Bronchopulmonary dysplasia and perinatal glucocorticoids in preterm infants: changing practice based on evidence
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Late (≥ 7 days) inhalation corticosteroids to reduce bronchopulmonary dysplasia in preterm infants

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Abstract

Background: Bronchopulmonary dysplasia (BPD), defined as oxygen dependence at postmenstrual age of 36 weeks, remains an important complication of prematurity. Pulmonary inflammation plays a central role in the pathogenesis of BPD. Attenuating pulmonary inflammation with postnatal systemic corticosteroids reduces the incidence of bronchopulmonary dysplasia in preterm infants but may be associated with an increased risk of adverse neurodevelopmental outcome. Local administration of corticosteroids via the inhalation route might be an effective and safe alternative.

Objectives: To determine if administration of inhalation corticosteroids after the first week of life to preterm infants at high risk of developing BPD, is effective and safe in reducing the incidence of the separate or combined outcome death or BPD.

Search methods: We identified randomised, controlled trials within the Pubmed, EMBASE, CINAHL and the Cochrane Database, references from retrieved trials and hand searches of journals.

Selection criteria: Randomised controlled trials comparing inhalation corticosteroids, started ≥ 7 days PNA but before 36 weeks postmenstrual age (PMA), to placebo in ventilated and non-ventilated infants at risk of BPD were included. Trials investigating systemic corticosteroids versus inhalation corticosteroids were excluded.

Data collection and analysis: Data on patient characteristics, trial methodology, and inhalation regimens were collected. The primary outcomes were death and/or BPD at 28 days PNA or 36 weeks PMA. Secondary outcomes were short-term respiratory outcomes, such as failure to extubate, total days of mechanical ventilation and oxygen use, and the need for systemic corticosteroids. The original trialists’ were contacted to verify the validity of extracted data and to provide data currently missing. All data were analyzed using RevMan 5.0.24. When possible, meta-analysis was performed using typical risk ratio (TRR) for dichotomous outcomes and weighted mean difference (WMD) for continuous outcomes, along with their 95% confidence intervals (CI). Ventilated and non-ventilated participants were analyzed separately.

Results: Eight trails randomising 232 preterm infants were included in this review. Inhalation corticosteroids did not reduce the separate or combined outcomes death or BPD. Furthermore, inhalation steroids did not impact short term respiratory outcomes such as failure to extubate and total duration of mechanical ventilation or oxygen dependency. There was a trend to a reduced use of systemic corticosteroids in favour of inhalation corticosteroids (TRR 0.51; 95%CI 0.26, 1.00). There was a paucity of data on short-term and long term adverse effects. These results should be interpreted with caution because the total number of randomized patients is
relatively small and most trials differed considerably in patient characteristics, inhalation therapy and outcome definitions.

Authors’ conclusions: Based on the results of the currently available evidence inhalation corticosteroids initiated at ≥ 7 days of life for preterm infants at high risk of developing BPD cannot be recommended at this point in time. More and larger randomised, placebo-controlled trials are needed to establish the efficacy and safety of inhalation corticosteroids.

Background

Description of the condition

Bronchopulmonary dysplasia (BPD), defined as oxygen dependency at 36 weeks postmenstrual age (PMA) is the most important complication of prematurity with a reported incidence of 23% in infants born at 28 weeks, increasing to 73% in infants born at 23 weeks.1 BPD is characterized by prolonged respiratory support, a compromised lung function and recurrent respiratory infections during the first years of life. Furthermore, BPD is considered an independent risk factor for neurodevelopmental impairment.2-4 BPD is a multifactorial disease with mechanical ventilation, oxygen toxicity and pre- and postnatal infection as the most important risk factors and pulmonary inflammation playing a central, mediating role.

Description of the intervention

The intervention of interest is inhaled corticosteroids administered to either ventilated or non-ventilated newborn infants at risk of developing BPD. Budesonide, beclomethasone and fluticasone are the most frequently used inhaled corticosteroids in newborn infants and these drugs are almost exclusively delivered using a pressurized metered dose inhaler or a nebulizer. Studies in preterm infants revealed that the metered-dose inhalation results in a far better deposition than nebulisation. In addition, inhalation via an endotracheal tube provides better deposition than inhalation via a face mask.5

How the intervention might work

As previously mentioned, pulmonary inflammation plays a central, modulating role in the pathogenesis of BPD.6,7 Corticosteroids have a strong anti-inflammatory effect, making them an ideal candidate to attenuate the inflammatory response associated with BPD. Randomized controlled trials (RCTs) have shown that systemic administration of corticosteroids reduces the incidence of BPD and the combined outcome death or BPD in ventilated preterm infants. However, systemic corticosteroids are also associated with short-term (e.g. hyperglycemia,
hypertension, infection) and long-term (neurodevelopmental impairment) adverse effects. This balance between beneficial and adverse effects of corticosteroids may be more favourable when using the inhalation route, because, ideally, inhaled corticosteroids should demonstrate high pulmonary deposition, in addition to a low systemic bioavailability and rapid systemic clearance.

**Why it is important to do this review**

The association between early (< 7 days of life) systemic corticosteroids use and adverse neurodevelopmental outcome has resulted in a reduction in the overall use of corticosteroids in ventilated preterm infants. Administering corticosteroids by inhalation might be a safe and effective alternative. A systemic review of the randomized evidence on inhaled corticosteroids in preterm infants was first published in the Cochrane Library in 1999, followed by an update in 2002. The conclusions of that review were that in ventilated infants administration of inhalation corticosteroids resulted in an improved rate of extubation without any apparent adverse effects. No firm conclusions could be drawn for non-ventilated infants. The present systematic review provides a second update, including a discussion of RCTs published after 2002. In addition, we extended the inclusion criteria by including all RCTs initiating inhalation corticosteroids after the first week of life, in line with the Cochrane reviews on systemic corticosteroids.

**Objectives**

The primary objective was to compare the effectiveness of inhaled corticosteroids versus placebo administered after the first week of life in preterm infants at high risk of developing BPD on the incidence of death or BPD at 36 weeks PMA. The secondary objective was to compare the effectiveness of inhaled corticosteroids versus placebo on respiratory support, the need for systemic corticosteroids, and adverse effect during hospitalization and long-term follow-up.

**Methods**

**Criteria for considering studies for this review**

*Types of studies*
Randomised or quasi-randomised placebo controlled trials (RCT).

*Types of participants*
Preterm infants ≥ 7 days PNA needing mechanical ventilation and/or supplemental oxygen.
Types of interventions
Trials were included if infants were randomised to treatment with inhalation corticosteroid or placebo. The intervention had to be a standardized (non-individualized) dosage regimen of inhalation corticosteroids, initiated between 7 days of life and 36 weeks PMA. Studies investigating inhalation corticosteroids compared to or in addition to systemic corticosteroids (dexamethasone, hydrocortisone or methylprednisolone) were excluded.

Types of outcome measures
To be included in the review, the trials had to report on one or more of the following outcome parameters:
- Death at 28 days PNA, 36 weeks PMA and hospital discharge
- BPD (defined by the need for supplemental oxygen) at 28 days PNA and 36 weeks PMA
- The combined outcome death or BPD at at 28 days PNA and 36 weeks PMA
- Failure to extubate at day 7 and 14 after initiating therapy and at the latest reported timepoint
- Days of mechanical ventilation
- Days of supplemental oxygen
- Days of hospitalization
- The use of systemic corticosteroids
- Sepsis, defined as clinical suspected or culture proven
- Hypertension
- Hyperglycemia
- Gastrointestinal bleeding or perforation (SIP)
- Necrotizing enterocolitis
- Patent ductus arteriosus (PDA)
- Intraventricular hemorrhage (IVH) any grade
- Periventricular leucomalacia (PVL)
- Retinopathy of prematurity (ROP) any grade
- Long-term neurodevelopmental sequelae, assessed after at least 1 year corrected gestational age (CGA) and before a CGA of 4 year including cerebral palsy and Bayley’s Scales of Infant Development (Mental Development Index, MDI)
- Blindness
- Deafness

Search methods for identification of studies
We used the following Medical Subject Heading terms and text words:
steroids or glucocorticoids or flixotide or fluticasone or becotide or beclomethasone or pulmicort or budesonide or anti inflammatory agents) and (inhal* or nebulis* or nebuliz*)
or aerolis* or aeroliz*) and (neonatal chronic lung disease or bronchopulmonary dysplasia or neonatal respiratory distress syndrome or chronic lung disease of prematurity or chronic lung disease of infancy).
No search limits were used.

Electronic searches
Clinical trials were identified by electronic searches of MEDLINE (from 1966 onwards), EMBASE (from 1974 onwards), CINAHL (from 1982 onwards) and the CENTRAL in the Cochrane Library.

Searching other resources
Reference lists of published trials and review articles, and the abstracts of the Pediatric Academic Societies and the European Society for Pediatric Research from 1990 onwards were hand searched.

Data collection and analysis
Selection of studies
The relevant citations found following the database search, were further classified into three groups by two reviewers (WO and AvK), namely ‘clearly a RCT’, ‘clearly not a RCT’ and ‘possibly a RCT’. Full text review was done on all, except those ‘clearly not a RCT’. Disagreements were solved by consensus.

Data extraction and management
In addition to the predefined outcome parameters, the following clinical data were extracted independently by two reviewers (WO and AvK) using a preset data extraction form: patient characteristics (birth weight, gestational age, gender), number of patients randomized, treatment with antenatal glucocorticoids, postnatal surfactant. Disagreement was resolved by consensus. Original investigators of the included RCTs were asked to confirm whether the data extraction was accurate, and where necessary, to provide additional (unpublished) data.

Assessment of risk of bias in included studies
The methodological qualities of the included trials were assessed using the standard methods of the Cochrane Neonatal Review Group. Trial quality assessment of the included trials was performed independently by two reviewers (WO and AvK) rating the following: risk for bias by insufficient allocation sequence and concealment, blinding of intervention, completeness of follow-up and blinding of
outcome measurements. Disagreement was resolved by consensus. If necessary, the original investigators were asked to provide additional information.

**Measures of treatment effect**
Meta-analysis of the extracted data was performed using the standard methods of the Cochrane Neonatal Review Group. The extracted data were processed using the Cochrane statistical package, RevMan 5.0.24. Treatment effect estimates for all trials were calculated, expressed as typical relative risk (TRR) for dichotomous outcomes, and weighted mean difference (WMD) for continuous outcomes, all with a 95% confidence interval (CI).

**Unit of analysis issues**
This review did not include trials with non-standard designs and no effect measures for counts and rates were necessary.

**Dealing with missing data**
All trials were performed on an intention-to-treat analysis. Original investigators of the included RCTs were asked to provide additional (unpublished) data.

**Assessment of heterogeneity**
Due to clinical and methodological heterogeneity, subgroup analyses were performed as described below. In the absence of statistical heterogeneity \( (p > 0.05) \), fixed-effects models were used for the meta-analyses, otherwise random effects models were used.

**Assessment of reporting biases**
Funnel plots were planned to assess possible reporting biases. No language restriction was used in the search strategy.

**Data synthesis**
*Fixed-effect models were used when appropriate.*

Subgroup analysis and investigation of heterogeneity
Data on outcomes of ventilated and non-ventilated patients at trial entry were handled as two separate subgroups.
Sensitivity analysis
Sensitivity analyses were planned to examine the potential influence of treatment variation (type and dose of inhalation corticosteroid, duration of treatment and delivery system).

Results
Results of the search
The search strategy identified 46 relevant manuscripts (27 published in MEDLINE and 19 by hand search) (Figure 1). Electronic searches of EMBASE, CINAHL and the CENTRAL in the Cochrane library revealed no new relevant manuscripts. The abstract of these studies were reviewed independently by the two reviewers for inclusion in this meta-analysis. There was consensus between the reviewers.

Included studies
Eight randomized controlled trials reported in a total of 12 manuscripts met the inclusion criteria for this review. Seven trials were available as full-text publications12-18 and one as an abstract.19

Description of separate trials
Arnon 199613: This double-blind trial included 20 preterm infants with a birthweight < 2000 gram and a gestational age < 33 weeks, still in need of mechanical ventilation at 14 days PNA with a fraction of inspired oxygen (FiO2) ≥ 30%. Patients with PDA, sepsis, air leak or congenital malformation were not included. Eligible patients were randomly assigned to budesonide 600 μg twice daily or placebo given by MDI inserted into small volume spacer for 7 days or until extubation, whichever came first. From the reported outcome parameters, only the rate of PDA and sepsis rate during the study period could be used for this review. The authors provided additional data on extubation rate.
Denjean 199815: This was a double blinded placebo controlled multicenter trial conducted in 6 centres in France over a 2 year period. A total of 86 preterm infants with gestational age < 31 weeks, respiratory distress syndrome (RDS) and in need of mechanical ventilation or nasal ventilation or CPAP at 10 days PNA were included in this study. Patients with PDA, sepsis, pulmonary infections, major malformation or prior treatment with corticosteroids or bronchodilators were excluded. Although this study consisted of four treatment arms, only those patients treated with beclomethasone, 250 μg/puff delivered by a MDI (inserted into a small volume spacer) four times a day or placebo were included in this review. Therapy was started on the 10th or 11th day and given for 28 days with a tapering dose for the last 8
Effects of late (≥ 7 days) inhalation glucocorticoids

Figure 1 Flow of inclusion randomized controlled trials in different phases of search.

216 Potentially relevant citations screened for retrieval
   197 Identified by Pubmed Search
   19 Identified by search of meeting abstracts and other sources

170 Citations excluded (clearly not relevant)

46 Abstracts retrieved for more detailed evaluation
   27 From Pubmed Search
   19 From meeting abstracts and other sources

28 Reports excluded
   9 Not RCT\(^{(20-28)}\)
   3 Initiation of therapy < 7 days PNA\(^{(38-43)}\)
   4 Initiation of therapy > 36 weeks PNA\(^{(35-36)}\)
   4 Inhalation versus systemic steroids\(^{(35-38)}\)
   1 Both index and placebo arm systemic steroids\(^{(48)}\)
   1 Systemic steroids followed by inhalation\(^{(49)}\)
   6 Double publications of excluded trials\(^{(42-47)}\)

18 Full-text manuscripts or meeting abstracts retrieved for detailed information

6 Manuscripts excluded
   2 Original RCTs initiating therapy < 7 days PNA\(^{(46,49)}\)
   4 Double publications of excluded trials

12 Manuscripts of original placebo controlled RCTs included in the systematic review
   7 Full text manuscripts\(^{(22,28)}\)
   1 Abstract\(^{(49)}\)
   4 Double publications of included trials

days. The primary outcome was BPD, defined as oxygen dependency at 28 days PNA in combination with radiographic abnormalities consistent with BPD. However, except for the total duration of supplemental oxygen, all outcomes of interest for this review were presented for the combined group of ventilated and non-ventilated infants and were therefore excluded from the final analysis. The use of intravenous
corticosteroids was only reported for the ventilated infants. The author provided additional data on the randomization process.

Dugas 2005: This was a double blinded randomised trial of 32 infants with a gestational age ≤ 32 weeks, a postnatal age between 28 and 60 days, and a diagnosis of BPD, which was defined as a $\text{FiO}_2 \geq 0.25$ to maintain oxygen saturation between 88 and 92%, a $p\text{CO}_2 \geq 45$ mmHg and chest radiography consistent with BPD. Reasons for exclusion were hypertension, hyperglycemia, sepsis, pneumonia, renal failure, treatment with corticosteroids 5 days prior to inclusion, a $\text{FiO}_2 \geq 0.30$ in ventilated or a $\text{FiO}_2 \geq 0.40$ in non-ventilated infants, and congenital heart disease. The participants were treated with placebo or fluticasone propionate 125 μg/puff given by MDI inserted into small volume spacer and interposed between an anesthesia bag and the tube or a face mask. Infants with a birth weight between 500 - 1200 grams received one puff twice daily for 3 weeks and once daily in the 4th week. The number of puffs was double if the infant’s weight was ≥ 1200 grams. The primary outcome was the total duration of supplemental oxygen. Other outcomes, such as total duration of hospitalization or duration of mechanical ventilation, were only reported for the combined group of ventilated and non-ventilated infants and could therefore not be used for this review. From the reported outcome parameters, only mortality at 36 weeks PMA, mortality at hospital discharge, open label intravenous glucocorticoids and hyperglycemia during the study period in the ventilated subgroup could be used for this review. The original authors did not provide additional data.

Giep 1996: A total of 19 patients were included in this feasibility and safety study with a randomized design. Patients were eligible if their birth weight was between 500 and 1500 grams, the X-ray showed signs of RDS or BPD, the postnatal age was at least 14 days, and they were still mechanically ventilated with a $p\text{O}_2 > 0.40$ and a peak inspiratory pressure (PIP) > 14 cm H₂O after failing an extubation attempt. Patients with PDA, sepsis, congenital heart disease, congenital malformations or previous postnatal or concurrent administration of corticosteroids were not included. The participating infants were randomized to be treated with beclomethasone (1 mg/kg/day) or placebo delivered by MDI and Aerochamber. Infants weighing 500 to 799, 800 to 1000, 1001 to 1300 and above 1300 grams were treated with, respectively, three, four, five and six puffs every 8 hours for a total duration of 7 days. The reported outcomes failure to extubate, use of systemic corticosteroids, sepsis rate and IVH were included in this review. Although data on blood pressure and blood glucose were reported on a daily basis, the number of infants with hypertension and hyperglycemia were not reported. Attempts to contact the original authors failed.

Jonsson 2000: In this double-blind placebo controlled study 30 very low birth weight infants, either mechanically ventilated or supported by continuous positive airway pressure with $\text{FiO}_2 \geq 0.3$, were randomized to budesonide or placebo, delivered by an electronic dosimetric jet nebulizer. Infants with malformations, congenital heart disease, IVH grades III-IV, deteriorating ventilator settings or on high frequency
ventilation were excluded. Starting on day 7 of life, infants were treated with a dose of 500 μg twice a day, for a total duration of 14 days. Reported outcomes of interest for this review were use of open label corticosteroids, failure to extubate on day 14 in the ventilated subgroup and mortality at hospital discharge and at 36 weeks PMA. The authors provided data on the outcomes, oxygen requirements at 28 days of age and at 36 weeks PMA duration of supplemental oxygen, duration of mechanical ventilation, failure to extubate and the adverse outcomes hyperglycemia, hypertension and sepsis for the ventilated and non-ventilated subgroups, separately.

LaForce 1993: This prospective, randomized, paired analysis study included infants with a birth weight < 1500 gram and RDS, who were ventilator dependent at 14 days with X-ray abnormalities indicative for BPD. Patients with a PDA, pneumonia, sepsis, congenital heart disease or air leak were not included. Those allocated to the intervention group were treated with nebulized beclomethasone dipropionate 50 μg 3 times a day for 28 days. Medication was delivered via a Whisper Jet nebulizer system in the ventilator circuit or a blowby with 8 litre of humidified gas per minute in, respectively, ventilated and non-ventilated infants. Reported outcome of interest for this review was mortality at hospital discharge. The original authors provided data on randomisation and sepsis rates.

Pappagallo 1998: This single center study included preterm infants with a birthweight < 1500 gram, more than 7 days PNA with a high probability of developing BPD based on a prediction model or ventilator dependency. This study had two phases, with only the second phase having a randomized placebo controlled design. Data on the 18 infants included in this second phase were used for this review. Infants with sepsis, pulmonary hypoplasia, congenital anomalies or heart diseases were excluded. Patients were randomly assigned to dexamethasone inhalation 1 mg/kg 8-hourly for 7 days, followed by 0.5 mg/kg for three days or placebo using a jet nebulizer. The reported outcomes of interest for this review were the use of intravenous corticosteroids, duration of mechanical ventilation, days on supplemental oxygen and total duration of hospitalization. The rate of failure to extubate was found in a hand searched abstract, reporting on the preliminary outcomes of 10 patients. The original authors could not provide additional data.

Pokriefka 1993: In this study, only published in as an abstract, 14 ventilator-dependent preterm infants with moderate to severe BPD were enrolled and treated with flunisolide or placebo for 28 days, followed with a weaning schedule. No inclusion or exclusion criteria were described. This RCT including is only available as an abstract, reporting clinical and respiratory outcomes without dichotomous or continuous data. Continuous data on mean number of intubation days were reported with neither standard deviations nor standard errors. Therefore these data could not be used. The rates of extubation were stated, although not on which day after initiating therapy. These data were used in the outcome failure to extubate.
at the latest reported timepoint. All attempts to contact the original authors were failed.

**Description of aggregated patient characteristics and intervention**

Five trials\textsuperscript{12-14,16,19} included only ventilated infants at trial entry, whereas three trials\textsuperscript{15-17} included both ventilated and non-ventilated preterm infants. Criteria for including participants were comparable between trials, i.e. ventilator and/or oxygen dependency at \( \geq 7 \) days PNA. The exclusion criteria were the presence of a persistent ductus arteriosus, signs of sepsis, congenital malformations and treatment with postnatal corticosteroids prior to inclusion. Most trials started therapy moderately early (7-21 days PNA), whereas one study started therapy \( > 21 \) days PNA (delayed onset).\textsuperscript{16} The gestational age and birth weight of the included infants was comparable between trials.

Three trials did not report on the use of antenatal corticosteroids or postnatal surfactant.\textsuperscript{14,18,19} In the remaining trials the use of antenatal corticosteroids and postnatal surfactant varied from 25\% to 80\% and 69\% to 100\%, respectively. Within the trials, subjects in the treatment and placebo groups were similar with regards to clinical characteristics, such as birth weight, gestational age, gender, use of antenatal corticosteroids and surfactant, Apgar scores, FiO\textsubscript{2} and ventilator settings or respiratory support at trial entry.

Interventions differed in every trial with regard to the type of corticosteroid, dosage, delivery system and duration of treatment. The corticosteroids used included beclomethasone, flunisolide, budesonide and dexamethasone. Delivery systems included MDI with a spacer device and nebulisation. Total duration of study medication ranged from 7 - 28 days.

**Description of aggregated outcome parameters**

Table 2 summarizes the aggregated outcomes. Three trials\textsuperscript{14,16,17} reported or provided data on mortality in the ventilated infants at the different points in hospitalization (mortality at 28 days PNA, 36 weeks PMA and at hospital discharge), whereas Jonsson provided us with additional data on non-ventilated infants. None of the manuscripts reported the incidence of BPD at 28 days PNA or 36 weeks PMA for the ventilated and non-ventilated infants separately, however by personal communication these data was obtained for the study of Jonsson.\textsuperscript{17} Failure to extubate 7 days after initiating therapy was reported by 5 trials\textsuperscript{12,13,16-18}, whereas Pokriefka reported failure to extubate at an unknown date.\textsuperscript{19} Three trials reported on the duration of mechanical ventilation for the subgroup of ventilated infants at trial entry.\textsuperscript{16-18} Four trials reported data on the total days of supplemental oxygen in the subgroup of ventilated infants\textsuperscript{15-18} and two in the subgroup of
non-ventilated infants. Total days of hospitalization in the intervention and placebo arm were reported by Pappagallo. Five trials reported the incidence of open label corticosteroids use outside the study protocol in both arms. Four studies reported or provided additional data on the outcome sepsis. Four studies also reported or provided additional data on one of the following outcomes in both arms: persistent ductus arteriosus, hypertension, necrotising enterocolitis and intraventricular hemorrhage. In three studies, no increase in adverse side effects such as impaired glucose homeostasis and hypertension was reported, but the actual data were not provided in the manuscripts. None of the included trials reported on gastrointestinal bleeding or perforation, periventricular leucomalacia, retinopathy of prematurity and long term neurodevelopmental sequelae. None of the original authors were able to provide data on these outcomes.

Excluded studies
Twenty-eight trials (16 full-text publications and 12 abstracts) were excluded for the following reasons (Figure 1): non-randomised design or without placebo (N=9), initiation of therapy before 7 days PNA or after 36 weeks PMA (N=7), administration of systemic steroids as co-intervention (N=6) and double publications of excluded trials (N=6). Two trials met the inclusion criteria of this review, but all attempts to contact the original trialist requesting for subgroup data failed and therefore these trials were excluded.

Risk of bias in included studies
All of the included trials were randomised, double-blinded with placebo controls. Five studies provided additional methodological information. The quality of the trials ranged from moderate to high, with some trials failing to provide sufficient details on the randomization process, method of blinding and the management of withdrawals.

Risk of bias in individual studies
Arnon 1996: Method of randomisation was not mentioned in the manuscript. Personal communication revealed that randomisation was performed by the pharmacy. Code and drugs were kept until the end of the trial and released from the hospital pharmacy in sealed envelopes. Blinding was established by using identical MDIs for corticosteroids and placebo administration. Ten patients were withdrawn and did not complete the study: 5 because of sepsis (3 placebo, 2 treatment group),...
4 because of PDA (2 in each group) and 1 because of an air leak (treatment group). These infants were excluded from the analysis in the original manuscript, but were included in this review. It was unclear whether the study was free of selective reporting.

Denjean 1998\textsuperscript{15}: The method of allocation concealment or randomization process were not mentioned in the manuscript, however accuracy was confirmed by personal communication. Randomization by pre-established tables was stratified by center, gestational age and type of ventilator support. Method of blinding was not clearly stated in the manuscript, but again ensured by personal communication to be genuine. Due to severe clinical deterioration, for 3 patients the code was broken. Furthermore, it was stated that of the 178 infants randomised, informed consent was either not obtained or withdrawn for 5 patients for unclear reasons. It was unclear whether the study was free of selective reporting.

Dugas 2005\textsuperscript{16}: Method of concealment was not mentioned in the manuscripts. Infants were assigned to treatment or placebo arm by block randomization with stratification of intubated and extubated infants separately. Blinding was ensured by identical MDIs supplied by the drug manufacturer. Pharmacist in charge of the medication, the treating physician and the investigators were unaware of treatment allocation. Three infants in the placebo group did not complete the study protocol (two because of clinical pulmonary deterioration and one because central line sepsis). All participants were analyzed on an intention-to-treat basis. Mean supplemental oxygen at study enrolment differed between treatment and placebo arm, being significantly lower in the treatment group. The predefined outcomes were reported accurately.

Giep 1996\textsuperscript{12}: Methods of allocation concealment or randomisation of the participants were not described in the manuscript. Observers were blinded to treatment allocation, however the method ensuring this was not reported. Three infants in the placebo group and two in the treatment group received systemic corticosteroids after study entry and continuous data which were not of interest for this review were excluded from analysis thereafter.

Jonsson 2000\textsuperscript{17}: Randomization was computer generated, and sealed envelopes were consecutively numbered. Clinical staff was blinded to group assignment and the code was broken after the last patient finished the treatment. Blinding of the intervention was ensured by supplying the study drug in identical opaque, unmarked plastic vials. Outcome assessments were also blinded. Two patients were withdrawn by attending clinician due to deterioration and received systemic corticosteroids and one died on 9th day of life. Outcomes for all enrolled infants were provided. The predefined outcomes were reported accurately.

LaForce 1993\textsuperscript{14}: The attending neonatologist was unaware of the treatment regimen. However, the used method of allocation concealment or blinding was unclear. Nine patients were withdrawn from analysis due to technical problems with equipment (2
in each group), lost to referring hospital (2 in each group) and one because of sudden
death before start of study (in treatment group). These patients were not included
in the analyses of the original manuscript, but were used for the dichotomous
outcomes during the study period in this review. It was unclear whether the study
was free of selective reporting.
Pappagello 199818: The manuscript revealed no information regarding the method
of sequence generation, allocation concealment or randomization. Clinical staff was
unaware of intervention since the vials were prepared by the pharmacist labelled
with a code and both study and placebo medications were clear solutions and dosage
was calculated on basis of volume. Outcomes were given for all infants enrolled.
Pokriefka 199319: The authors in the abstract state that this was a double-blind
randomized trial but in its brevity no information was available regarding the
method of randomization, blinding of intervention or outcome assessments.
Outcomes for all enrolled infants were provided.

**Summarized risk of bias**

*Allocation*
Allocation concealment was blinded in 5 trials13-17 and unclear in the remaining
trials. Adequate sequence generation, however, was only clear in 2 trials.15,17

*Blinding*
Based on the reported data and/or personal communications, all studies were
judged as having a double blind design. The double blind design was not clearly
stated in the abstract of Pokriefka.19

*Incomplete outcome data*
Five trials12,16-19 reported the outcomes of all included participants, whereas in
2 trials13,15 participants were not included for not obtaining informed consent or
excluded for the outcomes and in 1 trial it was unclear.14

*Selective reporting*
Five trials reported the predefined outcome data completely. In three trials, it was
unclear whether all predefined outcome data were reported.13-15

*Other potential sources of bias*
With the exception of three trials12,13,17 other potential sources of bias could not be
excluded based on the available information.
Table 1. Data and analyses

<table>
<thead>
<tr>
<th>Outcome or Subgroup</th>
<th>Studies</th>
<th>Participants</th>
<th>Statistical Method</th>
<th>Effect Estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 Mortality</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.1 Outcome at 28 days PNA</td>
<td>2</td>
<td>43</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>3.00 [0.14, 65.90]</td>
</tr>
<tr>
<td>1.1.1 Ventilated infants</td>
<td>2</td>
<td>33</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>3.00 [0.14, 65.90]</td>
</tr>
<tr>
<td>1.1.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.2 Outcome at 36 weeks PMA</td>
<td>3</td>
<td>53</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>3.00 [0.35, 25.78]</td>
</tr>
<tr>
<td>1.2.1 Ventilated infants</td>
<td>3</td>
<td>43</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>3.00 [0.35, 25.78]</td>
</tr>
<tr>
<td>1.2.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>1.3 Outcome at hospital discharge</td>
<td>3</td>
<td>53</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>3.00 [0.35, 25.78]</td>
</tr>
<tr>
<td>1.3.1 Ventilated infants</td>
<td>3</td>
<td>43</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>3.00 [0.35, 25.78]</td>
</tr>
<tr>
<td>1.3.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td><strong>2 Bronchopulmonary dysplasia</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2.1 Outcome at 28 days PNA</td>
<td>1</td>
<td>30</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.93 [0.72, 1.21]</td>
</tr>
<tr>
<td>2.1.1 Ventilated infants</td>
<td>1</td>
<td>20</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.89 [0.61, 1.29]</td>
</tr>
<tr>
<td>2.1.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.71, 1.41]</td>
</tr>
<tr>
<td>2.2 Outcome at 36 weeks PMA</td>
<td>1</td>
<td>30</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.59, 1.70]</td>
</tr>
<tr>
<td>2.2.1 Ventilated infants</td>
<td>1</td>
<td>20</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.34 [0.69, 1.98]</td>
</tr>
<tr>
<td>2.2.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.50 [0.06, 3.91]</td>
</tr>
<tr>
<td><strong>3 Combined outcome mortality or bronchopulmonary dysplasia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.1 Outcome at 28 days PNA</td>
<td>1</td>
<td>30</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.85, 1.18]</td>
</tr>
<tr>
<td>3.1.1 Ventilated infants</td>
<td>1</td>
<td>20</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.83, 1.20]</td>
</tr>
<tr>
<td>3.1.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.71, 1.41]</td>
</tr>
<tr>
<td>3.2 Outcome at 36 weeks PMA</td>
<td>1</td>
<td>30</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.10 [0.74, 1.63]</td>
</tr>
<tr>
<td>3.2.1 Ventilated infants</td>
<td>1</td>
<td>20</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.24 [0.87, 1.75]</td>
</tr>
<tr>
<td>3.2.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.50 [0.06, 3.91]</td>
</tr>
<tr>
<td><strong>4 Other respiratory outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.1 Failure to extubate day 7</td>
<td>5</td>
<td>79</td>
<td>RR (M-H, Random, 95% CI)</td>
<td>0.85 [0.62, 1.18]</td>
</tr>
<tr>
<td>4.2 Failure to extubate day 14</td>
<td>2</td>
<td>27</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.36 [0.10, 1.33]</td>
</tr>
<tr>
<td>4.3 Failure to extubate at the latest reported timepoint</td>
<td>5</td>
<td>80</td>
<td>RR (M-H, Random, 95% CI)</td>
<td>0.47 [0.16, 1.42]</td>
</tr>
<tr>
<td>4.4 Days of mechanical ventilation</td>
<td>3</td>
<td>45</td>
<td>MD (IV, Random, 95% CI)</td>
<td>2.79 [-2.47, 9.06]</td>
</tr>
<tr>
<td>4.5 Days of supplemental oxygen</td>
<td>4</td>
<td>141</td>
<td>MD (IV, Fixed, 95% CI)</td>
<td>0.57 [-5.90, 7.07]</td>
</tr>
<tr>
<td>4.5.1 Ventilated infants</td>
<td>4</td>
<td>100</td>
<td>MD (IV, Fixed, 95% CI)</td>
<td>5.53 [-3.99, 15.03]</td>
</tr>
<tr>
<td>4.5.2 Non-ventilated infants</td>
<td>2</td>
<td>41</td>
<td>MD (IV, Fixed, 95% CI)</td>
<td>-3.74 [-12.63, 5.14]</td>
</tr>
<tr>
<td><strong>5 Adverse effects during hospitalization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.1 Open label intravenous corticosteroids</td>
<td>4</td>
<td>74</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.51 [0.26, 1.00]</td>
</tr>
<tr>
<td>5.1.1 Ventilated infants</td>
<td>4</td>
<td>64</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.51 [0.26, 1.00]</td>
</tr>
<tr>
<td>5.1.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.2 Sepsis</td>
<td>5</td>
<td>99</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.92 [0.51, 1.63]</td>
</tr>
<tr>
<td>5.2.1 Ventilated infants</td>
<td>5</td>
<td>89</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.89 [0.45, 1.76]</td>
</tr>
<tr>
<td>5.2.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.36, 2.75]</td>
</tr>
<tr>
<td>5.3 Persistent ductus arteriosus</td>
<td>1</td>
<td>30</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.16, 6.20]</td>
</tr>
<tr>
<td>5.3.1 Ventilated infants</td>
<td>1</td>
<td>30</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>1.00 [0.16, 6.20]</td>
</tr>
<tr>
<td>5.4 Hypertension (&gt; 2SD)</td>
<td>1</td>
<td>27</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.4.1 Ventilated infants</td>
<td>1</td>
<td>17</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.4.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.5 Necrotising enterocolitis</td>
<td>1</td>
<td>27</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.5.1 Ventilated infants</td>
<td>1</td>
<td>17</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.5.2 Non-ventilated infants</td>
<td>1</td>
<td>10</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>Not estimable</td>
</tr>
<tr>
<td>5.6 Intraventricular hemorrhage (any grade)</td>
<td>1</td>
<td>19</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.60 [0.13, 2.82]</td>
</tr>
<tr>
<td>5.6.1 Ventilated infants</td>
<td>1</td>
<td>19</td>
<td>RR (M-H, Fixed, 95% CI)</td>
<td>0.60 [0.13, 2.82]</td>
</tr>
<tr>
<td>5.7 Days of hospitalization</td>
<td>1</td>
<td>18</td>
<td>MD (IV, Fixed, 95% CI)</td>
<td>-24.70 [-41.75, -7.65]</td>
</tr>
<tr>
<td>5.7.1 Ventilated infants</td>
<td>1</td>
<td>18</td>
<td>MD (IV, Fixed, 95% CI)</td>
<td>-24.70 [-41.75, -7.65]</td>
</tr>
</tbody>
</table>
Effects of interventions

Mortality or BPD:
Meta-analysis of separate or combined outcomes mortality and BPD at 28 days PNA or 36 weeks PMA did not show a significant difference between the treatment and placebo arm in either the ventilated or non-ventilated subgroup (see table 1; typical risk ratio (TRR) 0.93 (95% confidence interval (CI): 0.72, 1.21) and 1.00 (95% CI: 0.59, 1.70), respectively).

Other respiratory outcomes:
Due to statistical significant clinical heterogeneity, data on failure to extubate were analyzed using a random effects model (Figure 2). The overall typical risk ratio (TRR) of failure to extubate at 7 days (5 studies), 14 days (2 studies) and latest reported timepoint (1 study) after treatment onset was, respectively, 0.85 (95% CI: 0.61, 1.18), 0.36 (95% CI: 0.10, 1.33) and 0.57 (95% CI: 0.27, 1.20).

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Events Total</th>
<th>Placebo Events Total</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnon 1996</td>
<td>9 9 11</td>
<td>11 11 32.3%</td>
<td>1.00 [0.83, 1.20]</td>
</tr>
<tr>
<td>Dugas 2005</td>
<td>4 5 4 5 9 11</td>
<td>4 5 15.5%</td>
<td>1.00 [0.54, 1.86]</td>
</tr>
<tr>
<td>Giep 1996</td>
<td>4 10 8 9 11</td>
<td>4 11.4%</td>
<td>0.45 [0.20, 0.99]</td>
</tr>
<tr>
<td>Jonsson 2000</td>
<td>10 10 10 10 32.4%</td>
<td>10 10 32.4%</td>
<td>1.00 [0.83, 1.20]</td>
</tr>
<tr>
<td>Pappagallo 1998</td>
<td>2 5 5 5 8.4%</td>
<td>2 5 8.4%</td>
<td>0.45 [0.17, 1.21]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>39 40 100.0%</td>
<td>39 40 100.0%</td>
<td>0.85 [0.62, 1.18]</td>
</tr>
<tr>
<td>Total events</td>
<td>29 38</td>
<td>29 38</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.08; Chi² = 14.73, df = 4 (P = 0.005); P² = 73%
Test for overall effect: Z = 0.95 (P = 0.34)

The meta-analysis of the outcome duration of mechanical ventilation in the ventilated infants showed no significant statistical difference between the treatment arms. In both subgroups (ventilated and non-ventilated participants) meta-analysis showed no significant difference between the treatment and placebo arm regarding duration of supplemental oxygen for the ventilated: (WMD 5.53 (95% CI: -3.99, 15.05) and non-ventilated infants (-3.74 (95% CI: -12.63, 5.14).

Adverse effects during hospitalization:
Meta-analysis showed that open label intravenous corticosteroids were less often used in ventilated infants treated with inhaled corticosteroids, but this difference only approached statistical significance (Figure 3). Only one trial reported on the use of open label intravenous corticosteroids in non-ventilated infants showing that this intervention was not used in any of the included infants.17
Five trials reported either suspected or documented sepsis rates and the meta-analysis of these results failed to show a significant difference between the inhaled corticosteroids and placebo group (TRR 0.98 (95% CI: 0.54, 1.76). 12-14,16,17 Subgroup analysis did not change this finding.

We were unable to perform meta-analysis on the outcomes persistent ductus arteriosus, hypertension, necrotising enterocolitis, intraventricular hemorrhage and total days of hospitalization because these outcomes were only reported in single trials. None of these trials reported a significant difference in these outcomes, except for total days of hospitalization. Pappagello showed a significant decrease in the total days of hospitalization in favour of the inhaled corticosteroids group (WMD -24.70 (95%CI: -41.75, -7.65). 18

Discussion

Summary of main results

Based on the predefined inclusion criteria, this systematic review identified eight, relatively small, randomized controlled trials comparing inhalation corticosteroids to placebo in a total of 232 ventilated and non-ventilated preterm infants. These trials
differed considerably in the patient characteristics, the intervention (medication, dose, duration, and delivery), the reported outcomes and the definitions of these outcomes. This heterogeneity and the small number of randomized patients should be taken into account when interpreting the results of this review.

As the aim was to examine effects to prevent BPD, the end-point of inclusion was chosen to exclude those trials investigating inhaled glucocorticoids in preterms with established BPD after 36 weeks PMA. It is – to our knowledge – unknown how much time before the end point inhaled glucocorticoids will be effective. One could argue for 2 weeks before, 4 weeks before, it is not really clear. There needs to be an exposure for some time to reduce inflammation. The only trial which could have theoretically included patients around the corrected gestation of 36 weeks PMA could not provide us data on the primary outcome BPD at 36 weeks PMA. All other trials treated for at an average of 8 weeks (i.e. 36 weeks - GA at inclusion, on average). Therefore, we feel that the inclusion criteria are fulfilling for the purpose of this review.

Meta-analysis of reported and provided data showed that inhalation corticosteroids do not improve the separate or combined outcomes mortality or BPD at any timepoint during hospitalization. In addition, there were no significant differences in the short-term respiratory outcomes such as failure to extubate at 7, 14 days or at the latest reported time point, the total days of mechanical ventilation or days of supplemental oxygen. This despite the fact that several studies reported that inhalation corticosteroids improved resistance and compliance of the respiratory system, sometimes resulting in a reduction in FiO$_2$ or respiratory rate. However, the heterogeneity in how lung function was measured and the data were reported, prevented a valid meta-analysis of these outcomes.

Our meta-analysis did show a trend to a reduced use of systemic corticosteroids for the reduction of BPD in the inhaled corticosteroids group. In light of the growing concerns on the adverse effects of systemic corticosteroids, this might prove to be an important and clinically relevant finding. However, the lack of data on short and long-term adverse effects in most trials precludes firm conclusions at this point in time.

**Overall completeness and applicability of evidence**

The overall completeness and applicability of this review is low for several reasons. First, few trials were of randomised, placebo-controlled design and therefore eligible for inclusion. The numbers of participants within each of these included trials were small, which limits their power to detect small but clinically important effects of treatment. Second, most placebo-controlled trials investigating inhalation corticosteroids differed considerably in terms of patient characteristics and study...
design, including differences in type of inhalation medication, dose, duration of therapy, and delivery systems. It is unknown if and how these factors modify the treatment effect of inhalation corticosteroids on the outcome parameters reported in this review since no sensitivity analysis could be done to assess the potential impact of different drugs, dosages, delivery systems and treatment duration on the magnitude of expected benefit. Third, not all trials reported the primary and secondary outcome parameters. Various definitions were used, and outcomes were assessed at different points in time. Our extended attempts to retrieve unpublished data did not change this shortcoming.

Quality of the evidence
Three out of the 8 included studies did not report allocation concealment and the majority did not report adequacy of allocation sequence. However, all but one trial reported adequate blinding of intervention, therefore the quality of these RCTs was judged as moderate to high.

Potential biases in the review process
Due to the lack of possible aggregation data reported in the eligible trials no funnelplots could be performed. Therefore, the potential risk of publication bias cannot be excluded.

Authors’ conclusions
Implications for practice
Inhalation corticosteroids administered after the first week of life to preterm infants do not improve the separate or combined outcomes mortality or BPD at any timepoint during hospitalization. Although there are indication that inhalation corticosteroids improve lung function, this does not seem to impact short-term respiratory outcomes such as failure to extubate or the duration of mechanical ventilation. Inhalation corticosteroids may reduce the use of systemic corticosteroids but the clinical relevance of this treatment effect is unclear as short and long term adverse effects of inhalation corticosteroids are underreported. The results of this meta-analysis are compromised by the fact that most trials are underpowered and they are heterogeneous in design. Based on these results the use of inhalation corticosteroids initiated at ≥ 7 days of life for preterm infants at high risk of developing BPD cannot be recommended at this point in time.
Implications for research

Studie are needed to determine the optimal inhaled corticosteroids drug, dose, duration and device, using short term markers of lung function and inflammation. The optimal treatment regimen should be tested in a randomized placebo-controlled trial, including a large number of preterm infants at high risk of developing BPD. The trial design should avoid bias by using adequate allocation concealment and a double-blinded intervention and outcome assessment. Outcomes should be reported using predefined modern definitions and timing, using accepted diagnostic tests for these outcomes. Data on the following primary outcome parameters should be collected: BPD at 36 weeks’ PMA, mortality at 36 weeks’ PMA and at discharge, and a complete assessment of major neurosensory impairment using predefined definitions. Short-term benefits (ie, time of extubation, duration of ventilation) and adverse effects (ie, hypertension, infection, hyperglycemia, and the use of open label intravenous corticosteroids) can be reported as secondary outcomes.

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Chapter 6

References


