

# Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants (Review)

Shah SS, Ohlsson A, Halliday H, Shah VS



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Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants (Review)

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## ABSTRACT

### Background

Chronic lung disease (CLD) remains a serious and common problem among very low birth weight infants despite the use of antenatal steroids and postnatal surfactant therapy to decrease the incidence and severity of respiratory distress syndrome. Due to their anti-inflammatory properties, corticosteroids have been widely used to treat or prevent CLD. However, the use of systemic steroids has been associated with serious short and long-term adverse effects. Administration of corticosteroids topically through the respiratory tract might result in beneficial effects on the pulmonary system with fewer undesirable systemic side effects.

### Objectives

To determine the effect of inhaled versus systemic corticosteroids administered to ventilator dependent preterm neonates with birth weight  $\leq 1500$  g or gestational age  $\leq 32$  weeks after two weeks of life for the treatment of evolving CLD.

### Search strategy

Randomized and quasi-randomized trials were identified by searching the Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2007), MEDLINE (1966 - June 2007), EMBASE (1980 - June 2007), CINAHL (1982 - June 2007), reference lists of published trials and abstracts published in *Pediatric Research* or electronically on the Pediatric Academic Societies website (1990 - April 2007).

### Selection criteria

Randomized or quasi-randomized trials comparing inhaled versus systemic corticosteroid therapy (irrespective of the dose and duration of therapy) starting after the first two weeks of life in ventilator dependent very low birth weight preterm infants.

### Data collection and analysis

Data were extracted regarding clinical outcomes including CLD at 28 days or 36 weeks postmenstrual age (PMA), mortality, combined outcome of death or CLD at 28 days of age or 36 weeks PMA, other pulmonary outcomes and adverse effects. All data were analyzed using RevMan 4.2.10. When appropriate, meta-analysis was performed using relative risk (RR), risk difference (RD), and weighted mean difference (WMD) along with their 95% confidence intervals (CI). If RD was statistically significant, the number needed to treat (NNT) was calculated.

### Main results

Data from one additional trial were available for inclusion in this update. Thus, five trials comparing inhaled versus systemic corticosteroids in the treatment of CLD were identified. Two trials were excluded as both included non-ventilator dependent patients and three trials qualified for inclusion in this review.

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Halliday et al (Halliday 2001) randomized infants at < 72 hours, while Rozycki et al (Rozycki 2003) and Suchomski et al (Suchomski 2002) randomized at 12 - 21 days. The data from the two trials of Rozycki et al and Suchomski et al are combined using meta-analytic techniques. The data from the trial by Halliday et al are reported separately, as outcomes were measured over different time periods from the age at randomization.

In none of the trials was there a statistically significant difference between the groups in the incidence of CLD at 36 weeks PMA among all randomized infants. The estimates for the trial by Halliday et al (Halliday 2001) were RR 1.10 (95% CI 0.82, 1.47), RD 0.03 (95% CI -0.08, 0.15); number of infants (n = 292).

For the trials by Rozycki et al (Rozycki 2003) and Suchomski et al (Suchomski 2002) the typical RR was 1.02 (95% CI 0.83, 1.25) and the typical RD 0.01 (95% CI -0.11, 0.14); (number of infants = 139). There were no statistically significant differences between the groups in either trial for oxygen dependency at 28 days of age, death by 28 days or 36 weeks PMA, the combined outcome of death by or CLD at 28 days or 36 weeks PMA, duration of intubation, duration of oxygen dependence, or adverse effects. Information on the long-term neurodevelopmental outcomes was not available.

### Authors' conclusions

This review found no evidence that inhaled corticosteroids confer net advantages over systemic corticosteroids in the management of ventilator dependent preterm infants. Neither inhaled steroids nor systemic steroids can be recommended as standard treatment for ventilated preterm infants. There was no evidence of difference in effectiveness or side-effect profiles for inhaled versus systemic steroids. A better delivery system guaranteeing selective delivery of inhaled steroids to the alveoli might result in beneficial clinical effects without increasing side-effects. To resolve this issue, studies are needed to identify the risk/benefit ratio of different delivery techniques and dosing schedules for the administration of these medications. The long-term effects of inhaled steroids, with particular attention to neurodevelopmental outcome, should be addressed in future studies.

## PLAIN LANGUAGE SUMMARY

Preterm babies (babies who are born before term, 40 weeks pregnancy) often need breathing support (ventilator support) for breathing difficulties. Babies who need breathing support for a prolonged period of time often develop chronic lung disease (CLD). It is thought that inflammation in the lungs may be part of the cause. Corticosteroid drugs when given orally or through a vein reduces this inflammation (swelling) in the lungs and are used to treat such conditions. However, the use of corticosteroids is associated with serious side effects. Its use has been associated with cerebral palsy (motor problem) and developmental delay. Inhaling steroids, so that the drug directly reaches the lung, has been tried as a way to limit adverse effects. This review of trials found that inhaled steroids do not offer any advantages. More research is needed to show whether any form of routine use of steroids results in overall health improvements for babies at risk of CLD.

## BACKGROUND

Chronic lung disease (CLD) remains a serious and common problem among very low birth weight infants despite the use of antenatal steroids (Crowley 2002) and postnatal surfactant therapy (Yost 2002; Soll 2002) to decrease the incidence and severity of respiratory distress syndrome. The incidence of CLD varies between 23 - 26% (Lee 2000; Lemons 2001) in very low birth weight infants (< 1500 g) and has an inverse relationship to both gestational age and birth weight (Sinkin 1990; Lee 2000).

Several randomized controlled trials (Avery 1985; CDTG 1991; Cummings 1989; Harkavy 1989; Kazzi 1990; Ohlsson 1992) and systematic reviews (Shah 2001; Halliday 1999; Halliday 2002a; Halliday 2002b) have demonstrated that among infants with CLD, treatment with systemic corticosteroids facilitates extuba-

tion and improves respiratory system compliance. Marked heterogeneity regarding the dose and duration of dexamethasone administration has been noted among trials. However, corticosteroids appear to have little effect on the duration of supplemental oxygen, the duration of hospitalisation or mortality (Avery 1985; CDTG 1991; Harkavy 1989; Kazzi 1990; Ohlsson 1992). There are concerns regarding the short and long-term side effects of systemic steroids in this population. These include hyperglycemia, hypertension, hypertrophic cardiomyopathy, gastrointestinal hemorrhage and perforation, enhanced catabolism and growth failure, nephrocalcinosis, poor bone mineralization and susceptibility to infection (Ng 1993; Stark 2001).

The potential effects on brain growth and neurodevelopment are most alarming. Animal models (rat and rhesus monkey) at a similar stage of ontogeny to the human fetus have shown that steroids

permanently affect brain cell division, differentiation, and myelination, as well as the ontogeny of cerebral cortical development (Johnson 1979; Weichsel 1977). These effects are long-lasting and associated with decreased head circumference and neuromotor abnormalities. Several follow-up studies of postnatal systemic corticosteroid therapy in preterm infants have shown a higher incidence of neurodevelopmental abnormalities in surviving dexamethasone treated infants (O'Shea 1999; Shinwell 2000; Yeh 1998).

In recent statements released by the European Association of Perinatal Medicine (Halliday 2001a), American Academy of Pediatrics (CFN/AAP 2002) and the Canadian Pediatric Society (FNC/CPS 2002), routine use of systemic dexamethasone for the prevention or treatment of CLD is not recommended. Outside the context of randomized, controlled trials, the use of corticosteroids should be limited to exceptional clinical circumstances. This recommendation was based on concerns regarding short and long-term complications, especially cerebral palsy.

Thus, alternatives to systemic corticosteroids that may have fewer adverse consequences need to be investigated. Administration of corticosteroids topically through the respiratory tract might result in beneficial effects on the pulmonary system with fewer undesirable systemic side effects.

This review aimed to examine the effectiveness of inhaled versus systemic corticosteroids administered to ventilator dependent very low birth weight neonates of 1500 g or less after the first two weeks of life, for the treatment of evolving CLD.

## OBJECTIVES

The primary objective was to compare the effectiveness of inhaled versus systemic corticosteroids administered to ventilator dependent preterm neonates with birth weight  $\leq$  1500 g or gestational age  $\leq$  32 weeks after two weeks of life on the incidence of CLD at 36 weeks corrected postmenstrual age (PMA)

Secondary objectives were to compare the effectiveness of inhaled versus systemic corticosteroids on:

### 1. Other indicators of CLD including:

- Requirement for supplemental oxygen at 28 days of age
- Duration of requirement for supplemental oxygen (days)
- Duration of assisted ventilation (days)
- Duration of hospitalization (days)
- Change in pulmonary function tests (lung compliance and resistance)

### 2. The incidence of adverse events including:

- Mortality (expressed as neonatal mortality by 28 days of age or by 36 weeks PMA)

- Hyperglycemia (defined as a blood glucose of  $>$  10 mmol/l) during the course of intervention
  - Hypertension [defined as systolic or diastolic blood pressure  $>$  2 standard deviations (SD) above the mean for infant's gestational and postnatal age (Zubrow 1995)] during the course of intervention
  - Gastrointestinal hemorrhage (defined as presence of bloody nasogastric or orogastric aspirate)
  - Necrotizing enterocolitis (NEC) (Bell's stage II and III) (Bell 1978)
  - Intraventricular hemorrhage (IVH) any grade [defined as per Papile et al (Papile 1978)]
  - Periventricular leucomalacia (PVL) (defined as cysts in the periventricular area on US or CT scan)
  - Retinopathy of prematurity (ROP) any grade based on the international classification (ICROP 1984)
  - Patent ductus arteriosus (PDA) defined by presence of clinical symptoms and signs and/or demonstration by echocardiography
  - Hypertrophic cardiomyopathy defined as thickening of the intraventricular septum and/or of the left ventricular wall on echocardiography
  - Sepsis defined by the presence of clinical symptoms and signs of infection and a positive culture from a normally sterile site
  - Pneumonia based on clinical and radiological signs and a positive endotracheal tube aspirate culture
  - Growth (weight, length/height and head circumference) at 36 weeks PMA
  - Cataracts (defined by presence of opacities in the lens)
  - Hypertrophy of the tongue
  - Nephrocalcinosis (defined by the presence of echodensities in the medulla of the kidney on ultrasound) (Saarela 1999)
  - Suppression of the hypothalamic-pituitary-adrenal axis assessed by metyrapone or ACTH stimulation test
3. Long-term neurodevelopmental outcome: Neurodevelopmental impairment is defined as presence of cerebral palsy and/or mental retardation [Bayley Scales of Infant Development (BSID), Mental Development Index (MDI)  $<$  70] and/or legal blindness ( $<$  20/200 visual acuity) and/or deafness (aided or  $<$  60 dB on audiometric testing) assessed at 18-24 months.

## CRITERIA FOR CONSIDERING STUDIES FOR THIS REVIEW

### Types of studies

Randomized or quasi-randomized clinical trials.

### Types of participants

Ventilator dependent preterm infants with birth weight  $\leq$  1500 g or gestational age  $\leq$  32 weeks and postnatal age of more than two weeks.

### Types of intervention

Inhaled versus systemic corticosteroid therapy (irrespective of the dose or duration of therapy).

### Types of outcome measures

Studies reported on at least one of the following outcomes:

1. Amongst all randomized:

- CLD at 36 weeks PMA (defined as requirement for supplemental oxygen at 36 weeks PMA)
- CLD at 28 days of age (defined as requirement for supplemental oxygen at 28 days of age)
- Death by 36 weeks PMA
- Death by 28 days of age
- Death by or CLD at 36 weeks PMA
- Death by or CLD at 28 days of age
- Additional administration of systemic corticosteroids
- Adverse events: infection, hyperglycemia, hypertension, gastrointestinal bleeding, cataracts, IVH, PVL, NEC, ROP, PDA and suppression of hypothalamic-pituitary-adrenal axis

2. Amongst survivors:

- CLD at 36 weeks PMA
- CLD at 28 days of age

3. Long-term neurodevelopmental outcome: Neurodevelopmental impairment is defined as presence of cerebral palsy and/or mental retardation [Bayley Scales of Infant Development (BSID), Mental Development Index (MDI)  $<$  70] and/or legal blindness ( $<$  20/200 visual acuity) and/or deafness (aided or  $<$  60 dB on audiometric testing) assessed at 18 - 24 months.

## SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

Randomized controlled trials comparing inhaled versus systemic corticosteroid therapy in preterm neonates were identified

from MEDLINE (1996 - June 2007) using MeSH headings: infant-newborn, chronic lung disease, bronchopulmonary dysplasia, anti-inflammatory agents, steroids, dexamethasone, administration, inhalation; aerosols, budesonide, beclomethasone dipropionate, flunisolide and fluticasone propionate.

Other databases were searched including: Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library, Issue 3, 2007), EMBASE (1980 - June 2007), CINAHL (1982 - June 2007), reference lists of published trials, and abstracts published in Pediatric Research or electronically on the Pediatric Academic Societies website (1990 - June 2007). No language restrictions were applied. For the original review, the articles were screened by four review authors (SS, VS, AO, HH) to identify articles eligible for inclusion in the review. For this update, two review authors (VS, AO) conducted the literature search and have reviewed the articles obtained.

## METHODS OF THE REVIEW

Criteria and methods used to assess the methodological quality of the trials: the standard method of Cochrane Collaboration and its Neonatal Review Group was used. For each trial, information was sought regarding the method of randomization, blinding and reporting of outcomes of all infants enrolled in the trial. Data from the primary investigator were obtained for unpublished trials or when published data were incomplete. Retrieved articles were assessed and data abstracted independently by four review authors (SS, VS, AO, HH). The update of this review was performed by two review authors (VS, AO). Discrepancies were resolved by discussion and consensus. The statistical analyses used were relative risk (RR), risk difference (RD), and weighted mean difference (WMD) when appropriate along with their 95% confidence intervals (CI). If RD was significant, number needed to treat (NNT) was calculated. A fixed effect model was used for meta-analysis. Heterogeneity tests [including the I squared ( $I^2$ ) test] were to be performed to assess the appropriateness of pooling the data.

## DESCRIPTION OF STUDIES

Five trials comparing inhaled versus systemic corticosteroids in treatment of CLD were identified. Two trials (Dimitriou 1997; Nicholl 2002) were excluded as both included non-ventilator dependent patients and the groups of ventilated infants could not be identified separately. Three trials fulfilled the inclusion criteria and are included in this updated review: Halliday et al (Halliday 2001), Suchomski et al (Suchomski 2002) and Rozycki et al (Rozycki 2003) (published since our initial review). Even though Rozycki et al (Rozycki 2003) enrolled preterm infants with birth weights between 650 - 2,000 g, on review of the published data, 93% of the subjects enrolled had birth weights  $<$  1,000 g with PMA ranging from 23 - 31 weeks. Therefore, the data from this

trial are included in this review. Each of these trials have been published as a full text article. Details of each trial are given in the table "Characteristics of included studies".

Halliday et al (Halliday 2001) - This trial enrolled infants born at < 30 weeks gestation, postnatal age < 72 hours, needing mechanical ventilation and fractional inspired oxygen concentration (FiO<sub>2</sub>) > 0.30. Infants of 30 and 31 weeks could also be included if they needed FiO<sub>2</sub> > 0.50. Infants with lethal congenital anomalies, severe IVH (grade 3 or 4), or proven systemic infection before entry were excluded from the trial. The trial was designed to evaluate the effectiveness of early (< 72 hours) or delayed (> 15 days) administration of systemic dexamethasone or inhaled budesonide. Infants were randomly allocated to one of four treatment groups in a factorial design: early (< 72 hours) dexamethasone, early budesonide, delayed selective (> 15 days) dexamethasone and delayed selective budesonide. Only the delayed budesonide and delayed dexamethasone groups are included in this review. One hundred and forty two babies were randomized to the delayed selective budesonide policy while 150 were randomized to the delayed selective dexamethasone policy. Budesonide was administered by metered dose inhaler and a spacing chamber in a dose of 400 µg/kg twice daily for 12 days. Dexamethasone was given intravenously (IV) or orally (PO) in a tapering course beginning with 0.5 mg/kg/day in two divided doses for three days reducing by half every three days for a total of 12 days of therapy. Delayed selective treatment was started if infants needed mechanical ventilation and more than 30% oxygen for > 15 days. Out of 142 infants randomized to the delayed selective budesonide group, 33 received a full course, 21 received a partial course while 88 did not receive budesonide. Out of 150 infants randomized to the delayed selective dexamethasone group, 35 received a complete course, 25 received a partial course while 90 infants did not receive dexamethasone. An intention to treat analysis was performed by the investigators in their report of this study, and by us in this review. The primary outcome was death or oxygen dependency at 36 weeks. Secondary outcome measures included death or major cerebral abnormality, duration of oxygen treatment, and complications of preterm birth.

Suchomski et al (Suchomski 2002) - This trial compared inhaled beclomethasone, either 400 or 800 µg/d, to intravenous dexamethasone in preterm infants dependent on conventional mechanical ventilation and supplemental oxygen at two weeks of age. Seventy eight preterm infants with birth weight ≤ 1500 g, gestational age ≤ 30 weeks and ventilatory dependence at 12 - 21 days of age with rate > 15/min and FiO<sub>2</sub> > 0.30 with a persistence of these ventilator settings for a minimum of 72 hours were included in the study. Infants on high frequency ventilation were ineligible for the study. Infants were excluded from the study if they had major congenital malformations, culture proven sepsis, hypertension or hyperglycemia needing treatment, or persistent patent ductus arteriosus. Infants were randomly assigned to one of the three treatment groups: inhaled beclomethasone at 400 µg/d, at 800 µg/d, or intravenous dexamethasone. Inhaled beclometha-

sone was continued until extubation. Post-extubation the same dose was continued for another 48 hours. After that, the dose was halved every other day for six days, after which the steroids were stopped. Based on our inclusion criteria (to include all studies regardless of dosage of inhaled steroids), and because there was no significant difference in the effects of the two different doses, the two inhaled beclomethasone groups in the trial by Suchomski et al (Suchomski 2002) were combined to form one group in the present review. Intravenous dexamethasone was given as a 42 day tapering course starting with 0.5 mg/kg/day in two divided doses (Avery 1985). Crossover from either of the inhaled beclomethasone groups to intravenous dexamethasone was allowed if after four to five days of inhaled beclomethasone, the infant's ventilator and oxygen support had not decreased and the attending neonatologist felt that the infant could benefit from intravenous dexamethasone. Eighteen infants from the inhaled steroid group crossed over to systemic dexamethasone. An intention to treat analysis was performed by the investigators in their report of this study, and by us in this review. Outcome measures included adverse effects like sepsis, hypertension and hyperglycemia; short term ventilatory requirements, duration of mechanical ventilation, duration of supplemental oxygen, length of stay in the hospital and need for respiratory support at 28 days or 36 weeks PMA. For infants completing a 10 day course of either inhaled or intravenous steroids, an ACTH (adrenocorticotrophic hormone) stimulation test was done two weeks after completion of the steroid course.

Rozycki et al (Rozycki 2003) enrolled 61 preterm infants with birth weights between 650 - 2,000 g if at 14 days of age they were at significant risk of developing moderate to severe CLD, defined as the need for mechanical ventilation and oxygen, along with X-ray changes beyond 28 days of life. Infants with culture proven sepsis and who were receiving FiO<sub>2</sub> of ≥ 0.30 were eligible if they had a ventilatory index (10,000/Ventilator rate x peak pressure x pCO<sub>2</sub>) of < 0.8. Infants without previous sepsis were eligible if the ventilatory index was < 0.51. Infants meeting these criteria had a 75% risk of developing moderate-severe CLD. Infants with the following conditions were excluded: preexisting hyperglycemia with blood glucose > 200 mg/dl for > 24 hours, hypertension with systolic pressures > 70-90 mm Hg, depending on birth weight, surgery within previous seven days, active bacterial infection unless repeat blood, urine or cerebrospinal fluid cultures were sterile after 72 hours of antibiotics, thrombocytopenia with a platelet count of < 100,000, any gastrointestinal bleeding within the previous seven days, significant weaning from ventilator support in the previous three days and previous exposure to postnatal steroids. Eligibility was determined at 14 days of age but the study could be delayed up to six days while awaiting resolution of infections. Infants were randomized to the following four groups: Group A: aerosol placebo-systemic dexamethasone; Group B: high beclomethasone-systemic placebo; Group C: medium beclomethasone-systemic placebo; and Group D: low beclomethasone-systemic placebo. Those receiving aerosol steroids who re-

mained ventilator-dependent after seven days were switched to standard 42-day tapering doses of systemic dexamethasone. The primary outcome variable was extubation within the first seven days of the study. Secondary outcome measures included: changes in ventilatory settings and oxygen delivery over the first 7 days, the incidence of hypertension, hyperglycemia, infection and growth.

## METHODOLOGICAL QUALITY

Halliday et al (Halliday 2001) - This was a multicentre randomized controlled trial involving 47 centres. The interventions and outcome measures were not blinded in all the centres. However, in 11 centres the trial was conducted double blind. In these centres, placebo metered dose inhalers and intravenous saline were used to mask treatment allocation. After identifying an eligible infant, the clinician telephoned the randomization centre to enroll the infant and determine the treatment group. Outcomes were reported for all infants enrolled in the study. Comparisons were also made for the primary outcome variables between the centres observing double blind strategy and the other centres.

Suchomski et al (Suchomski 2002) - This was a prospective randomized controlled trial. Three sets of 27 cards were assembled followed by placement of one card each into one of 81 opaque envelopes. As infants were enrolled, a card was sequentially pulled and the infant assigned to the appropriate study group. Blinding of intervention was not performed. Blinding of outcome measurement was not ensured. Cross-over from inhaled steroid groups to intravenous dexamethasone was allowed at the discretion of attending neonatologist. Outcome measures were reported for all babies enrolled in the study.

Rozycki et al (Rozycki 2003) - This was a prospective randomized double-blind controlled trial. The infants were randomized using a random table number and only the pharmacy was aware of the individual group assignment. Blinding of intervention was performed. Blinding of outcome measurement was not ensured. Outcome measures were reported for all infants enrolled in the study.

## RESULTS

The data from two trials (Rozycki 2003; Suchomski 2002) were combined for meta-analysis, while the data from the study by Halliday 2001 are presented separately due to clinical differences between these trials. Halliday et al (Halliday 2001) randomized infants < 72 hours, while Suchomski et al (Suchomski 2002) randomized at 12 - 21 days and Rozycki et al (Rozycki 2003) randomized after 14 days. Each trial reported outcomes from the age of randomization. Although the infants received steroids after the first two weeks of life in all these trials, the time period over which outcomes were measured differed between the studies.

## INHALED VS. SYSTEMIC STEROIDS (INFANTS RANDOMIZED BETWEEN 12-21 DAYS OF AGE) (COMPARISON 01):

### PRIMARY OUTCOMES:

#### *CLD at 36 weeks PMA (Outcome 01.01):*

Two trials enrolling 139 neonates reported on the incidence of CLD at 36 weeks PMA. There was no statistically significant difference in the incidence of CLD by 36 weeks PMA in the inhaled steroid compared to systemic steroid group [typical RR 1.02 (95% CI 0.83, 1.25); typical RD 0.01 (95% CI - 0.11, 0.14)]. There was high heterogeneity for this outcome for RR ( $p=0.03$ ,  $I^2=80%$ ) and for RD ( $p=0.02$ ,  $I^2=81%$ ).

### SECONDARY OUTCOMES:

#### *CLD at 28 days of age (Outcome 01.02):*

One trial enrolling 78 neonates reported on the incidence of CLD at 28 days of age. There was no statistically significant difference in the incidence of CLD at 28 days of age [RR 0.97 (95% CI 0.90, 1.05), RD - 0.04 (95% CI -0.12, 0.04)].

#### *Death by 36 weeks PMA (Outcome 01.03):*

One trial enrolling 78 neonates reported on the incidence of death by 36 weeks PMA. There was no statistically significant effect on death by 36 weeks PMA [RR 2.69 (95% CI 0.13, 54.15), RD 0.04 (95% CI -0.04, 0.12)].

#### *Death by 28 days of age (Outcome 01.04):*

One trial enrolling 78 neonates reported on the incidence of death by 28 days. No statistically significant effect on mortality by 28 days was noted [RR 2.69 (95% CI 0.13, 54.15), RD 0.04 (95% CI 0.04, 0.12)].

#### *Death by or CLD at 36 weeks PMA (Outcome 01.05):*

One trial enrolling 78 neonates reported on the incidence of death by or CLD at 36 weeks PMA. There was no statistically significant difference between the groups for the combined outcome of death by or CLD at 36 weeks PMA [RR 0.94 (95% CI 0.83, 1.05), RD -0.06 (95% CI -0.17, 0.05)].

#### *Death by or CLD at 28 days of age (Outcome 01.06):*

One trial enrolling 78 neonates reported on the incidence of death by or CLD at 28 days. All enrolled infants (51 in the inhaled steroid group and 27 in the systemic steroid group) had this outcome and therefore the RR was not estimable. The RD for this outcome was 0.00 (95% CI -0.06, 0.06).

#### *Need for ventilation amongst survivors at 36 weeks PMA (Outcome 01.07):*

One trial reported on this outcome ( $n=76$ ). There was no statistically significant difference for this outcome between groups [RR 1.10 (95% CI 0.30, 4.06), RD 0.01 (95% CI -0.14, 0.16)].

***Duration mechanical ventilation among survivors (days) (Outcome 01.08):***

One trial reported on this outcome for 77 neonates. The duration of mechanical ventilation was not statistically significantly different between groups (MD - 3 days, 95% CI -16, 10).

***Duration of supplemental oxygen amongst survivors (days) (Outcome 01.09):***

One trial reported on this outcome for 76 neonates. The duration of supplemental oxygen was not statistically significantly different between the two groups (MD -15 days, 95% CI -37, 7).

***Length of hospital stay amongst survivors (days) (Outcome 01.10):***

One trial reported on this outcome for 76 neonates. There was no statistically significant difference in the length of hospital stay amongst survivors between groups (MD -13, 95% CI -33, 7).

***Hyperglycemia (Outcome 01.11):***

Two trials enrolling 139 neonates reported on the incidence of hyperglycemia. There was no statistically significant difference in the incidence of hyperglycemia between groups [typical RR 0.33 (95% CI 0.05, 2.12); typical RD -0.04 (95% CI -0.11, 0.04)]. There was low heterogeneity for this outcome for RD ( $p=0.17$ ,  $I^2=47%$ ).

***Hypertension (Outcome 01.12):***

Two trials enrolling 139 neonates reported on the incidence of hypertension. There was no statistically significant difference in the incidence of hypertension between groups (typical RR 0.70, 95% CI 0.31, 1.58; typical RD -0.06, 95% CI -0.19, 0.08). There was no heterogeneity for this outcome for RR ( $p=0.88$ ,  $I^2=0%$ ) and for RD ( $p=0.88$ ,  $I^2=0%$ ).

***Necrotizing enterocolitis (Outcome 01.13):***

One trial enrolling 78 neonates reported on the incidence of NEC. There was no statistically significant difference in the incidence of NEC between groups (RR 2.12, 95% CI 0.25, 18.02; RD 0.04, 95% CI -0.06, 0.14).

***Gastrointestinal bleed (Outcome 01.14):***

One trial enrolling 78 neonates reported on the incidence of gastrointestinal bleed. None of the enrolled infants had this outcome and therefore the RR was not estimable. The RD was -0.00, 95% CI -0.06, 0.06).

***Periventricular leucomalacia (Outcome 01.15):***

Two trials enrolling 139 neonates reported on this outcome. There was no statistically significant difference in the incidence of periventricular malacia between groups (typical RR 0.83, 95% CI 0.33, 2.08; typical RD -0.02, 95% CI -0.15, 0.10 ).

***Retinopathy of prematurity  $\geq$  stage 3 (Outcome 01.16):***

Two trials enrolling 139 neonates reported on the incidence of ROP  $\geq$  stage 3. There was no statistically significant difference in the incidence of ROP  $\geq$  stage 3 between groups (typical RR 1.33, 95% CI 0.64, 2.74; typical RD 0.06, 95% CI -0.08, 0.21). There was no heterogeneity for this outcome for RR ( $p=0.59$ ,  $I^2=0%$ ) and for RD ( $p=0.62$ ,  $I^2=0%$ ).

***Culture proven sepsis (Outcome 01.17):***

One trial enrolling 78 neonates reported on this outcome. There was no statistically significant difference in the incidence of culture proven sepsis between groups (typical RR 1.24, 95% CI 0.35, 4.4; RD 0.03, 95% CI -0.13, 0.18).

**INHALED VS. SYSTEMIC STEROIDS (INFANTS RANDOMIZED AT < 72 HOURS OF AGE) (COMPARISON 02):**

**PRIMARY OUTCOME:**

***CLD at 36 weeks PMA (Outcome 02.01):***

One trial enrolling 292 neonates reported on the incidence of CLD at 36 weeks PMA. There was no statistically significant difference in the incidence of CLD at 36 weeks PMA in the inhaled steroid compared to systemic steroid group [RR 1.10 (95% CI 0.82, 1.47); RD 0.03 (95% CI - 0.08, 0.15)].

**SECONDARY OUTCOMES:**

***CLD at 28 days of age (Outcome 02.02):***

One trial enrolling 292 neonates reported on the incidence of CLD at 28 days of age. There was no statistically significant difference in the incidence of CLD at 28 days [RR 1.06 (95% CI 0.88, 1.26), RD 0.03 (95% CI -0.08, 0.15)].

***Death by 36 weeks PMA (Outcome 02.03):***

One trial enrolling 292 neonates reported on the incidence of death by 36 weeks PMA. There was no statistically significant effect on death by 36 weeks PMA [RR 0.96 (95% CI 0.62, 1.49), RD -0.01 (95% CI -0.10, 0.09)].

***Death by 28 days of age (Outcome 02.04):***

One trial enrolling 292 neonates reported on the incidence of death by 28 days of age. No statistically significant effect on mortality by 28 days was noted [RR 0.85 (95% CI 0.52, 1.37), RD -0.03 (95% CI -0.12, 0.06)].

***Death by or CLD at 36 weeks PMA (Outcome 02.05):***

One trial enrolling 292 neonates reported on the incidence of death by or CLD at 36 weeks PMA. There was no statistically significant difference between the groups for the combined outcome of death by or CLD at 36 weeks PMA [RR 1.04 (95% CI 0.86, 1.26), RD 0.03 (95% CI -0.09, 0.14)].

***Death by or CLD at 28 days of age (Outcome 02.06):***

One trial enrolling 292 neonates reported on the incidence of death by or CLD at 28 days of age. There was no statistically significant difference between the groups for the combined outcome of death by or CLD at 28 days of age [RR 1.00 (95% CI 0.90, 1.12), RD 0.00 (95% CI -0.09, 0.09)].

***Pneumothorax (Outcome 02.07):***

One trial reported on this outcome (n=292). There was no statistically significant difference for this outcome between groups [RR 0.92 (95% CI 0.53, 1.60), RD -0.01 (95% CI -0.09, 0.07)].

***Other air leaks (Outcome 02.08):***

One trial reported on this outcome (n=292). There was no statistically significant difference for this outcome between groups [RR 1.00 (95% CI 0.55, 1.83), RD 0.00 (95% CI -0.08, 0.08)].

***Pulmonary hemorrhage (Outcome 02.09):***

One trial enrolling 292 neonates reported on this outcome. There was no statistically significant difference for this outcome between groups [RR 0.86 (95% CI 0.43, 1.72), RD -0.02 (95% CI -0.08, 0.05)].

***Duration mechanical ventilation (days) (Outcome 02.10):***

One trial reported on this outcome for 292 neonates. The duration of mechanical ventilation was not statistically significantly different between groups (MD 0.1 days, 95% CI -5.2, 5.4).

***Duration of supplemental oxygen (days) (Outcome 02.11):***

One trial reported on this outcome for 292 neonates. The duration of supplemental oxygen was not statistically significantly different between the two groups (MD 7 days, 95% CI -17, 30).

***Hyperglycemia (Outcome 02.12):***

One trial enrolling 292 neonates reported on the incidence of hyperglycemia. There was no statistically significant difference in the incidence of hyperglycemia between groups (RR 0.90, 95% CI 0.63, 1.28; RD -0.03, 95% CI -0.14, 0.07).

***Hypertension (Outcome 02.13):***

One trial enrolling 139 neonates reported on the incidence of hypertension. There was no statistically significant difference in the incidence of hypertension between groups (RR 0.87, 95% CI 0.74, 1.02; RD -0.09, 95% CI -0.20, 0.01).

***Necrotizing enterocolitis (Outcome 02.14):***

One trial enrolling 292 neonates reported on the incidence of NEC. There was no statistically significant difference in the incidence of NEC between groups (RR 0.86, 95% CI 0.43, 1.72; RD -0.02, 95% CI -0.08, 0.05).

***Gastrointestinal bleed (Outcome 02.15):***

One trial enrolling 292 neonates reported on the incidence of gastrointestinal bleed. There was no statistically significant difference in the incidence of NEC between groups (RR 0.89, 95% CI 0.41, 1.93; RD -0.01, 95% CI -0.07, 0.05).

***Gastrointestinal perforation (Outcome 02.16):***

One trial enrolling 292 neonates reported on this outcome. There was no statistically significant difference in the incidence of gastrointestinal perforation between groups (RR 0.85, 95% CI 0.23, 3.08; RD -0.01, 95% CI -0.04, 0.03).

***Patent ductus arteriosus (Outcome 02.17) :***

One trial enrolling 292 neonates reported on this outcome. There was no statistically significant difference in the incidence of PDA between groups (RR 0.90, 95% CI 0.73, 1.11; RD -0.06, 95% CI -0.17, 0.06).

***Retinopathy of prematurity, at any stage (Outcome 02.18):***

One trial enrolling 292 neonates reported on the incidence of ROP at any stage. There was no statistically significant difference in the incidence of ROP groups (RR 1.27, 95% CI 0.86, 1.89; RD 0.06, 95% CI -0.04, 0.16).

***Culture proven sepsis (Outcome 02.19):***

One trial enrolling 292 neonates reported on this outcome. There was no statistically significant difference in the incidence of culture proven sepsis between groups (RR 1.06, 95% CI 0.78, 1.44; RD 0.02, 95% CI -0.09, 0.13).

**OTHER OUTCOMES:**

**ACTH stimulation test:**

The ACTH test was completed in one trial (Suchomski 2002) on 24 infants. The baseline cortisol levels before the ACTH stimulation test for the 800 µg/d inhaled group ( $3 \pm 2.3$  µg/dl; n = 7) and the intravenous group ( $1.6 \pm 1.3$  µg/dl; n = 10) were statistically significantly lower than for the 400 µg/d inhaled group ( $7.3 \pm 4.2$  µg/dl; n = 7). However, the response to ACTH (i.e., relative rise in cortisol level) was similar in all the three groups:  $12 \pm 5.7$  µg/dl in the 400 µg/d inhaled group,  $15.6 \pm 8.5$  µg/dl in the 800 µg/d inhaled group and  $10.7 \pm 4.6$  µg/dl in the intravenous group, p = 0.408. Post ACTH stimulation cortisol levels were  $18.4 \pm 8.0$  µg/dl in the 800 µg/d inhaled group,  $19.3 \pm 5.9$  µg/dl in the 400 µg/d inhaled group and  $12.3 \pm 5.7$  µg/dl in the intravenous group, p = 0.048.

No relevant data for the following outcomes were available for analysis: long-term neurodevelopmental outcome, measurement of pulmonary functions, growth, nephrocalcinosis, hypertrophy of tongue, cataract, pneumonia or hypertrophic cardiomyopathy.

## DISCUSSION

This review found no evidence that inhaled as compared to systemic steroids decrease the incidence of CLD at 36 weeks PMA, CLD at 28 days of age, mortality by 28 days or 36 weeks PMA, or the combined outcome of death by or CLD at 28 days of age or 36 weeks PMA. There was no evidence of effect on the duration of ventilation, duration of oxygen supplementation or the incidence of adverse effects.

The data from the two trials (Rozycki 2003; Suchomski 2002) were combined as they enrolled infants between 12 - 21 days of age, while data from the trial by Halliday et al (Halliday 2001) were reported separately as they randomized infants < 72 hours of age. The period of measurement of outcomes varied between the studies by Halliday et al (Halliday 2001) and the other trials (Rozycki 2003; Suchomski 2002) making combination of results inappropriate. This may possibly explain the differences in the incidence of adverse events like CLD, mortality, etc. Halliday et al (Halliday 2001) counted deaths from < 72 hours onwards while Suchomski et al (Suchomski 2002) did so from 12 - 21 days onwards. This means that in Halliday 2001, all deaths from < 72 hours were attributed to the randomized treatment policy, whereas in Suchomski 2002, only deaths from 12 - 21 days were so attributed. Looking at the control event rate we see what we would expect - a much higher death rate in Halliday 2001 than in Suchomski 2002 (death by 36 weeks was 33/150 in Halliday 2001 and 0/27 in Suchomski 2002). Similar explanations could be provided for the other outcomes of interest. Due to these concerns, aggregation of the data in the two trials was not performed.

A systematic review (Halliday 2002a) of postnatal corticosteroid therapy begun after three weeks postnatal age showed a borderline significant decrease in incidence of CLD, but no evidence of effect on survival at discharge or duration of hospitalization. Also, systematic reviews of systemic postnatal corticosteroid therapy instituted between 7 -14 days postnatal age (Halliday 2002b, Shah 2001) showed a decrease in the incidence of CLD at 36 weeks PMA and mortality. However, the duration of hospitalization was not decreased.

A major concern with studies of inhaled steroid therapy is the uncertainty regarding drug delivery and deposition of steroids in the oropharynx and in the peripheral airways. Numerous factors affect drug delivery and deposition including the number of particles in the respirable range, the delivery technique (use of MDI with or without a spacer), nebulizers (jet or ultrasonic) and the presence or absence of an endotracheal tube. Previous workers have shown that the amount of aerosol delivery varies from 0.4% to 14% based on the technique used (Arnon 1992; Grigg 1992; O'Callaghan 1992). The delayed onset of activity (Dimitriou 1997; LaForce 1993) and a similar risk profile of inhaled steroids (Shah 2002) suggests that their effects may be secondary to systemic absorption.

Inhaled steroids are believed to be less effective compared to systemic steroids. The type, dosage and delivery methods may be inadequate. More refinements in the inhalational drug delivery system guaranteeing selective delivery in the alveoli and smaller airways may improve the clinical efficacy and decrease the side-effect profile of inhaled steroids. In the present review, there is no evidence of difference in effectiveness or side-effect profiles for inhaled versus systemic steroids. A better delivery system/higher dose of inhaled steroids may result in equivalence of effectiveness for the two modes of administration, but may also show evidence of side-effects. To resolve this issue, studies are needed to identify the risk/benefit ratio of different delivery techniques and dosing schedules for the administration of these medications.

This review found no evidence that inhaled steroids confer any net advantages over systemic steroids in the management of ventilator dependent preterm infants. Systemic steroids given late (after one week) do not show clear evidence of neurodevelopmental problems (Halliday 2002a; Halliday 2002b). However, systemic steroids, especially dexamethasone given early (< 96 hours), are associated with an increase in cerebral palsy (Halliday 2002c). Further studies with particular attention to long-term neurodevelopmental outcome need to be performed before delayed steroids, either inhaled or systemic, can be recommended as safe for treatment of evolving CLD in preterm infants. Follow-up studies are extremely important and all surviving infants in the OSECT study (Halliday 2001) are currently being traced and examined by pediatricians and psychologists.

## AUTHORS' CONCLUSIONS

### Implications for practice

This updated review of three trials found no evidence that inhaled corticosteroids confer net advantages over systemic corticosteroids in the management of ventilator dependent preterm infants. Neither inhaled nor systemic steroids can be recommended as standard treatment for ventilated preterm infants.

### Implications for research

Studies are needed to identify the risk/benefit ratio of different delivery techniques and dosing schedules for the administration of steroids. Studies are needed to address the long-term effects of inhaled steroids, with particular attention to neurodevelopmental outcome.

## POTENTIAL CONFLICT OF INTEREST

None

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### External sources of support

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- Mount Sinai Hospital, Toronto, Ontario CANADA

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**T A B L E S****Characteristics of included studies**

Study	Halliday 2001
Methods	<p>Multicentre, randomized open study.</p> <ol style="list-style-type: none"> <li>1. Blinding of randomization: Yes.</li> <li>2. Blinding of intervention: Not in all centres. 11 centres - Yes; 36 centres - No</li> <li>3. Blinding of outcome measurement: No</li> <li>4. Complete follow up: Yes</li> </ol>
Participants	<p>570 infants from 47 neonatal intensive care units worldwide (United Kingdom, Ireland, Canada, Switzerland, Norway, Greece, Portugal, Sweden, Slovenia, Poland, Singapore, UAE) were enrolled. Inclusion criteria: Gestational age &lt; 30 weeks, postnatal age &lt; 72 hours and need for mechanical ventilation and inspired FiO<sub>2</sub> &gt; 30%. Delayed selective treatment was started if infants needed mechanical ventilation and &gt; 30% FiO<sub>2</sub> for &gt; 15 days. Infants of 30 - 31 weeks GA could also be included if they needed &gt; 50% FiO<sub>2</sub>.</p> <p>Demographic data: values presented as mean (SD) or as appropriate</p> <p><b>Budesonide group</b> n = 142 Gestational age (weeks): 27 (2) Birth weight (grams): 994 (279) Gender (female/male) (number of infants): 64/78 Antenatal steroids (number and percentage): 89 (63%) Surfactant treatment: 132 (93%) Clinical Risk Index for Babies score: Median 6, Range 1-18</p> <p><b>Dexamethasone group</b> n = 150 Gestational age (weeks): 27.1 (1.9) Birth weight (grams): 1007 (283) Gender (female/male) (number): 71/79 Antenatal steroids (number and percentage): 82 (55%) Surfactant treatment (number and percentage): 138 (92%) Clinical Risk Index for Babies score: median 7, range 1-16</p> <p>Exclusion criteria: congenital lethal anomalies, severe IVH (grade 3 or 4) and proven systemic infection before entry. A strong suspicion of infection, uncontrolled hypertension and hyperglycemia were considered to be indications to postpone trial entry until they resolved, provided that this occurred within 72 hours of birth.</p> <p>Study period: February 1994 to December 1998.</p>

## Characteristics of included studies (Continued)

	<p>The trial had factorial design and a similar number of infants was allocated to each group. Group 1 received early (&lt; 72 hours) dexamethasone (n = 135); group 2 received delayed (&gt; 15 days) dexamethasone (n = 150); group 3 received early budesonide (n = 143); Group 4 received delayed selective budesonide (n = 142).</p>
Interventions	<p>1. Dexamethasone was administered IV or PO in initial dose of 0.5 mg/kg/day in 2 divided doses for 3 days, followed by 0.25 mg/kg/day in 2 divided doses for 3 days, then 0.10 mg/kg/day for 3 days, and finally 0.05 mg/kg/day in 2 divided doses for 3 days for a total of 12 days of treatment.</p> <p>2. Budesonide was administered using a metered dose inhaler (MDI; 200µg/puff; Pulmicort, Astra Draco, Lund, Sweden) connected to spacing device (Aerochamber MV 15; Trudell Medical, Canada). The aerochamber was a rigid, clear plastic cylinder, 11 by 4.1 cm with an approximate capacity of 145 ml. After endotracheal suctioning, the MDI was shaken and inserted into the spacing chamber. The spacer was then filled with 100% oxygen and the infant's FiO<sub>2</sub> was increased by 20%. The aerochamber was connected into the ventilatory circuit and manual inflations were given through the chamber using an inflatable bag. Budesonide was administered as soon as chest wall movements were established. A 500-1000 g infant was given 2 puffs twice daily and 1000-1500 g infant was given 3 puffs twice daily. The puffs were given one at a time, activating MDI at end expiration and allowing 10 breaths after each activation. After each administration, the chamber was removed from the ventilator circuit and the infant was reconnected to the ventilator at the previous settings. The duration of budesonide treatment was up to 12 days provided the infant remained intubated. If the infant was extubated before 12 days budesonide was discontinued.</p>
Outcomes	<p>1. Primary outcome measure was death or oxygen dependency at 36 weeks CGA.</p> <p>2. Secondary outcome measures included death or major cerebral abnormality on ultrasound nearest to 6 weeks postnatal age, death or oxygen dependency at 28 days and expected date of delivery, duration &gt;40% FiO<sub>2</sub>, duration of any supplemental oxygen, duration of assisted ventilation by endotracheal tube and duration of hospital stay.</p> <p>3. Complications such as pneumothorax, other pulmonary air leaks, NEC, acquired pneumonia, PDA requiring treatment, pulmonary hemorrhage requiring increased ventilation, seizures treated with anticonvulsants, recurrent apnea needing treatment, ROP at 36 weeks CGA, gastric hemorrhage and GI perforation were noted. All neonates were monitored daily for blood pressure and blood glucose. Also, withdrawals from the intervention because of hypertension, hyperglycemia, sepsis, gastric bleeding, or intestinal perforation were noted. An intention to treat analysis was performed.</p>
Notes	<p>The study was performed double blind in 11 centres, and in these centres placebo MDIs and intravenous saline were used to mask treatment allocation.</p>
Allocation concealment	<p>A – Adequate</p>

Study	Rozycki 2003
Methods	<p>Prospective randomized controlled trial.</p> <p>1. Blinding of randomization: Yes After parental consent, infants were stratified into two birth weight groups (650-1,000 grams and 1,001-2,000 g birth weight) and then into four dosing group using a random table number</p> <p>2. Blinding of intervention: Yes</p> <p>3. Blinding of outcome assessment: No</p> <p>4. Complete follow up: Yes</p>
Participants	<p>61 preterm infants with birth weights between 650-2,000 grams if at 14 days of age were at significant risk for developing moderate to severe CLD, defined as need for mechanical ventilation and oxygen, along with X-ray changes beyond 28 days of life were enrolled.</p> <p>Infants with proven sepsis and receiving FiO<sub>2</sub> of &gt; or equal 0.3 and had a ventilatory index of &lt; 0.8 were eligible while for infants without culture proven sepsis, the oxygen requirement was the same but the ventilatory index threshold was &lt; 0.510.</p>

## Characteristics of included studies (Continued)

Demographic data: values presented as mean (SE) or as appropriate

Group A: Dexamethasone group

n = 15

Birth weight (grams): 773 (132)

Gestational age (weeks): 26 (24-27)

Gender (male/female): 7/8

Prenatal steroids: 2/15

Inborn: 12

Prestudy sepsis: 8

Initial ventilation index: 0.252 (0.094)

Group B: High dose beclomethasone group

n = 16

Birth weight (grams): 710 (148)

Gestational age (weeks): 26 (23-29)

Gender (male/female): 6/10

Prenatal steroids: 1/15

Inborn: 13

Prestudy sepsis: 10

Initial ventilation index: 0.300 (0.184)

Group C: Medium dose beclomethasone group

n = 15

Birth weight (grams): 796 (152)

Gestational age (weeks): 26 (24-30)

Gender (male/female): 8/7

Prenatal steroids: 3/16

Inborn: 11

Prestudy sepsis: 7

Initial ventilation index: 0.294 (0.106)

Group D: Low dose beclomethasone group

n = 15

Birth weight (grams): 760 (124)

Gestational age (weeks): 25 (24-31)

Gender (male/female): 9/6

Prenatal steroids: 2/15

Inborn: 13

Prestudy sepsis: 9

Initial ventilation index: 0.293 (0.158)

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### Interventions

Infants were randomized into 4 groups:

Group A: aerosol placebo-  
systemic dexamethasone

Group B: high dose beclomethasone-systemic placebo

Group C: medium dose beclomethasone-systemic placebo

Group D: low dose beclomethasone-systemic placebo

Dexamethasone group: 42 day course of dexamethasone as described by Avery et al followed by a 7 day course of placebo to ensure that all subjects ended the study at the same time.

Subjects in the aerosol steroid groups (B, C, or D) began a similar 42-day systemic dexamethasone course on day 8 if extubation was unsuccessful while on inhaled steroids.

Aerosol steroid groups randomized to receive:

High dose beclomethasone group (2.4-3.69 micrograms/kg/day)

Medium dose beclomethasone group (1.0-1.85 micrograms/kg/

## Characteristics of included studies (Continued)

	<p>day) Low dose beclomethasone group (0.48-0.74 micrograms/kg/day) Beclomethasone dipropionate (42 micrograms/actuation, Vanceril, Schering-Plough, Kenilworth, NJ) was administered using a metered dose inhaler (MDI) placed between the bag and the spacer. After disconnecting the ventilator circuit, a 250-ml Laerdal resuscitation bag with oxygen reservoir connected to an oxygen source (&gt; 90% FiO<sub>2</sub>) was connected through a spacer to the endotracheal tube. After activating the MDI, infants were given three manual breaths. Infants &lt; 1,001 grams at birth received one dose of beclomethasone every 12 hourly while larger infants received a dose every 8 hourly. Inhaled steroids were administered for a maximum of 7 days. The medication was stopped if the infant was successfully extubated for more than 12 hours even if not all doses had been administered.</p>
Outcomes	<p>1. Primary outcome measure was extubation within the first 7 days of the study 2. Secondary outcome measures included changes in ventilator settings and oxygen delivery over the first 7 days. The rates of hypertension, hyperglycemia, infection and growth over the first 7 days were also analyzed. Long-term outcomes not included.</p>
Notes	<p>Infants were ventilated with time-cycled, pressure limited, nonsynchronized ventilators during this study. Ventilator management was prescribed during the first 2 weeks of the study. If the pCO<sub>2</sub> was &lt; 50 mm Hg, the peak pressure was lowered until it was &lt; 15 cm H<sub>2</sub>O. Then, if the pCO<sub>2</sub> was &lt; 50 mm Hg, the ventilator rate was lowered, FiO<sub>2</sub> was adjusted to maintain oxygen saturation between 88-92%. No subjects received bronchodilators during the study period. The use of caffeine or diuretics was left to the discretion of the attending physician.</p>
Allocation concealment	A – Adequate

Study	Suchomski 2002
Methods	<p>Prospective randomized controlled trial. 1. Blinding of randomization: Yes Random allocation using 3 sets of 27 assembled, opaque envelopes. As infants were enrolled, a card was sequentially pulled and infant assigned to appropriate study group. In case of multiple gestation, all eligible siblings were assigned to same group to minimize parental anxiety. 2. Blinding of intervention: No 3. Blinding of outcome measurement: No 4. Complete follow up: Yes</p>
Participants	<p>78 preterm infants &lt; or = 30 weeks, birth weight &lt; or = 1500 g and conventional ventilator dependence at 12-21 days of age with rate &gt; 15/min and FiO<sub>2</sub> &gt; 0.30 with persistence of these ventilator settings for a minimum of 72 hours were enrolled in the study. Demographic data: Values presented as mean (SD) or as appropriate Inhaled beclomethasone 800 µg/d group n = 25 Gestational age (weeks): 26 (1) Birth weight (grams): 843 (177) Gender (female/male) (number of infants): 14/11 Maternal steroids (number and percentage): 12 (48%) Age of commencement of steroids (days): 17 (3) Baseline mean airway pressure: 7.1 (1.2)</p>

## Characteristics of included studies (Continued)

Baseline FiO<sub>2</sub>: 0.44 (0.10)

Inhaled beclomethasone 400 µg/day group  
n = 26

Gestational age (weeks): 26 (2)

Birth weight (grams): 846 (139)

Gender (female/male) (number of infants): 12/14

Maternal steroids (number and percentage): 22 (84.6%)

Age of commencement of steroids (days): 18 (3)

Baseline mean airway pressure: 7.3 (1.9)

Baseline FiO<sub>2</sub>: 0.42 (0.13)

Intravenous dexamethasone group

n=27

Gestational age (weeks): 26 (2)

Birth weight (grams): 843 (227)

Gender (female/male) (number of infants): 8/19

Maternal steroids (number and percentage): 16 (59.2%)

Age of commencement of steroids (days): 17 (2)

Baseline mean airway pressure: 7.9 (1.6)

Baseline FiO<sub>2</sub>: 0.49 (0.13)

Infants were ineligible if they were on high frequency oscillatory ventilation. Exclusion criteria: major congenital malformations, culture positive sepsis, hypertension which required medical management, persistent PDA, or hyperglycemia requiring insulin. Infants were also excluded if they received any postnatal steroid therapy (either inhaled or intravenous) before 12 days of age or before entry in the study.

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### Interventions

1. The inhaled beclomethasone was delivered through a metered dose inhaler with a spacer device (Aerovent) connected in line with the ventilator at 50 µg per puff. Between each puff, the infant was ventilated with 4 or 5 manual breaths delivered at a peak pressure identical to that delivered during mechanical ventilation. The 400 µg/d group (n=26) received 4 puffs every 12 hours. The 800 µg/puff group (n=25) received 4 puffs every 6 hours. Beclomethasone was continued until extubation. If the infant was successfully extubated, then the same dose was administered for 48 hours more. Thereafter, the steroid dose was halved every other day for 6 days, after which the steroid was stopped. After extubation, the inhaled beclomethasone was given using a face mask with inhaler and spacer device.

2. The intravenous dexamethasone group (n=27) received a 42 day tapering course (Avery 1985), starting with 0.5 mg/kg/day, divided every 12 hours. Cross over from either of the inhaled beclomethasone groups to intravenous dexamethasone was allowed if, after 4 to 5 days of inhaled beclomethasone, the infant's ventilator and oxygen support had not decreased and the attending neonatologist felt that the infant might benefit from intravenous dexamethasone.

3. All data were analysed according to original group assignment.

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### Outcomes

1. Primary outcome measures: hypertension or hyperglycemia needing treatment or culture positive sepsis.

2. Other outcome variables: ventilatory settings, specifically rate, mean airway pressure (MAP), peak inspiratory pressure (PIP), positive end expiratory pressure (PEEP), and supplemental oxygen requirement every 6 hours daily on all enrolled patients starting from 5 days before initiation of steroid therapy and daily thereafter, until extubation. After extubation, the supplemental oxygen was recorded daily until patient was discharged or supplemental oxygen was discontinued.

3. The occurrence of the following was also recorded: IVH, PVL, NEC, ROP, GI bleed and death.

4. For babies who completed at least a 10 day course of either inhaled or intravenous steroids, an ACTH stimulation test was done 2 weeks after completion of steroid course. The test was completed in 24 neonates and the morning cortisol levels were noted before and one hour after intravenous bolus of 36 µg/kg synthetic ACTH

(Cortrosyn, Organon, West Orange, NJ).

Notes Sample size was determined by assuming a rate of adverse effects (as defined by sepsis or hyperglycemia or hypertension requiring treatment) of 80% in intravenous steroid -treated infants. The sample size was calculated to detect a 30% difference in adverse effects at 80% power and  $p < 0.05$ .  
There was a statistically significant difference between the groups regarding some maternal characteristics such as maternal steroid use and need for caesarean section.

Allocation concealment A – Adequate

Abbreviations:

CGA: corrected gestational age

IVH: intraventricular hemorrhage

MDI: metered dose inhaler

NEC: necrotising enterocolitis

PDA: patent ductus arteriosus

PIP: peak inspiratory pressure

PEEP: positive end expiratory pressure

PO: per orally

ROP: retinopathy of prematurity

### Characteristics of excluded studies

Study	Reason for exclusion
Dimitriou 1997	The authors included non ventilator dependent infants and the age of commencement of steroids varied from 5 to 118 days of life.
Nicholl 2002	Non-ventilator dependent infants were included in the study.

## ANALYSES

### Comparison 01. Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 CLD at 36 weeks PMA	2	139	Relative Risk (Fixed) 95% CI	1.02 [0.83, 1.25]
02 CLD at 28 days of age	1	78	Relative Risk (Fixed) 95% CI	0.96 [0.91, 1.02]
03 Death by 36 weeks PMA	1	78	Relative Risk (Fixed) 95% CI	2.69 [0.13, 54.15]
04 Death by 28 days of age	1	78	Relative Risk (Fixed) 95% CI	2.69 [0.13, 54.15]
05 Death by or CLD at 36 weeks PMA	1	78	Relative Risk (Fixed) 95% CI	0.94 [0.83, 1.05]
06 Death by or CLD at 28 days of age	1	78	Relative Risk (Fixed) 95% CI	Not estimable
07 Need for ventilation amongst survivors at 36 weeks PMA	1	76	Relative Risk (Fixed) 95% CI	1.10 [0.30, 4.06]
08 Duration of mechanical ventilation amongst survivors (days)	1	77	Weighted Mean Difference (Fixed) 95% CI	-3.00 [-16.28, 10.28]
09 Duration of supplemental oxygen amongst survivors (days)	1	76	Weighted Mean Difference (Fixed) 95% CI	-15.00 [-36.83, 6.83]
10 Length of hospital stay amongst survivors (days)	1	76	Weighted Mean Difference (Fixed) 95% CI	-13.00 [-33.22, 7.22]
11 Hyperglycemia	2	139	Relative Risk (Fixed) 95% CI	0.33 [0.05, 2.12]

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12 Hypertension	2	139	Relative Risk (Fixed) 95% CI	0.70 [0.31, 1.58]
13 Necrotizing enterocolitis	1	78	Relative Risk (Fixed) 95% CI	2.12 [0.25, 18.02]
14 Gastrointestinal bleed	1	78	Relative Risk (Fixed) 95% CI	Not estimable
15 Periventricular leucomalacia	2	139	Relative Risk (Fixed) 95% CI	0.83 [0.33, 2.08]
16 Retinopathy of prematurity > or equal to stage 3	2	139	Relative Risk (Fixed) 95% CI	1.33 [0.64, 2.74]
17 Culture proven sepsis	1	78	Relative Risk (Fixed) 95% CI	1.24 [0.35, 4.40]

### Comparison 02. Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 CLD at 36 weeks PMA	1	292	Relative Risk (Fixed) 95% CI	1.10 [0.82, 1.47]
02 CLD at 28 days of age	1	292	Relative Risk (Fixed) 95% CI	1.06 [0.88, 1.26]
03 Death by 36 weeks PMA	1	292	Relative Risk (Fixed) 95% CI	0.96 [0.62, 1.49]
04 Death by 28 days of age	1	292	Relative Risk (Fixed) 95% CI	0.85 [0.52, 1.37]
05 Death by or CLD at 36 weeks PMA	1	292	Relative Risk (Fixed) 95% CI	1.04 [0.86, 1.26]
06 Death by or CLD at 28 days of age	1	292	Relative Risk (Fixed) 95% CI	1.00 [0.90, 1.12]
07 Pneumothorax	1	292	Relative Risk (Fixed) 95% CI	0.92 [0.53, 1.60]
08 Other air leaks	1	292	Relative Risk (Fixed) 95% CI	1.00 [0.55, 1.83]
09 Pulmonary hemorrhage	1	292	Relative Risk (Fixed) 95% CI	0.86 [0.43, 1.72]
10 Duration of mechanical ventilation (days)	1	292	Weighted Mean Difference (Fixed) 95% CI	0.13 [-5.17, 5.43]
11 Duration of supplemental oxygen (days)	1	292	Weighted Mean Difference (Fixed) 95% CI	6.72 [-16.70, 30.14]
12 Hyperglycemia	1	292	Relative Risk (Fixed) 95% CI	0.90 [0.63, 1.28]
13 Hypertension	1	292	Relative Risk (Fixed) 95% CI	0.87 [0.74, 1.02]
14 Necrotizing enterocolitis	1	292	Relative Risk (Fixed) 95% CI	0.86 [0.43, 1.72]
15 Gastrointestinal bleed	1	292	Relative Risk (Fixed) 95% CI	0.89 [0.41, 1.93]
16 Gastrointestinal perforation	1	292	Relative Risk (Fixed) 95% CI	0.85 [0.23, 3.08]
17 Patent ductus arteriosus	1	292	Relative Risk (Fixed) 95% CI	0.90 [0.73, 1.11]
18 Retinopathy of prematurity, any stage	1	292	Relative Risk (Fixed) 95% CI	1.27 [0.86, 1.89]
19 Culture proven sepsis	1	292	Relative Risk (Fixed) 95% CI	1.06 [0.78, 1.44]

## INDEX TERMS

### Medical Subject Headings (MeSH)

Administration, Inhalation; Beclomethasone [administration & dosage]; Chronic Disease; Dexamethasone [administration & dosage]; Glucocorticoids [\*administration & dosage]; Infant, Newborn; Infant, Premature; Infant, Premature, Diseases [\*drug therapy]; \*Infant, Very Low Birth Weight; Lung Diseases [\*drug therapy]; Respiration, Artificial

### MeSH check words

Humans

## COVER SHEET

**Title** Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants (Review) 18

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<b>Authors</b>	Shah SS, Ohlsson A, Halliday H, Shah VS
<b>Contribution of author(s)</b>	Sachin Shah: performance of literature search, identification of studies, abstraction of the data, analysis of data and writing of the review. Arne Ohlsson: writing of the protocol, identification of studies (literature search), abstraction of data, analysis of data and editing of the review. Henry Halliday: writing of protocol, identification of studies, abstraction of data, analysis of data and editing of review. Vibhuti Shah: writing of the protocol, identification of studies (literature search), abstraction of data, analysis of data and editing of the review. This update was conducted by Vibhuti Shah and Arne Ohlsson.
<b>Issue protocol first published</b>	2000/2
<b>Review first published</b>	2003/2
<b>Date of most recent amendment</b>	17 August 2007
<b>Date of most recent SUBSTANTIVE amendment</b>	03 August 2007
<b>What's New</b>	This updates the review "Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants" published in The Cochrane Library Issue 2, 2003 (Shah 2003). For this update, one additional trial was identified and included in this review. The conclusions of the review did not change.
<b>Date new studies sought but none found</b>	Information not supplied by author
<b>Date new studies found but not yet included/excluded</b>	Information not supplied by author
<b>Date new studies found and included/excluded</b>	Information not supplied by author
<b>Date authors' conclusions section amended</b>	Information not supplied by author
<b>Contact address</b>	Dr Vibhuti Shah Staff Neonatologist Department of Paediatrics Mount Sinai Hospital Room 775A 600 University Avenue Toronto Ontario M5G 1X5 CANADA E-mail: vshah@mtsinai.on.ca Tel: 416 586 4816 Fax: 416 586 8745
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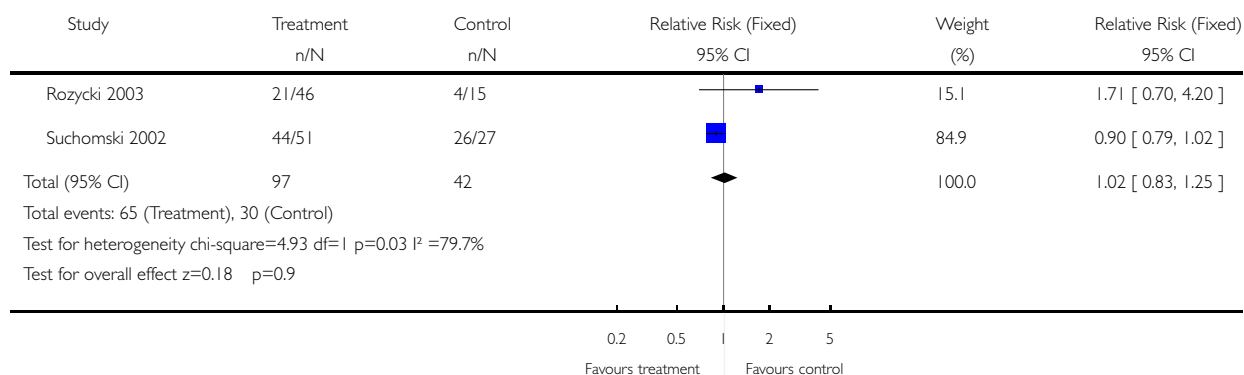
## GRAPHS AND OTHER TABLES

### Analysis 01.01. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 01 CLD at 36 weeks PMA

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 01 CLD at 36 weeks PMA

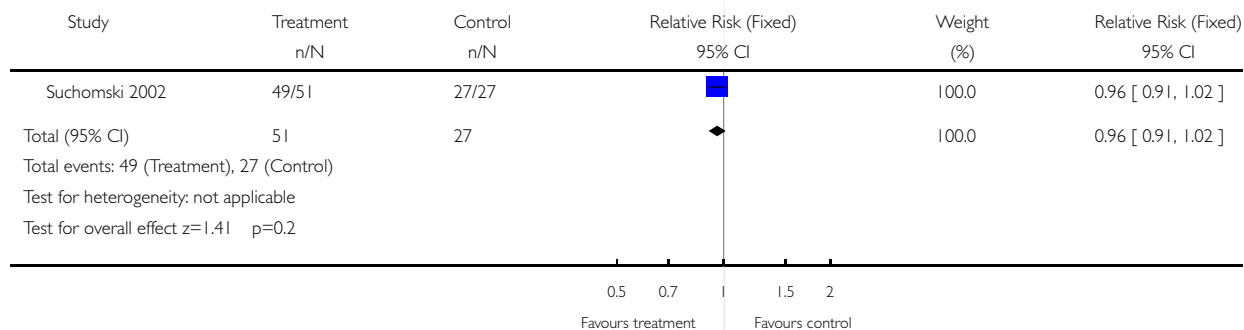


### Analysis 01.02. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 02 CLD at 28 days of age

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

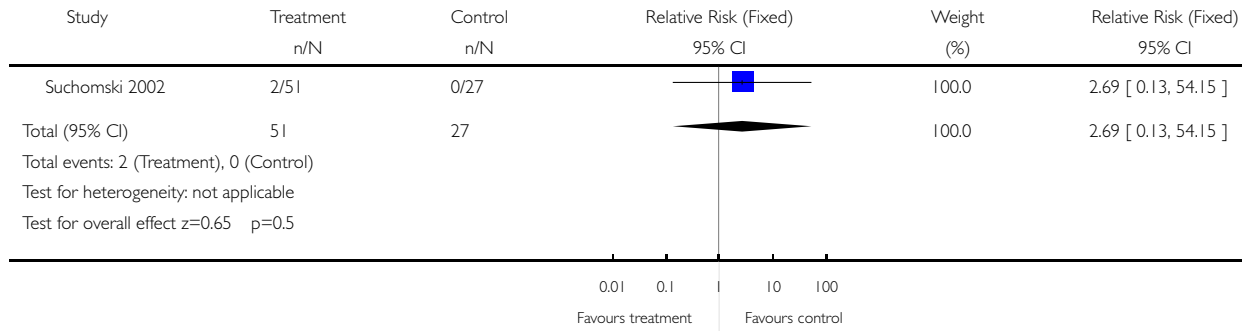
Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 02 CLD at 28 days of age



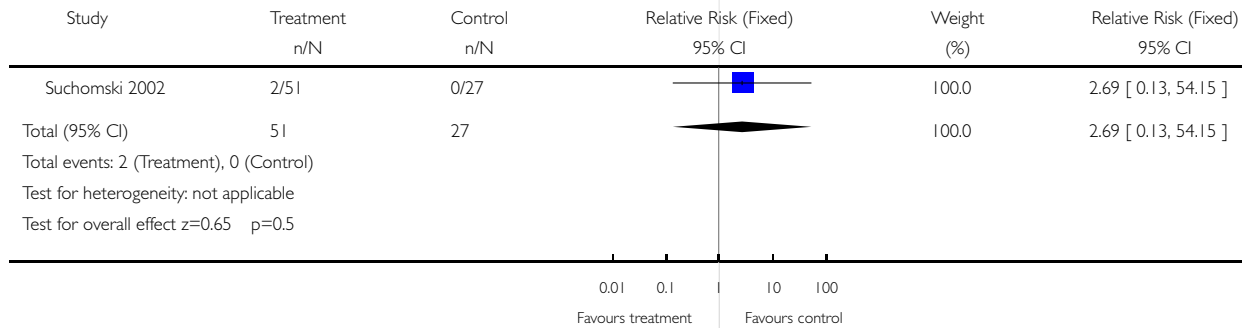
**Analysis 01.03. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 03 Death by 36 weeks PMA**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants  
 Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)  
 Outcome: 03 Death by 36 weeks PMA



**Analysis 01.04. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 04 Death by 28 days of age**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants  
 Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)  
 Outcome: 04 Death by 28 days of age

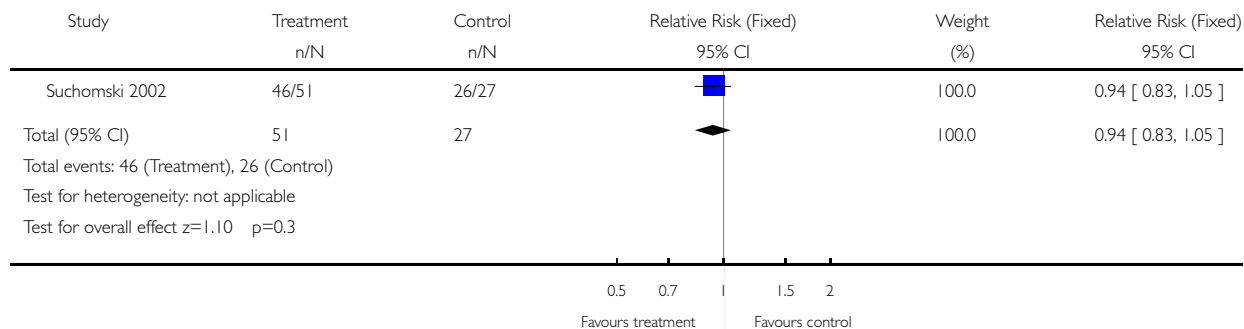


**Analysis 01.05. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 05 Death by or CLD at 36 weeks PMA**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 05 Death by or CLD at 36 weeks PMA

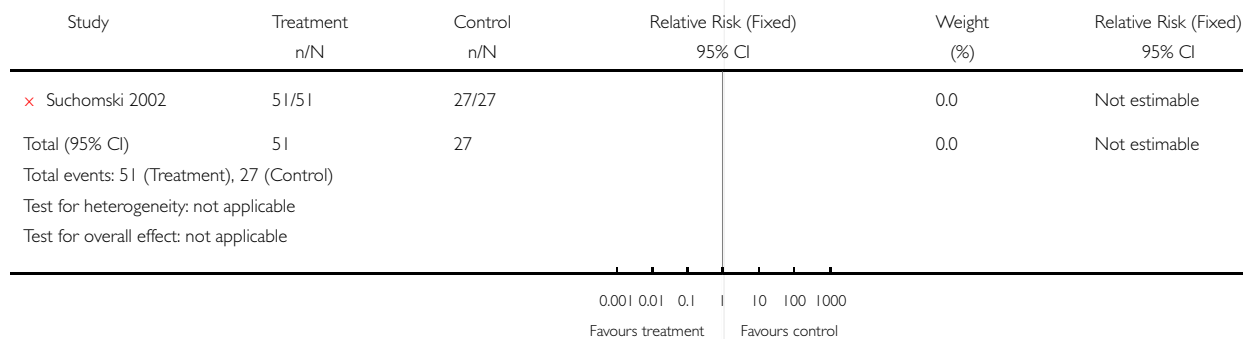


**Analysis 01.06. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 06 Death by or CLD at 28 days of age**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 06 Death by or CLD at 28 days of age

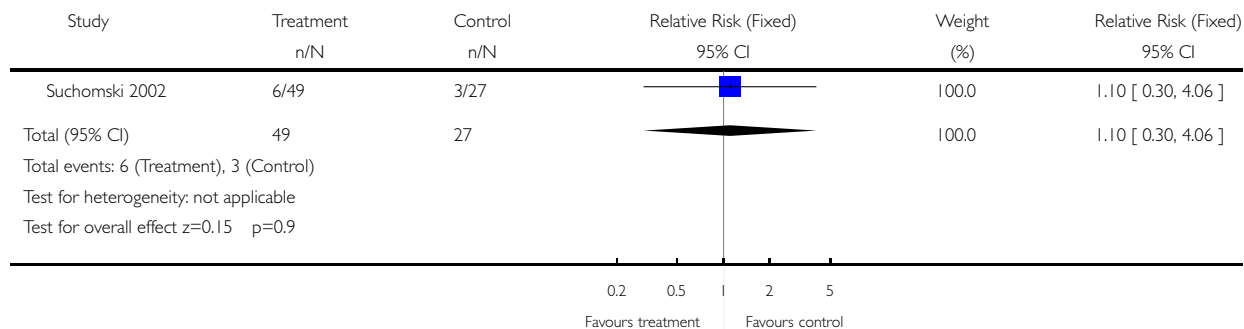


**Analysis 01.07. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 07 Need for ventilation amongst survivors at 36 weeks PMA**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 07 Need for ventilation amongst survivors at 36 weeks PMA

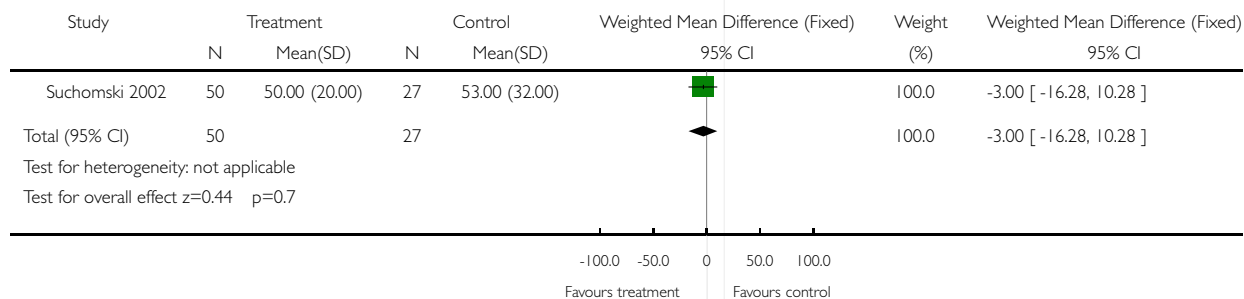


**Analysis 01.08. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 08 Duration of mechanical ventilation amongst survivors (days)**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 08 Duration of mechanical ventilation amongst survivors (days)

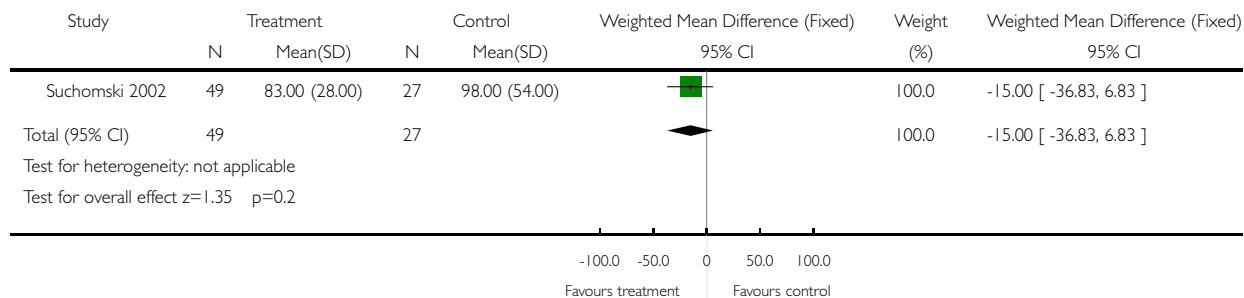


**Analysis 01.09. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 09 Duration of supplemental oxygen amongst survivors (days)**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 09 Duration of supplemental oxygen amongst survivors (days)

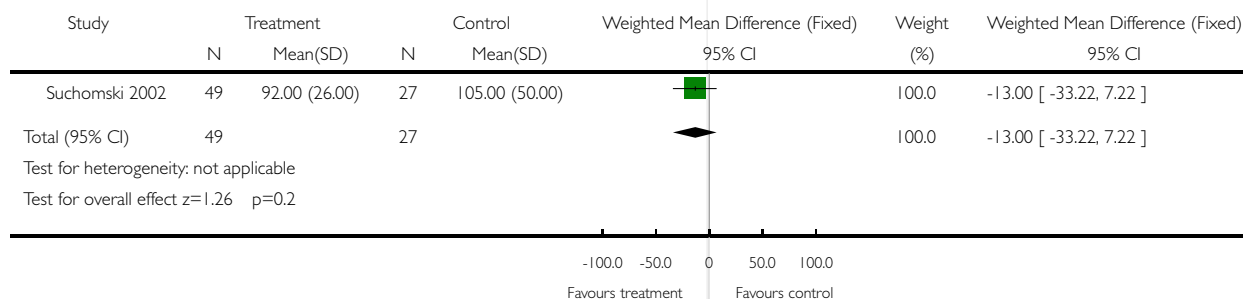


**Analysis 01.10. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 10 Length of hospital stay amongst survivors (days)**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 10 Length of hospital stay amongst survivors (days)

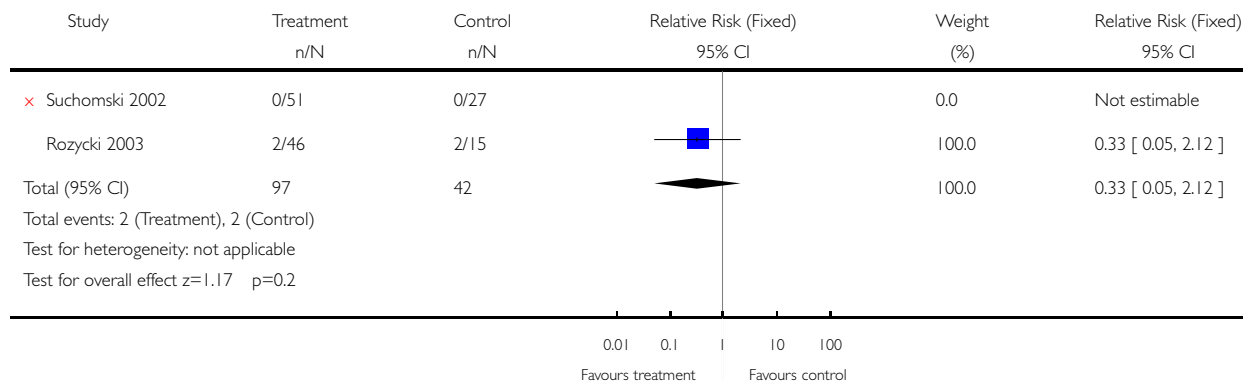


### Analysis 01.11. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 11 Hyperglycemia

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 11 Hyperglycemia

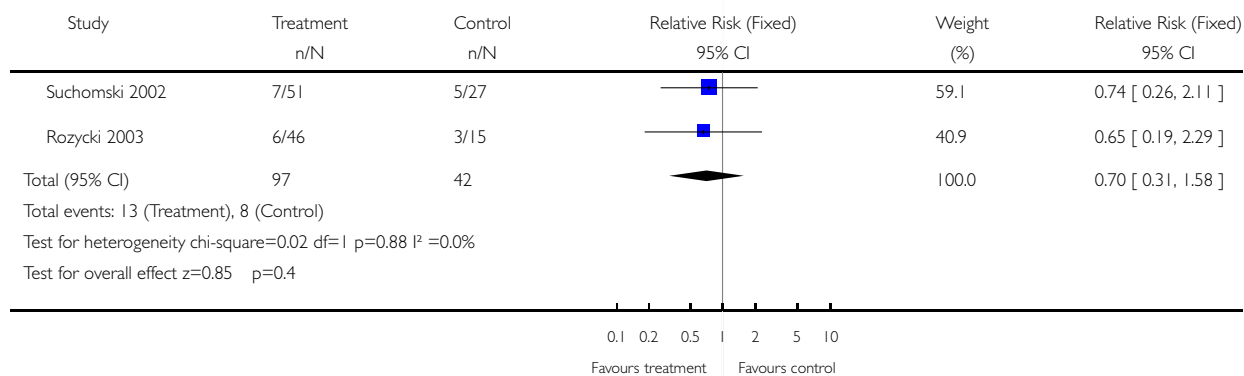


### Analysis 01.12. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 12 Hypertension

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 12 Hypertension

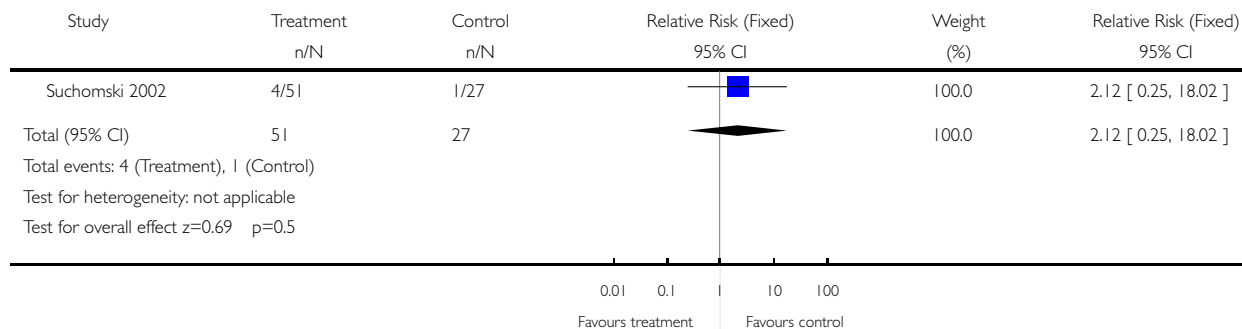


**Analysis 01.13. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 13 Necrotizing enterocolitis**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 13 Necrotizing enterocolitis

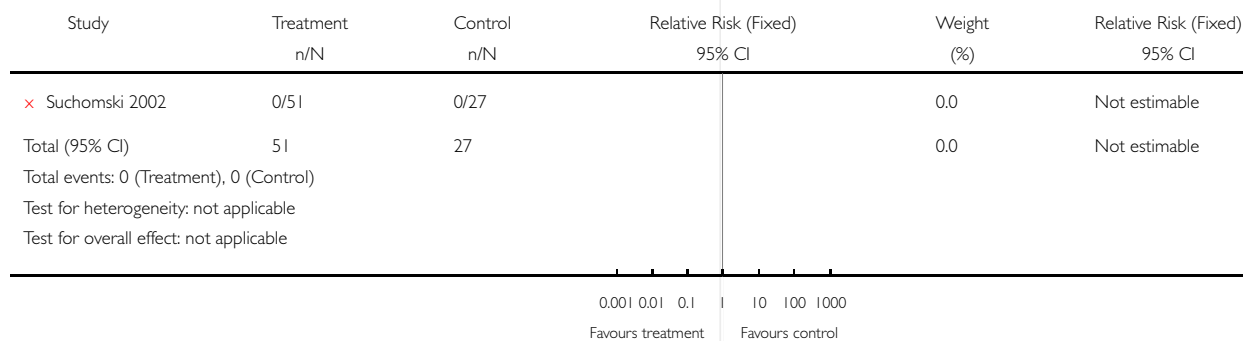


**Analysis 01.14. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 14 Gastrointestinal bleed**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 14 Gastrointestinal bleed

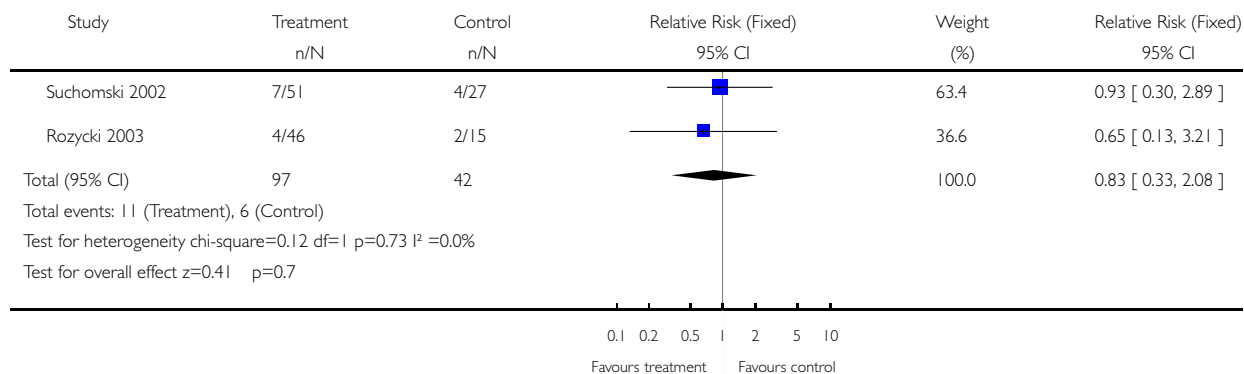


**Analysis 01.15. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 15 Periventricular leucomalacia**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 15 Periventricular leucomalacia

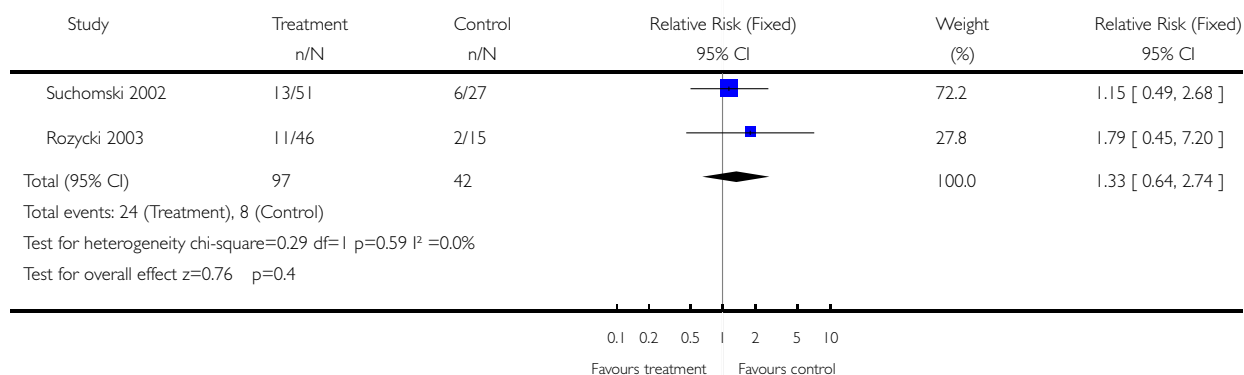


**Analysis 01.16. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 16 Retinopathy of prematurity > or equal to stage 3**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 16 Retinopathy of prematurity > or equal to stage 3

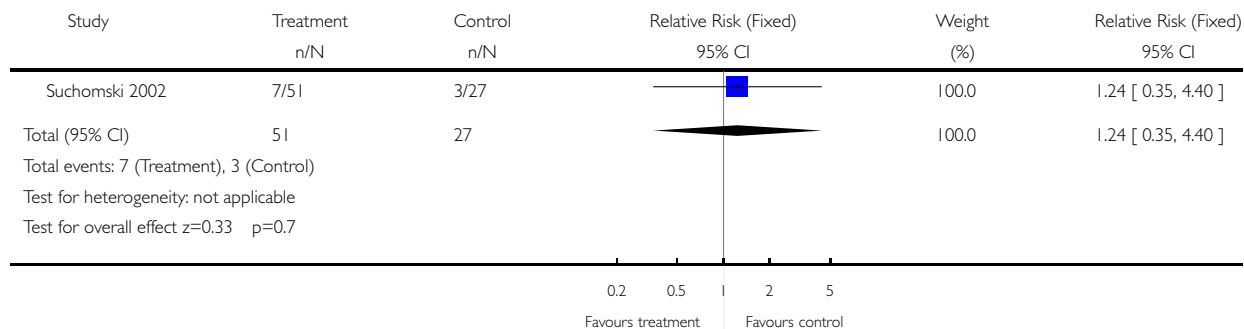


**Analysis 01.17. Comparison 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age), Outcome 17 Culture proven sepsis**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 01 Inhaled vs. systemic steroids (Infants randomized between 12-21 days of age)

Outcome: 17 Culture proven sepsis

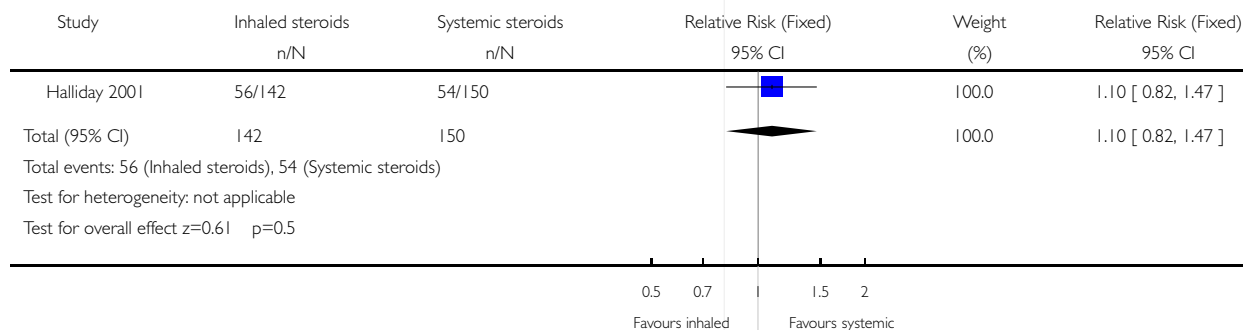


**Analysis 02.01. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 01 CLD at 36 weeks PMA**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 01 CLD at 36 weeks PMA

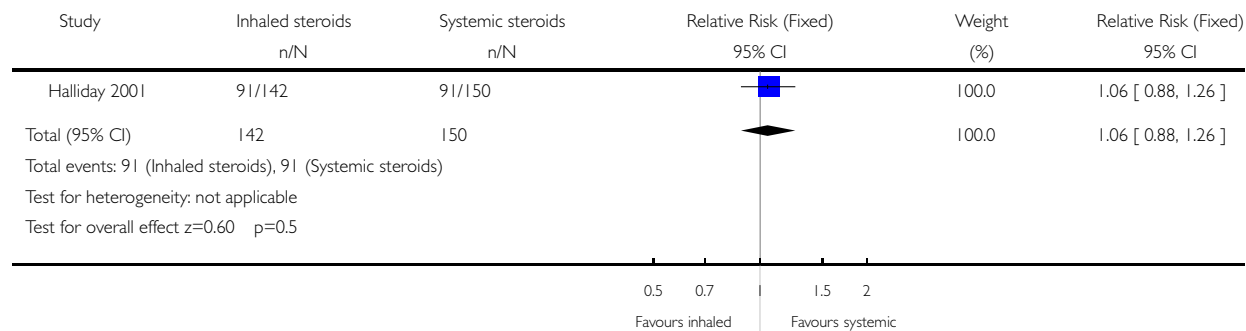


**Analysis 02.02. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 02 CLD at 28 days of age**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 02 CLD at 28 days of age

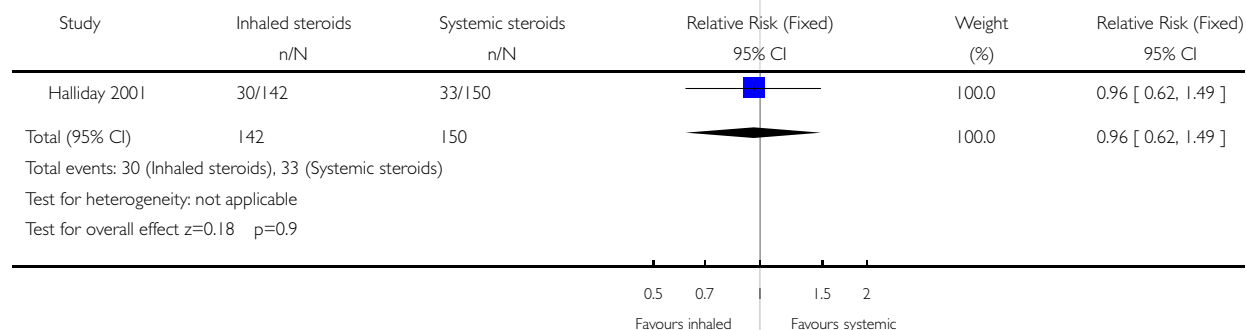


**Analysis 02.03. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 03 Death by 36 weeks PMA**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 03 Death by 36 weeks PMA

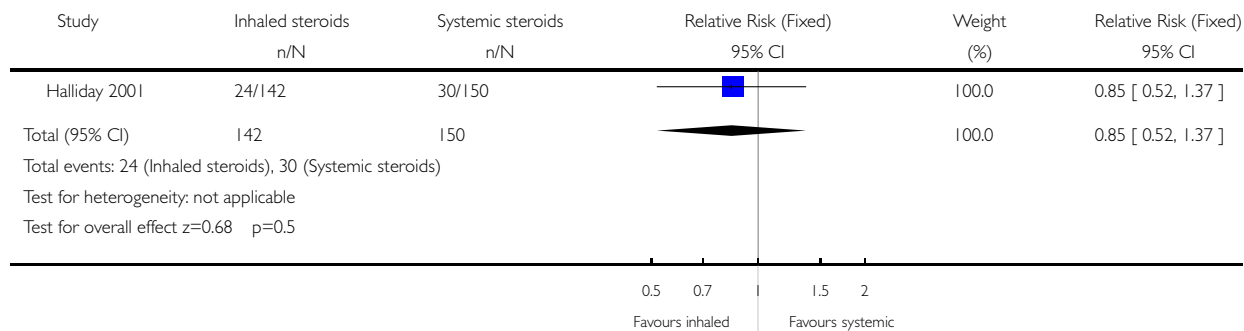


**Analysis 02.04. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 04 Death by 28 days of age**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 04 Death by 28 days of age

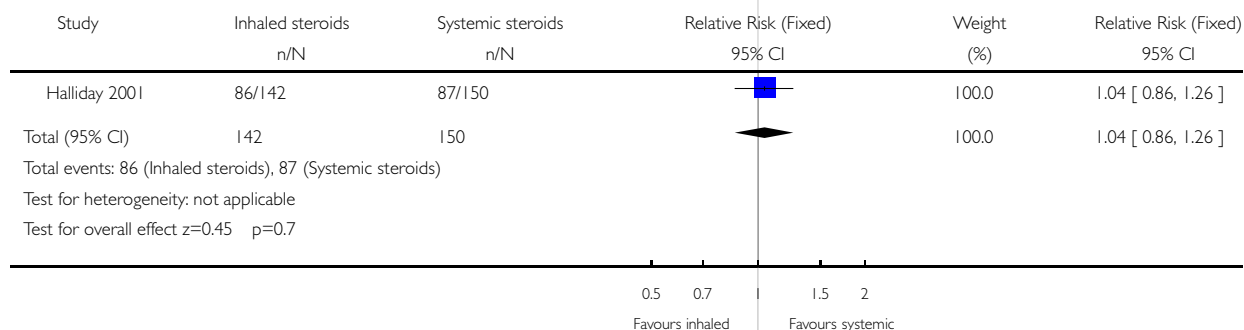


**Analysis 02.05. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 05 Death by or CLD at 36 weeks PMA**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 05 Death by or CLD at 36 weeks PMA

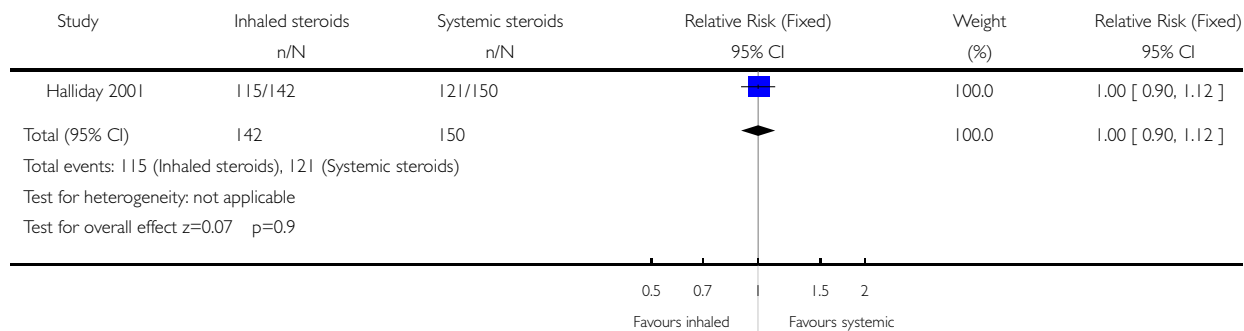


**Analysis 02.06. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 06 Death by or CLD at 28 days of age**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 06 Death by or CLD at 28 days of age

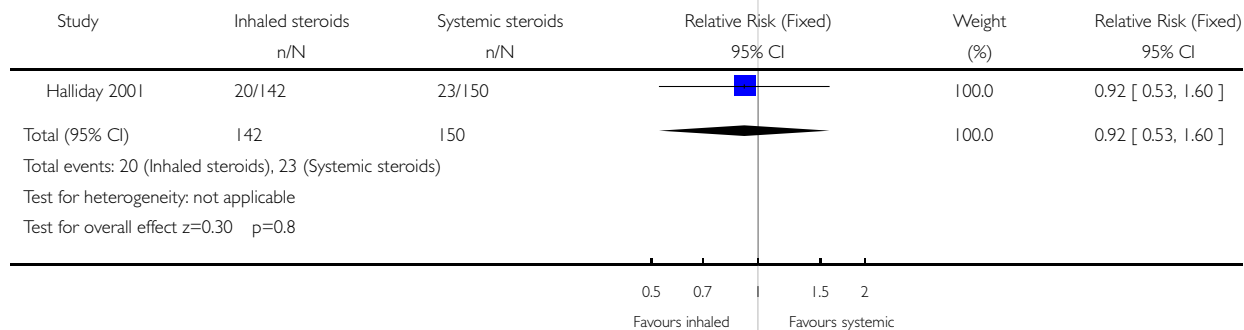


**Analysis 02.07. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 07 Pneumothorax**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 07 Pneumothorax

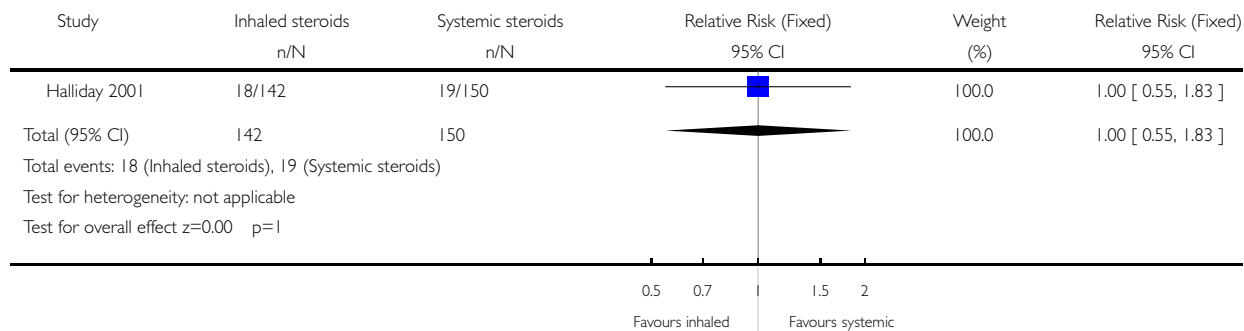


**Analysis 02.08. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 08 Other air leaks**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 08 Other air leaks

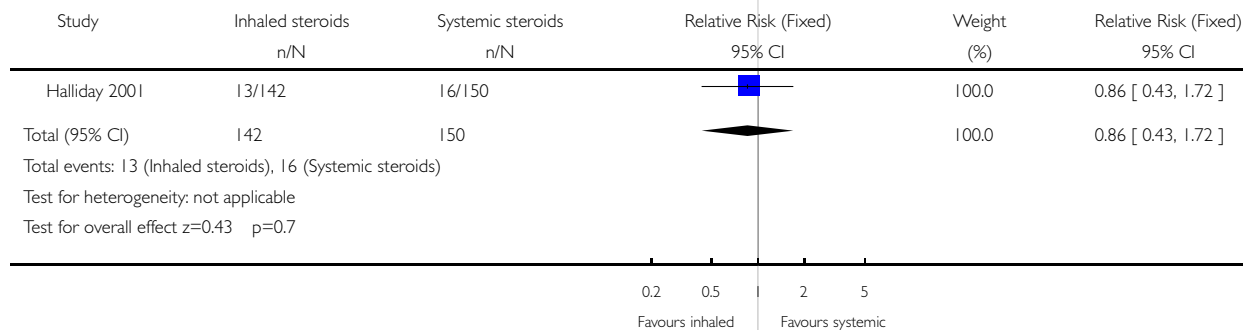


**Analysis 02.09. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 09 Pulmonary hemorrhage**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 09 Pulmonary hemorrhage

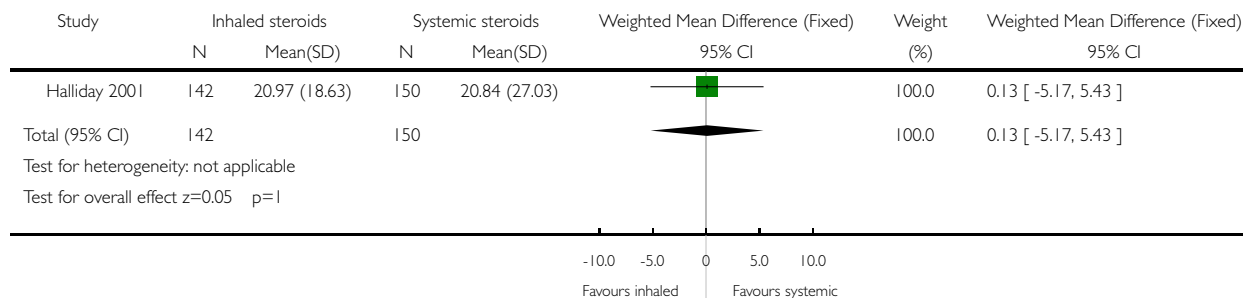


**Analysis 02.10. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 10 Duration of mechanical ventilation (days)**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 10 Duration of mechanical ventilation (days)

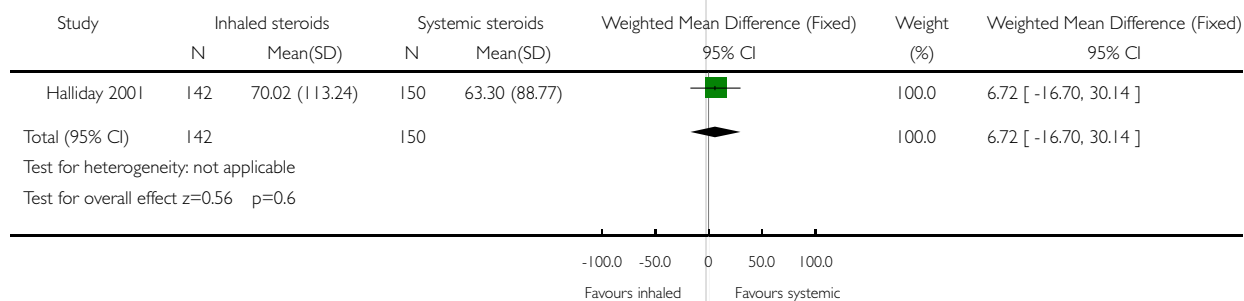


**Analysis 02.11. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 11 Duration of supplemental oxygen (days)**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 11 Duration of supplemental oxygen (days)

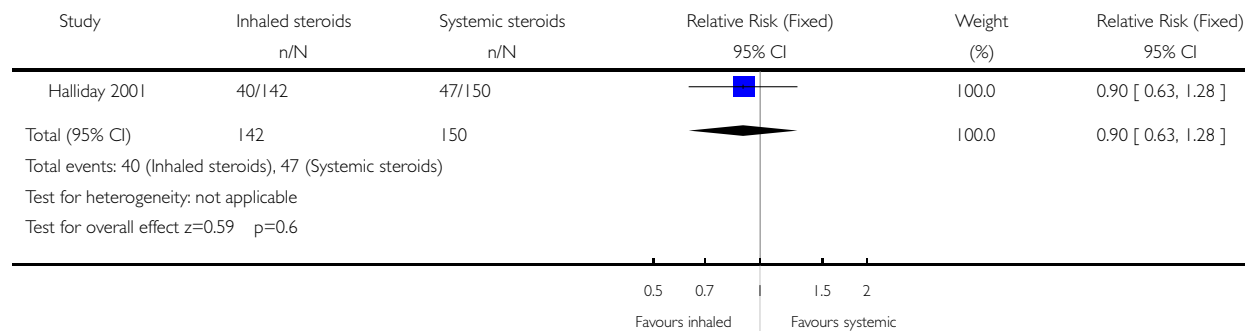


**Analysis 02.12. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 12 Hyperglycemia**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 12 Hyperglycemia

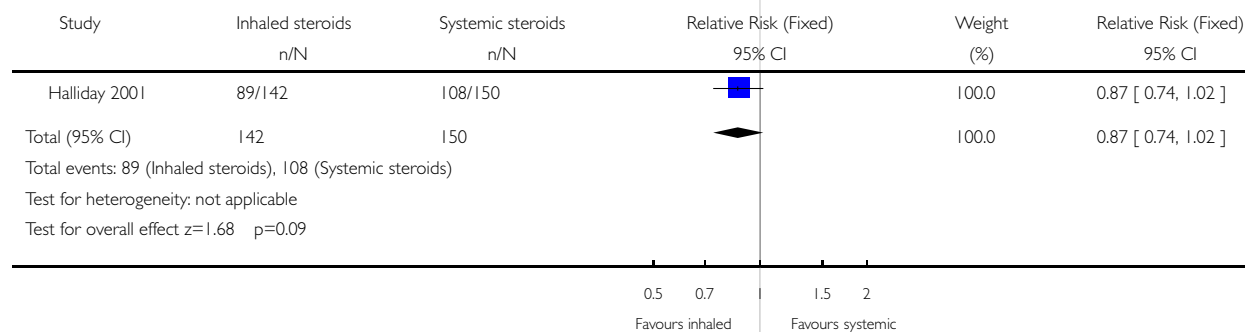


**Analysis 02.13. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 13 Hypertension**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 13 Hypertension

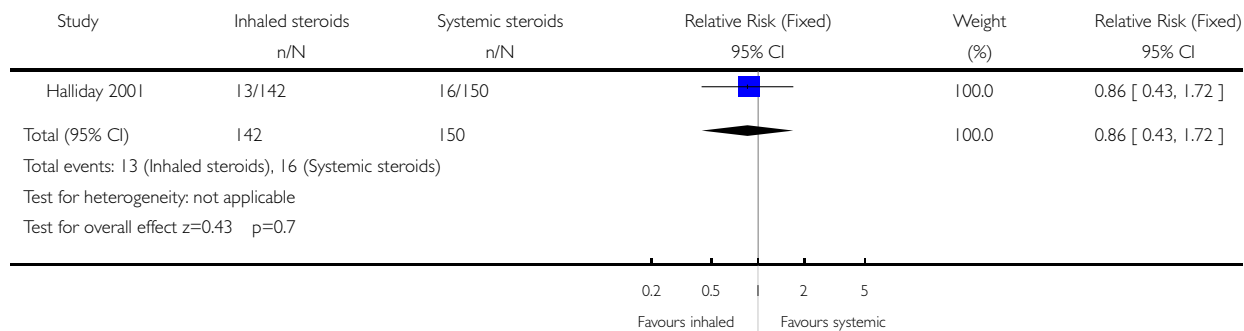


**Analysis 02.14. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 14 Necrotizing enterocolitis**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 14 Necrotizing enterocolitis

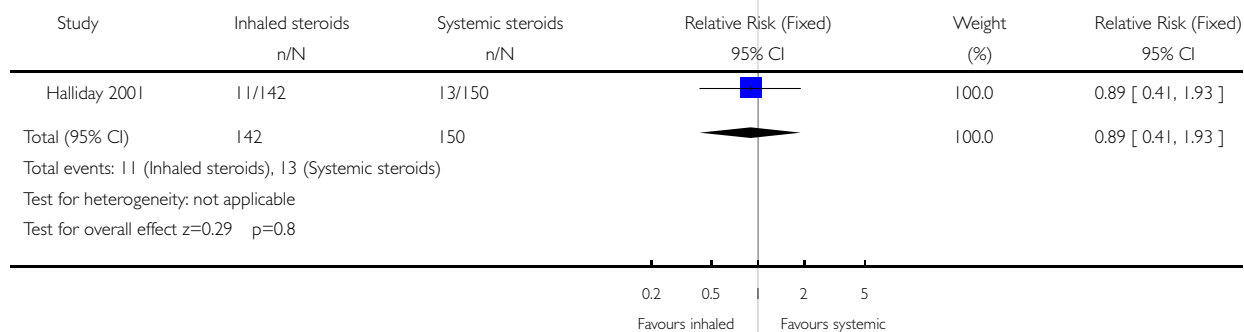


**Analysis 02.15. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 15 Gastrointestinal bleed**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 15 Gastrointestinal bleed

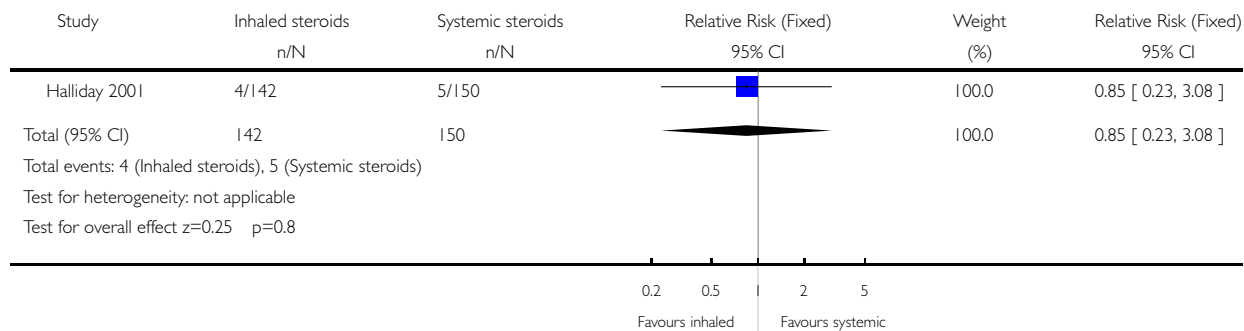


**Analysis 02.16. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 16 Gastrointestinal perforation**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 16 Gastrointestinal perforation

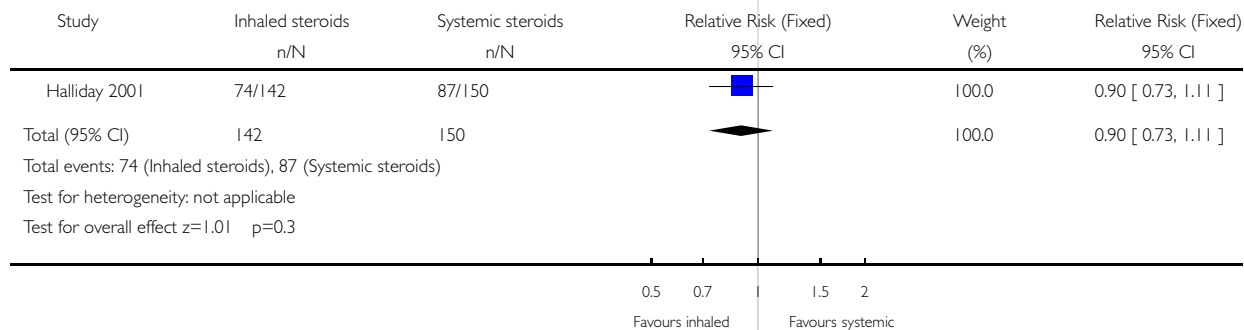


**Analysis 02.17. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 17 Patent ductus arteriosus**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 17 Patent ductus arteriosus

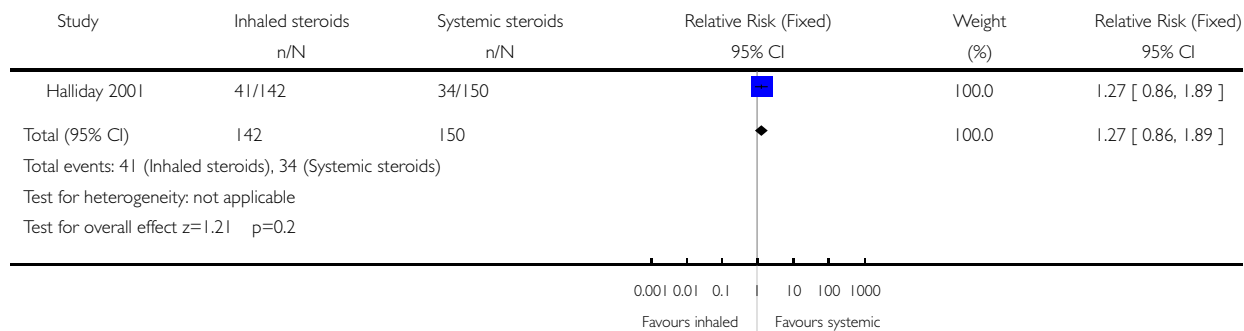


**Analysis 02.18. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 18 Retinopathy of prematurity, any stage**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 18 Retinopathy of prematurity, any stage



**Analysis 02.19. Comparison 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age), Outcome 19 Culture proven sepsis**

Review: Inhaled versus systemic corticosteroids for the treatment of chronic lung disease in ventilated very low birth weight preterm infants

Comparison: 02 Inhaled vs. systemic steroids among all randomized (Infants randomized at < 72 hrs of age)

Outcome: 19 Culture proven sepsis

