# A Network Meta-analysis of Dexamethasone for Preventing Post-Extubation Upper Airway Obstruction in Children

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responsible for abstract and full text screening and data extraction. N.P.I., M.Z. and Y.Z performed statistical analysis. N.P.I., S.A.S., and R.K. are responsible for study data integrity. All authors reviewed the manuscript and approved its final submitted version.

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**Abstract**

**Rationale:** Peri-extubation corticosteroids are commonly used in children to prevent upper airway obstruction (UAO). However, the best timing and dose combination of corticosteroids is unknown.

**Objectives:** To compare effectiveness of different corticosteroid regimens in preventing UAO and reintubation.

**Methods:** MEDLINE, CINAHL and Embase search identified randomized trials in children using corticosteroids to prevent UAO. All studies used dexamethasone. The studies were categorized based on timing of initiation of dexamethasone (early use: >12 hours prior to extubation) and the dose (high dose: (>/= 0.5mg/kg/dose). We performed Bayesian network meta-analysis (NMA) with studies grouped into four regimens- High dose, Early use (HE); Low dose, Early use (LE); High dose, Late use (HL) and Low dose, Late use (LL).

**Results:** 8 trials (n=903) were included in the analysis. For preventing UAO, (odds ratio, 95% credible interval), HE (0.13; 0.04, 0.36), HL (0.39; 0.19, 0.74) and LE (0.15; 0.04, 0.58) regimens appear to be more effective compared to no dexamethasone (low certainty). HE and LE had the highest probability of being the top ranked regimens for preventing UAO [surface under the cumulative ranking (SUCRA) 0.901 and 0.808 respectively]. For preventing reintubation, the effect estimate was imprecise for all four dexamethasone regimens compared to no dexamethasone (very low certainty). HE and LE were the top ranked regimens (SUCRA 0.803 and 0.720 respectively) for preventing reintubation. Sensitivity analysis showed that regimens which started >12 hours prior to extubation were likely more effective than regimens started >6 hours prior to extubation.

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**Conclusions:** Peri-extubation dexamethasone can prevent post-extubation UAO in children but effectiveness is highly dependent on timing and dosing regimen. Early initiation (ideally >12 hours prior to extubation) appears to be more important than the dose of dexamethasone. Ultimately the specific steroid strategy should be personalized considering the potential for adverse events associated with dexamethasone and the individual risk of UAO and reintubation.

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Post-extubation upper airway obstruction (UAO) is a common complication of pediatric endotracheal intubation. While the causes and anatomic locations are multiple, edema in the subglottic space is amongst the most common etiologies for post-extubation UAO, which can lead to increased respiratory load after extubation and extubation failure (1). Post-extubation UAO is reported to contribute to reintubation in 37% of children undergoing elective extubation (2).

Pre-extubation corticosteroids have been used for decades to prevent post-extubation UAO and extubation failure (3). However, corticosteroid treatment regimens vary substantially based on the medication used, dose, timing and the number of doses administered. The optimal combination of dose and timing of corticosteroids to prevent post-extubation UAO in children is unknown, despite numerous randomized controlled trials. Standard meta-analysis with statistical pooling have been conducted, but they are not able to determine if one dosing regimen is superior to another (4). Network meta-analysis (NMA) can distinguish the relative efficacy of different regimen of corticosteroids in preventing post extubation UAO (5).

The objective of this study is to perform a standard pairwise meta-analysis and a network meta-analysis of all the pediatric trials of pre-extubation corticosteroids to determine a) whether corticosteroids are effective in preventing or reducing the severity of post extubation UAO and re-intubation; and b) what combination of corticosteroid dose and timing is most effective in preventing post-extubation UAO and reintubation.

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## Methods

We used the preferred reporting items for systematic reviews and metanalyses (PRISMA) checklist for network metanalyses to prepare this report (Table E1)(6). This review was conducted as part of a project to develop clinical practice guidelines for ventilator liberation in children. The protocol for the systematic review was submitted to the international prospective register for systematic reviews, PROSPERO, at the University of York, United Kingdom and the application was accepted in January 2021 (registration number CRD42021228702). Details of the protocol for the systematic review can be accessed at https://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42021228702.

### Review question

In acutely hospitalized children receiving invasive mechanical ventilation (IMV) for more than 24 hours should systemic corticosteroids be administered prior to extubation to prevent post-extubation UAO?

Outcomes were selected prior to the literature search. We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to rate outcomes into three categories based on their importance for decision-making: a) critical, b) important but not critical and c) outcomes of limited importance (7). Using this process, the panel of experts categorized the outcomes as following:

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a) *Critical outcomes:* mortality, failure to liberate from IMV (i.e., re-intubation), total duration of IMV, pediatric intensive care unit (PICU) length of stay (LOS), post-extubation UAO.

b) *Important outcomes:* liberation from non-invasive respiratory support, ventilator free days, new tracheostomy rate, total duration of non-invasive respiratory support, hospital length of stay, pressure injuries, effort of breathing, cross-over to other treatments.

c) *Outcome of limited importance:* gastrointestinal bleeding, transient hypertension.

**Literature search**

Comprehensive search strategies were composed and conducted by two medical librarians in MEDLINE (Ovid), Embase (Elsevier) and CINAHL Complete (EBSCO) on March 10, 2021 and rerun again on January 18, 2022 for all human studies that include children 18 years or younger. There were no language or date limitations. The complete search strategy is provided in Table E2. Pairs of reviewers independently screened the title and abstracts and performed full text review. Any conflicts were resolved by a third reviewer. Title, abstract screening and full text review were performed using the systematic review software, Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Vic, Australia. (www.covidence.org). We used the following eligibility criteria:

a) *Patients:* We included studies conducted in the PICU or the pediatric cardiac intensive care unit (CICU) that were performed on critically ill children up to age 18 years, receiving IMV for more than 24 hours who underwent or were scheduled for planned

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ventilator liberation. We excluded studies involving preterm infants or where extubation occurred outside the intensive care units (e.g. operating rooms).

b) *Study type:* We included randomized trials evaluating the use of corticosteroids prior to extubation.

**Data collection**

Data abstraction was done by a pair of independent reviewers using standardized data extraction forms in Redcap (8).

**Risk of bias within individual studies**

Risk of bias of included studies was assessed using the Cochrane tool for the assessment of risk of bias in randomized trials (RoB 2.0)(9).

**Data synthesis**

We planned two meta-analyses; a standard pairwise meta-analysis with different corticosteroid regimens pooled as one and a NMA where we lumped studies based on the dose used and the timing of initiation of corticosteroids relative to the time of extubation.

A. Pairwise meta-analysis:

Based on a previously published meta-analysis, we expected most studies to compare corticosteroids with a placebo or no corticosteroids (4). Expecting different dosing regimens, we planned a random effects model for the analysis.

B. Network meta-analysis:

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Nodes (interventions in a network plot) were determined by the dose of systemic corticosteroid used and the timing of the first dose in relation to the extubation. The only corticosteroids used in the included studies was dexamethasone. Therefore, nodes were determined based on dexamethasone dose and timing. Intravenous dexamethasone ≥ 0.5mg/kg/dose was considered high dose. Initiation of systemic corticosteroids ≥12 hours prior to extubation was considered early corticosteroid use (12-hour model). These criteria test the hypotheses that the effectiveness of dexamethasone in reducing upper airway edema may be dependent on the dose of corticosteroid used as well as the number and timing of pre-extubation doses administered. This classification of interventions led to four nodes: Early use of High dose corticosteroids (HE), Early use of Low dose corticosteroid (LE), Late use of High dose corticosteroids (HL) and Late use of Low dose corticosteroids (LL). The arm with no corticosteroid or placebo constituted the fifth node. A sensitivity analysis was planned with early use being defined as >6 hour prior to extubation (6-hour model). The 6-hour duration was tested based on the notion that initiation of corticosteroid at least 12 hours prior to extubation is more likely to delay extubation by 1 day compared to corticosteroid initiation 6 hours or less prior to extubation.

**Statistical analysis**

We performed the NMA using a Bayesian analytic framework. A Bayesian approach has been preferred for network meta-analysis since it is better able to handle studies with very few or zero events and produce probability and ranking outputs that are intuitive to end users (5). The effect of the intervention for dichotomous outcomes was summarized as odds ratio and 95%

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credible intervals (CrI); for continuous measures data was summarized as mean difference and 95% CrI. A Bayesian random effects model for network meta-analysis was adopted because it assumes and accounts for unexplained heterogeneity across studies.

Due to relatively sparse data, imposing a random effects model generally requires the adoption of Bayesian methods with informative priors on between-trials heterogeneity. An empirical study conducted by Turner et al. provides the basis for choosing a plausible prior for the between-studies variance parameter [in our analysis a log normal distribution (-3.02, 1.852)], which is assumed to be equal across comparisons (10).

The analysis was conducted with the Markov Chain Monte Carlo methods (11). Four Markov chains, yielding 400,000 iterations (100,000 iterations per chain after an initial burn-in of 10,000 and a thinning of 10) generating the posterior distributions of the model parameters, were carried out.

Convergence was checked by using the Brooks-Gelman-Rubin diagnostic (12). The goodness of fit of the model was assessed with residual deviance (11). The $I^2$ statistic was used to assess statistical heterogeneity. We used the node splitting approach to calculate the Bayesian P value to determine inconsistency (13).

Different interventions were ranked using the Surface Under the Cumulative Ranking curve (SUCRA) and the rank probabilities generated by the Bayesian approach. SUCRA is expressed as a percentage and provides the relative probability of an intervention being the best among all the options (14). SUCRA of 1 for an intervention indicates that the intervention is certain to be the best among all the interventions tested, while a SUCRA of 0 indicates that the intervention is certain to be the worst among the treatments tested. It is recommended

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that the ranks be interpreted in the context of the certainty of evidence and the absolute risk reduction (ARR) of the pair-wise comparisons (15, 16).

The standard pair wise meta-analysis with all systemic corticosteroid regimens pooled as one was performed using RevMan 5.4 (The Cochrane Collaboration, 2020). The network meta-analysis was conducted using the GeMTC package of R version 3.5.3 (RStudio, Boston, MA)(17).

**Assessment of certainty of the evidence**

We assessed certainty of evidence using recently published guidance by the GRADE working group (18-20). Thresholds for ARR were determined by a survey of authors. The authors considered a difference of >3% (>30 per 1000 ARR) in reintubations, a difference of >10% (>100 per 1000 ARR) in UAO (assuming a third of patients with UAO get reintubated), a difference in PICU LOS of >24 hours and a difference in length of IMV difference of >12 hours as clinically significant.

## Results

A total of 11,235 records were screened of which 11,107 were excluded. The full texts of 128 records were assessed for eligibility. A total of 8 randomized trials fulfilled the eligibility criteria and were included in the analysis (21-28). All the included studies used Dexamethasone as the corticosteroid. Thus, results and conclusions of this review are limited to the use of

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Dexamethasone for the prevention of post-extubation UAO. Figure 1 shows the reason for exclusion of records during the full text review (29, 30).

The 8 trials had a total sample size of 903 subjects. Three studies performed per-protocol analysis (21, 26, 27) and we included 835 total subjects in our meta-analysis. One randomized trial was not included in our analysis because stridor was reported as a continuous outcome rather than a dichotomous outcome, it included two neonates, and three participants in the placebo group received dexamethasone (31). Details of the study characteristics are provided in Table E3. Six trials compared dexamethasone to either isotonic saline or no placebo (21-25, 28). Two studies compared different dosing regimens of dexamethasone to each other (26, 27). The dexamethasone dose used in the trials ranged from 0.15mg/kg/dose to 1mg/kg/dose with a maximum dose of 10mg. Time of initiation of dexamethasone ranged from 1 to 24 hours prior to extubation. Total number of doses ranged from 3 to 6 doses, with some doses given post extubation. All studies employed a 6-hour dosing interval. All studies reported reintubation and UAO, 5 studies reported length of IMV, 3 studies reported PICU LOS, 4 studies reported gastrointestinal bleeding and 3 studies reported the incidence of hypertension. Only data for reintubation and UAO was available for all the nodes in the network analysis.

There was some risk of bias across the studies included in the NMA for both reintubation and UAO (Figure E1a and Figure E1b). One study had a high risk for bias in the assessment of UAO due to lack of blinding (23). In addition, in two studies the concealment of allocation was not clear (22, 24) and one study performed per protocol analysis without sufficient reason to do so (21).

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**Effects of the interventions**

In the standard pairwise meta-analysis, we combined the six studies (n= 473) that compared intravenous dexamethasone to no dexamethasone. Data for reintubation, UAO, length of IMV, PICU LOS, gastrointestinal bleeding and hypertension were pooled across studies (Figure 2). Dexamethasone was associated with a trend for a lower rate of reintubation (odds ratio 0.55, 95% CI 0.21 to 1.46, low certainty). Dexamethasone use was associated with a significantly lower rate of UAO (odds ratio 0.40, 95% CI 0.21 to 0.73, moderate certainty). Three studies (n=298) reported a decrease in length of IMV (mean difference -0.27 days, 95% CI -0.89, 0.35) with Dexamethasone use (23, 24, 28), although this did not meet the threshold for either clinical or statistical significance. Dexamethasone was associated with (two studies, n= 145) a modest and statistically non-significant increase in PICU LOS (mean difference 0.44 days, 95% CI -0.66 to 1.55, very low certainty)(23, 28). There were very few adverse events reported: two studies (n= 146) reported one subject with gastrointestinal bleeding (in the dexamethasone group)(21, 25) and three studies (n=235) reported two subjects with hypertension (one each in dexamethasone and placebo groups)(21, 23, 25).

In the NMA, we grouped the 8 trials (n=835) into five nodes evaluating outcomes of UAO and reintubation. In the 12-hour model (early use defined as dexamethasone initiation ≥12 hours prior to extubation), three studies were included in the high early node (n= 447)(23, 26, 27), 4 studies in the high late node (n= 400)(21, 24, 26, 28), 1 study in low early node (n= 238)(27), 2 studies in low late node (n= 112)(22, 25) and six studies were included in the no corticosteroid node (n=473)(21-25, 28). Table 1a and 1b describe the relative effect estimates and absolute estimates for UAO and reintubation of the nodes with dexamethasone compared

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to the no dexamethasone node. For UAO, the largest absolute risk reduction (34-36% reduction), with the baseline risk of 46%, was seen with early dosing regimens (number needed to treat of 2.8). For preventing UAO, HE, HL and LE all appear to be effective. High early had the highest probability of being the first ranked intervention with a SUCRA of 0.901. The effect estimate for reintubation was imprecise for all four intervention groups when compared to no dexamethasone. Among the interventions, HE had the highest probability of being the first rank for preventing reintubation with a SUCRA of 0.803. The summary effects of all the comparisons along with the GRADE certainty of evidence estimates is provided in Table 2 (a,b). Analysis for both outcomes reached convergence using the Brooks-Gelman-Rubin diagnostic with the overall Potential Scale Reduction Factor (PSRF) < 1.005. Closed network loops for both UAO and reintubation did not show any inconsistency.

Sensitivity analysis which used 6 hours instead of 12 as the cut off for early initiation of corticosteroids showed similar results, although the benefits of early use of steroids were less clear, with odds ratios closer to 1 (Table 1b) compared to the 12-hour model (Table 1a). In this six-hour model, HE and HL appeared to be associated with lower rates of reintubation, while HE and LE were the most effective regimens for preventing UAO. The cumulative rankings in the 12-hour model and the 6-hour model for reintubation and UAO (Figure 3) gives another perspective of the relative efficacy of the different regimens.

Two participants developed GI bleeding in the four trials (n= 512) included in the NMA. Because only two events were reported, it was and not feasible to statistically pool the outcome of GI bleeding in the NMA.

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## Discussion

Systemic corticosteroids have been used across the age spectrum for the prevention of upper airway edema following endotracheal intubation (4). In this review we used a Bayesian NMA framework to study the relative efficacy of different regimens of systemic corticosteroids in preventing post-extubation UAO and reintubation. Our analysis suggests that earlier administration of dexamethasone (at least 6-12 hours prior to extubation) is perhaps more important than the dose of administration (0.5mg/kg/dose versus <0.5mg/kg/dose), with high dose (0.5mg/kg/dose) dexamethasone administered early (>12 hours prior to extubation) likely to be the most effective strategy. These findings with regards to the use of multiple repeated doses administered > 12 hours prior to extubation are consistent with previous systematic reviews conducted in adults (4).

However, most of these findings are driven by the outcome of post-extubation UAO. Reintubation rates were not statistically different between the dexamethasone and placebo groups. Reintubation rates specifically attributable to UAO were not reported separately in the studies, although this is difficult to surmise because re-intubation, even when UAO is present, is often multi-factorial (i.e. UAO plus muscle weakness, poor respiratory drive etc) (1). Hence, a larger sample size may be required to show a benefit on the outcome of re-intubation.

This analysis showed a large UAO prevention effect for early dosing (at least 6-12 hours prior to extubation) of dexamethasone. However, the effect sizes may have been influenced by the high incidence of UAO (46%) in the control groups of the trials. It is possible that the trial population was somehow at higher risk of developing post-extubation UAO than standard

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patients, or that the assessment tools used were very sensitive for the diagnosis of UAO. Two studies described high proportions of intubations taking place in uncontrolled environments with a subsequent higher likelihood for post-extubation UAO (26, 27) and one study included only children at high risk for extubation failure (23, 26, 27). In other studies which used objective assessment tools to diagnose sub-glottic UAO were used, the incidence of UAO was reported to be 12% (1). Nevertheless, even with a 12% UAO incidence the absolute effect of dexamethasone use would be a 10.3% UAO reduction, a clinically significant effect based on our *a priori* threshold of effect sizes. Dexamethasone dosing within 6 hours of planned extubation appeared to be less effective than earlier dosing. Comparing the effect sizes of dexamethasone timing (>12 hours versus >6 hours versus ≤6 hours), a 'time- response relationship' is observed, with dosing >12 hours being the most effective and dosing <6 hours of extubation being the least effective in preventing UAO. If steroids are started within 6 hours of a planned extubation, a higher dose of 0.5mg/kg/dose may be more effective than 0.25mg/kg/dose- with an absolute effect of 21% less UAO. This would be clinically significant if the baseline incidence of UAO is high (i.e. close to 46% like what is seen in the placebo arm of the RCTs); but the absolute effect may not be clinically significant with lower baseline rates of UAO.

A pairwise meta-analysis of trials in adults using pre-extubation systemic corticosteroids reported clinically important effects only in participants who failed a cuff-leak test (suggesting higher likelihood of post-extubation UAO) (32). In children the air leak test is probably predictive of post-extubation UAO only in children with cuffed ET tubes (1). While none of the pediatric trials restricted inclusion based on cuff-leak test, it is likely dexamethasone will have the greatest benefit in a group of children at high risk for developing post-extubation UAO.

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Potential risk factors for the development of post-extubation UAO in children include abnormal cuff-leak test in children with cuffed ETT, multiple airway instrumentations, excessive positive fluid balance, sedation level prior to extubation and previous history of stridor (1), although there is some inconsistency in these variables in the literature.

Use of pre-extubation dexamethasone involves some trade-offs. In our review, there were very few major adverse events reported. This is like the meta-analysis in adults (n=2472) where no cases of hyperglycemia or GI bleeding were reported (32). The trade-offs for using dexamethasone, therefore, mostly depends on the risk of prolonging IMV (to administer corticosteroid) versus a patient's risk of reintubation due to post-extubation UAO.

**Limitations**

Our pairwise analysis showed moderate heterogeneity for reintubation and UAO. An important source of heterogeneity is the variability in the rates of UAO. Some studies included in our review had high rates of UAO in the 'no dexamethasone' arm with one study having a UAO rate of 87.5% (21). Similarly, the reintubation rates were highly variable ranging from 5% to 63%. These differences may be attributed to the subjectivity in diagnosing UAO, wide age range for subjects included in the studies as well as the multifactorial nature of extubation failure in children. Nevertheless, the NMA did not show any inconsistency and it offered more precise effect estimates. Our ability to describe the trade-offs of benefits and harms associated with dexamethasone was limited by the rarity of adverse effects in the included studies. The lack of adverse effects could be due to inadequate reporting as has been suggested recently, but adult studies have reported similarly low rates of adverse effects (33). Our review includes trials that

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span nearly 30 years. Recently, there has been a suggestion that trials more than 20 years old may overestimate effect size (34). In our review, two studies are more than twenty years old, one showed large effect size for both reintubation and UAO in favor of dexamethasone (21) while the other did not find any difference between dexamethasone and placebo. Therefore, we don't believe the age of trials on their own influenced our results (24).

**Conclusions**

Evidence from this network meta-analysis suggests early initiation of dexamethasone (12 hours prior to extubation) using a high dose (0.5mg/kg/dose) is the most effective strategy to prevent post-extubation UAO and possibly reintubation due to UAO. Early initiation with doses less than 0.5mg/kg/dose are probably as effective as early initiation of high dose dexamethasone in preventing UAO. Given the complex nature of trade-offs with each patient, the decision to use a specific strategy of dexamethasone should be personalized taking into consideration the risk of post-extubation UAO, risk factors for extubation failure (such as respiratory muscle weakness), the potential for adverse effects (such as GI bleeding and hypertension) and the time available before planned extubation.

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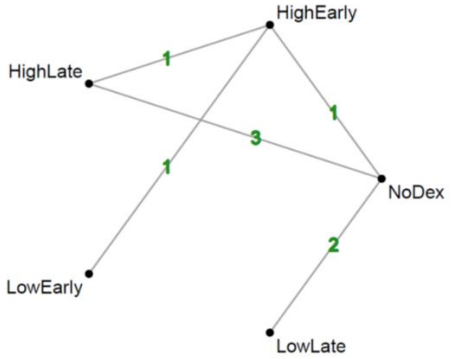
## Table 1a. Summary of Findings for 12-hour model

**Effects of estimates and certainty of evidence for Dexamethasone for the prevention of post-extubation UAO: 12-hour model**

**Population:** Critically ill children intubated and mechanically ventilated for at least 24 hours.

**Interventions:** Dexamethasone
High Early: >/= 0.5mg/kg/dose given > 12 hours pre-extubation
Low Early: <0.5mg/kg/dose given > 12 hours pre-extubation
High Late: >/= 0.5mg/kg/dose given < 12 hours pre-extubation
Low Late: <0.5mg/kg/dose given < 12 hours pre-extubation

**Comparator:** Placebo/No steroids (reference)




**Outcomes:** Reintubation; Upper airway obstruction

**Setting:** PICU, CICU

**Outcome: Reintubation. Rate in reference population: 18.9%**

| Intervention, Total studies, Total participants | Odds ratio (95% CrI) | Anticipated absolute effect (95% CrI) | | | Certainty of evidence | Ranking (SUCRA) |
|---|---|---|---|---|---|---|
| | | *Without intervention* | *With intervention* | Difference | | |
| High early, 3 trials, 447 participants | 0.24 (0.04, 1.17) | 189 per 1000 | 52 per 1000 | 137 fewer per 1000 (181 fewer to 25 more) | Very low* | 0.803 |
| High late, 4 trials, 400 participants | 0.43 (0.10, 1.27) | 189 per 1000 | 93 per 1000 | 96 fewer per 1000 (167 fewer to 40 more) | Very low† | 0.566 |
| Low early, 1 trial, 238 participants | 0.26 (0.02, 3.40) | 189 per 1000 | 57 per 1000 | 132 fewer per 1000 (185 fewer to 254 more) | Very low‡ | 0.720 |
| Low late, 2 trials, 112 participants | 1.1 (0.15, 7.77) | 189 per 1000 | 200 per 1000 | 11 more per 1000 (156 fewer to 456 more) | Very low§ | 0.227 |
| No dexamethasone 6 trials, 473 participants | Reference | Reference | Reference | Reference | Reference | 0.182 |

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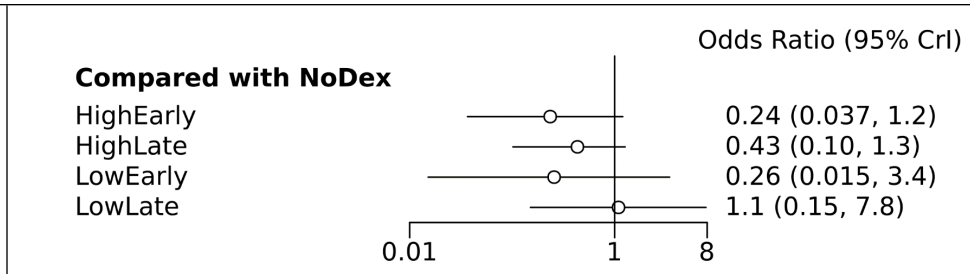
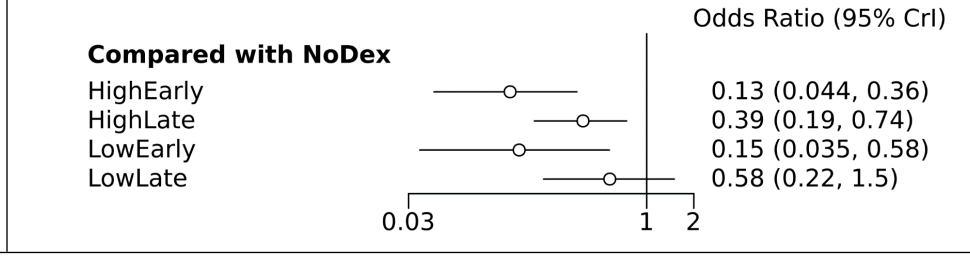
| | | | | | | |
|---|---|---|---|---|---|---|
| Relative effects with No Dexamethasone as reference |  | | | | | |
| **Outcome: UAO. Assessed clinically. Rate in reference population: 46%** | | | | | | |
| High early, 3 trials, 447 participants | 0.13 (0.04, 0.36) | 460 per 1000 | 100 per 1000 | 360 fewer per 1000 (427 fewer to 225 fewer) | Low‖ | 0.901 |
| High late, 4 trials, 400 participants | 0.39 (0.19, 0.74) | 460 per 1000 | 249 per 1000 | 211 fewer per 1000 (321 fewer to 73 fewer) | Low** | 0.460 |
| Low early, 1 trial, 238 participants | 0.15 (0.04, 0.58) | 460 per 1000 | 113 per 1000 | 347 fewer per 1000 (427 fewer to 126 fewer) | Low†† | 0.808 |
| Low late, 2 trials, 112 participants | 0.58 (0.22, 1.52) | 460 per 1000 | 331 per 1000 | 129 fewer per 1000 (302 fewer to 104 more) | Low‡‡ | 0.296 |
| No dexamethasone 6 trials, 473 participants | Reference | Reference | Reference | Reference | Reference | 0.033 |
| Relative effects with No Dexamethasone as reference |  | | | | | |

*One study with high risk of bias, indirectness (single direct study), imprecision

†All studies with some risk of bias, serious inconsistency in direct comparison, imprecision

‡No direct comparison, imprecision

§Some risk of bias, very serious imprecision in direct comparison

‖ One study with high risk of bias, indirectness (single direct study)

**All studies with some risk of bias, serious inconsistency in direct comparison

††No direct comparison

‡‡Some risk of bias, serious imprecision in direct comparison

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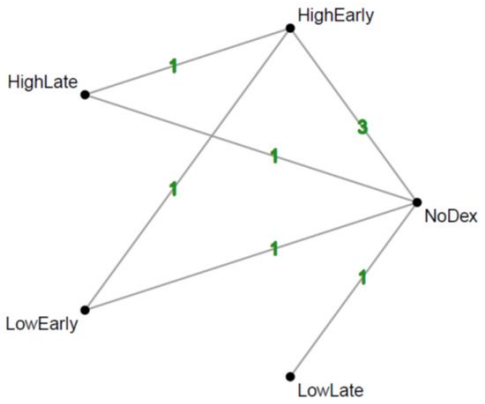
## Table 1b. Summary of Findings for 6-hour model

**Effects of estimates and certainty of evidence for Dexamethasone for the prevention of post-extubation UAO: 6-hour model**

**Population:** Critically ill children intubated and mechanically ventilated for at least 24 hours.

**Interventions:** Dexamethasone
High Early: >/= 0.5mg/kg/dose given > 6 hours pre-extubation
Low Early: <0.5mg/kg/dose given > 6 hours pre-extubation
High Late: >/= 0.5mg/kg/dose given </=6 hours pre-extubation
Low Late: <0.5mg/kg/dose given </= 6 hours pre-extubation

**Comparator:** Placebo/No steroids (reference)




**Outcomes:** Reintubation; Upper airway obstruction

**Setting:** PICU, CICU

**Outcome: Reintubation. Rate in reference population: 18.9%**

| **Intervention, Total studies, Total participants** | **Odds ratio (95% CrI)** | **Anticipated absolute effect (95% CrI)** | | | **Certainty of evidence** | **Ranking (SUCRA)** |
|---|---|---|---|---|---|---|
| | | ***Without intervention*** | ***With intervention*** | **Difference** | | |
| High early, 5 trials, 658 participants | 0.41 (0.09, 1.21) | 189 per 1000 | 87 per 1000 | 102 fewer per 1000 (169 fewer to 31 more) | Very low* | 0.728 |
| High late, 2 trials, 179 participants | 0.44 (0.06, 2.4) | 189 per 1000 | 93 per 1000 | 96 fewer per 1000 (176 fewer to 170 more) | Very low† | 0.657 |
| Low early, 2 trials, 318 participants | 0.63 (0.10, 3.78) | 189 per 1000 | 128 per 1000 | 61 fewer per 1000 (167 fewer to 280 more) | Very low† | 0.482 |
| Low late, 1 trial, 32 participants | 0.99 (0.015, 69) | 189 per 1000 | 187 per 1000 | 2 fewer per 1000 (188 fewer to 752 more) | Very low† | 0.394 |
| No dexamethasone 6 trials, 473 participants | Reference | Reference | Reference | Reference | Reference | 0.238 |

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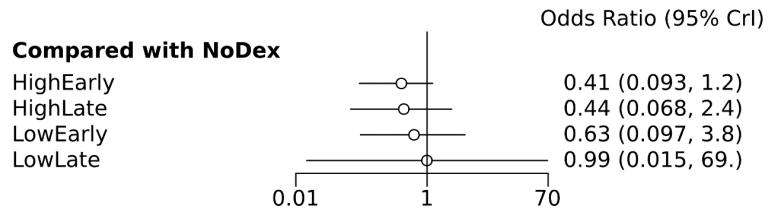
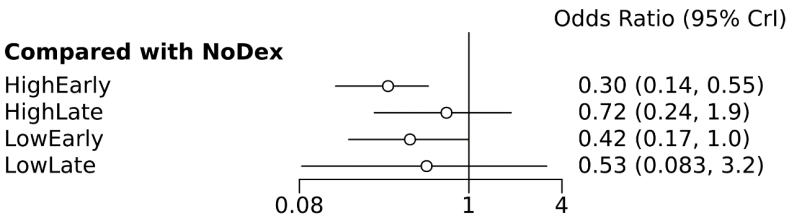
| | | | | | | |
|---|---|---|---|---|---|---|
| Relative effects with No Dexamethasone as reference |  | | | | | |
| **Outcome: UAO. Assessed clinically. Rate in reference population: 46%** | | | | | | |
| High early, 5 trials, 658 participants | 0.30 (0.13, 0.55) | 460 per 1000 | 204 per 1000 | 256 fewer per 1000 (353 fewer to 141 fewer) | Low‡ | 0.880 |
| High late, 2 trials, 179 participants | 0.72 (0.24, 1.9) | 460 per 1000 | 380 per 1000 | 80 fewer per 1000 (290 fewer to 158 more) | Low§ | 0.337 |
| Low early, 2 trials, 318 participants | 0.42 (0.17, 1.0) | 460 per 1000 | 264 per 1000 | 196 fewer per 1000 (333 fewer to 0 fewer) | Low§ | 0.646 |
| Low late, 1 trial, 32 participants | 0.53 (0.08, 3.2) | 460 per 1000 | 311 per 1000 | 149 fewer per 1000 (396 fewer to 272 more) | Very low† | 0.512 |
| No dexamethasone 6 trials, 473 participants | Reference | Reference | Reference | Reference | Reference | 0.125 |
| Relative effects with No Dexamethasone as reference |  | | | | | |

*Multiple studies with some risk of bias, serious inconsistency due in direct comparison, imprecision

†Indirectness (Single direct study), very serious imprecision in direct comparison

‡Multiple studies with some risk of bias, serious inconsistency due in direct comparison

§Indirectness (Single direct study), serious imprecision in direct comparison

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**Table 2a. Effect estimates (95% credible intervals) and GRADE certainty of effect estimate for all comparisons in the 12-hour model**

| **Reintubation** | | | | |
|---|---|---|---|---|
| HighEarly | - | - | - | - |
| 0.54 (0.11,3.20)<br>Very low | HighLate | - | - | - |
| 0.92 (0.11,7.07)<br>Very low | 1.69 (0.11,22.93)<br>Very low | LowEarly | - | - |
| 0.22 (0.01,2.73)<br>Very low | 0.40 (0.03,3.59)<br>Very low | 0.24 (0.01,5.98)<br>Very low | LowLate | - |
| 0.24 (0.04,1.17)<br>Very low | 0.44 (0.10,1.27)<br>Very low | 0.26 (0.02,3.40)<br>Very low | 1.07 (0.15,7.77)<br>Very low | NoDex |
| **UAO** | | | | |
| HighEarly | - | - | - | - |
| 0.34* (0.12,0.88)<br>Low | HighLate | - | - | - |
| 0.88 (0.34,2.19)<br>Low | 2.57 (0.68,9.84)<br>Low | LowEarly | - | - |
| 0.23* (0.05,0.92)<br>Very low | 0.67 (0.20,2.12)<br>Very low | 0.26 (0.05,1.38)<br>Very low | LowLate | - |
| 0.13* (0.04,0.36)<br>Low | 0.39* (0.19,0.74)<br>Low | 0.15* (0.04,0.59)<br>Low | 0.58 (0.22,1.52)<br>Low | NoDex |

**GRADE Certainty of evidence:** High | Medium | Low | Very low

*Effect estimate with 95% credible intervals not crossing the line of no effect. Odds ratios (OR) and 95% credible interval (Crl) are presented. Comparisons between treatments should be read from left to right, and their OR is in the cell in common between the column-defining treatment and the row-defining treatment. OR less than 1 favors the column-defining treatment for the network estimates.

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**Table 2b. Effect estimates (95% credible intervals) and GRADE certainty of effect estimate for all comparisons in the 6-hour model**

| **Reintubation** | | | | |
|---|---|---|---|---|
| HighEarly | - | - | - | - |
| 0.92 (0.13, 5) Very low | HighLate | - | - | - |
| 0.64 (0.09,3.33) Very low | 0.70 (0.06,7.1) Very low | LowEarly | - | - |
| 0.40 (0.001,30.3) Very low | 0.44 (0.004,40) Very low | 0.63 (0.006,59) Very low | LowLate | - |
| 0.41 (0.09,1.21) Very low | 0.44 (0.06,2.4) Very low | 0.63 (0.10,3.78) Very low | 0.99 (0.01,69) Very Low | NoDex |
| **UAO** | | | | |
| HighEarly | - | - | - | - |
| 0.42 (0.15,1.08) Very low | HighLate | - | - | - |
| 0.72 (0.28,1.56) Low | 1.72 (0.48,5.7) Low | LowEarly | - | - |
| 0.56 (0.07,3.90) Very low | 1.34 (0.16,10.8) Very low | 0.78 (0.10,6.25) Very low | LowLate | - |
| 0.30* (0.13,0.55) Low | 0.72 (0.24,1.9) Low | 0.42* (0.17,1.0) Low | 0.53 (0.08,3.2) Very low | NoDex |

**GRADE Certainty of evidence:** High | Medium | Low | Very low

*Effect estimate with 95% credible intervals not crossing the line of no effect. Odds ratios (OR) and 95% credible interval (Crl) are presented. Comparisons between treatments should be read from left to right, and their OR is in the cell in common between the column-defining treatment and the row-defining treatment. OR less than 1 favors the column-defining treatment for the network estimates.

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**Figure Legends**

**Figure 1.** Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) Flow diagram showing flow of information through the different phases of the systematic review.

**Figure 2.** Forest plot of effect estimates and 95% confidence intervals of the pairwise meta-analysis.

**Figure 3.** Cumulative probability curves and SUCRA values for different dexamethasone regimens. For each regimen, the cumulative probability of being ranked 1st through 5th is displayed. The more the curve for a certain regimen is located toward the upper left corner, the higher its SUCRA value and the better its effectiveness.

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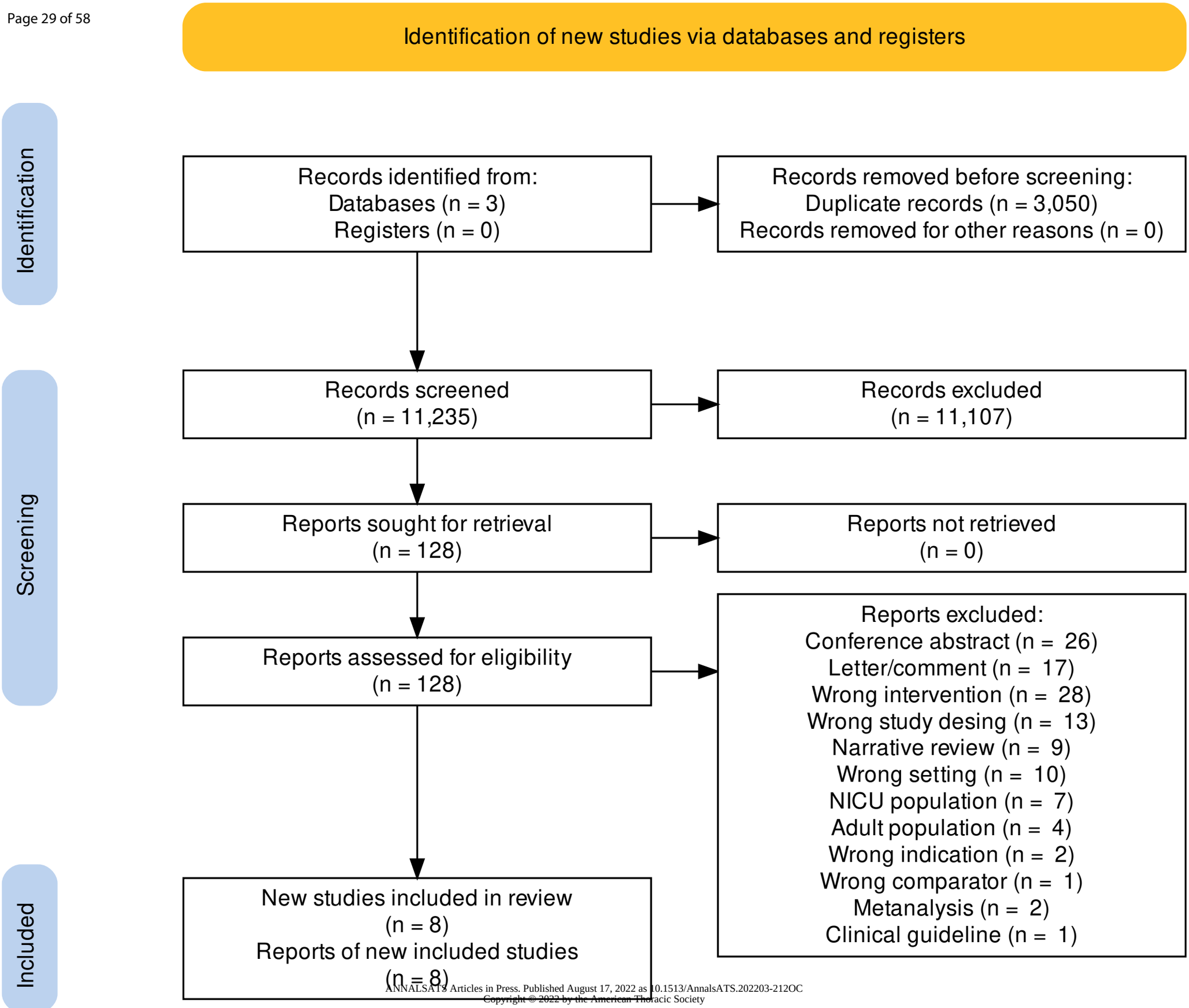


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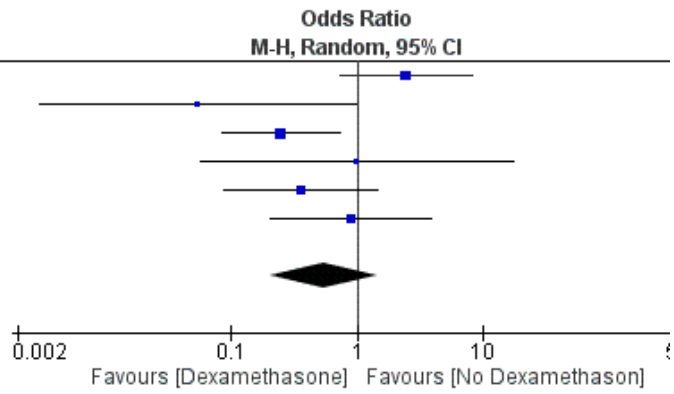
## 2A (Analysis 1.1)

| Study or Subgroup | Dexamethasone Events | Dexamethasone Total | No Dexamethasone Events | No Dexamethasone Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Tellez 1991 (0.5mg/kg/dose) | 9 | 76 | 4 | 77 | 21.5% | 2.45 [0.72, 8.33] | 1991 |
| Anene 1996 (0.5mg/kg/dose) | 0 | 31 | 7 | 32 | 8.4% | 0.05 [0.00, 0.99] | 1996 |
| Malhotra 2009 (0.5mg/kg/dose) | 9 | 30 | 19 | 30 | 23.3% | 0.25 [0.08, 0.73] | 2009 |
| Cesar 2009 (0.2mg/kg/dose) | 1 | 16 | 1 | 16 | 8.6% | 1.00 [0.06, 17.51] | 2009 |
| de Carvalho 2020 (0.25mg/kg/dose) | 3 | 41 | 8 | 44 | 19.4% | 0.36 [0.09, 1.45] | 2020 |
| Ritu 2020 (0.15mg/kg/dose) | 4 | 42 | 4 | 38 | 18.8% | 0.89 [0.21, 3.86] | 2020 |
| **Total (95% CI)** | | **236** | | **237** | **100.0%** | **0.55 [0.21, 1.46]** | |
| Total events | 26 | | 43 | | | | |

Heterogeneity: Tau² = 0.77; Chi² = 11.28, df = 5 (P = 0.05); I² = 56%

Test for overall effect: Z = 1.20 (P = 0.23)



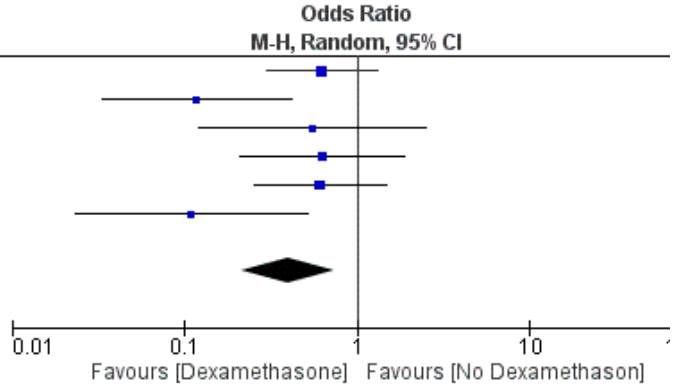

Forest plot of comparison: 1 Dexamethasone versus No Dexamethasone, outcome: 1.1 **Reintubation**.

## 2B (Analysis 1.2)

| Study or Subgroup | Dexamethasone Events | Dexamethasone Total | No Dexamethasone Events | No Dexamethasone Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Tellez 1991 (0.5mg/kg/dose) | 16 | 76 | 23 | 77 | 24.6% | 0.63 [0.30, 1.31] | 1991 |
| Anene 1996 (0.5mg/kg/dose) | 14 | 31 | 28 | 32 | 14.6% | 0.12 [0.03, 0.42] | 1996 |
| Cesar 2009 (0.2mg/kg/dose) | 10 | 16 | 12 | 16 | 11.4% | 0.56 [0.12, 2.54] | 2009 |
| Malhotra 2009 (0.5mg/kg/dose) | 8 | 30 | 11 | 30 | 17.2% | 0.63 [0.21, 1.88] | 2009 |
| Ritu 2020 (0.15mg/kg/dose) | 18 | 42 | 21 | 38 | 21.2% | 0.61 [0.25, 1.47] | 2020 |
| de Carvalho 2020 (0.25mg/kg/dose) | 2 | 41 | 14 | 44 | 11.0% | 0.11 [0.02, 0.52] | 2020 |
| **Total (95% CI)** | | **236** | | **237** | **100.0%** | **0.40 [0.21, 0.73]** | |
| Total events | 68 | | 109 | | | | |

Heterogeneity: Tau² = 0.26; Chi² = 9.20, df = 5 (P = 0.10); I² = 46%

Test for overall effect: Z = 2.95 (P = 0.003)




Forest plot of comparison: 1 Dexamethasone versus No Dexamethasone, outcome: 1.2 **Upper airway obstruction**.



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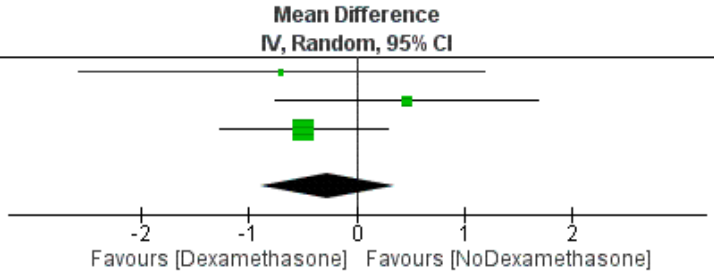
## 2C (Analysis 1.3)

| Study or Subgroup | Dexamethasone Mean | SD | Total | No Dexamethasone Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI |
|---|---|---|---|---|---|---|---|---|
| de Carvalho 2020 (0.25mg/kg/dose) | 5.76 | 2.6 | 41 | 6.46 | 5.77 | 44 | 10.8% | -0.70 [-2.58, 1.18] |
| Malhotra 2009 (0.5mg/kg/dose) | 5.9 | 2.76 | 30 | 5.43 | 2.01 | 30 | 25.7% | 0.47 [-0.75, 1.69] |
| Tellez 1991 (0.5mg/kg/dose) | 3.03 | 2.44 | 76 | 3.52 | 2.46 | 77 | 63.5% | -0.49 [-1.27, 0.29] |
| **Total (95% CI)** | | | **147** | | | **151** | **100.0%** | **-0.27 [-0.89, 0.35]** |

Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)

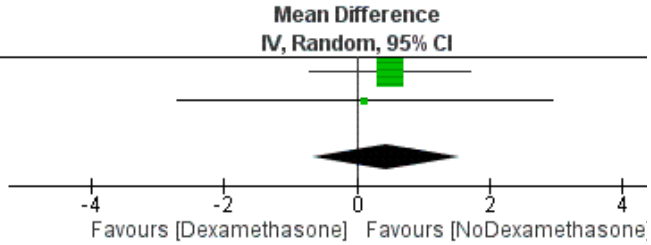



Forest plot of comparison: 1 Dexamethasone versus No Dexamethasone, outcome: 1.3 **Length of IMV**.

## 2D (Analysis 1.4)

| Study or Subgroup | Dexamethasone Mean | SD | Total | No Dexamethasone Mean | SD | Total | Weight | Mean Difference IV, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|---|---|
| Malhotra 2009 (0.5mg/kg/dose) | 5.9 | 2.7 | 30 | 5.4 | 2 | 30 | 84.7% | 0.50 [-0.70, 1.70] | 2009 |
| de Carvalho 2020 (0.25mg/kg/dose) | 7.83 | 6.7 | 41 | 7.71 | 6.57 | 44 | 15.3% | 0.12 [-2.70, 2.94] | 2020 |
| **Total (95% CI)** | | | **71** | | | **74** | **100.0%** | **0.44 [-0.66, 1.55]** | |

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.43)

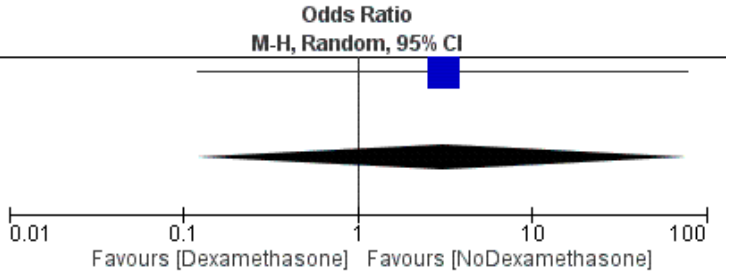



Forest plot of comparison: 1 Dexamethasone versus No Dexamethasone, outcome: 1.4 **PICU length of stay**.

## 2E (Analysis 1.5)

| Study or Subgroup | Dexamethasone Events | Total | No Dexamethasone Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Anene 1996 (0.5mg/kg/dose) | 1 | 33 | 0 | 33 | 100.0% | 3.09 [0.12, 78.70] | 1996 |
| Ritu 2020 (0.15mg/kg/dose) | 0 | 42 | 0 | 38 | | Not estimable | 2020 |
| **Total (95% CI)** | | **75** | | **71** | **100.0%** | **3.09 [0.12, 78.70]** | |
| Total events | 1 | | 0 | | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)




Forest plot of comparison: 1 Dexamethasone versus No Dexamethasone, outcome: 1.5 **GI Bleeding**.



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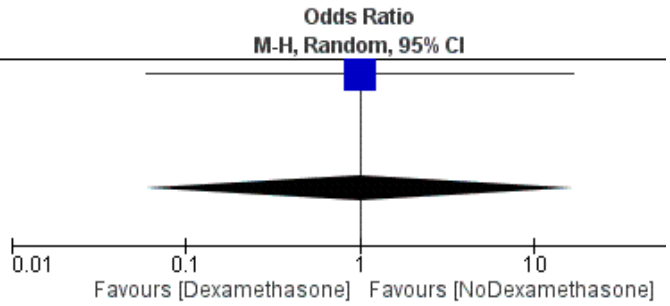
## 2F (Analysis 1.6)

| Study or Subgroup | Dexamethasone Events | Total | No Dexamethasone Events | Total | Weight | Odds Ratio M-H, Random, 95% CI | Year |
|---|---|---|---|---|---|---|---|
| Anene 1996 (0.5mg/kg/dose) | 1 | 33 | 1 | 33 | 100.0% | 1.00 [0.06, 16.69] | 1996 |
| de Carvalho 2020 (0.25mg/kg/dose) | 0 | 41 | 0 | 44 | | Not estimable | 2020 |
| Ritu 2020 (0.15mg/kg/dose) | 0 | 42 | 0 | 38 | | Not estimable | 2020 |
| **Total (95% CI)** | | **116** | | **115** | **100.0%** | **1.00 [0.06, 16.69]** | |
| Total events | 1 | | 1 | | | | |

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)




Forest plot of comparison: 1 Dexamethasone versus No Dexamethasone, outcome: 1.6 **Hypertension**.



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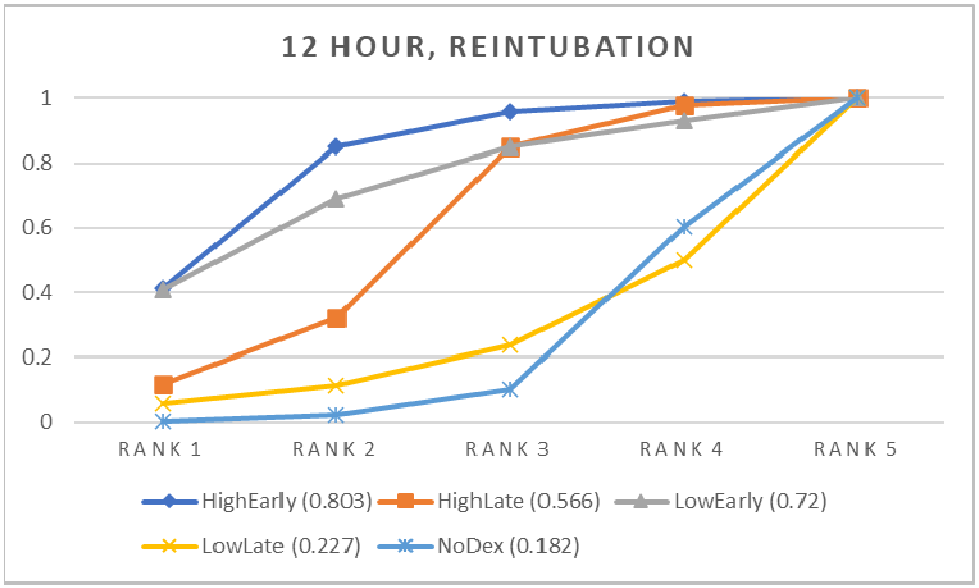
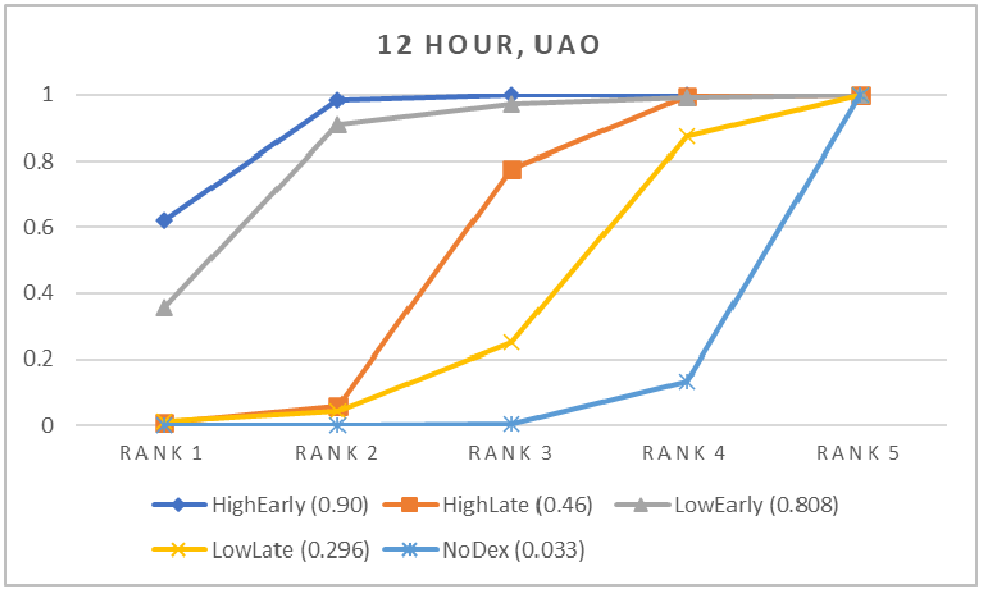
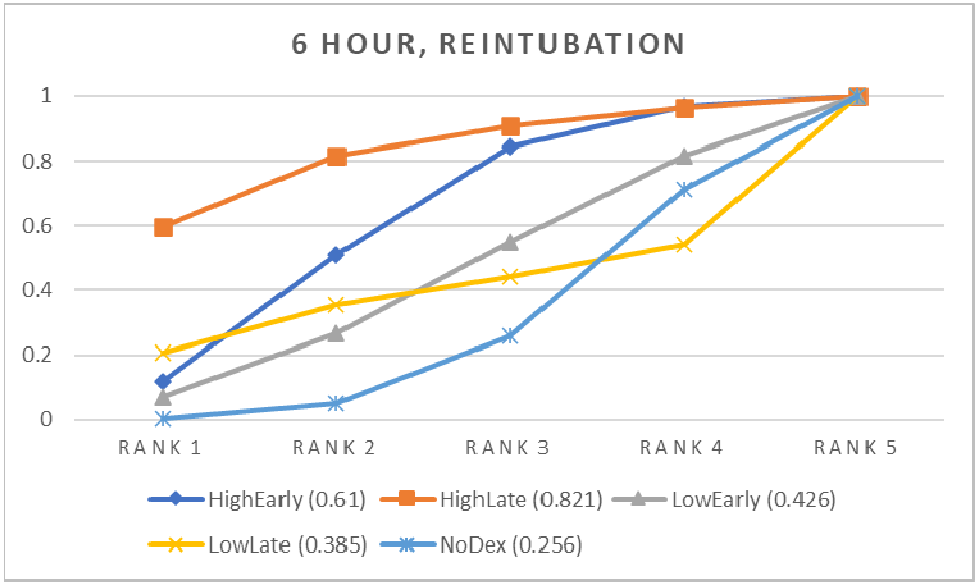
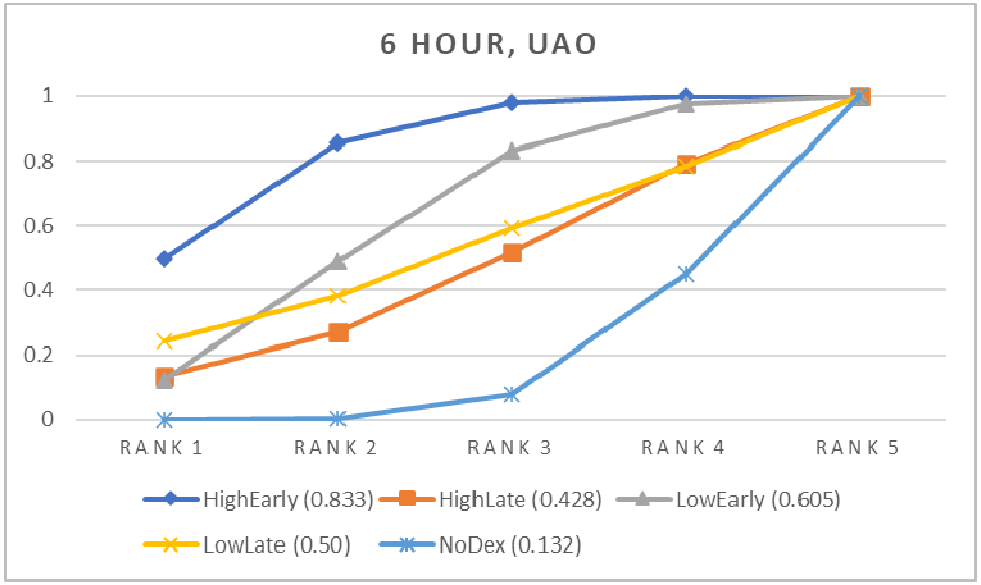
## Cumulative rankograms with SUCRA values

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**Online Data Supplement**

# A Network Meta-analysis of Dexamethasone for Preventing Post-Extubation Upper Airway Obstruction in Children

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**Table E1.** PRISMA NMA Checklist of Items to Include When Reporting A Systematic Review Involving a Network Meta-analysis

| Section/Topic | Item # | Checklist Item | Reported on Page # |
|---|---|---|---|
| **TITLE** | | | |
| Title | 1 | Identify the report as a systematic review *incorporating a network meta-analysis (or related form of meta-analysis).* | ***1*** |
| **ABSTRACT** | | | |
| Structured summary | 2 | Provide a structured summary including, as applicable:<br>**Background:** main objectives<br>**Methods:** data sources; study eligibility criteria, participants, and interventions; study appraisal; and *synthesis methods, such as network meta-analysis.*<br>**Results:** number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; *treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.*<br>**Discussion/Conclusions:** limitations; conclusions and implications of findings.<br>**Other:** primary source of funding; systematic review registration number with registry name. | 4 |
| **INTRODUCTION** | | | |
| Rationale | 3 | Describe the rationale for the review in the context of what is already known*, including mention of why a network meta-analysis has been conducted.* | ***6*** |
| Objectives | 4 | Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS). | 6-8 |
| **METHODS** | | | |
| Protocol and registration | 5 | Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number. | 7 |

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| | | | |
|---|---|---|---|
| Eligibility criteria | 6 | Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. *Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification).* | 7,8 |
| Information sources | 7 | Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched. | 8 |
| Search | 8 | Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated. | Online supplement, Table 1 |
| Study selection | 9 | State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis). | 8 |
| Data collection process | 10 | Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators. | 9 |
| Data items | 11 | List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made. | 7,8 |
| **Geometry of the network** | **S1** | Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers. | ***10, Table 3*** |
| Risk of bias within individual studies | 12 | Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis. | 9 |
| Summary measures | 13 | State the principal summary measures (e.g., risk ratio, difference in means). *Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.* | 11, 12 |

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| | | | |
|---|---|---|---|
| Planned methods of analysis | 14 | Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to:<br>• *Handling of multi-arm trials;*<br>• *Selection of variance structure;*<br>• *Selection of prior distributions in Bayesian analyses; and*<br>• *Assessment of model fit.* | 11,12 |
| **Assessment of Inconsistency** | **S2** | Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found. | 11 |
| Risk of bias across studies | 15 | Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies). | **12** |
| Additional analyses | 16 | Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following:<br>• Sensitivity or subgroup analyses;<br>• Meta-regression analyses;<br>• *Alternative formulations of the treatment network; and*<br>• *Use of alternative prior distributions for Bayesian analyses (if applicable).* | ***12*** |
| **RESULTS†** | | | |
| Study selection | 17 | Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram. | 13 |
| **Presentation of network structure** | **S3** | Provide a network graph of the included studies to enable visualization of the geometry of the treatment network. | ***Table 3*** |
| **Summary of network geometry** | **S4** | Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure. | ***13,14*** |

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| | | | |
|---|---|---|---|
| Study characteristics | 18 | For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations. | Table 2 |
| Risk of bias within studies | 19 | Present data on risk of bias of each study and, if available, any outcome level assessment. | Online supplement, Figure E1a, E1b |
| Results of individual studies | 20 | For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. *Modified approaches may be needed to deal with information from larger networks.* | Table 2 |
| Synthesis of results | 21 | Present results of each meta-analysis done, including confidence/credible intervals. *In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.* If additional summary measures were explored (such as treatment rankings), these should also be presented. | ***14, Table 3, Table 4*** |
| **Exploration for inconsistency** | **S5** | Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, *P* values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network. | ***15*** |
| Risk of bias across studies | 22 | Present results of any assessment of risk of bias across studies for the evidence base being studied. | Online supplement, Figure E1a, E1b |
| Results of additional analyses | 23 | Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses*, alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses,* and so forth). | ***15, Table 3*** |
| **DISCUSSION** | | | |
| Summary of evidence | 24 | Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers). | 16 |
| Limitations | 25 | Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., | 18 |

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| | | | |
|---|---|---|---|
| | | incomplete retrieval of identified research, reporting bias). *Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).* | |
| Conclusions | 26 | Provide a general interpretation of the results in the context of other evidence, and implications for future research. | 19 |
| **FUNDING** | | | |
| Funding | 27 | Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network. | ***3*** |

PICOS = population, intervention, comparators, outcomes, study design.
* Text in italics indicateS wording specific to reporting of network meta-analyses that has been added to guidance from the PRISMA statement.

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**Table E2. APPENDIX for PICO 7 (Air leak test) & 8 (systemic steroids)**
**Search strategies for MEDLINE, Embase, and CINAHL**

**MEDLINE (Ovid)**
Databases selected: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)

| Line | Query |
|---|---|
| 1 | Adolescent/ |
| 2 | Adolescen*.mp. |
| 3 | Teen*.mp. |
| 4 | Youth*.mp. |
| 5 | exp Child/ |
| 6 | Child*.mp. |
| 7 | Infant/ |
| 8 | Infant, Newborn/ |
| 9 | Infant*.mp. |
| 10 | Infanc*.mp. |
| 11 | Newborn*.mp. |
| 12 | Neonat*.mp. |
| 13 | Pediatrics/ |
| 14 | P?ediatric*.mp. |
| 15 | Hospitals, Pediatric/ |
| 16 | Intensive Care Units, Pediatric/ |
| 17 | PICU*.mp. |
| 18 | (Kid or kids).mp. |
| 19 | Toddler*.mp. |
| 20 | 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 |
| 21 | (Adaptive adj2 Support Ventilat*).mp. |
| 22 | Airway Extubation/ |
| 23 | Airway extubat*.mp. |
| 24 | Artificial Respirati*.mp. |
| 25 | ((intubation or extubation*) adj3 (airway or tracheal or intratracheal or endotracheal)).mp. |
| 26 | exp Intermittent Positive-Pressure Breathing/ |
| 27 | Intermittent Positive-Pressure Breathing.mp. |
| 28 | exp Intermittent Positive-Pressure Ventilation/ |
| 29 | Intermittent Positive-Pressure Ventilat*.mp. |
| 30 | Intubation, Intratracheal/ |
| 31 | Mechanical Ventilat*.mp. |
| 32 | Neurally Adjusted Ventilatory Assist*.mp. |
| 33 | open lung ventilat*.mp. |
| 34 | Peep.mp. |
| 35 | Positive End Expiratory Pressure*.mp. |
| 36 | exp Positive-Pressure Respiration/ |

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| | |
|---|---|
| 37 | Positive-Pressure Ventilat*.mp. |
| 38 | pressure controlled ventilat*.mp. |
| 39 | Proportional Assist Ventilat*.mp. |
| 40 | Reintubat*.mp. |
| 41 | Respiration, Artificial/ |
| 42 | Respirator Weaning*.mp. |
| 43 | Ventilator*.mp. |
| 44 | (Ventilat* adj3 Liberation*).mp. |
| 45 | exp Ventilators, Mechanical/ |
| 46 | exp Ventilator Weaning/ |
| 47 | Ventilator* Weaning*.mp. |
| 48 | Ventilation Weaning*.mp. |
| 49 | 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 |
| 50 | Dexamethasone/ |
| 51 | Dexamethasone*.mp. |
| 52 | Adrenal Cortex Hormones/ |
| 53 | ((adrenal or adreno or adrenocortical or corticoadrenal) adj2 (steroid* or hormone*)).mp. |
| 54 | adrenocorticosteroid*.mp. |
| 55 | Corticoid*.mp. |
| 56 | Corticosteroid*.mp. |
| 57 | Cortico steroid*.mp. |
| 58 | Cortical steroid*.mp. |
| 59 | Glucocorticoids/ |
| 60 | Glucocorticoid*.mp. |
| 61 | Hydrocortisone/ |
| 62 | Hydrocortisone*.mp. |
| 63 | Cortisone/ |
| 64 | Cortisone*.mp. |
| 65 | Prednisolone/ |
| 66 | prednisolone*.mp. |
| 67 | Predonine*.mp. |
| 68 | Methylprednisolone/ |
| 69 | Methylprednisolone*.mp. |
| 70 | Prednisone/ |
| 71 | Prednison*.mp. |
| 72 | Anti-Inflammatory Agents/ |
| 73 | Anti inflammator*.mp. |
| 74 | Antiinflamator*.mp. |
| 75 | Antiinflammation*.mp. |
| 76 | Anti inflammation*.mp. |
| 77 | 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 |
| 78 | airleak test*.mp. |

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| | |
|---|---|
| 79 | leak test*.mp. |
| 80 | (leak adj5 extubation*).mp. |
| 81 | (leak adj3 endotracheal).mp. |
| 82 | tube leak*.mp. |
| 83 | cuff leak*.mp. |
| 84 | cuffleak*.mp. |
| 85 | leak pressure*.mp. |
| 86 | stridor*.mp. |
| 87 | inspiratory flow limitation*.mp. |
| 88 | (puls* adj2 paradox*).mp. |
| 89 | laryngeal ultrasound*.mp. |
| 90 | larynx ?edema*.mp. |
| 91 | laryngeal ?edema*.mp. |
| 92 | Racepinephrine/ |
| 93 | Racepinefrine*.mp. |
| 94 | Racepinephrine*.mp. |
| 95 | racinephrine*.mp. |
| 96 | (racemic adj2 (epinephrine* or adrenaline*)).mp. |
| 97 | Racadrenalin*.mp. |
| 98 | vaponephrin*.mp. |
| 99 | Vaponefrin*.mp. |
| 100 | Micronefrin*.mp. |
| 101 | Micronephrine*.mp. |
| 102 | Mikronephrin*.mp. |
| 103 | 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 |
| 104 | 77 or 103 |
| 105 | 20 and 49 and 104 |

**Embase (Elsevier)**

| Line | Query |
|---|---|
| #122 | #22 AND #61 AND #121 |
| #121 | #92 OR #120 |
| #120 | #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 |
| #119 | 'anti inflammation*' |
| #118 | antiinflammation* |
| #117 | antiinflamator* |
| #116 | 'anti inflammator*' |
| #115 | 'antiinflammatory agent'/de |
| #114 | prednison* |
| #113 | 'prednisone'/exp |
| #112 | methylprednisolone* |
| #111 | 'methylprednisolone'/exp |

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| | |
|---|---|
| #110 | predonine* |
| #109 | prednisolone* |
| #108 | 'prednisolone'/de |
| #107 | cortisone* |
| #106 | 'cortisone'/exp |
| #105 | hydrocortisone* |
| #104 | 'hydrocortisone'/exp |
| #103 | glucocorticoid* |
| #102 | 'glucocorticoid'/de |
| #101 | 'cortical steroid*' |
| #100 | 'cortico steroid*' |
| #99 | corticosteroid* |
| #98 | 'corticosteroid'/de |
| #97 | corticoid* |
| #96 | adrenocorticosteroid* |
| #95 | (adrenal OR adreno OR adrenocortical OR corticoadrenal) NEAR/2 (steroid* OR hormone*) |
| #94 | dexamethasone* |
| #93 | 'dexamethasone'/de |
| #92 | #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 |
| #91 | mikronephrin* |
| #90 | micronephrine* |
| #89 | micronefrin* |
| #88 | vaponefrin* |
| #87 | vaponephrin* |
| #86 | racadrenalin* |
| #85 | racemic NEAR/2 (epinephrine* OR adrenaline*) |
| #84 | racinephrine* |
| #83 | racepinephrine* |
| #82 | racepinefrine* |
| #81 | 'racepinefrine'/exp |
| #80 | 'laryngeal $edema*' |
| #79 | 'larynx $edema*' |
| #78 | 'larynx edema'/exp |
| #77 | 'laryngeal ultrasound*' |
| #76 | paradox* NEAR/2 puls* |
| #75 | 'paradoxical pulse'/exp |
| #74 | 'inspiratory flow limitation*' |
| #73 | stridor* |
| #72 | 'stridor'/exp |
| #71 | 'leak pressure*' |
| #70 | 'cuff leak*' OR cuffleak* |
| #69 | 'cuff leak test'/exp |

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| | |
|---|---|
| #68 | 'tube leak*' |
| #67 | leak NEAR/3 endotracheal |
| #66 | leak NEAR/5 extubation* |
| #65 | 'leak test*' |
| #64 | 'airleak test*' |
| #63 | 'air leak test'/exp |
| #62 | 'air leak'/exp |
| #61 | #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 |
| #60 | 'artificial respirati*' |
| #59 | 'volume controlled ventilation'/exp |
| #58 | 'ventilation weaning*' |
| #57 | 'ventilator* weaning*' |
| #56 | 'ventilator weaning'/de |
| #55 | 'mechanical ventilator'/de |
| #54 | ventilat* NEAR/3 liberation* |
| #53 | ventilator* |
| #52 | 'ventilator'/de |
| #51 | 'tracheal extubation'/de |
| #50 | 'respirator weaning*' |
| #49 | 'artificial ventilation'/de |
| #48 | reintubat* |
| #47 | 'protective ventilation'/exp |
| #46 | 'proportional assist ventilat*' |
| #45 | 'pressure support ventilation'/de |
| #44 | 'pressure controlled ventilat*' |
| #43 | 'pressure controlled ventilation'/de |
| #42 | 'positive-pressure ventilat*' |
| #41 | 'positive pressure ventilation'/de |
| #40 | 'positive end expiratory pressure*' |
| #39 | 'positive end expiratory pressure ventilation'/exp |
| #38 | peep |
| #37 | 'open lung ventilat*' |
| #36 | 'noninvasive positive pressure ventilation'/exp |
| #35 | 'neurally adjusted ventilatory assist*' |
| #34 | 'mechanical ventilat*' |
| #33 | 'inverse ratio ventilation'/de |
| #32 | 'invasive ventilation'/exp |
| #31 | 'endotracheal intubation'/exp |
| #30 | 'intermittent positive-pressure ventilat*' |
| #29 | 'intermittent positive pressure ventilation'/exp |
| #28 | 'intermittent positive-pressure breathing' |
| #27 | 'intermittent mandatory ventilation'/exp |

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| | |
|---|---|
| #26 | (intubation* OR extubation*) NEAR/3 (airway OR tracheal OR intratracheal OR endotracheal) |
| #25 | 'airway extubat*' |
| #24 | 'extubation'/de |
| #23 | adaptive NEAR/2 support NEXT/1 ventilat* |
| #22 | #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 |
| #21 | toddler* |
| #20 | 'toddler'/exp |
| #19 | kid OR kids |
| #18 | picu* |
| #17 | 'pediatric intensive care unit'/de |
| #16 | p$ediatric* |
| #15 | 'pediatrics'/de |
| #14 | neonat* |
| #13 | newborn* |
| #12 | infanc* |
| #11 | infant* |
| #10 | 'newborn'/exp |
| #9 | 'infancy'/exp |
| #8 | 'infant'/exp |
| #7 | child* |
| #6 | 'child'/exp |
| #5 | youth* |
| #4 | teen* |
| #3 | adolescen* |
| #2 | 'adolescence'/de |
| #1 | 'adolescent'/exp |

**CINAHL Complete (EBSCO)**

| **Line** | **Query** |
|---|---|
| S105 | S70 AND S103 AND S104 |
| S104 | S26 OR S51 |
| S103 | S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102 |
| S102 | adaptive N2 support ventilat* |
| S101 | (MH "Extubation") |
| S100 | airway extubat* |
| S99 | artificial respirati* |
| S98 | (intubation* OR extubation*) N3 (airway OR tracheal OR intratracheal OR endotracheal) |

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| | |
|---|---|
| S97 | (MH "Intermittent Positive Pressure Breathing") |
| S96 | Intermittent Positive- Pressure Breathing |
| S95 | (MH "Intermittent Positive Pressure Ventilation") |
| S94 | Intermittent Positive- Pressure Ventilat* |
| S93 | (MH "Intubation, Intratracheal") |
| S92 | (MH "Inverse Ratio Ventilation") |
| S91 | (MH "Mandatory Minute Volume Ventilation") |
| S90 | mechanical ventilat* |
| S89 | neurally adjusted ventilatory assist* |
| S88 | open lung ventilat* |
| S87 | peep |
| S86 | (MH "Positive End- Expiratory Pressure") |
| S85 | Positive End Expiratory Pressure* |
| S84 | (MH "Positive Pressure Ventilation") |
| S83 | positive-pressure ventilat* |
| S82 | pressure controlled ventilat* |
| S81 | (MH "Pressure Support Ventilation") |
| S80 | proportional assist ventilat* |
| S79 | reintubat* |
| S78 | (MH "Respiration, Artificial") |
| S77 | 'respirator weaning*' |
| S76 | ventilator* |
| S75 | ventilat* N3 liberation* |
| S74 | (MH "Ventilators, Mechanical") |
| S73 | (MH "Ventilator Weaning") |
| S72 | ventilator* weaning* |
| S71 | Ventilation Weaning* |
| S70 | S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 |
| S69 | (MH "Adolescence+") |
| S68 | Adolescen* |
| S67 | Teen* |
| S66 | Youth* |
| S65 | (MH "Child") OR (MH "Child, Hospitalized") OR (MH "Child, Medically Fragile") OR (MH "Child, Preschool") |
| S64 | Child* |
| S63 | (MH "Infant") OR (MH "Infant, Hospitalized") OR (MH "Infant, High Risk") |
| S62 | (MH "Infant, Newborn") |
| S61 | Infant* |
| S60 | Infanc* |
| S59 | Newborn* |
| S58 | Neonat* |
| S57 | (MH "Pediatrics") |
| S56 | P#ediatric* |
| S55 | (MH "Intensive Care Units, Pediatric") |

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| | |
|---|---|
| S54 | PICU* |
| S53 | Kid OR kids |
| S52 | Toddler* |
| S51 | S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 |
| S50 | (MH "Dexamethasone") |
| S49 | Dexamethasone* |
| S48 | (MH "Adrenal Cortex Hormones") |
| S47 | (adrenal OR adreno OR adrenocortical OR corticoadrenal) N2 (steroid* OR hormone*) |
| S46 | adrenocorticosteroid* |
| S45 | Corticoid* |
| S44 | Corticosteroid* |
| S43 | "Cortico steroid*" |
| S42 | "Cortical steroid*" |
| S41 | (MH "Glucocorticoids+") |
| S40 | Glucocorticoid* |
| S39 | Hydrocortisone* |
| S38 | Cortisone* |
| S37 | (MH "Prednisolone+") |
| S36 | prednisolone* |
| S35 | Predonine* |
| S34 | Methylprednisolone* |
| S33 | (MH "Prednisone") |
| S32 | Prednison* |
| S31 | (MH "Antiinflammatory Agents") |
| S30 | "Anti inflammator*" |
| S29 | Antiinflamator* |
| S28 | Antiinflammation* |
| S27 | "Anti inflammation*" |
| S26 | S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 |
| S25 | mikronephrin* |
| S24 | micronephrine* |
| S23 | micronefrin* |
| S22 | vaponefrin* |
| S21 | vaponephrin* |
| S20 | Racadrenalin* |
| S19 | racemic N2 (epinephrine* OR adrenaline*) |
| S18 | racinephrine* |
| S17 | racepinephrine* |
| S16 | racepinefrine* |
| S15 | "laryngeal #edema*" |

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| | |
|---|---|
| S14 | (MH "Laryngeal Edema") |
| S13 | "larynx #edema*" |
| S12 | "laryngeal ultrasound*" |
| S11 | paradox* N2 puls* |
| S10 | "inspiratory flow limitation*" |
| S9 | stridor* |
| S8 | "leak pressure*" |
| S7 | Cuffleak* |
| S6 | "cuff leak*" |
| S5 | "tube leak*" |
| S4 | leak N3 endotracheal |
| S3 | leak N5 extubation* |
| S2 | "leak test*" |
| S1 | "airleak test*" |

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**Table E3. Studies comparing steroid versus no steroids.**

| **PICO8, Anene, 1996** | |
|---|---|
| **Study design** | RCT |
| **Aim of study (brief)** | To determine whether dexamethasone is effective in the prevention of postextubation airway obstruction in these young children |
| **Inclusion criteria** | All children <5 yrs of age, intubated for >48 hrs, and undergoing their first elective extubation |
| **Exclusion criteria** | Patients admitted for laryngotracheal infections and those patients who had received corticosteroids within 7 days before extubation |
| **Total number of participants** | 66, 63 analyzed |
| **Intervention details** | Intravenous dexamethasone (Fujisawa USA, Deerfield, IL) 0.5 mg/kg per dose up to a maximum dose of 10 mg, or an equal volume of saline. The first dose was administered 6 to 12 hrs before extubation and subsequently was provided every 6 hrs for a total of six doses. |
| **Comparator/Control details** | Equal volume of iv normal saline |
| **Outcomes** | Failure to liberate from invasive MV (or failed extubation), Total duration of invasive MV, Post-extubation upper airway obstruction, GI bleeding |
| **PICO8, Cesar, 2009** | |
| **Study design** | RCT |
| **Aim of study (brief)** | To investigate the effect of intravenous dexamethasone and nebulized L-epinephrine, administered separately or combinedly, on the clinical development of postextubation laryngeal edema |

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| | |
|---|---|
| **Inclusion criteria** | All patients admitted to PICU needing invasive mechanical ventilation due to respiratory failure or elective surgical procedures reaching at least 15 blocks of four matched subjects |
| **Exclusion criteria** | Vocal cord anomalies and other anatomic abnormalities of the upper airways before intubation; Previous use of corticosteroids during hospitalization; Clinical contraindication for the use of corticosteroids or epinephrine; Clinical abnormalities, such as anemia, arterial hypotension or methemoglobinemia Bad ventilation conditions verified by the RR and transcutaneous oxygen saturation. |
| **Total number of participants** | 32 |
| **Intervention details** | 0.2 mg/k dexamethasone sodium phosphate one hour prior extubation every 6 h during 24 h of follow-up Maximum dose 2.6 mg |
| **Comparator/Control details** | Isotonic saline solution (control) 1h prior extubation, every 6h during 24 h of follow-up Nebulization of 0.5m/kg of epinephrine hydrochloride (1 mg/ml) by using facial mask (max dose 5 ml), diluted in 5 ml of isotonic saline solution by nebulization with oxygen (at a flow rate of 2-7 l/min). |
| **Outcomes** | Failure to liberate from invasive MV (or failed extubation), Post-extubation upper airway obstruction |
| **PICO8, de Carvalho, 2020** | |
| **Study design** | RCT |
| **Aim of study (brief)** | To evaluate the efficacy of iv dexamethasone to prevent extrathoracic airway obstruction and extubation failure in children and adolescents. |
| **Inclusion criteria** | Patients aged 28 days to 15 years, who had undergone mechanical ventilation for 48 hours or more and who had at least one of the following risk factors for extubation failure: MV for >15 days, use of inotropic agents for >48 hours, ages 1 to 3 months, mPaw > 8.5 cm H2O or OI > 4.5, FiO2 > 0.4 shortly before extubation, |

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| | |
|---|---|
| | cardiac or chronic pulmonary diseases, congestive heart failure, PaCO2> 45 mm Hg), patients with > 1 intubation during hospital stay because of endotracheal tube exchange or accidental extubation, OI > 10 at any time of ventilation, septic and other types of shock and ARDS. |
| **Exclusion criteria** | Tracheostomy prior to admission, Airway anomalies, Neuromuscular diseases, Already receiving steroids for any reason. |
| **Total number of participants** | 85 |
| **Intervention details** | iv dexamethasone disodium phosphate loading dose of 1 mg/kg (maximum 10 mg) followed by 0.25 mg/kg every 6 hours, being able to receive up to five doses before extubation. |
| **Comparator/Control details** | Nothing |
| **Outcomes** | Failure to liberate from invasive MV (or failed extubation),Total duration of invasive MV, PICU length of stay, Post-extubation upper airway obstruction |
| **PICO8, Malhotra, 2009** | |
| **Study design** | RCT |
| **Aim of study (brief)** | To determine the role of iv dexamethasone in preventing postextubation laryngeal edemal stridor. To determine whether multiple doses of dexamethasone are effective to reduce or prevent postextubation airway obstruction. To investigate whether an after-effect exists 24 hours after the dis-continuation of dexamethasone |
| **Inclusion criteria** | The patients who were on ventilators for more than 24 hours with a first elective extubation in an ICU. |

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| | |
|---|---|
| **Exclusion criteria** | Upper airway disease. Neck surgery. Any anatomical deformity of upper airways Patients already on steroids. History of extubation during the same hospitalization |
| **Total number of participants** | 60 This study also include adults (60), but results data are completely split. |
| **Intervention details** | Dexamethasone 0.5 mg/kg (maximum 8mg) bolus i.v was given 4 hours prior to planned extubation, at extubation and at 6 and 12 hours after extubation. |
| **Comparator/Control details** | Placebo saline at similar intervals than dexa. The placebo was prepared in identical volume and labeled as B (A for dexa) in a syringe to ensure administration in double blind fashion; |
| **Outcomes** | Failure to liberate from invasive MV (or failed extubation),Total duration of invasive MV, PICU length of stay, Post-extubation upper airway obstruction |
| **PICO8, Ritu, 2020** | |
| **Study design** | RCT |
| **Aim of study (brief)** | To study the effects of dexamethasone therapy in preventing postextubation stridor in children |
| **Inclusion criteria** | Children of 2 months to 12 years who were ventilated for at least 48 hours and in whom extubation was planned in next 6-12 hours |
| **Exclusion criteria** | Children who have received steroids within 7 days prior to extubation, previous failed extubations, self-extubations, and tracheostomized patients |
| **Total number of participants** | 80 |
| **Intervention details** | dexamethasone at 0.15 mg/kg/dose every 6 hourly for 6 doses with the first dose administered at least 6-12 hours prior to planned extubation. |

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| | |
|---|---|
| **Comparator/Control details** | Normal Saline every 6 hourly for 6 doses with the first dose administered at least 6-12 hours prior to planned extubation. Equivalent volume and at same timings than dexamethasone |
| **Outcomes** | Mortality, Failure to liberate from invasive MV (or failed extubation),Total duration of invasive MV, PICU length of stay, Post-extubation upper airway obstruction, New tracheostomy rate, GI bleeding |
| **PICO8, Tellez, 1991** | |
| **Study design** | RCT |
| **Aim of study (brief)** | To evaluate the effectiveness of dexamethasone in reducing the incidence of postextubation stridor in routine cases of tracheal intubation and MV, free of any previously known UAO problem. |
| **Inclusion criteria** | All patients undergoing intubation except those that meet one or more of the exclusion criteria. |
| **Exclusion criteria** | (1) Corticosteroids therapy within the previous 7 days, (2) A primary pharyngeal or laryngeal infection, (3) Surgical trauma to the upper airway, (4) A history of previous UAO (such as subglottic stenosis), (5) A medical condition that contraindicated the use of corticosteroids. |
| **Total number of participants** | 153 |
| **Intervention details** | Dexamethasone sodium posphate 0.5 mg/kg per administration (maximum dose: 10 nag) iv 6-12 hours before anticipated extubation and then every 6 hours for a total of 6 doses. |
| **Comparator/Control details** | Isotonic saline solution (placebo), identical volume, iv 6-12 hours before anticipated extubation and then every 6 hours for a total of 6 doses. |
| **Outcomes** | Failure to liberate from invasive MV (or failed extubation), Total duration of invasive MV, Post-extubation upper airway obstruction |

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**Studies comparing different steroid regimens.**

| **Parajuli, 2021** | |
|---|---|
| **Study design** | RCT |
| **Aim of study (brief)** | To assess if Low dose dexamethasone (LDD) is noninferior to high dose dexamethasone (HDD) in reducing the risk of post extubation airway obstruction (PEAO), and also to assess risk factors for the development of PEAO amongst children. |
| **Inclusion criteria** | Eligibility criteria included age more than 3 months and less than 12 years, intubation for more than 48 h, and anticipation of having their first planned extubation during the next 24 h |
| **Exclusion criteria** | Patients with actual or potential poor airway reflexes, Glasgow Coma Score (GCS) less than 8, pre-existing airway issues, previous tracheal intubation or tracheostomy, chronic lung disease, contraindications for steroid, gastrointestinal bleeding, hypertension (>95th centile), hyperglycemia, steroid, or chronic nonsteroidal anti-inflammatory drug therapy were excluded. |
| **Total number of participants** | 287, 238 analyzed |
| **Intervention details** | Patients in the control group (HDD) were planned to receive six doses of intravenous dexamethasone (0.5 mg/kg/dose, max 8 mg/dose), the first dose 24 h before anticipated extubation and then after every 6 h for a total of six doses. |
| **Comparator/Control details** | Patients in the study group (LDD) were planned to receive six doses of intravenous dexamethasone (0.25 mg/kg/dose, max 4 mg/dose) using the aforementioned protocol. |
| **Outcomes** | Failure to liberate from invasive MV (or failed extubation),Post-extubation upper airway obstruction, GI bleeding |

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| Baranwal, 2014 | |
|---|---|
| **Study design** | RCT |
| **Aim of study (brief)** | To compare the effect of 24-h pretreatment with dexamethasone (24hPD) versus 6-h pretreatment (6hPD) on PEAO and reintubation in children. |
| **Inclusion criteria** | Eligibility criteria included age >3 months and <12 years, intubation for >48 h, and anticipated first planned extubation during the next 24 h. |
| **Exclusion criteria** | Patients with actual or potential poor airway reflexes (e.g., Guillain–Barre´ syndrome with unstable airway, tetanus, etc.), Glasgow Coma Score (GCS) B8 (only best motor and eye responses), congenital anomalies, infection, burns, trauma and surgery involving airway, history of previous tracheal intubation or tracheostomy, chronic lung disease, contraindications for steroid, gastrointestinal bleeding, hypertension ([95th centile), hyperglycemia, steroid treatment in preceding 7 days or chronic nonsteroidal anti-inflammatory drug (NSAID) therapy were excluded. |
| **Total number of participants** | 140 randomized; 124 analyzed |
| **Intervention details** | 24hPD patients received six doses of intravenous dexamethasone (0.5 mg/kg/dose, maximum 8 mg/dose): the first dose 24 h before anticipated extubation and then every 6 h for a total of six doses. Extubation was done in the morning immediately after fifth dose. |
| **Comparator/Control details** | 6hPD patients received intravenous sterile water in equal volume for initial three doses, followed by dexamethasone (0.5 mg/kg/dose) for next three doses: 1st dose 6 h prior to and 2nd dose at extubation, and 3rd dose 6 h after extubation, |
| **Outcomes** | Failure to liberate from invasive MV (or failed extubation), Post-extubation upper airway obstruction, GI bleeding |

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**Supplemental Figure Legends:**

**Figure E1a.** Risk of bias assessment, using RoB-2, of trials included in the pairwise and network meta-analysis. Outcome: Reintubation.

**Figure E1b.** Risk of bias assessment, using RoB-2, of trials included in the pairwise and network meta-analysis. Outcome: UAO.

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**Reintubation**

| Study ID | Experimental | Comparator | Outcome | Weight | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|---|---|---|
| Tellez 1991 | Dexamethasone | NA | Reintubation | 1 | ! | + | + | + | + | ! |
| Anene 1996 | Dexamethasone | Saline | Reintubation | 1 | + | ! | + | + | + | ! |
| Cesar 2009 | Dexamethasone | NA | NA | 1 | ! | + | + | + | + | ! |
| Malhotra 2009 | Dexamethasone | Saline | Reintubaiton | 1 | + | + | + | + | + | + |
| Baranwal 2014 | Dexamethasone | NA | Reintubation | 1 | + | + | + | + | + | + |
| de Carvalho 2020 | Dexamethasone | NA | Reintubation | 1 | + | + | + | ! | + | ! |
| Parajuli 2021 | Dexamethasone 0.5mg/kg/dose | Dexamethasone 0.25mg/kg/dose | Reintubation | 1 | + | + | + | + | + | + |
| Ritu 2020 | Dexamethasone | Saline | Reintubation | 1 | + | + | + | + | + | + |

| | |
|---|---|
| D1 | Randomisation process |
| D2 | Deviations from the intended interventions |
| D3 | Missing outcome data |
| D4 | Measurement of the outcome |
| D5 | Selection of the reported result |

| | |
|---|---|
| + | Low risk |
| ! | Some concerns |
| - | High risk |

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**UAO**

| Study ID | Experimental | Comparator | Outcome | Weight | D1 | D2 | D3 | D4 | D5 | Overall |
|---|---|---|---|---|---|---|---|---|---|---|
| Tellez 1991 | Dexamethasone | NA | Stridor | 1 | ! | + | + | + | + | ! |
| Anene 1996 | Dexamethasone | Saline | Stridor | 1 | + | ! | + | + | + | ! |
| Cesar 2009 | Dexamethason | Saline | PLE Clinical scoring syst | 1 | ! | + | + | + | + | ! |
| Malhotra 2009 | Dexamethasone | Saline | Laryngeal edema by lar | 1 | + | + | + | + | + | + |
| Baranwal 2014 | Dexamethasone | NA | UAO | 1 | + | + | + | + | + | + |
| de Carvalho 2020 | Dexamethasone | No dexamethasone | Westley Croup Score- U | 1 | + | + | + | - | + | - |
| Ritu 2020 | Dexamethasone | Saline | Stridor | 1 | + | + | + | + | + | + |
| Parajuli 2021 | Dexamethasone 0.5mg/kg/dose | Dexamethasone 0.25mg/kg/dose | PEAO-Wesley Croup Sc | 1 | + | + | + | + | + | + |

| | |
|---|---|
| D1 | Randomisation process |
| D2 | Deviations from the intended interventions |
| D3 | Missing outcome data |
| D4 | Measurement of the outcome |
| D5 | Selection of the reported result |

| | |
|---|---|
| + | Low risk |
| ! | Some concerns |
| - | High risk |

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