Postnatal steroids in the treatment of bronchopulmonary dysplasia

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ABSTRACT

Bronchopulmonary dysplasia (BPD) is an adverse outcome of prematurity which affects approximately 40% of newborns with a gestational age (GA) <29 weeks. This review article describes the current consensus over the use of postnatal steroids in the treatment of BPD, providing an insight into historical clues, optimal patient selection, timing of the therapy, alternative routes of administration, and therapeutic strategies.

Keywords: neonates, steroids, bronchopulmonary dysplasia

List of abbreviations (in alphabetical order):

BPD — bronchopulmonary dysplasia
CNS — central nervous system
CP — cerebral palsy
FiO₂ — inspired oxygen fraction
GA — gestational age
GI — gastrointestinal
MRI — magnetic resonance imaging
MV — mechanical ventilation
PDA — patent ductus arteriosus
RCT — randomized controlled trial
RDS — respiratory distress syndrome

INTRODUCTION

Bronchopulmonary dysplasia (BPD) is an adverse outcome of prematurity that affects approximately 40% of newborns with a gestational age (GA) <29 weeks [1]. BPD involves a permanent impairment of respiratory function and represents a major risk factor for mortality and neurodevelopmental morbidity. Exposure to pro-inflammatory stimuli, in utero and after birth, contributes to the physiopathology of BPD. It has been observed, in fact, that the recruitment of inflammatory cells in the lung already begins during gestation in the setting of clinical or histological chorioamnionitis. After birth, mechanical ventilation (MV), exposure to oxygen, sepsis, and other intercurrent acute pathologies can support the inflammatory process which, by favoring the recruitment of pro-inflammatory mediators and inflammatory cells at the level of immature lung tissue, can result in necrosis, fibrosis, inappropriate septation, simplification of the alveoli and dysregulation of microvascular growth, which represent the characteristic aspects of evolving BPD [2]. Postnatal steroids, due to their strong anti-inflammatory action, are used to prevent or reduce the severity of BPD.

Historical notes on the use of postnatal steroids in neonatal intensive care

In the 1990s, postnatal steroids were widely used, and approximately 80% of preterm infants weighing <750 g were treated with dexamethasone. Subsequent follow-up studies, however, highlighted a correlation between unrestrained postnatal steroid administration and an increased incidence of adverse neurobehavioral outcomes [3-5], to the point that their use to
prevent or treat BPD became contraindicated around the year 2006. As expected, this limitation led to a significant increase in the incidence of the disease [7] in the following decade. Furthermore, data in the literature progressively highlighted a countervariant: systematic reviews of randomized trials (RCTs) demonstrated how postnatal steroids reduced, rather than increased, the incidence of cerebral palsy (CP) when administered to preterm infants at high risk of developing BPD [8]. These findings forced the scientific world to rethink the indications for the use of postnatal steroids [9]. To date, with almost a hundred RCTs on the prevention and treatment of BPD, postnatal steroids are among the most studied drugs in neonatology. However, clear answers are still lacking [10] to questions such as which newborns to treat, what the optimal timing is for starting therapy, what the advantages are of alternative administration routes to the systemic, and what the best therapeutic scheme is.

### Patient selection

All endogenous and synthetic steroids perform glucocorticoid and mineralocorticoid action in different combinations. Glucocorticoid action reduces inflammation, has an immunosuppressive effect, influences the metabolism of some nutrients, and optimizes the stress response. Mineralocorticoid action promotes renal absorption of sodium and excretion of potassium, the passive reabsorption of water, increased intravascular volume, and increased blood pressure [9]. Corticosteroids decrease lung inflammation through genomic and nongenomic actions [9-11]. Nongenomic activities include stabilizing cellular membranes and inhibiting phospholipase A2 and cyclooxygenase expression. Genomic modifications decrease lymphocyte production and pulmonary sequestration, suppress proinflammatory cytokines, and increase expression of anti-inflammatory cytokines and their membrane receptors [11]. At the brain level, glucocorticoid receptors are widely expressed in glia and at the level of neurons of the cerebrum and cerebellum. In contrast, mineralocorticoid receptors are found mainly at the level of the hippocampus and in limbic structures. The activation of glucocorticoid receptors appears to suppress synaptic plasticity and inhibit neuronal development, while the activation of mineralocorticoids promotes plasticity and neuronal survival [11]. The synthetic steroid hormones most used in neonatology are hydrocortisone and dexamethasone, which have a predominantly glucocorticoid action. Hydrocortisone is a short-acting (8-12 hours) steroid with mineralocorticoid activity at supraphysiological doses, while dexamethasone is a long-acting steroid (>36 hours), which has a power of action 25 times greater than hydrocortisone. Dexamethasone binds preferentially to glucocorticoid receptors in the central nervous system (CNS), while hydrocortisone preferentially activates mineralocorticoid receptors [11]. A recent literature review aimed at evaluating the correlation between systemic postnatal steroid and cerebral anomalies in premature infants using magnetic resonance imaging (MRI) reported an association between the use of dexamethasone and reduction of cerebral and cerebellar volume, while the use of hydrocortisone is often, but not always, associated with the absence of structural variations [12]. These findings discourage the routine use of postnatal corticosteroids. In choosing which infants to treat, clinicians are helped by studies that demonstrate how the effect of postnatal steroids on neurobehavioral development is modified based on the individual infant’s risk of developing BPD. One meta-regression of data from 20 RCTs reported how the use of postnatal steroids increased the risk of PC if these were used in preterm infants who have a risk of developing BPD <35%, while the risk of CP is reduced when postnatal steroids are administered to infants who have a risk of developing BPD >65% [8]. This association is also confirmed by a more recent meta-analysis, which considers the most current therapy schemes [13]. It remains quite difficult for neonatologists to predict the risk of BPD accurately. Possible tools include the trend of inspired oxygen fraction (FiO₂) in the first 2 weeks of life [14], the National Institute of Child Health and Human Development (NICHD) Neonatal BPD outcome estimator (https://neonatal.rti.org/index.cfm), lung ultrasound [15,16], and artificial intelligence [17].

### Timing of the therapy

Timing for steroid therapy includes an early approach (<7 days) to prevent BPD and a late approach, between 7 days and 36 weeks of postmenstrual age (PMA), to treat evolving BPD.

#### Early Systemic Corticosteroids (<7 days)

- **A 2021 Cochrane review, which included 33 RCTs published between 1972 and 2016 on 4,395 newborns at high risk of developing BPD, 22 of which were on dexamethasone and 11 on hydrocortisone, both administered within the first 6 days of life, showed that early dexamethasone significantly reduces the risk of BPD at 36 weeks and also the combined outcome of death or BPD, but significantly increases the risk of adverse events such as gastrointestinal (GI) perforation, CP and the combined outcome of death or CP.**

By contrast, hydrocortisone is less effective in reducing the incidence of BPD at 36 weeks and increases the risk of GI perforation more, especially when administered in association with cyclo-oxygenase inhibitors for closure of a patent ductus arteriosus (PDA), but significantly reduces mortality without being associated with adverse neurobehavioral outcomes (Table 1) [18]. A meta-analysis of RCTs seems to indicate that hydrocortisone is particularly effective in reducing the risk of the combined outcome of death or BPD in premature infants weighing <1000g and exposed to chorioamnionitis [19].
Late Systemic Corticosteroids (7 days – 36 weeks)

A 2021 Cochrane review, which included 23 RCTs published between 1985 and 2019 on 1,817 newborns with evolving BPD, 21 of which were on dexamethasone and 2 on hydrocortisone, both administered between 7 days of life and 36 weeks of PMA, showed that dexamethasone administered starting from the 7th day of life significantly reduces the risk of BPD at 36 weeks and of the combined outcome of death or BPD without increasing the risk of adverse events such as PC or the combined outcome of death or PC. By contrast, hydrocortisone was not shown to be effective in treating evolving BPD (Table 1) [20]. The US Stop BPD trial [21] subsequently confirmed the data on the poor effectiveness of late hydrocortisone. Finally, a retrospective cohort study on a population of 1,472 newborns of GA <30 weeks independently associated a dosage of hydrocortisone >2mg/kg/day in the first 14 days of life with an increase in overall mortality [22].

Alternative routes of administration

Inhaled steroids – The administration of steroids via inhalation is usually perceived as more advantageous than the systemic route, as the drug is delivered directly to the site of action, the dose required for the therapeutic effect is lower, the onset of action is more rapid and systemic bioavailability is reduced, as are side effects. The inhaled steroids used in neonatology include budesonide, beclomethasone, dexamethasone, fluticasone, and flunisolide. The NEUROSIS trial, published in 2015, included 863 premature infants of 23-27 weeks GA at high risk of developing BPD. The study showed how the use of aerosolized budesonide, starting from the first 24 hours of life and continued for the entire duration of ventilatory support or up to 32 weeks postmenstrual age (PMA), can reduce the combined outcome of death or BPD at 36 weeks of PMA compared to placebo; however, it also showed an increased risk of mortality, calculated at between 18 and 22 months of corrected age (Table 1) [23,24]. Two Cochrane reviews subsequently published in 2017 and 2022 compared both early inhaled steroids (within the first 14 days of life) [25] and late inhaled steroids (>7 days of life) [26] with placebo. The first article showed a slight reduction in both the incidence of BPD and the combined outcome of death or BPD at 36 weeks of PMA, while the second did not show any significant difference in primary outcomes. Finally, a Cochrane review published in 2020, which

### Table 1. Effect of postnatal corticosteroid therapy (adapted from: Jensen EA, Watterberg KL. Postnatal Corticosteroids to Prevent Bronchopulmonary Dysplasia. Neoreviews. 2023 Nov 1;24(11):e691-e703)

<table>
<thead>
<tr>
<th>Drug, Route and Timing of Initiation</th>
<th>Death or BPD at 36 Weeks’ PMA</th>
<th>BPD at 36 Weeks’ PMA</th>
<th>Death at the Last Reported Age</th>
<th>Death or Cerebral Palsy</th>
<th>Cerebral Palsy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Systemic</strong></td>
<td></td>
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<tr>
<td>&lt;7 days of age (reference 18)</td>
<td></td>
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<tr>
<td>Dexamethasone</td>
<td>0.88 (0.81-0.95)</td>
<td>0.72 (0.63-0.82)</td>
<td>1.02 (0.90-1.16)</td>
<td>1.18 (1.01-1.37)</td>
<td>1.85 (1.31-2.61)</td>
</tr>
<tr>
<td></td>
<td>17 trials, n=2791</td>
<td>15 trials, n=1948</td>
<td>20 trials, n=2940</td>
<td>7 trials, n=921</td>
<td>7 trials, n=587</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>0.90 (0.82-0.99)</td>
<td>0.89 (0.78-1.02)</td>
<td>0.80 (0.65-0.99)</td>
<td>0.86 (0.71-1.05)</td>
<td>1.01 (0.65-1.58)</td>
</tr>
<tr>
<td></td>
<td>9 trials, n=1376</td>
<td>9 trials, n=1145</td>
<td>11 trials, n=1433</td>
<td>6 trials, n=1052</td>
<td>6 trials, n=742</td>
</tr>
<tr>
<td>≥7 days of age (references 20,21)</td>
<td></td>
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<tr>
<td>Dexamethasone</td>
<td>0.75 (0.67-0.84)</td>
<td>0.80 (0.69-0.93)</td>
<td>0.85 (0.66-1.11)</td>
<td>0.95 (0.77-1.16)</td>
<td>1.14 (0.75-1.74)</td>
</tr>
<tr>
<td></td>
<td>12 trials, n=553</td>
<td>7 trials, n=278</td>
<td>19 trials, n=993</td>
<td>15 trials, n=855</td>
<td>15 trials, n=591</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>0.97 (0.92-1.02)</td>
<td>0.98 (0.92-1.04)</td>
<td>0.83 (0.64-1.06)</td>
<td>0.95 (0.75-1.19)</td>
<td>1.25 (0.85-1.83)</td>
</tr>
<tr>
<td></td>
<td>3 trials, n=1235</td>
<td>3 trials, n=1099</td>
<td>3 trials, n=1235</td>
<td>3 trials, n=1184</td>
<td>3 trials, n=951</td>
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<tr>
<td><strong>Inhaled</strong></td>
<td></td>
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<tr>
<td>≤24 hours of age (references 23,24)</td>
<td></td>
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<tr>
<td>Budesonide</td>
<td>0.86 (0.75-1.00)</td>
<td>0.74 (0.60-0.91)</td>
<td>1.37 (1.01-1.86)</td>
<td>Not reported</td>
<td>1.18 (0.67-2.07)</td>
</tr>
<tr>
<td></td>
<td>1 trial, n=865</td>
<td>1 trial, n=726</td>
<td>1 trial, n=813</td>
<td></td>
<td>1 trial, n=670</td>
</tr>
<tr>
<td>≤14 days of age (references 10,25)</td>
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<tr>
<td>Variable</td>
<td>0.86 (0.75-0.99)</td>
<td>0.76 (0.62-0.92)</td>
<td>1.36 (1.02-1.81)</td>
<td>1.26 (1.00-1.58)</td>
<td>1.05 (0.67-1.65)</td>
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<tr>
<td></td>
<td>6 trials, n=1285</td>
<td>6 trials, n=1285</td>
<td>3 trials, n=1127</td>
<td>3 trials, n=1127</td>
<td>3 trials, n=1127</td>
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<tr>
<td><strong>Intratracheal</strong></td>
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<tr>
<td>&lt;8 days of age (reference 29)</td>
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<tr>
<td>Budesonide</td>
<td>0.59 (0.50-0.70)</td>
<td>0.64 (0.55-0.74)</td>
<td>0.63 (0.43-0.93)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>6 trials, n=771</td>
<td>12 trials, n=1377</td>
<td>6 trials, n=771</td>
<td></td>
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</tr>
</tbody>
</table>

Legend: Green boxes indicate a statistically significant beneficial effect, red boxes indicate a statistically significant adverse effect, and white boxes indicate no significant difference between treated neonates and controls; Data are expressed as RR (95% CI)
included 3 RCTs and 370 newborns, was conducted to compare the effectiveness of inhaled steroids with systemic steroids in newborns with a birth weight ≤1500g and/or GA ≤32 weeks ventilator-dependent beyond the 7th day of life, did not show any advantage of one over the other in modifying the incidence of combined outcomes such as death or BPD at 36 weeks of corrected age [27].

**Surfactant + budesonide** – The administration of budesonide conveyed by supplementary surfactant is extremely promising. In an RCT, Yeh and collaborators included 265 extremely low birth weight newborns affected by severe respiratory distress (RDS) (defined as the need for invasive MV and FiO₂ >0.5), randomized to receive budesonide delivered by surfactant within the first 4 hours of life or just surfactant. The group of infants treated with budesonide showed a significant reduction in the combined outcome of death or BPD at 36 weeks without short-term complications [28]. A meta-analysis published in 2022, which included 12 studies, confirmed that combining surfactant + budesonide reduces the incidence of BPD, death or BPD, and mortality (Table 1). Follow-up at 36 months of corrected age showed no negative effect on neuromotor or cognitive development [29]. Two large RCTs are currently underway and will provide information on the long-term outcomes of this strategy [9].

**Therapeutic strategies**

A systematic review and “network” meta-analysis published in 2021, which included 62 RCTs and 5,559 newborns with an average GA of 26 weeks, compared 14 therapeutic strategies for using postnatal steroids. These included moderately early (8-14 days) or late (14-28 days) use of dexamethasone at low (<2 mg/kg), medium (2-4 mg/kg), or high (>4 mg/kg) doses; early (<8 days) or late (≥8 days) hydrocortisone; early (<8 days) or late (≥8 days) inhaled steroids; and budesonide delivered by surfactant. The systematic review also included, among the variables, the duration of therapy, defined as short (<8 days), medium (8-14 days) or long (>14 days). The results of this study indicated that medium-dose dexamethasone started between 8 and 14 days of life as the most effective therapeutic strategy in reducing the combined outcome of death or BPD at 36 weeks, albeit with low-quality evidence [30]. This strategy, together with inhaled steroids, is also among the most effective in ensuring the success of extubation despite being associated with an increased risk of hypertension. The meta-analysis confirmed the increased incidence of GI perforation associated with early hydrocortisone [20]. However, it did not report any evaluation of short- or long-term outcomes such as intracranial hemorrhage, necrotizing enterocolitis, periventricular leukomalacia, and PC at 18-24 months of corrected age [30]. These observations confirm what is reported in the Cochrane review on the use of late systemic steroids, which indicates that only cumulative doses of dexamethasone ≥ 2mg/kg are effective in reducing the outcome of death or BPD significantly. Regarding the duration of therapy, Puia-Dumitrescu and coworkers highlighted how exposure to dexamethasone for more than 14 days is associated with a worse neurobehavioral outcome at 2 years of corrected age, both in the motor and language domains [31]. Furthermore, when systemic steroid therapies last more than 14 days, it is always necessary to consider the risk of adrenergic suppression, a condition that must be promptly recognized and treated[11,32]. Finally, it is important to remember that the therapeutic scheme of low-dose dexamethasone or “mini-dex” used in the DART trial [33], equal to a cumulative dose of dexamethasone <1 mg/kg, does not seem as useful in treating evolving BPD, although it is extremely effective in promoting extubation of newborns still on mechanical ventilation beyond the 10th day of life [33].

**CONCLUSIONS**

Overall, questions remain regarding the correct use of postnatal steroids. Available data indicate that the most effective and safest therapeutic scheme is to use dexamethasone at a cumulative dose of 1-2 mg/kg, administered over 7-10 days, starting from the second-third week of life. The recently published policy statement of the American Academy of Pediatrics confirms that the use of postnatal steroids must be individualized, the duration of exposure predefined and limited, and suspension is indicated in cases of failure to respond within 72 hours. The statement also suggests that early hydrocortisone may be a viable strategy for those born from chorioamnionitis-complicated pregnancies. At the same time, inhaled steroids do not appear to offer any advantage over systemic steroids and may increase mortality. Finally, the use of budesonide in association with surfactant is very promising, but data on long-term outcomes are still missing [34].

**Conflict of interest:**

The authors have no relevant financial or non-financial interests to disclose.

**Author’s contributions:**

All authors have contributed, read and agreed to the published version of the manuscript.

**Statement on human and animal rights:**

The research conducted complied with the ethical standards in accordance with Helsinki Declaration (of 1975, revised in 2013), as well as national regulations in the field.

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32. Yates HL, Newell SJ. Minidex: very low dose dexamethasone (0.05 mg/kg/day) in chronic lung disease. Arch Dis Child Fetal Neonatal Ed. 2011;96(3):F190-4. doi: 10.1136/adc.2010.187203.25.
