at 18–22 months, there were more deaths in the budesonide arm (20% [82/419] vs 14% [58/400],. Interpretation of the results and how this translates to clinical practice is difficult. However, the increase in mortality in the absence of clear long-term benefit would argue against routine clinical use of inhaled budesonide **(16)**.

### Delayed (≥7 days after birth) inhaled corticosteroids:

The evidence for delayed (≥7 days) inhaled corticosteroids was updated in the Cochrane review. There were some short- term benefits of reduced risk of failure to extubate; 5 studies, 79 infants) and at the latest reported time point after treatment onset (6 studies, 90 infants). There was no difference in the individual or combined outcomes of death or BPD. None of the eight

included trials (total 232 infants) reported long-term outcomes beyond the neonatal period **(17).**

**Intratracheal corticosteroids:**

Several investigators reported that the evidence for intratracheal administration of budesonide-surfactant mixture **(18).** There were two trials by **Yeh et al. (12)** that randomized a total of 381 infants to budesonide-surfactant or surfactant alone if they met the inclusion criteria of < 1500 g birth weight, chest X-ray changes consistent with RDS, intubated and ventilated, < 4 h after birth and receiving ≥50% supplemental oxygen. The risk of BPD was lower in the budesonide-surfactant group vs surfactant, as was the combined outcome of death or BPD (budesonide-surfactant 39% vs surfactant only 65%) **(18)**.

Follow up to 30 months is underway but there are no substantial differences re- ported in neurodevelopmental outcomes to date. There are several other trials of intratracheal budesonide either actively recruiting or about to start using a different surfactant as the budesonide vehicle. The long-term neurodevelopmental outcomes from all trials will be informative when judging the risks versus benefits of intratracheal administration of PCS (**12).**

**Systemic corticosteroids**

The most data on the risks and benefits of PCS for prevention or treatment of BPD come from systemic administration, in particular, of dexamethasone. The systematic review and meta-analyses have been updated in two Cochrane reviews **(5).**

**Early (<8 days after birth) systemic corticosteroids:**

Of the 32 trials (21 dexamethasone, and 11 hydrocortisone) randomizing 4395 participants, there were significant beneficial short- term effects of early systemic PCS for respiratory outcomes. Benefits included lower rates of extubating failure, BPD (at 28 days and 36 weeks), death or BPD, patent ductus arteriosus and severe retinopathy of prematurity. There were also early adverse effects noted, such as gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure. Long-term concerns centered around the increased risk of cerebral palsy from the 13 trials that reported long-term neurosensory outcomes. For the combined outcome of death or cerebral palsy, there was little difference between treatment and placebo but it must be noted that heterogeneity between the studies was high **(5).**

It is important to note that all the studies reporting long-term outcomes in early childhood were not powered to find differences in neuro development, but were powered for primary out-comes in the neonatal period, e.g., BPD, or death or BPD. Weighing up the current evidence, there are benefits and harms in the short-term, but serious long-term harms associated with early use of systemic PCS, especially dexamethasone. It would be wise to use early systemic PCS judiciously to prevent BPD in clinical practice **(5).**

**Late (> 7 days after birth) systemic corticosteroids**

Data from 21 RCTs of 1424 participants also demonstrated short- term benefits similar to those of early systemic corticosteroids**.** All but one of the trials used dexamethasone. Compared with placebo, there was a reduction in mortality at 28 days, but not at later ages; reduction in extubating failure, BPD and the combined outcome of mortality or BPD (both at 28 days or 36 weeks); and the need

for late rescue dexamethasone. Harms associated with delayed use of PCS included a trend towards increased risks of infection and gastrointestinal bleeding. The risks of hyperglycemia, glycosuria, hypertension, and severe retinopathy of prematurity were increased. However, necrotizing enterocolitis and blindness were not increased**.** Long-term neurosensory outcomes were available from 16 studies (940 participants). There were no significant differences in reported long-term neurosensory outcomes between corticosteroid and control groups: cerebral palsy, death or cerebral palsy, neurosensory disability, and the combined outcome of death or major neurosensory disability.

In addition, outcomes in later childhood including respiratory health or function, blood pressure, or growth were similar between group**.** As with the early systemic corticosteroids trials, most of the studies reporting long-term outcomes were not powered to detect clinically important neurodevelopmental differences between the corticosteroid and control groups **(5).**

Another is a trial being run by the National Institutes of Child Health and Human Development in the USA of a 10-day tapering course of hydrocortisone for infants < 30 weeks who are still ventilated at age 14–28 days. The study is powered for its primary outcome of survival free of moderate-severe BPD, and survival without moderate-severe neurodevelopmental impairment at 18–22 months **(19).**

## Inhaled vs Systemic Corticosteroids:

There are limited data on the long-term outcomes of inhaled vs systemic corticosteroids. The open-labelled study of early corticosteroid treatment (OSECT) was a RCT of early vs late, and inhaled vs systemic corticosteroids. Participants were randomized into four groups with a factorial design which enabled two major comparisons, i.e., early (< 72 h) versus delayed treatment (> 15 days), and systemic dexamethasone versus inhaled budesonide. Of the 570 infants enrolled in the larger trial, (84%) who were born in the United Kingdom and Ireland were followed up to 7 years of age, 52 of whom received early corticosteroids.

There were no significant differences in cognitive, behavior, cerebral palsy, moderate/severe disability or the combined outcome of death or moderate/severe disability. Systolic or diastolic hypertension were similar between early inhaled and early systemic corticosteroid groups. There was, however, a lower risk of a diagnosis of asthma in the inhaled corticosteroid group compared with the systemic corticosteroid group **(14).**

When the delayed treatment groups (delayed budesonide, n = 38; delayed dexamethasone, n = 37) were compared, there were no significant differences in any of the neurodevelopmental or medical outcomes listed above. The findings from these subgroup analyses must be interpreted with caution as there is little information about how representative the groups were of the larger trial. Further replication is needed before firm conclusions can be drawn **(14).**

## Recommendations for use:

Despite improvements in perinatal respiratory care, very preterm neonates continue to develop BPD. Corticosteroids are effective in reducing BPD, but the concerns about harms need to temper their use. For the choice of corticosteroid, there is most evidence around the efficacy of systemic corticosteroids, more so with dexamethasone, in preventing or treating BPD**.** If given to infants at highest risk of BPD, postnatal dexamethasone

would potentially be "protective" against complications like death or cerebral palsy **(5).**

Some evidence points to the efficacy of systemic hydrocortisone **(5)**, although several studies reported stop-BPD RCT is discouraging, and to a lesser degree, inhaled budesonide in improving short-term respiratory outcomes, but data on long-term safety are lacking **(15, 19).**

In regard to timing of administration, it would be prudent to avoid giving systemic corticosteroids early, i.e., < 7 days after birth, as the risk of cerebral palsy is highest when given early **(5).** Hydrocortisone is potentially associated with fewer neurological side effects compared with dexamethasone if given "early" but there are few data on long- term neurodevelopment for "delayed" hydrocortisone therapy. With inhaled corticosteroids, given "early" or "delayed", the systematic re- views do not suggest any adverse neurodevelopmental outcomes at 2–3 years, but there are few benefits and more data are required. The early trials of intratracheal budesonide-surfactant show promise in reducing BPD, but firm recommendations about its clinical use will need to wait until the current RCTs are completed **(14).**

## Surfactant therapy in Bronchopulmonary dysplasia:

### Pulmonary surfactant:

Pulmonary surfactant is a complex mixture of phospholipids, primarily phosphatidylcholine, and the surfactant proteins SP-A, SP-B, SP-C and SP-D, which together define the physical structure, function and metabolism of surfactant in the alveolus (Fig. 1). Synthesis of surfactant lipids and proteins depends on the differentiation of AT2 cells, which occurs fairly late in gestation. Consequently, a lack of pulmonary surfactant as a result of incomplete differentiation of AT2 cells causes RDS in preterm infants. Assisted ventilation, continuous airway pressure and supplemental oxygen can initially support ventilation after birth. Furthermore, administration of exogenous pulmonary surfactant has greatly facilitated the transition to air breathing, decreasing the requirement for oxygen and assisted ventilation and thereby improving survival but secondarily increasing the number of infants at risk of BPD.

In conclusion, postnatal adaptation of the preterm lungs to breathing at birth is challenged by initial lung injury owing to surfactant deficiency, exposure to increased oxygen, mechanical ventilation, inadequate nutrition, infection and inflammation, which together provide considerable hurdles to normal pulmonary growth and repair and result in a loss of alveolar surface area that has lifelong consequences **(20).**

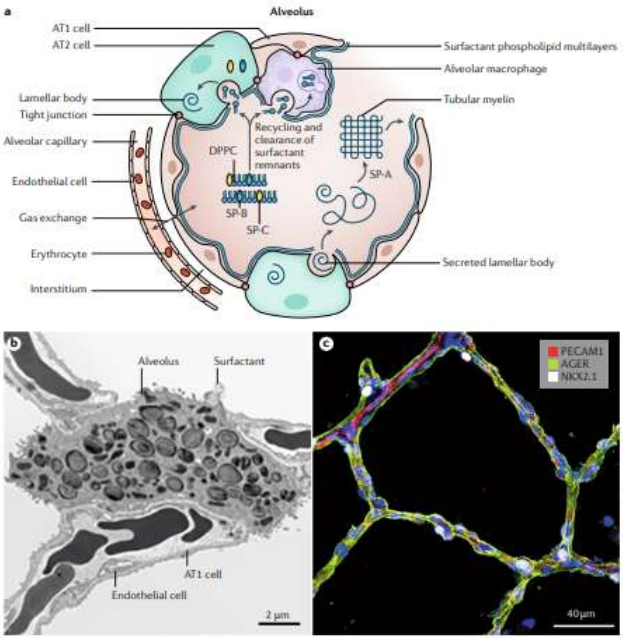


**Figure (1):** Structure of the alveolar gas exchange region **(21)**.

## Surfactant protein D therapy in Bronchopulmonary dysplasia:

Surfactant protein D (SP-D) is a collection protein that is found in the lungs as well as an other extra-pulmonary mucosa. In the fetal lung, SP-D has been detected at 10–20 weeks of age and the levels of pulmonary SP-D increase during gestation until term labor. SP-D accomplishes a critical role in the innate immune function of the lungs where it recognizes, opsonizes and promotes the phagocytosis and clearance of invading infectious pathogens and other noxious entities such as nano- or micro-particles accidentally inhaled from the environment**.** In addition, SP-D regulates inflammatory responses by modulating several inflammatory signaling pathways, such as the toll-like receptor 4 (TLR4) pathway. SP-D also influences pulmonary surfactant lipids homeostasis and ultrastructure with a relevant role in the newborn period by decreasing surfactant pool sizes**(22).**

SP-D is synthesized by alveolar type II pneumocytes as different oligomeric forms: trimers (minimal protein unit secreted by alveolar type II cells), hexamers, dodecamers and higher order oligomers that are variable in size (also called "fuzzy balls") **(23, 24)**.

## Recombinant Human Surfactant protein D targets BPD inflammation:

Multiple studies have demonstrated that inflammation generated as a result of all the different factors previously described is the central player in BPD pathogenesis, leading to lung injury. The application of rhSP-D as a therapy to prevent and treat BPD would reduce inflammation by down-regulating pro-inflammatory signaling pathways and mediators, and at the same time, it would specifically target some of the external factors, such as neonatal infection, that induce the pro-inflammatory responses. Inflammatory pathways mediated by toll-like receptor asTLR2 and TLR4 are activated in BPD by damage-associated molecular patterns (DAMPs) that are endogenous molecules released by damaged cells, or by pathogen-associated molecular patterns (PAMPs) when there is a pathogen- mediated infection associated **(25).**

## Surfactant protein D in premature infants:

The prematurity and underdevelopment of the lungs in preterm infants influence endogenous pulmonary SP-D concentrations and functionality. In ventilated preterm infants that received exogenous pulmonary surfactant treatment during their first week of life, low pulmonary SP-D concentrations at postnatal days 2 and 3 correlated with a worse outcome measured as supplemental oxy- gen needs at 28 postnatal days. Specifically, infants with low SP-D levels were still on supplemental oxygen therapy at postnatal day 28 while infants with higher SP-D levels were on room air. Lower pulmonary SP-D concentrations at postnatal day 1 have been observed in preterm infants that developed chronic pulmonary disease compared to those that did not **(26, 27).**

In addition to lower SP-D concentrations, SP-D function was evaluated by binding assays, showing low activity associated with a predominance of low oligomeric forms of SP-D(trimers, which have been associated with lower lectin activity of the protein) in the BALF from preterm infants that developed chronic lung disease **(26).**

**A Cochrane review**, which include also, the comparison between the effect of intratracheal administration of surfactant/budesonide with that of

surfactant alone on the incidence of death or BPD. A clinical trial was conducted in 265 very-low-birth-weight infants with severe respiratory distress syndrome who required mechanical ventilation and inspired oxygen (fraction of inspired oxygen, >50%) within 4 hours of birth were randomly assigned to one of two groups (131 intervention and 134 control). The intervention infants received surfactant (100 mg/kg) and budesonide (0.25 mg/kg), and the control infants received surfactant only (100 mg/kg), until each infant required inspired O2 at less than 30% or was extubated. Moreover, these study concluded that in very-low-birth-weight infants with severe respiratory distress syndrome, intratracheal administration of surfactant/budesonide compared with surfactant alone significantly decreased the incidence of BPD or death without immediate adverse effect **(12).**

**Pan et al. (28)** described that the clinical efficacy of intratracheal instillation of pulmonary surfactant (PS) combined with budesonide for preventing bronchopulmonary dysplasia (BPD) in very low birth weight (VLBW) infants. Thirty VLBW infants with gestational age <32 weeks who developed neonatal respiratory distress syndrome (NRDS) (grade III-IV) suffering from intrauterine infection were randomly assigned into a PS with budesonide group and a PS alone group.

The changes were compared between the two groups in arterial blood gas indexes, oxygenation index (OI), duration of mechanical ventilation, duration of oxygen supplementation, incidence of BPD, mortality rate at 36 weeks corrected gestational age and incidences of other complications except BPD. Compared with the PS alone group, the PS with budesonide group had a lower incidence of BPD, shorter duration of mechanical ventilation and oxygen supplementation. On the $2^{nd}$ to $6^{th}$ day after treatment, the PS with budesonide group had higher pH value of arterial blood gas and OI and lower carbon dioxide partial pressure compared with the PS alone group. There were no significant differences in the mortality rate at 36 weeks corrected gestational age and the incidences of other complications except BPD between the two groups. So, they concluded that the intratracheal instillation of PS combined with budesonide can effectively reduce the incidence of BPD in VLBW premature infants with severe NRDS.

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