Interventions to Improve Rates of Successful Extubation in Preterm Infants
A Systematic Review and Meta-analysis

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IMPORTANCE Clinicians aim to extubate preterm infants as early as possible, to minimize the risks of mechanical ventilation. Extubation is often unsuccessful owing to lung disease or inadequate respiratory drive.

OBJECTIVE To conduct a systematic review and meta-analysis of interventions to improve rates of successful extubation in preterm infants.

DATA SOURCES Searches were undertaken in PubMed and The Cochrane Library.

STUDY SELECTION The review was conducted using the methods of the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Studies were included if they were randomized clinical trials published in English, enrolled intubated preterm infants (born <37 weeks' gestation), and reported 1 or both of the primary outcomes.

DATA EXTRACTION AND SYNTHESIS One thousand three hundred seventy-nine titles were screened independently by 2 investigators to assess need for full-text review. Disagreements were resolved via consensus of all authors. Where no Cochrane Review existed for an intervention, or not all identified studies were included, a new pooled analysis was performed.

MAIN OUTCOMES AND MEASURES Primary outcomes were treatment failure or reintubation within 7 days of extubation.

RESULTS Fifty studies were eligible for inclusion. Continuous positive airway pressure reduced extubation failure in comparison with head-box oxygen (risk ratio [RR], 0.59; 95% CI, 0.48-0.72; number needed to treat [NNT], 6; 95% CI, 3-9). Nasal intermittent positive pressure ventilation was superior to continuous positive airway pressure in preventing extubation failure (RR, 0.70; 95% CI, 0.60-0.81; NNT, 8; 95% CI, 5-13). High-flow nasal cannula therapy and continuous positive airway pressure had similar efficacy (RR, 1.11; 95% CI, 0.84-1.47). Methylxanthines reduced extubation failure (RR, 0.48; 95% CI, 0.32-0.71; NNT, 4; 95% CI, 2-7) compared with placebo or no treatment. Corticosteroids (RR, 0.18; 95% CI, 0.04-0.97; NNT, 12; 95% CI, 6-100) and chest physiotherapy (RR, 0.32; 95% CI, 0.13-0.82; NNT, 15; 95% CI, 7-50) both reduced extubation failure rates but were associated with significant adverse effects. Doxapram did not aid successful extubation (RR, 0.80; 95% CI, 0.22-2.97).

CONCLUSIONS AND RELEVANCE Preterm infants should be extubated to noninvasive respiratory support. Caffeine should be used routinely, while corticosteroids should be used judiciously, weighing up the competing risks of bronchopulmonary dysplasia and neurodevelopmental harm.
The introduction of mechanical ventilation for the treatment of respiratory failure in preterm infants has led to improvements in survival. However, prolonged mechanical ventilation can result in unintended harm. Mechanically ventilated preterm infants are at increased risk of developing bronchopulmonary dysplasia, sepsis, neurological injury, and retinopathy of prematurity. To minimize these risks, clinicians aim to extubate preterm infants as early as possible. In the most preterm infants, extubation is often unsuccessful owing to lung disease or inadequate respiratory drive.

Given that approximately two-thirds of infants born before 29 weeks’ gestation require intubation, it is important that clinicians are aware of strategies to improve rates of extubation success. We conducted a systematic review and meta-analysis of interventions aimed at improving rates of successful extubation in preterm infants.

Methods

Search Strategy

This review was conducted using the methods of the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0. Relevant studies were identified by searching PubMed, The Cochrane Library, and the reference lists of included articles. The PubMed search strategy was (Infant, Premature[Mesh] OR Infant, Low birth weight[Mesh] OR Infant, Newborn[Mesh]) AND (Airway Extubation[Mesh] OR Intubation, Intratracheal[Mesh] OR Ventilator Weaning[Mesh]) AND (Randomized Controlled Trial [Publication Type] OR Letter [Publication Type] OR Review [Publication Type] OR Clinical Trial [Publication Type] OR Evaluation Studies OR Comparative Study [Publication Type]).

The primary outcomes were (1) treatment failure (as defined in the studies), and/or (2) reintubation, both within 7 days of extubation. Studies were included if they were randomized clinical trials published in English, enrolled intubated preterm infants (born <37 weeks’ gestation), and reported 1 or both primary outcomes. Studies were excluded if they reported intubation solely for surfactant administration followed by rapid extubation. Study protocols, cohort studies, retrospective studies, review articles, abstracts, editorials, and animal studies were excluded.

The titles and abstracts of all retrieved articles were screened independently by 2 investigators (C.T.R. and K.N.F.) to assess the need for further review. Full-text articles were then assessed for inclusion. Disagreements were resolved via consensus of all authors.

Included studies were grouped by intervention tested. Where current Cochrane Reviews included all identified studies of an intervention, the Cochrane Review was cited. When no Cochrane Review existed for an intervention, or the review did not include all identified studies, a new pooled analysis was performed and reported in keeping with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Statistical Analysis

Additional analyses were performed using the Cochrane Review process (Revman, version 5.3). Consistent with recommendations made by the Cochrane Neonatal Review Group, a fixed-effects model was used. Where significant heterogeneity between studies was detected (I² >50%), an additional random-effects analysis was undertaken (eTable 1 in the Supplement). Outcomes are reported as risk ratio (RR), risk difference (RD), and where a significant difference exists, number needed to treat (NNT). Risk ratio, RD, and NNT are presented as point estimate (95% confidence interval).

Risk of Bias Assessment

Risk of bias was assessed using the Cochrane Collaboration tool (eTable 2 in the Supplement). Strength of evidence across studies was assessed against Grading of Recommendations, Assessment, Development, and Evaluation guidelines (eTables 3-9 in the Supplement).

Results

The search was conducted on December 23, 2015, yielding 1379 articles. An additional 39 articles were identified from Cochrane Reviews. Full-text reviews were conducted on 100 articles, of which 50 were included: 36 were already included in Cochrane Reviews (Figure 1). Three studies had an unacceptably high risk of bias and were excluded.

Continuous Positive Airway Pressure

Continuous positive airway pressure (CPAP) aims to deliver gas flow at pressures sufficient to maintain airway patency, reducing obstruction, work of breathing, and apnea. Continuous positive airway pressure improves oxygenation and maintains lung volume. Continuous-flow CPAP devices, such as ventilator-generated and bubble CPAP devices, direct a constant gas flow against the resistance of the expiratory limb of the circuit and alter set pressure by varying the area of the expiratory valve opening (ventilator-generated) or underwater depth of the expiratory limb (bubble). Variable-flow CPAP devices, such as the Infant Flow system (Carefusion Corp) use flow changes to generate different pressures. Continuous positive airway pressure can be delivered by various nasal interfaces. Fifteen articles studied CPAP post-extubation.
**Interventions for Successful Extubation in Preterm Infants**

**CPAP vs Head-Box Oxygen**

Nine studies were identified: all were included in the existing Cochrane Review. The study by Tapia et al was not a randomized clinical trial and was excluded. Continuous positive airway pressure significantly reduced respiratory failure within 7 days of extubation (RR, 0.59; 95% CI, 0.48-0.72; RD, −0.19; 95% CI, −0.26 to −0.12; NNT, 6; 95% CI, 3-9; \( I^2 \), 46%)(Figure 2A). There was no significant difference in reintubation rates within 7 days (RR, 0.83; 95% CI, 0.66-1.04; RD, −0.06; 95% CI, −0.13 to 0.01; \( I^2 \), 31%) (Figure 2B), possibly because many studies used “rescue CPAP” successfully when head-box oxygen had failed.

**CPAP Device**

**Bubble vs Ventilator-Generated CPAP** | Yadav et al randomized 32 infants at less than 32 weeks’ gestation with birth weights less than 1500 g to either bubble or ventilator-generated CPAP, both delivered by short binasal prongs. This small study found no significant difference in rate of extubation failure: bubble, 4 of 16 (25%) vs ventilator-generated, 9 of 16 (56%) (RR, 0.44; 95% CI, 0.17-1.15; RD, −0.31; 95% CI, −0.64 to 0.01).

**Variable Flow vs Ventilator-Generated CPAP** | Stefanescu et al compared Infant Flow with ventilator-generated CPAP in 162 extremely low-birth-weight infants (birth weight <1000 g). They found no difference in rates of extubation failure: Infant Flow, 30 of 78 (38%) vs ventilator-generated, 32 of 84 (38%) (RR, 1.01; 95% CI, 0.68-1.49; RD, 0.00; 95% CI, −0.15 to 0.15).

**Bubble vs Variable Flow CPAP** | Gupta et al compared bubble with Infant Flow CPAP, both delivered by short binasal prongs, for preventing extubation failure in 140 preterm infants at 24 weeks’ to 29 weeks' gestation, or with birth weight 600 g to 1500 g. At 72 hours, 12 of 71 of the bubble group (17%) vs 19 of 69 of the Infant Flow group (28%) had failed extubation (RR, 0.61; 95% CI, 0.32-1.17; RD, −0.11; 95% CI, −0.24 to 0.03). At 7 days post-extubation, the outcome was similar (RR, 0.68; 95% CI, 0.37-1.24; RD, −0.09; 95% CI, −0.23 to 0.05).

**Lower vs Higher CPAP Pressure** | Buzzella et al randomized 93 infants at 23 weeks' to 30 weeks’ gestation, with birth weights 500 g to 1000 g, to be extubated to either 4 cm to 6 cm H2O (lower) or 7 cm to 9 cm H2O (higher) CPAP pressure. There was a borderline reduction in extubation failure at 96 hours in the “higher” group: 11 of 46 (24%) vs 20 of 47 (43%) (RR, 0.56; 95% CI, 0.30-1.04; RD, −0.19; 95% CI, −0.37 to 0.00). Reintubation rates within 7 days were reduced in the “higher” group: 14 of 46 (30%) vs 24 of 47 (51%) (RR, 0.60; 95% CI, 0.35-1.00; RD, −0.21; 95% CI, −0.40 to −0.01; NNT, 5; 95% CI, 2-100).

**CPAP Interface**

**Binasal vs Single-Nasal Prongs** | Davi et al randomized 87 extremely low-birth-weight infants to receive CPAP via binausal or single-nasal prong post-extubation. Bi-nasal prongs were significantly associated with reduced extubation failure: 10 of 46 (21%) vs 26 of 46 (57%) (RR, 0.43; 95% CI, 0.24-0.78; RD, −0.32; 95% CI, −0.52 to −0.13; NNT, 4; 95% CI, 1-8). This was a borderline reduction in reintubation in infants treated with binausal prongs: 9 of 41 (22%) vs 19 of 46 (41%) (RR, 0.53; 95% CI, 0.27-1.04; RD, −0.19; 95% CI, −0.38 to 0.00).

**Nasal Mask vs Short Binasal Prongs** | Kieran et al randomized 63 extremely low-birth-weight infants to receive CPAP via nasal mask or binausal prongs post-extubation. The

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**Figure 1. Search Results**

1379 Records identified through database searching
39 Additional records identified through other sources
1394 Records after duplicates removed
1394 Records screened
100 Full-text articles assessed for eligibility
50 Studies included in qualitative synthesis
34 Studies included in qualitative synthesis (meta-analysis)

1294 Records excluded
50 Full-text articles excluded with reasons
11 Not randomized clinical trial
11 Extubation failure not an outcome
8 Extubation not planned
2 Study groups not comparable
1 Intubation solely for surfactant administration
1 Not in English

1344 Records after duplicates removed
1344 Records screened
1294 Records excluded
100 Full-text articles assessed for eligibility
50 Studies included in qualitative synthesis
34 Studies included in qualitative synthesis (meta-analysis)
nasal mask group had significantly fewer reintubations within 72 hours: 5 of 31 (16%) vs 13 of 32 (41%) (RR, 0.40; 95% CI, 0.16-0.98; RD, −0.24; 95% CI, −0.46 to −0.03; NNT, 5; 95% CI, 2-34). However, there was no difference in rates of reintubation overall: 15 of 31 infants with nasal mask (48%) vs 19 of 32 infants with binalar prongs (59%) (RR, 0.81; 95% CI, 0.51-1.29; RD, −0.11; 95% CI, −0.35 to 0.13).

Nasal Intermittent Positive Pressure Ventilation and Biphasic Positive Airway Pressure

Nasal intermittent positive pressure ventilation (NIPPV) uses a mechanical ventilator to deliver positive pressure inflations on a background of CPAP. The rate, inflation time, and peak inflation pressures used are similar to mechanical ventilation. Nasal intermittent positive pressure ventilation may be synchronized (S-NIPPV) with the infant’s spontaneous breathing, or nonsynchronized (NS-NIPPV). Biphasic positive airway pressure (BiPAP) is a variant that cycles between higher and lower set pressures, without coordination with the infant’s breathing, and commonly delivered using “variable-flow” devices. 29

Ten studies were identified investigating post-extubation NIPPV or BiPAP. Eight of these were included in a 2014 Cochrane Review. 29

Nonsynchronized NIPPV vs Head-Box Oxygen

Kumar et al 30 compared NS-NIPPV via a single prong with head-box oxygen as post-extubation support for preterm infants weighing less than 2000 g, mechanically ventilated for more than 24 hours, and younger than 28 days of age. 30 In the NS-NIPPV group, 7 of 45 infants (16%) failed extubation vs 28 of 45 infants (62%) in the head-box oxygen group (RR, 0.25; 95% CI, 0.12-0.51; RD, −0.47; 95% CI, −0.64 to −0.29; NNT, 3; 95% CI, 1-4).

Any Mode of NIPPV or BiPaP vs CPAP

Kirpalani et al 31 compared the use of either mode of NIPPV or BiPaP (NIPPV group) with CPAP in 1009 infants at less than 30 weeks’ gestation, with birth weight less than 1000 g, at first use of noninvasive support. 31 The 845 infants randomized post-extubation are included in this analysis. There was a borderline reduction in extubation failure (RR, 0.86; 95% CI, 0.72-1.01; RD, −0.06; 95% CI, −0.13 to 0.00) (eFigure 1 in the Supplement).

However, the Cochrane Review meta-analysis of 8 studies, with the addition of Kahramaner et al, 32 using any mode of NIPPV or BiPaP, found a significant reduction in respiratory failure compared with CPAP (RR, 0.70; 95% CI, 0.60-0.81; RD, −0.13; 95% CI, −0.18 to −0.08; NNT, 8; 95% CI, 5-13; I2, 66%) (Figure 3A 23-39 and eTable 1 in the Supplement). 32 Nasal inter-
mittent positive pressure ventilation or BiPAP use were also associated with significantly reduced reintubation (RR, 0.74; 95% CI, 0.64-0.85; RD, −0.10; 95% CI, −0.15 to −0.05; NNT, 10; 95% CI, 6-20; I², 51%) (Figure 3B33-39 and eTable 1 in the Supplement).

Nonsynchronized NIPPV or BiPAP vs CPAP
Three studies were identified. Nonsynchronized NIPPV/BiPAP associated with significantly reduced extubation failure (RR, 0.64; 95% CI, 0.44-0.95; RD, −0.24 to 0.02; NNT, 10; 95% CI, 4-50; I², 51%) (Figure 3B35-39 and eTable 1 in the Supplement).

Synchronized NIPPV vs CPAP
Five studies were identified; all were included in the Cochrane Review.29 Synchronized NIPPV was associated with significantly reduced extubation failure (RR, 0.25; 95% CI, 0.15-0.41; RD, −0.33; 95% CI, −0.43 to −0.23; NNT, 4; 95% CI, 2-5; I², 0%) (eFigure 1 in the Supplement).

Nonsynchronized NIPPV or S-NIPPV vs CPAP
Seven studies were identified. Nasal intermittent positive pressure ventilation use was associated with a significant decrease in extubation failure (RR, 0.28; 95% CI, 0.18-0.43; RD, −0.28; 95% CI, −0.36 to −0.20; NNT, 4; 95% CI, 2-5; I², 0%).

High-Flow Nasal Cannula Therapy
High-flow nasal cannula (HFNC) uses binasal cannula to deliver heated and humidified blended air and oxygen at gas flows greater than 1 L/min.40

Six studies investigated HFNC therapy post-extubation: 3 studies were included in the 2011 Cochrane Review, and a further 3 studies were identified by our search.40

HFNC vs CPAP
Four studies were identified. Campbell et al41 compared HFNC (mean flow, 1.8 L/min) with Infant Flow CPAP in 40 preterm infants with birth weight 1250 g or less.41 More infants in the HFNC group required reintubation within 7 days: 12 of 20 infants (60%) vs 3 of 20 infants (15%); P = .003.

In 2013, 3 larger RCTs using higher gas flows were published. The primary outcome for all was treatment failure, determined by objective parameters including oxygenation, apnea, and acidosis. Collins et al42 compared HFNC (Vapotherm Inc) 8 L/min with CPAP in 132 very preterm infants.42

\[ \text{RR, Fixed (95\% CI)} \]
\[ 0.74 (0.64-0.85) \]

\[ \text{Total (95\% CI)} \]
\[ 693 \quad 675 \]

\[ \text{Total events} \]
\[ 200 \]

\[ \text{Heterogeneity: } \chi^2 = 16.36, df = 8 (P = .004); I^2 = 51\% \]

\[ \text{Test for overall effect: } z = 4.06 (P < .001) \]
was no difference in treatment failure within 7 days: 15 of 67 infants receiving HFNC (22%) vs 22 of 65 receiving CPAP (34%) (P = .14). Intubation after treatment failure was not mandated, and there was no difference in reintubation within 7 days (7 of 67 infants in the HFNC group [10%] vs 8 of 65 infants in the CPAP group [12%]; P = .74).

Yoder et al43 randomized 432 preterm and term infants to either HFNC 3 L/min to 5 L/min or CPAP as either primary or post-extubation support.43 The 223 preterm infants in the post-extubation arm were included in our analysis. There was no difference between the HFNC and CPAP groups in treatment failure: 11 of 107 infants in the HFNC groups (10%) vs 9 of 116 infants in the CPAP group (8%) (P = .51). There was also no difference in the rate of reintubation within 7 days: 11 of 107 infants (10%) vs 12 of 116 infants (10%) (P = .99).

Manley et al44 conducted a noninferiority randomized clinical trial, comparing HFNC 5 L/min to 6 L/min with CPAP as post-extubation support in 303 very preterm infants.44 Treatment failure within 7 days occurred in 52 of 152 (34%) of the HFNC group vs 39 of 151 (26%) of the CPAP group (P = .11). About half the infants with treatment failure in the HFNC group were “rescued” from reintubation by CPAP. The rates of reintubation within 7 days were therefore similar: 27 of 152 infants in the HFNC group (18%) vs 38 of 151 infants in the CPAP group (25%) (P = .12).

On pooled analysis, there was no difference between HFNC and CPAP in treatment failure within 7 days (RR, 1.11; 95% CI, 0.84-1.47; RD, 0.02; 95% CI, −0.04 to 0.09; I², 55%) (Figure 4A and eTable 1 in the Supplement) or reintubation within 7 days (RR, 0.94; 95% CI, 0.68-1.31; RD, −0.01; 95% CI, −0.06 to 0.04; I², 64%) (Figure 4B and eTable 1 in the Supplement). It should be noted that several studies allowed the use of “rescue” CPAP/NIPPV if HFNC had failed prior to reintubation. For the outcome of reintubation, restricting the analysis to trials delivering heated and humidified gas flows of at least 2 L/min reduced the heterogeneity to 0% (RR, 0.78; 95% CI, 0.55-1.12; RD, −0.04; 95% CI, −0.09 to 0.02) (eFigure 2 in the Supplement).

Humidified vs Nonhumidified HFNC
Woodhead et al45 enrolled 30 preterm infants immediately post-extubation in a crossover study comparing nonhumidified with Vapotherm (humidified) HFNC.45 The study was underpowered to detect a difference in reintubation rates: 0 of 15 infants in the Vapotherm group (0%) vs 2 of 13 infants in the nonhumidified HFNC group (15%) (RR, 0.17; 95% CI, 0.01-3.34; RD, −0.15; 95% CI, −0.37 to 0.06).

Comparison of Different HFNC Devices
Miller and Dowd46 compared the efficacy of Fisher and Paykel (Fisher and Paykel Healthcare) and Vapotherm HFNC in 40 preterm infants.46 There was no difference in rates of reintubation within 72 hours: 3 of 17 in the Fisher and Paykel group (18%) vs 3 of 23 in the Vapotherm group (13%) (RR; 1.35, 95% CI, 0.31-5.90; RD, 0.05; 95% CI, −0.18 to 0.27) or 7 days: 5 of 17 infants in the Fisher and Paykel group (29%) vs 7 of 23 infants in the Vapotherm group (30%) (RR, 0.97; 95% CI, 0.37-2.53; RD, −0.01; 95% CI, −0.30 to 0.28).

Methylxanthines
Methylxanthines reduce apneic episodes by increasing respiratory drive. The existing Cochrane Review of this topic included 6 studies, and our search identified an additional 3.47

### Table: Treatment Failure and Reintubation

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>HFNC Total No.</th>
<th>NCPAP Total No.</th>
<th>RR M-H Fixed (95% CI)</th>
<th>Favors HFNC</th>
<th>Favors NCPAP</th>
<th>Weight, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yoder et al, 2013</td>
<td>11</td>
<td>107</td>
<td>9</td>
<td>116</td>
<td>1.33 (0.57-3.07)</td>
<td></td>
</tr>
<tr>
<td>Manley et al, 2013</td>
<td>52</td>
<td>152</td>
<td>39</td>
<td>151</td>
<td>1.32 (0.91-1.88)</td>
<td></td>
</tr>
<tr>
<td>Collins et al, 2013</td>
<td>15</td>
<td>67</td>
<td>22</td>
<td>65</td>
<td>0.66 (0.38-1.16)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>78</td>
<td>326</td>
<td>332</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**A. Respiratory failure within 7 days of extubation. B. Reintubation within 7 days of extubation.**
Prophylactic Methylxanthines vs Placebo/No Treatment
Six studies included in the Cochrane Review compared prophylactic methylxanthines with placebo or no treatment for facilitating successful extubation. Methylxanthines were associated with a significantly reduced rate of extubation failure (RR, 0.48; 95% CI, 0.32-0.71; RD, −0.27; 95% CI, −0.39 to −0.15; NNT, 4; 95% CI, 2-7; I², 0%) (eFigure 3 in the Supplement).47

Theophylline vs Caffeine
Sims et al48 randomized 45 preterm infants to theophylline or caffeine at least 24 hours before planned extubation and daily for 5 days post-extubation.48 Within 72 hours of the loading dose, there was no difference in the number of infants who had not been successfully extubated: 4 of 23 infants in the theophylline group (17%) vs 5 of 22 infants in the caffeine group (23%) (RR, 0.77; 95% CI, 0.24-2.48; RD, −0.05; 95% CI, −0.29 to 0.18). There was also no difference in reintubation within 5 days: 3 of 23 infants in the theophylline group (13%) vs 3 of 22 infants in the caffeine group (14%) (RR, 0.96; 95% CI, 0.22-4.24; RD, −0.01; 95% CI, −0.20 to 0.19).

High- vs Low-Dose Caffeine
Two studies were identified. We considered it inappropriate to pool these data owing to the different dosages used.

Steer et al49 randomized 127 very preterm infants to 1 of 3 caffeine citrate dosing regimens (3 mg/kg/d, 15 mg/kg/d, or 30 mg/kg/d).49 Infants were given a daily dose of caffeine for 6 days beginning at least 24 hours before a planned extubation or within 6 hours following an unplanned extubation. Extubation failure was defined as either an inability to extubate within 48 hours of caffeine loading dose, reintubation, or doxapram given within 7 days of the caffeine load. Extubation failure rates were 19 of 42 infants (45%) vs 10 of 40 infants (25%) vs 11 of 45 infants (24%) for the 3 mg/kg, 15 mg/kg, and 30 mg/kg groups, respectively, and were not significantly different (P = .06).

The same group later compared 2 caffeine citrate dosing regimens (low dose 5 mg/kg/d and high dose 20 mg/kg/d) in 234 infants younger than 30 weeks’ gestation.50 The same dosing schedule and extubation failure criteria were used as in the previous study. A significant reduction in extubation failure was seen in the high-dose group: 17 of 113 infants (15%) vs 36 of 121 infants (30%) (RR, 0.51; 95% CI, 0.30-0.85; RD, −0.15; 95% CI, −0.25 to −0.04; NNT, 7; 95% CI, 4-25).

Corticosteroids
Endotracheal tubes, especially when used for a prolonged period or inserted multiple times, can cause upper airway injury. Exogenous corticosteroids help reduce inflammation, therefore preventing airway obstruction, potentially reducing extubation failure.31

Three studies of intravenous dexamethasone were identified and were included in the Cochrane Review.51 Intravenous dexamethasone given prophylactically was associated with reduced reintubation (RR, 0.18; 95% CI, 0.04-0.97; RD, −0.09; 95% CI, −0.16 to −0.01; NNT, 12; 95% CI, 6-100; I², 75%) (eFigure 4 in the Supplement).51 However, this difference was no longer significant when a random-effects model was used (RR, 0.20; 95% CI, 0.04-1.11; RD, −0.08; 95% CI, −0.23 to 0.07) (eTable 1 in the Supplement).

Doxapram
Doxapram hydrochloride is a respiratory stimulant. The Cochrane Review identified 3 studies comparing doxapram plus “standard treatment” (methylxanthines and CPAP) with standard treatment alone and 1 trial comparing doxapram with aminophylline.52 Two of these studies were excluded from analysis, either owing to open-label doxapram use in the control group or small sample size (8 infants).12,13

Huon et al53 compared doxapram and standard treatment with standard treatment alone in 29 preterm infants and found no significant difference in extubation failure (RR, 0.80; 95% CI, 0.22-2.97; RD, −0.05; 95% CI, −0.36 to 0.26) (eFigure 5 in the Supplement).53

Chest Physiotherapy
Mechanical ventilation increases lung secretions and can result in lung atelectasis. Active chest physiotherapy, including percussion and vibration, aims to assist in the removal of lung secretions.54

The Cochrane Review included 4 trials comparing the use of active chest physiotherapy both before and after extubation with no active physiotherapy. Meta-analysis found a significant reduction in reintubation within 24 hours with chest physiotherapy (RR, 0.32; 95% CI, 0.13-0.82; RD, −0.07; 95% CI, −0.13 to −0.02; NNT, 15; 95% CI, 7-50; I², 12%) (eFigure 6 in the Supplement).54

Discussion
As clinicians strive to reduce preterm infants’ exposure to mechanical ventilation, it is important they are aware of the evidence base for interventions available to aid extubation. To our knowledge, this is the first review compiling the evidence for multiple interventions aimed at improving rates of successful extubation in preterm infants.

Continuous positive airway pressure and NIPPV were superior to head-box oxygen. Limited evidence suggested that CPAP delivered at higher pressures (7-9 cm H2O) and via binaisal prongs was most effective. While CPAP delivered by nasal mask was associated with fewer intubations in the first 72 hours post-extubation in comparison with binaisal prongs, this effect was not sustained. No particular method of generating CPAP was found to be superior.

Nasal intermittent positive pressure ventilation was more effective than CPAP to prevent extubation failure, regardless of whether synchronization was used. There was substantial heterogeneity between included trials, partially explained by the inclusion of Kirpalani et al,31 which differs from other trials in its size, involvement of multiple centers, and different devices.31 Heterogeneity was partly explained by subgroup analysis, which demonstrated a differential treatment effect; S-NIPPV seemed to have a greater benefit than NS-NIPPV.
High-flow nasal cannula and CPAP appear to have similar efficacy in the prevention of reintubation, although some studies used CPAP as rescue therapy for babies whose HFNC failed. The use of different initial gas flows (range, 1.8-8 L/min) may account for the substantial heterogeneity. Excluding Campbell et al from the reintubation meta-analysis (eFigure 2 in the Supplement) on the basis that much lower gas flows and unheated gases were used resolves the heterogeneity of the overall pooled analysis. Current evidence does not support any particular HFNC device over another.

Methylxanthines improved rates of extubation success; however, doxapram did not. In the Caffeine for Apnea of Prematurity trial, caffeine use in preterm infants was shown to be safe and effective in the short and long term; however, extubation success was not reported. On subanalysis, it was shown that caffeine given pre-extubation reduced time spent in oxygen and rates of death or disability.

Fixed-effects analysis showed that corticosteroids reduced the rate of reintubation; however, this effect disappeared when a random-effects model was used. The considerable heterogeneity between studies of corticosteroids may be owing to the different doses used (total, 0.25 mg/kg to 1.5 mg/kg). Longer courses of corticosteroids are associated with increased risk of neurodevelopmental problems. Doyle et al demonstrated that infants with a high risk of bronchopulmonary dysplasia had a reduced risk of death or cerebral palsy when exposed to corticosteroids, whereas those at low risk of bronchopulmonary dysplasia had an increased risk.

Chest physiotherapy significantly improved extubation success; however, this must be interpreted cautiously. The trials have heterogeneous study populations and physiotherapy techniques and were conducted more than 10 years ago. The safety of chest physiotherapy is also questioned.

This review has several limitations. The large variations between studies in the defined duration of successful extubation and the inconsistent definition of “respiratory failure” make the analysis of pooled data challenging. We noted some instances of substantial heterogeneity ($I^2 > 50\%$) between studies, which were explored by conducting random-effects and subgroup analyses based on the characteristics of the intervention. In most cases, the additional analyses did not change our conclusions.

Conclusions

Preterm infants should be extubated to noninvasive respiratory support. Continuous positive airway pressure and NIPPV have the largest evidence base supporting their use. Continuous positive airway pressure should be delivered by binaisal prongs or nasal mask and at pressures of at least 5 cm H$_2$O. Meta-analysis, including post-extubation treatment by any mode of NIPPV or BiPAP, demonstrates superiority to CPAP in preventing extubation failure. However, translating the evidence for this heterogeneous group of treatments into clinical practice is difficult because there appear to be differences in efficacy between NIPPV and BiPAP modalities. High-flow nasal cannula appears to be a suitable alternative to CPAP, especially if “rescue” CPAP therapy is available. Caffeine should be routinely used in preterm infants undergoing extubation, using the dosages tested in the Caffeine for Apnea of Prematurity trial. Corticosteroids should be used judiciously, weighing up the competing risks of bronchopulmonary dysplasia and neurodevelopmental harm.

Further research is required to determine the best predictors of extubation readiness and the specific noninvasive respiratory support settings and interfaces to be used. A standard definition for defining extubation success and failure should be encouraged to enable synthesis of the evidence.
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Original Investigation Research

124-125.


after extubation for preventing morbidity in


Randomised, controlled trial of nasal continuous


27. Davis P, Davies M, Faber B. A randomised controlled trial of two methods of delivering nasal continuous positive airway pressure after extubation to infants weighing less than 1000 g: binasal (Hudson) versus single nasal prongs. *Arch Dis Child Fetal Neonatal Ed.* 2001;85(2):F82-F85.


