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Long-term effects of postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia: Balancing the risks and benefits

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ABSTRACT

Postnatal corticosteroids are effective in preventing or treating bronchopulmonary dysplasia (BPD) in preterm newborns, but their benefits need to exceed their risks. Several types of corticosteroids, and different timing and administration modes have been trialed. Systemic corticosteroids, given either early or late, have proven efficacy for reducing BPD and the combined outcome of death or BPD. Inhaled corticosteroids are less effective. However, systemic dexamethasone given early is associated with more neurosensory disability and cerebral palsy in survivors. The risk of adverse neurodevelopment is highest if dexamethasone is given to preterm infants at low risk of BPD. Current trials focus on corticosteroids, mixed with surfactant, delivered intratracheally directly to the lung, which may avoid some systemic adverse effects of corticosteroids. Early trials of intratracheal corticosteroids are encouraging, but more data are needed to determine whether this method of administration is preferable to systemic corticosteroids for preventing or treating BPD.

Practice points:

- Postnatal systemic corticosteroids, given to prevent or treat BPD, should be given only to those at high risk of BPD.
- If possible, postnatal systemic corticosteroids should be given after the first week of life to prevent or treat BPD.
- There is little evidence to support clinical use of inhaled corticosteroids at any time.
- Most evidence of respiratory efficacy is for systemic corticosteroids, but promising data are emerging for intratracheal corticosteroids, using surfactant as a vehicle.
- Long-term outcomes from the trials of intratracheal corticosteroids are needed before they can be recommended for widespread clinical use.

Research directions:

- Short and long-term outcomes from current intratracheal budesonide-surfactant trials are needed.
- The benefits and harms of low dose systemic corticosteroids need to be further clarified in large randomized controlled trials.

1. Introduction

Bronchopulmonary dysplasia (BPD) is a major complication of prematurity, particularly in infants who have respiratory distress syndrome (RDS) caused by a lack of surfactant after birth. The risk is highest in the most immature infants; approximately 50% of extremely preterm newborns (< 28 weeks' gestation) develop BPD [1], and rates as high as 80% have been reported for infants born < 25 weeks' gestation [2,3]. Although initially attributed to ventilator-induced injury, BPD exists despite the increasing use of less invasive modes of respiratory support, such as nasal continuous positive airway pressure. "New" BPD is an entity characterized by arrested alveolarization and vasculogenesis, with a strong inflammatory component [4]. It is thus reasonable to expect that anti-inflammatory treatments may be beneficial to prevent or treat BPD.

Corticosteroids are powerful anti-inflammatory agents and have been used to treat a wide range of inflammatory conditions [5]. The initial enthusiasm following reports of efficacy to treat or prevent BPD in preterm newborns resulted in widespread rollout of systemic postnatal 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 [6]. Nonetheless, as for any treatment, balancing the risks and benefits of PCS is important in clinical practice.

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This review will focus primarily on the long-term outcomes following PCS in preterm newborns to prevent or treat BPD, i.e., outcomes following discharge from the neonatal nursery. We will weigh up the benefits and risks, in relation to timing, mode of administration, and type of corticosteroid. Recommendations for the use of PCS, given the current evidence available, will also be presented.

2. 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 [7]. The commonest synthetic corticosteroids used in neonatology are dexamethasone, hydrocortisone, and more recently budesonide, which have different potencies and half-lives [8].

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 [9], and is critical to learning, memory and spatial processing [8]. 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 [9], which may, in part, explain the associations between dexamethasone and adverse long-term neurodevelopment in preterm infants.

3. History of 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 extubation from mechanical ventilation in preterm infants [10,11]. 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 [12]. 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 [13,14]. 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 [15,16]. 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 [17]. Since then, a meta-regression by Doyle et al. [18] 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 [18].

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 [19–21]. As these are not RCTs, only associations can be inferred, rather than causation.

More recent RCTs using hydrocortisone [10,22], 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 [23,24].

4. Long-term benefits and risks of PCS

We will consider the benefits and risks 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 [10,11,25,26].

4.1. Inhaled corticosteroids

4.1.1. 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 recent 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 [RR] 0.76, 95% confidence interval [CI] 0.63, 0.93, p = 0.005; 6 studies; 1088 participants), and reduced death or BPD at 36 weeks in all randomized neonates (early inhaled corticosteroids 35% [227/649] vs placebo 40% [256/636], RR 0.86, 95% CI 0.75, 0.99, p = 0.04; 6 studies; 1285 participants) [26]. The results are dominated by the largest trial, the Neonatal European Study of Inhaled Steroids (NEuroSIS) trial [27], 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 (RR 0.86, 95% CI 0.75, 1.00, p = 0.05). The rate of BPD was lower, but there was a small *increase* in mortality in the budesonide group [10]. 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 [28,29]. By two years' of age in the NEuroSIS trial, neurodevelopmental disability was similar between the groups (budesonide 48% [148/308] vs placebo 51% [165/321], adjusted RR 0.93, 95% CI 0.80, 1.09, p = 0.40) [30]. 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], RR 1.37, 95% CI 1.01, 1.86, p = 0.04). 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.

4.1.2. Delayed (≥7 days after birth) inhaled corticosteroids

The evidence for delayed (≥7 days) inhaled corticosteroids was recently updated in the Cochrane review [25]. There were some short-term benefits of reduced risk of failure to extubate (typical RR [TRR] 0.80, 95% CI 0.66, 0.98; 5 studies, 79 infants) and at the latest reported time point after treatment onset (TRR 0.60, 95% CI 0.45, 0.80; 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.

4.2. Intratracheal corticosteroids

Venkataraman reviewed the evidence for intratracheal administration of budesonide-surfactant mixture [31]. There were two trials by Yeh et al. [23,32] that randomized a total of 381 infants to budesonide-surfactant (Survanta®, AbbVie Inc, North Chicago, IL, USA) 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 (25% [47/191] vs surfactant only 44% [83/190]; absolute risk reduction (ARR) 0.19, 95% CI 0.10, 0.28; number needed to treat [NNT] 5 infants), as was the combined outcome of death or BPD (budesonide-surfactant 39% (74/191) vs surfactant only 65% (123/190); ARR 0.26, 95% CI 0.16, 0.35; NNT 4 infants) [31]. Follow up to 30 months is underway but there are no substantial differences reported in neurodevelopmental outcomes to date [23]. There are several other trials of intratracheal budesonide either actively recruiting (The PLUSS trial, ACTRN12617000322336, n = 1060; https://clinicaltrials.gov/ct2/show/NCT03521063, n = 108), or about to start (https://clinicaltrials.gov/ct2/show/NCT03275415, n = 380) using a different surfactant (Curosurf®, Chiesi Farmaceutici, Parma, Italy) 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.

4.3. 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 recently updated in two Cochrane reviews [10,11].

4.3.1. 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 extubation failure, BPD (at 28 days and 36 weeks), death or BPD, patent ductus arteriosus and severe retinopathy of prematurity [10]. There were also early adverse effects noted, such as gastrointestinal bleeding, intestinal perforation, hyperglycemia, hypertension, hypertrophic cardiomyopathy, and growth failure [10]. Long-term concerns centered around the increased risk of cerebral palsy (RR 1.42, 95% CI 1.06, 1.91) 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 (RR 1.03, 95% CI 0.91, 1.16) but it must be noted that heterogeneity between the studies was high.

When looking specifically at the type of corticosteroid used, cerebral palsy and the combined outcome of death or cerebral palsy were most commonly noted with dexamethasone (n = 7 studies) but not hydrocortisone (n = 6 studies). For cerebral palsy: typical RR dexamethasone: 1.75, 95% CI 1.20, 2.55; typical RR hydrocortisone: 1.05, 95% CI 0.66, 1.66. For the combined outcome of death or cerebral palsy: typical RR dexamethasone: 1.17, 95% CI 1.00, 1.37; typical RR hydrocortisone: 0.86, 95% CI 0.71, 1.05) [10]. It is important to note that all the studies reporting long-term outcomes in early childhood were not powered to find differences in neurodevelopment, but were powered for primary outcomes 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.

4.3.2. 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 [11]. 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 extubation 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 [11]. 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 (RR 1.16, 95% CI 0.82, 1.64), death or cerebral palsy (RR 0.95, 95% CI 0.78, 1.15), neurosensory disability (RR 1.15, 95% CI 0.86, 1.54), and the combined outcome of death or major neurosensory disability (RR 1.02, 95% CI 0.86, 1.21). In addition, outcomes in later childhood including respiratory health or function, blood pressure, or growth were similar between groups [10]. 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.

There are currently two trials of hydrocortisone given after the first week, but no long-term neurodevelopmental outcomes are available. The SToP-BPD study [33] is a RCT of hydrocortisone (cumulative dose 72.5 mg/kg) or placebo administered during a 22-day tapering schedule to infants born at < 30 weeks or with a birth weight < 1250 g who are ventilator-dependent at a postnatal age of 7–14 days. In results just reported, death or BPD at 36 weeks' postmenstrual age occurred in 71% (128/181) of infants randomized to hydrocortisone, compared with 74% (140/190) randomized to placebo (adjusted odds ratio 0.87 [95% CI, 0.54, 1.38]; p = 0.54) [34]. Two-year neurodevelopmental assessments are planned. Another is a trial being run by the National Institutes of Child Health and Human Development in the USA (https://clinicaltrials.gov/ct2/show/NCT01353313) 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.

5. 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 [35]. Of the 570 infants enrolled in the larger trial, 127/152 (84%) who were born in the United Kingdom and Ireland were followed up to 7 years of age, 52 of whom received early corticosteroids (early budesonide, n = 28; early dexamethasone, n = 24). 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 (RR 0.42, 95% CI 0.19, 0.94) [36].

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 [37].

The findings from these subgroup analyses must be interpreted with

Table 1
Long-term outcomes of PCS.

Steroid type and regimen	BPD at 36 weeks' PMA	Death or BPD	Death[@]	NDI or CP
	Relative risk (95% confidence interval)			
Inhaled corticosteroids: early [26]	0.97 (0.62, 1.52)	***0.86 (0.75, 0.99)***	1.07 (0.82, 1.40)*	1.33 (0.33, 5.42)
Inhaled corticosteroids: late [25]	1.00 (0.59, 1.70)	1.10 (0.74, 1.63)	3.00 (0.35, 25.78)*	No data
Intratracheal corticosteroids [31]	***0.57 (0.43, 0.76)***	***0.60 (0.49, 0.74)***	0.61 (0.34, 1.04)*	No data
Systemic corticosteroids: early (overall) [10]	***0.79 (0.72, 0.87)*** Dexamethasone: ***0.71 (0.62, 0.81)*** Hydrocortisone: 0.91 (0.80, 1.05)	***0.88 (0.83, 0.93)***	0.95 (0.85, 1.06)	NDI: 1.09 (0.89, 1.33) CP: ***1.42 (1.06, 1.91)***
Systemic corticosteroids: late [11]	***0.77 (0.67, 0.88)***	***0.77 (0.70, 0.86)***	0.84 (0.66, 1.07)	NDI: 1.15 (0.86, 1.54) CP: 1.16 (0.82, 1.64)
Inhaled vs systemic corticosteroids: early [36]	1.45 (0.99, 2.11)	1.09 (0.88, 1.35)	0.83 (0.56, 1.23)*	#Moderate/severe disability: 0.64 (0.16, 2.59) #CP: 1.76 (0.36, 8.70)
Inhaled vs systemic corticosteroids: late [37]	1.08 (0.88, 1.32)	1.04 (0.86, 1.26)	0.96 (0.62, 1.49)*	#Moderate/severe disability: 1.40 (0.49, 4.01) #CP: 0.97 (0.35, 2.72)

BPD – bronchopulmonary dysplasia, PMA – post menstrual age, NDI – neurodevelopmental impairment, CP – cerebral palsy, [@] at latest reported age, * at 36 weeks PMA, # data at 7 years of age from a subset of one study [35].

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.

A summary of the outcomes of the different types, modes of administration and timing of PCS are presented in Table 1.

6. 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 [10,11]. If given to infants at highest risk of BPD, postnatal dexamethasone would potentially be "protective" against complications like death or cerebral palsy [18]. Some evidence points to the efficacy of systemic hydrocortisone [10,11], although the recently reported SToP-BPD RCT [34] is discouraging, and to a lesser degree, inhaled budesonide [24] in improving short-term respiratory outcomes, but data on long-term safety are lacking.

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 [10]. 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 reviews do not suggest any adverse neurodevelopmental outcomes at 2–3 years, but there are few benefits and more data are required [25,26]. 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.

7. Conclusions

Even though there have been advances in respiratory management in preterm newborns, BPD continues to affect a significant number of very preterm infants. Thus, it is vital to continue to seek the best PCS regimen to prevent or treat BPD in preterm infants. Whilst there is some evidence to guide the use of systemic corticosteroids, other modes of administration may be preferable. Results of current trials of intratracheal budesonide-surfactant will be critical to refine the prevention and treatment of BPD in the future. However, as history has taught us, we must be cognizant of the long-term outcomes of new treatments before rolling them out on the basis of promising short-term outcomes.

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References

[1] Doyle LW, Carse E, Adams AM, Ranganathan S, Opie G, Cheong JLY. Ventilation in extremely preterm infants and respiratory function at 8 years. N Engl J Med 2017;377:329–37.
[2] Costeloe KL, Hennessy EM, Haider S, Stacey F, Marlow N, Draper ES. Short term outcomes after extreme preterm birth in England: comparison of two birth cohorts in 1995 and 2006 (the EPICure studies). BMJ 2012;345. e7976.
[3] Younge N, Goldstein RF, Bann CM, Hintz SR, Patel RM, Smith PB, et al. Survival and neurodevelopmental outcomes among periviable infants. N Engl J Med 2017;376:617–28.
[4] Jobe AH, Bancalari E. Bronchopulmonary dysplasia. Am J Respir Crit Care Med 2001;163:1723–9.
[5] Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids–new mechanisms for old drugs. N Engl J Med 2005;353:1711–23.
[6] Watterberg KL, Co Fetus, Newborn. Postnatal corticosteroids to prevent or treat bronchopulmonary dysplasia. Pediatrics 2010;126:800–8.
[7] Watterberg K. Evidence-based neonatal pharmacotherapy: postnatal corticosteroids. Clin Perinatol 2012;39:47–59.
[8] Meikle AW, Tyler FH. Potency and duration of action of glucocorticoids. Effects of hydrocortisone, prednisone and dexamethasone on human pituitary-adrenal function. Am J Med 1977;63:200–7.
[9] McEwen BS. The brain is an important target of adrenal steroid actions. A comparison of synthetic and natural steroids. Ann N Y Acad Sci 1997;823:201–13.
[10] Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Early (< 8 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev 2017;10:Cd001146.
[11] Doyle LW, Cheong JL, Ehrenkranz RA, Halliday HL. Late (> 7 days) systemic postnatal corticosteroids for prevention of bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev 2017;10:Cd001145.
[12] Cummings JJ, D'Eugenio DB, Gross SJ. A controlled trial of dexamethasone in preterm infants at high risk for bronchopulmonary dysplasia. N Engl J Med 1989;320:1505–10.
[13] Yeh TF, Lin YJ, Lin HC, Huang CC, Hsieh WS, Lin CH, et al. Outcomes at school age after postnatal dexamethasone therapy for lung disease of prematurity. N Engl J Med 2004;350:1304–13.
[14] Yeh TF, Lin YJ, Hsieh WS, Lin HC, Lin CH, Chen JY, et al. Early postnatal dexamethasone therapy for the prevention of chronic lung disease in preterm infants with respiratory distress syndrome: a multicenter clinical trial. Pediatrics 1997;100:E3.
[15] American Academy of Pediatrics. Postnatal corticosteroids to treat or prevent chronic lung disease in preterm infants. Pediatrics 2002;109:330–8.
[16] Barrington KJ. Hazards of systemic steroids for ventilator-dependent preterm infants: what would a parent want? CMAJ (Can Med Assoc J) 2001;165:33–4.
[17] Doyle LW, Davis PG, Morley CJ, McPhee A, Carlin JB. Low-dose dexamethasone facilitates extubation among chronically ventilator-dependent infants: a multicenter, international, randomized, controlled trial. Pediatrics 2006;117:75–83.
[18] Doyle LW, Halliday HL, Ehrenkranz RA, Davis PG, Sinclair JC. An update on the impact of postnatal systemic corticosteroids on mortality and cerebral palsy in preterm infants: effect modification by risk of bronchopulmonary dysplasia. J Pediatr 2014;165:1258–60.
[19] Cheong JL, Anderson P, Roberts G, Duff J, Doyle LW. the Victorian Infant

Collaborative Study Group. Postnatal corticosteroids and neurodevelopmental outcomes in extremely low birthweight or extremely preterm infants: 15-year experience in Victoria, Australia. Arch Dis Child Fetal Neonatal Ed 2013;98:F32–6.
[20] Walsh MC, Yao Q, Horbar JD, Carpenter JH, Lee SK, Ohlsson A. Changes in the use of postnatal steroids for bronchopulmonary dysplasia in 3 large neonatal networks. Pediatrics 2006;118:e1328–35.
[21] Stark AR, Carlo WA, Vohr BR, Papile LA, Saha S, Bauer CR, et al. Death or neurodevelopmental impairment at 18 to 22 months corrected age in a randomized trial of early dexamethasone to prevent death or chronic lung disease in extremely low birth weight infants. J Pediatr 2014;164. 34-9.e2.
[22] Baud O, Maury L, Lebail F, Ramful D, El Moussawi F, Nicaise C, et al. Effect of early low-dose hydrocortisone on survival without bronchopulmonary dysplasia in extremely preterm infants (PREMILOC): a double-blind, placebo-controlled, multicentre, randomised trial. Lancet 2016;387:1827–36.
[23] Yeh TF, Chen CM, Wu SY, Husan Z, Li TC, Hsieh WS, et al. Intratracheal administration of budesonide/surfactant to prevent bronchopulmonary dysplasia. Am J Respir Crit Care Med 2016;193:86–95.
[24] Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau PH, Carnielli V, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med 2015;373:1497–506.
[25] Onland W, Offringa M, van Kaam A. Late (> /= 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants. Cochrane Database Syst Rev 2017;8:Cd002311.
[26] Shah VS, Ohlsson A, Halliday HL, Dunn M. Early administration of inhaled corticosteroids for preventing chronic lung disease in very low birth weight preterm neonates. Cochrane Database Syst Rev 2017;1:Cd001969.
[27] Bassler D, Plavka R, Shinwell ES, Hallman M, Jarreau PH, Carnielli V, et al. Early inhaled budesonide for the prevention of bronchopulmonary dysplasia. N Engl J Med 2015;373:1497–506.
[28] Jangaard KA, Stinson DA, Allen AC, Vincer MJ. Early prophylactic inhaled beclomethasone in infants less than 1250 g for the prevention of chronic lung disease. Paediatr Child Health 2002;7:13–9.
[29] Nakamura T, Yonemoto N, Nakayama M, Hirano S, Aotani H, Kusuda S, et al. Early inhaled steroid use in extremely low birthweight infants: a randomised controlled trial. Arch Dis Child Fetal Neonatal Ed 2016 Apr 8. pii: fetalneonatal-2015-309943.
[30] Bassler D, Shinwell ES, Hallman M, Jarreau PH, Plavka R, Carnielli V, et al. Long-term effects of inhaled budesonide for bronchopulmonary dysplasia. N Engl J Med 2018;378:148–57.
[31] Venkataraman R, Kamaluddeen M, Hasan SU, Robertson HL, Lodha A. Intratracheal administration of budesonide-surfactant in prevention of bronchopulmonary dysplasia in very low birth weight infants: a systematic review and meta-analysis. Pediatr Pulmonol 2017;52:968–75.
[32] Yeh TF, Lin HC, Chang CH, Wu TS, Su BH, Li TC, et al. Early intratracheal instillation of budesonide using surfactant as a vehicle to prevent chronic lung disease in preterm infants: a pilot study. Pediatrics 2008;121:e1310–8.
[33] Onland W, Offringa M, Cools F, De Jaegere AP, Rademaker K, Blom H, et al. Systemic hydrocortisone to prevent bronchopulmonary dysplasia in preterm infants (the SToP-BPD study); a multicenter randomized placebo controlled trial. BMC Pediatr 2011;11:102.
[34] Onland W, Cools F, Kroon A, Rademaker K, Merkus MP, Dijk PH, et al. Effect of hydrocortisone therapy initiated 7 to 14 days after birth on mortality or bronchopulmonary dysplasia among very preterm infants receiving mechanical ventilation: a randomized clinical trial. J Am Med Assoc 2019;321:354–63.
[35] Halliday HL, Patterson CC, Halahakoon CW. A multicenter, randomized open study of early corticosteroid treatment (OSECT) in preterm infants with respiratory illness: comparison of early and late treatment and of dexamethasone and inhaled budesonide. Pediatrics 2001;107:232–40.
[36] Shah SS, Ohlsson A, Halliday HL, Shah VS. Inhaled versus systemic corticosteroids for preventing bronchopulmonary dysplasia in ventilated very low birth weight preterm neonates. Cochrane Database Syst Rev 2017;10. Cd002058.
[37] Shah SS, Ohlsson A, Halliday HL, Shah VS. Inhaled versus systemic corticosteroids for the treatment of bronchopulmonary dysplasia in ventilated very low birth weight preterm infants. Cochrane Database Syst Rev 2017;10. Cd002057.