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Optimising success of neonatal extubation: Respiratory support

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ABSTRACT

In this review, we examine lung physiology before, during and after neonatal extubation and propose a three-phase model for the extubation procedure. We perform meta-analyses to compare different modes of non-invasive respiratory support after neonatal extubation and based on the findings, the following clinical recommendations are made:

1) Continuous positive airway pressure support (CPAP) remains standard of care for most extubations.
2) For high-risk infants <28 weeks' gestation or infants with expected cardiorespiratory instability, either NIPPV or nHFOV may be used as post-extubation respiratory support. Synchronized, ventilator-generated NIPPV may be more effective than alternative modes. The use of nHFOV after extubation seems to confer the largest benefit but clinical experience is limited in most centres.
3) If backup CPAP is available, high-flow therapy may be preferred for infants ≥28 weeks with a low fraction of inspired oxygen.

1. Introduction

Non-invasive modes of ventilation are now considered superior to intubation at birth [1]. However, approximately 60 % of preterm infants are intubated in the first days of life, with rates highest in the most immature infants [2]. Prolonged endotracheal ventilation induces inflammation and tissue damage thereby disrupting lung development [3–6]. Thus, clinicians generally aim for early extubation. However, approximately 40 % of very preterm infants develop respiratory failure after extubation and require re-intubation, which in itself is associated with higher mortality rates and significant morbidity, including airway trauma, feeding difficulties and prolonged duration of respiratory support [2,7]. Achieving early, successful extubation is an important challenge for clinicians and researchers.

2. Physiology of neonatal extubation

Neonatal extubation remains a critical phase of a preterm infant's NICU journey. There are several factors contributing to the higher complexity compared with older infants or children, all of which are associated with an increased likelihood of extubation failure: (1) the upper airway of preterm infants is less stable [8], (2) the lung is more susceptible to collapse [9], (3) functional residual capacity (FRC) and total lung volumes are smaller and therefore, the ability to maintain adequate oxygen levels without respiratory support is poor [10], (4) susceptibility to adverse outcomes due to free oxygen radicals is higher (e.g. retinopathy of prematurity) [11], and (5) the upper respiratory tract is smaller and more fragile, therefore tissue damage is more likely to occur [12].

2.1. Three-phase model of extubation

There are three distinct yet connected phases of neonatal extubation: (1) before extubation, while the infant is still on invasive respiratory support, (2) during extubation, when no respiratory support is provided for a short period, and (3) after extubation, when non-invasive respiratory support is established (Fig. 1).

During phase one, the lung should be adequately recruited, and homogeneously well aerated. The airway is stabilized by the endotracheal tube and continuous distending pressure is guaranteed, thereby maintaining FRC and avoiding atelectasis. This leads to cardiorespiratory stability with stable peripheral oxygen saturation (SpO_2) and heart

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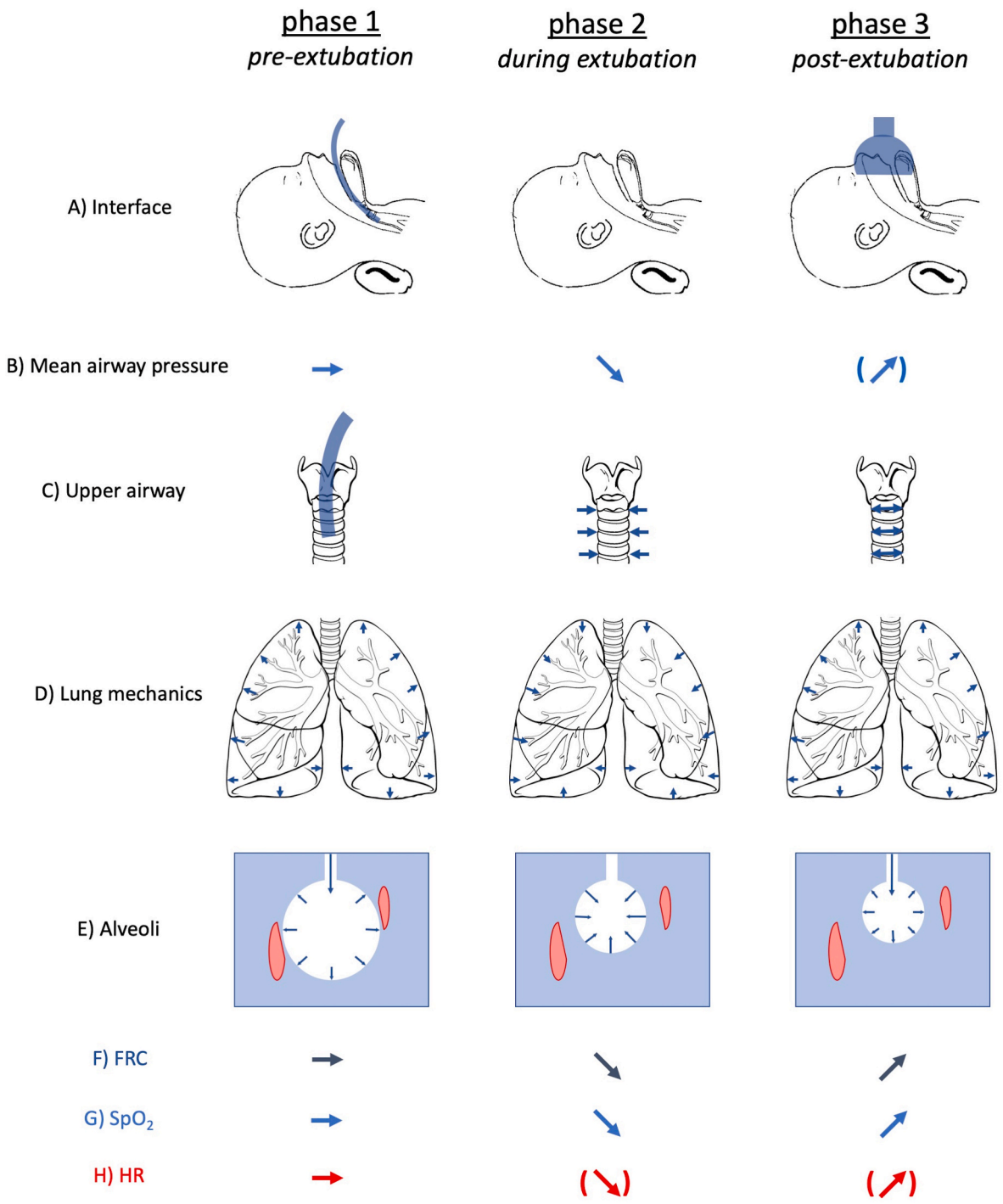

Fig. 1. Three-phase model of neonatal extubation. Changes in various parameters (A–H) are depicted before, during and after extubation (phases 1–3, respectively). Before extubation, the mean airway pressure is maintained continuously, the upper airway, the lung and the alveoli are stabilized by the positive distending pressure and functional residual capacity (FRC) as well as SpO_2 and heart rate (HR) are kept level. During extubation, a range of physiological changes occur – by taking away the interface and the corresponding positive distending pressure, mean airway pressure decreases, the larynx may collapse, the lung retracts, and alveoli are collapsing. Accordingly, FRC, SpO_2 and HR may decrease, depending on the infant's respiratory stability. Finally, after extubation, the re-initiation of non-invasive respiratory support may assist in recruiting lost lung capacity with an increased mean airway pressure, thereby stabilizing the larynx and collapsed lung tissue including the alveoli.

rate (HR) levels. Stability before extubation is critical in order to proceed into phase two when the risk of atelectasis is substantial.

During phase two, there are major changes in respiratory physiology: The thorax in preterm infants is highly compliant leading to an increased risk of atelectasis. FRC is often lost during the extubation process [13], particularly in the non-gravity-dependent regions of the lung [14]. Tidal volumes immediately after extubation and before the initiation of non-invasive respiratory support are increased compared with pre-extubation, presumably in an attempt to regain lost FRC [14]. "Floppiness" of the upper airway may lead to obstruction during this phase adding to the risk of desaturation and bradycardia [13].

Phase three is characterised by the need to restabilize the respiratory

system after extubation. Immediate application of a continuous positive distending pressure via face mask or nasal prongs is crucial after extubation. This stabilizes the larynx [15], avoiding upper airway obstruction. The positive distending pressure assists in regaining FRC after the loss during phase two [13]. These factors contribute to improvements in cardiorespiratory stability.

It is important to note that this model is most appropriate for more immature infants, as lung physiology is strongly dependent on gestational age and corresponding lung maturity. Immature infants are more susceptible to lung and airway collapse, reducing the likelihood of extubation success [2]. Accordingly, we will provide specific recommendations for different age groups, where appropriate.

3. Clinical data

3.1. Phase one

Signs of readiness for extubation are examined in the chapter of Shalish and Sant'Anna. (Chapter 9)

Preparation for extubation is important to avoid loss of FRC. High quality evidence regarding methods to improve this phase is lacking but we present the following suggestions based on physiological and observational data. A delay in removal of the adhesive tape is responsible for a large loss in FRC [13]. Thus, holding the endotracheal tube in place after adhesive tape removal but before removing the tube may be sensible. Alternatively, cutting the adhesive tape instead of removing it entirely in this sensitive phase may prevent further FRC loss before extubation. Minimal handling and pain-reducing sucrose administration may improve cardiorespiratory stability, thereby reducing the severity of desaturation and bradycardia [16]. Many centres routinely perform endotracheal suctioning before extubation. A small study has shown that lung volumes remained similar after endotracheal suctioning [13], but it may clear secretions from the airways, thereby reducing the risk of obstruction. Pre-oxygenation is routinely performed in older infants and children to facilitate a more stable transition to non-invasive respiratory support. However, there is evidence to suggest an increased susceptibility to free oxygen radicals and subsequent longer-term clinical harm in preterm infants [11]. We speculate that a higher FRC before initiation of extubation may provide a larger reserve and more overall stability. Accordingly, increasing the mean airway pressure before extubation or performing an "inspiratory hold" procedure (where the ventilator maintains the inspiratory pressure for the duration of the extubation), may increase lung volumes and provide increased stability. However, large pressures may also be injurious to the lung and no study to date has investigated this procedure. Therefore, we are not recommending the routine use of either pre-oxygenation or an inspiratory hold. As the dorsal aspect of the lung is larger than the ventral aspect due to the steep angle of diaphragmatic insertion at the rib cage, extubation in prone position may improve baseline FRC levels. None of these factors has been evaluated in rigorous studies with relevant clinical outcomes and thus, their clinical effects remain unknown.

3.2. Phase two

To our knowledge, there are no clinical studies evaluating respiratory support during the extubation procedure in preterm infants and thus, there is no evidence how to manage the phase immediately following extubation. However, from a physiological standpoint, continued respiratory support with a positive distending pressure (i.e. *PrePAP*) may prevent the loss of FRC and may assist in maintaining cardiorespiratory stability during extubation [13].

Worldwide, most preterm infants are intubated orally where a positive distending pressure may be provided throughout the extubation procedure via nasal prongs placed before extubation. This may help to maintain lung volumes and to avoid handling during the potentially unstable immediate post-extubation period. In most European countries, nasal intubation is common practice. In these infants, the endotracheal tube may be pulled back only marginally after extubation, thus keeping it in place as a nasopharyngeal tube temporarily until successful transition to non-invasive ventilation. The switch to a nasal mask/prongs can then be performed during the next round of care, possibly allowing the infant to stabilize before switching to an alternative interface. Finally, nasal/oral suctioning after extubation is controversial: On the one hand, it may decrease airway obstruction. Conversely, it may increase the time until non-invasive respiratory support is initiated, thereby potentially contributing to a larger loss in FRC. However, data are scarce and randomized controlled trials are needed to evaluate these ideas in the clinical setting.

3.3. Phase three

Nasal continuous positive airway pressure (CPAP) has become the standard of care for post-extubation respiratory support of preterm infants. CPAP maintains alveolar recruitment, prevents atelectasis, and reduces ventilation-perfusion mismatch, which improves oxygenation and work of breathing. As a result, CPAP reduces the incidence of respiratory failure among preterm infants after extubation without clinically important side effects [17].

Despite its physiological and clinical benefits, half of extremely preterm infants supported with CPAP after extubation require reintubation [18], which has been shown to be independently associated with adverse outcomes including a higher mortality before discharge, prolonged respiratory support, and hospitalization [19]. Therefore, methods to increase the effectiveness of post-extubation respiratory support have gained interest over the last years [20].

Non-invasive intermittent positive pressure ventilation (NIPPV) combines a continuous positive end-expiratory pressure (PEEP) with intermittent higher pressures delivered by nasal mask or nasal prongs. Two NIPPV modalities should be distinguished. On the one hand, there is traditional NIPPV, with settings designed to mimic ventilator settings. On the other hand, there are settings which are more reflective of bilevel CPAP, typically generated using flow-drivers [21]. Both devices are able to synchronize pressure changes with spontaneous breathing. Most commonly, Graseby capsules are used for NIPPV synchronisation but other options exist [22]. Neurally adjusted ventilator assist (NAVA) uses the electrical activity of the patient's diaphragm as a trigger to deliver synchronized inflations proportional to the infant's inspiratory effort [23].

Nasal high-flow therapy (hereafter, high-flow therapy) is an increasingly popular alternative to CPAP. During high-flow therapy, heated, humidified gas is delivered through narrow nasal cannulae. These appear to be more comfortable for infants than CPAP and NIPPV [24]. Commonly, gas flows greater than 2 L/min (e.g. 2–8 L/min) are used. With flows greater than 4 L/min, distending pressures are similar to those set with CPAP [25]. In contrast to CPAP, positive distending pressures generated during high-flow therapy are not measured and may be variable.

Non-invasive high-frequency oscillatory ventilation (nHFOV) is a relatively new method of augmenting CPAP support in preterm infants. Generated by a mechanical ventilator and transmitted via a nasal interface, it applies continuous airway pressures with superimposed oscillations during spontaneous breathing [26]. Electrical impedance tomography recordings demonstrate that these oscillations are transmitted to the lungs [27]. Thus, nHFOV could provide the advantages of both invasive high frequency oscillatory ventilation and CPAP. Surveys show that nHFOV is being used in clinical care in some European centres [28].

There is considerable uncertainty regarding the optimal non-invasive technique to support preterm infants after mechanical ventilation leading to a wide variability in clinical practice. The following meta-analyses will summarize the current evidence on the best form of respiratory support after extubation by examining data from RCTs

Table 1
Randomized controlled trials included in the meta-analyses.

Study	Patients [n]	GA [wk]	Comparisons	Primary outcomes	Enrolled population
1.1.1. Nonsynchronized NIPPV vs CPAP					
Khorana 2008 [37]	48	NDA	NIPPV vs CPAP	Reintubation <7 days	VLBW infants with RDS
O'Brien 2012 [38]	136	27.4	BiPAP vs CPAP	Reintubation <7 days	Infants <1250 g with RDS
Kahramaner 2014 [39]	67	28.8	NIPPV vs CPAP	Reintubation <48 h	Infants (<35 wks, <2000 g) with RDS
Jasani 2016 [40]	63	30.7	NIPPV vs CPAP	Reintubation <72 h	VLBW infants with RDS
Komatsu 2016 [41]	72	30.8	NIPPV vs CPAP	Reintubation <72 h	Infants (≤36 wks, >750 g)
Victor 2016 [42]	540	27.3	BiPAP vs CPAP	Reintubation <48 h	Preterm infants <30 wks
Esmaeilnia 2016 [43]	150	32.1	NIPPV vs CPAP	Reintubation <72 h	Preterm infants after INSURE
Ribeiro 2017 [44]	101	29.6	NIPPV vs CPAP	Reintubation <48 h	Infants (<34 wks, <1500 g) with RDS
Estay 2020 [45]	220	27.9	NIPPV vs CPAP	Reintubation <72 h	VLBW infants with RDS
Pan 2021 [46]	284	29.9	BiPAP vs CPAP	Reintubation <72 h	Infants <1500 g after INSURE
Li 2021 [47]	94	NDA	NIPPV vs CPAP (vs nHFOV)	Reintubation <7 days	Preterm Infants 25 + 0–33 + 6 wks
Zhu 2022 [31]	960	29.5	NIPPV vs CPAP (vs nHFOV)	Total duration of IMV	Preterm infants 25 + 0–32 + 6 wks
Yuan 2022 [48]	80	30.4	NIPPV vs CPAP (vs nHFOV)	Reintubation <72 h	Preterm infants with RDS
El-Farrash 2022 [49]	120	32.6	NIPPV vs BiPAP vs CPAP	Reintubation <48 h	Preterm infants ≤35 wks with RDS
1.1.2. Synchronized NIPPV vs CPAP					
Friedlich 1999 [50]	41	27.8	sNIPPV vs CPAP	Reintubation <48 h	VLBW infants with RDS
Barrington 2001 [51]	54	26.3	sNIPPV vs CPAP	Reintubation <72 h	Preterm infants ≤1250 g
Khalaf 2001 [52]	64	28.0	sNIPPV vs CPAP	Reintubation <72 h	Preterm infants ≤34 wks with RDS
Moretti 2008 [53]	63	27.0	sNIPPV vs CPAP	Reintubation <72 h	VLBW infants with RDS
Gao 2010 [54]	50	32.5	sNIPPV vs CPAP	NDA	Preterm infants with RDS
Ding 2020 [55]	120	29.6	sNIPPV vs CPAP	Reintubation <72 h	Preterm infants (<32 wks, <1250 g)
Shin 2022 [56]	78	26.9	NIV-NAVA vs CPAP	Reintubation <72 h	Preterm infants <30 wks
1.1.3. NIPPV (mixed methods) vs CPAP					
Kirpalani 2013 [57]	845	26.2	NIPPV/sNIPPV vs CPAP	Death/BPD <36 wks	Preterm infants (<30 wks, <1000g)
2.1.1. High-flow vs CPAP, < 28 weeks					
Collins 2013 [58]	59	NDA	High-flow vs CPAP	Reintubation <7 days	Preterm infants <32 wks
Manley 2013 [59]	174	NDA	High-flow vs CPAP	Reintubation <7 days	Preterm infants <32 wks
Soonsawad 2017 [60]	29	NDA	High-flow vs CPAP	Reintubation <72 h	Preterm infants <32 wks
Elkhwad 2017 [61]	43	26.8	High-flow vs CPAP	Reintubation <5 days	Preterm infants 24–28 wks
2.1.2. High-flow vs CPAP, ≥ 28 weeks					
Campbell 2006 [62]	40	27.5	High-flow vs CPAP	Reintubation <7 days	Preterm infants ≤1250 g
Collins 2013 [58]	73	NDA	High-flow vs CPAP	Reintubation <7 days	Preterm infants <32 wks
Manley 2013 [59]	129	NDA	High-flow vs CPAP	Reintubation <7 days	Preterm infants <32 wks
Yoder 2013 [63]	432	33.4	High-flow vs CPAP	Reintubation <72 h	Infants ≥28 wks
Mostafa-Gharehbaghi 2014 [64]	85	32.2	High-flow vs CPAP	Reintubation <72 h	Preterm infants (30–34 wks)
Liu 2014 [65]	255	35.5	High-flow vs CPAP	Reintubation <7 days	Preterm infants postextubation
Chen 2015 [66]	66	32.5	High-flow vs CPAP	Reintubation <7 days	VLBW infants with RDS
Soonsawad 2017 [60]	20	NDA	High-flow vs CPAP	Reintubation <72 h	Preterm infants <32 wks
Kadivar 2021 [67]	90	NDA	High-flow vs CPAP	Reintubation <72 h	Preterm infants after INSURE
Singh2022 [68]	30	30	High-flow vs CPAP	Reintubation <7 days	Preterm infants after INSURE
2.1.3. High-flow vs CPAP, mixed methods					
Kang 2016 [69]	161	NDA	High-flow vs CPAP	Reintubation <7 days	Preterm infants (30–32 wks)
Chen 2020 [70]	94	27.4	High-flow vs CPAP	Reintubation <72 h	VLBW infants with RDS
Uchiyama 2020 [71]	372	28.3	High-flow vs CPAP/NIPPV	Reintubation <7 days	Preterm infants <34 wks
3.1.1. nHFOV vs CPAP					
Lou 2017 [72]	65	32.5	nHFOV vs CPAP	Reintubation <7 days	Preterm infants with RDS
Chen 2019 [73]	206	32.6	nHFOV vs CPAP	Reintubation <7 days	Preterm infants <37 wks
Li 2021 [47]	92	NDA	nHFOV vs CPAP	Reintubation <7 days	Preterm infants (25–34 wks)
Yuan 2022 [48]	80	30.3	nHFOV vs CPAP (vs NIPPV)	Reintubation <72 h	Preterm infants with RDS
Zhu 2022 [31]	960	29.4	nHFOV vs CPAP (vs NIPPV)	Total duration of IMV	Preterm infants 25–33 wks
4.1.1. nHFOV vs NIPPV					
Wang 2019 [74]	103	29.7	nHFOV vs NIPPV	Reintubation <72 h	VLBW infants with RDS
Seth 2021 [75]	86	32	nHFOV vs NIPPV	Reintubation <72 h	Preterm infants 26–37 wks
Jia 2021 [76]	100	31.9	nHFOV vs NIPPV	Reintubation <72 h	Preterm infants with LBW
Zhuang 2021 [77]	90	29	nHFOV vs NIPPV	Reintubation <72 h	Preterm infants with severe BPD
Li 2021 [47]	92	29	nHFOV vs NIPPV	Reintubation <7 days	Preterm infants (25–34 wks)
Yuan 2022 [48]	80	30.5	nHFOV vs NIPPV (vs CPAP)	Reintubation <72 h	Preterm infants with RDS
Zhu 2022 [31]	960	29.4	nHFOV vs NIPPV (vs CPAP)	Total duration of IMV	Preterm infants 25 + 0–32 + 6 wks
Zhang 2022 [78]	41	35	nHFOV vs NIPPV	Reintubation <72 h	Preterm infants with PPHN

NDA: no data available, VLBW: very low birth weight, RDS: respiratory distress syndrome, Wks: weeks, INSURE: intubation – surfactant – extubation, LBW: low birth weight, NIV-NAVA: Noninvasive Neurally Adjusted Ventilatory Assist, BPD: bronchopulmonary dysplasia, PPHN: persistent pulmonary hypertension of the newborn.

comparing NIPPV, high-flow therapy and nHFOV as potential alternatives to CPAP for preterm infants after extubation.

4. Meta-analyses of trials for post-extubation respiratory support

A literature search was performed of PubMed, The Cochrane Library, and the reference lists of included articles. The search combined the individual form of respiratory support (see below) with the following terms: *preterm infant* and *extubation*. RCTs that enrolled preterm infants (born <37 weeks' gestation) and compared the following techniques were included.

- NIPPV (traditional NIPPV, bilevel CPAP, NIV-NAVA) versus CPAP
- Nasal high-flow versus CPAP
- nHFOV versus CPAP
- nHFOV versus NIPPV (traditional NIPPV, bilevel CPAP, NIV-NAVA)

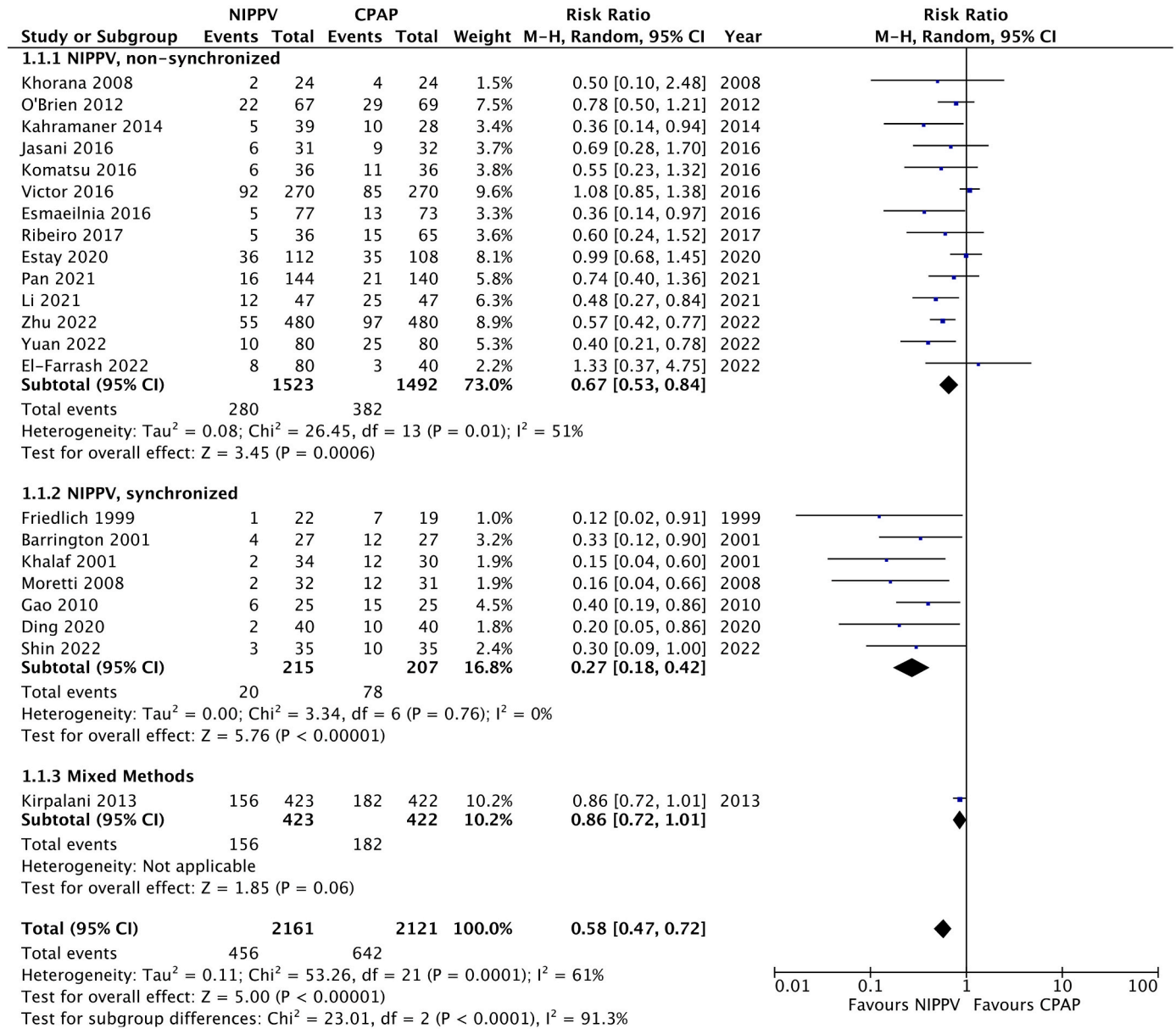

Fig. 2. Forest plot comparing NIPPV versus CPAP for post-extubation respiratory support (by synchronisation).

Data from included trials were extracted and cross-verified independently by the two authors of this review. Subgroup analyses were performed for the primary outcome by synchronisation (for the comparison NIPPV versus CPAP) and by gestational age at birth (for the comparison nasal high-flow versus CPAP). The primary outcome was defined as extubation failure (leading to additional ventilatory support/reintubation) within the first seven days post-extubation. Trials that reported extubation failure within a shorter time frame (e.g. within 72 h after extubation) or evaluated post-extubation respiratory support strategies after the INSURE (intubation – surfactant – extubation) procedure were included in the analysis. Publications in non-English languages were translated using Google translator. Meta-analyses were performed with RevMan (version 5.3) [29] using a random-effect model to pool data of included trials. Information on included trials is provided in Table 1.

4.1. NIPPV versus CPAP

We pooled data from 22 trials and 4282 preterm infants comparing NIPPV versus CPAP used as post-extubation respiratory support. Eleven of these trials reported a significant reduction in rates of respiratory failure in infants managed with NIPPV and the other 11 showed no difference between groups. In 14 trials, non-synchronized NIPPV was used. Seven trials applied NIPPV in a synchronized manner, and in one study, mixed methods were used. Since publication of the last Cochrane Review, twelve additional RCTs enrolling 2851 infants have addressed this question [30].

Overall, infants extubated to NIPPV had significantly lower rates of respiratory failure within the first week after extubation compared with those managed with CPAP, with a number needed to treat of 11 infants (combined subgroups 1.1.1, 1.1.2, and 1.1.3: RR 0.58, 95 % CI 0.47 to 0.72; RD -0.13, 95 % CI -0.17 to −0.08; Fig. 2). This beneficial effect was most obvious in the trials using synchronized NIPPV (subgroup 1.1.2: RR 0.27, 95 % CI 0.18 to 0.42; RD -0.27, 95 % CI -0.35 to −0.20). On average, only four infants would need to be extubated to synchronized NIPPV to prevent one extubation failure.

Irrespective of the NIPPV mode that was used, it is important to understand that the level of support differs considerably between

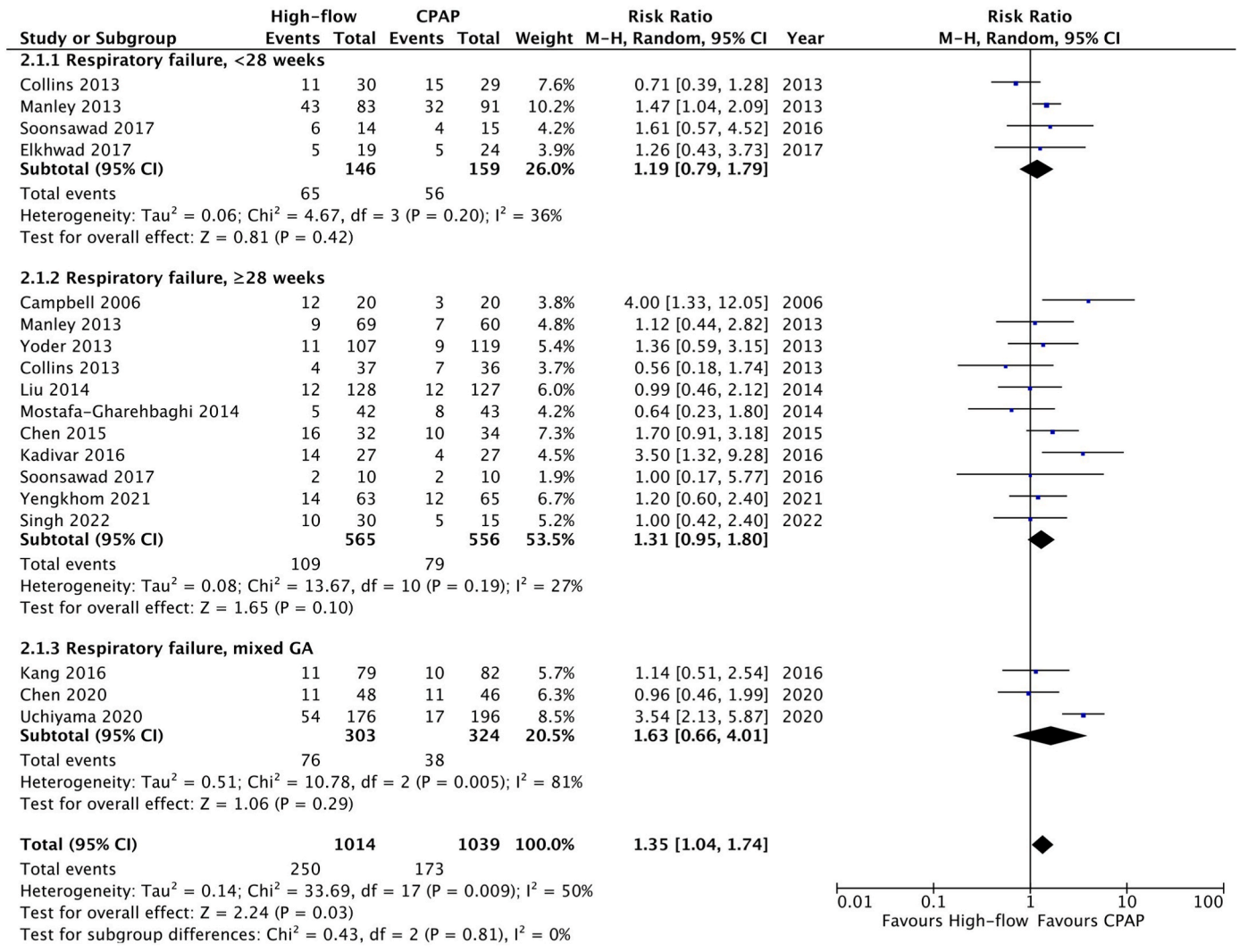

Fig. 3. Forest plot comparing high-flow therapy versus CPAP for post-extubation support (by gestational age).

ventilator-generated and flow-driver-generated NIPPV. We demonstrated previously that ventilator-generated synchronized NIPPV is most effective to prevent respiratory failure after extubation [21].

4.2. *Nasal high-flow versus CPAP*

In preterm infants, high-flow therapy for post-extubation respiratory support has been evaluated in 15 trials and 1948 infants. Since the 2016 Cochrane Review, ten additional RCTs including 1162 preterm infants have examined the efficacy of high-flow therapy to prevent extubation failure [24]. Four trials found a significant increase in rates of respiratory failure with high-flow therapy and no trial reported a significant reduction in respiratory failure with high-flow therapy.

Pooled data from all 15 trials demonstrated an increase in the risk of respiratory failure when infants were extubated to high-flow therapy (combined subgroups 2.1.1, 2.1.2, and 2.1.3: RR 1.35, 95 % CI 1.04 to 1.74; RD 0.07, 95 % CI 0.01 to 0.13; Fig. 3). In both subgroups (infants <28 and ≥28 weeks' gestation), there was no significant difference between high-flow therapy and CPAP in the rate of treatment failure after extubation (Fig. 3).

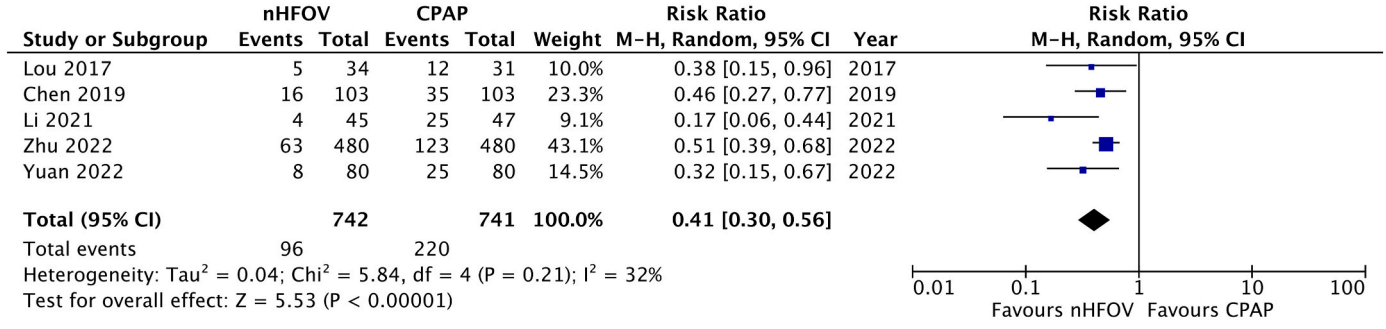

Fig. 4. Forest plot comparing nHFOV versus CPAP for post-extubation respiratory support.

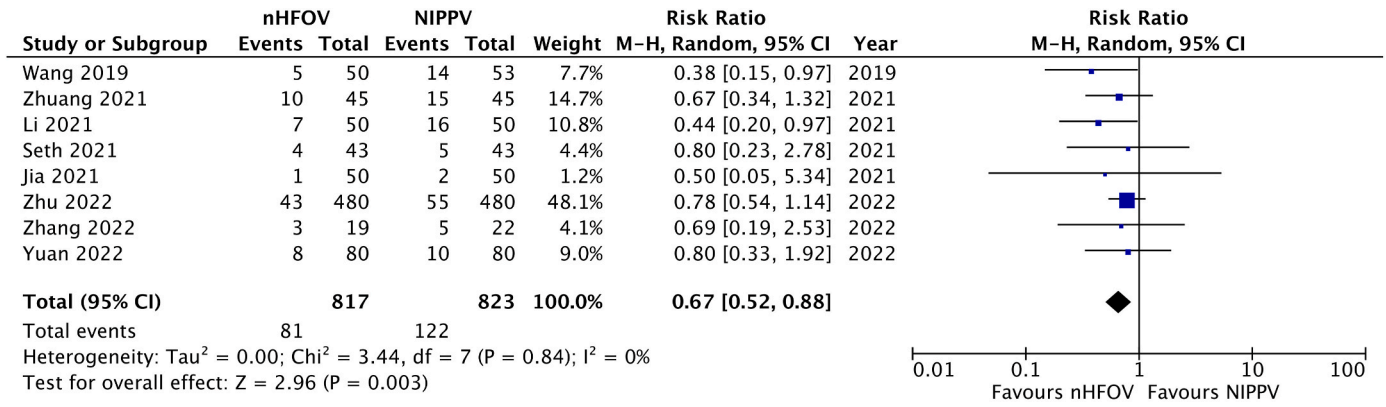

Fig. 5. Forest plot comparing nHFOV versus NIPPV for post-extubation respiratory support.

In most of the included trials, the use of rescue CPAP/NIPPV was permitted for infants meeting treatment failure criteria during high-flow therapy. Rescue CPAP/NIPPV has been shown to prevent a significant number of re-intubations in infants between 28 and 32 weeks' gestation with treatment failure under high-flow therapy (RR 0.51; 95 % CI, 0.27–0.97; 5 studies, 382 infants) [24].

4.3. *nHFOV versus CPAP*

Results from five trials enrolling 1483 infants were pooled for this analysis. All five individual trials reported a beneficial effect when nHFOV was used to avoid treatment failure after extubation. Overall, infants extubated to nHFOV had significantly lower rates of respiratory failure within the first week after extubation compared with those managed with CPAP (RR 0.41, 95 % CI 0.30 to 0.56; RD -0.22, 95 % CI -0.32 to −0.12, Fig. 4). Compared with CPAP, only six infants need to be treated with nHFOV after extubation to prevent one respiratory failure.

Of the five RCTs included in this comparison, the trial by Zhu et al. dominates the literature [31]. The multicentre NASal OscillatioN post-Extubation (NASONE) trial was conducted in 69 neonatal intensive care units in China. Preterm infants between 25 plus 0 days and 32 plus 6 days ready to be extubated were randomized to receive CPAP, NIPPV or nHFOV until discharge. Among 1440 preterm neonates with a mean gestational age of 29.4 weeks at birth, 497 were allocated to nHFOV, 480 of whom were included in the final analysis. Compared with CPAP, nHFOV halved the need for invasive respiratory support when used after extubation (reintubation rate: nHFOV 13.1 % versus CPAP 25.6 %; p-value <0.001).

4.4. *nHFOV versus NIPPV*

Since nHFOV is commonly regarded as rescue intervention in infants failing conventional non-invasive respiratory support such as NIPPV, we appended our updated meta-analyses with a direct comparison between nHFOV and NIPPV for preterm infants after extubation. We identified eight trials including 1640 preterm infants for the pooled analysis. Two trials reported a significant benefit for nHFOV, and six trials showed no significant difference between the two modalities. Of note, non-synchronized NIPPV was used in two trials. In the remaining six trials, exact methods could not be ascertained.

Pooled data demonstrated that infants extubated to nHFOV had a significantly lower risk for respiratory failure compared with infants extubated to NIPPV (RR 0.67, 95 % CI 0.52 to 0.88; RD -0.04, 95 % CI -0.08 to −0.01; Fig. 5). Extubation of 20 infants to nHFOV would prevent one case of extubation failure. Again, meta-analysis was dominated by the results of the NASONE trial. Although fewer infants failed their allocated therapy in the nHFOV group compared with the NIPPV group, this difference was not statistically significant (reintubation rate: nHFOV 13.1 % versus NIPPV 17.5 %; p-value 0.07).

4.5. *Positive end-expiratory pressure after extubation*

From a physiological perspective, a higher end-expiratory pressure may re-recruit lost FRC and prevent additional alveolar collapse more effectively than a lower pressure [32]. The as yet unpublished Extubation CPAP Level Assessment Trial (ECLAT) compared the effect of higher CPAP pressures of 9–11 cm H_2O with current standard pressures of 6–8 cm H_2O on extubation failure. The initial recruitment target of 200 extremely preterm infants was not reached; the trial was stopped early after 138 infants due to difficulties in recruitment [33]. Despite the smaller sample size, the authors demonstrated that extubation to higher CPAP pressures reduced the risk of extubation failure compared with the standard pressure range (35 % vs 57 %; risk difference −0.22, 95 % CI -0.37 to −0.04). There were no important differences in any of the safety outcomes [34]. Based on these results, higher CPAP pressures may be beneficial for extubation of extremely preterm infants.

4.6. *Safety*

CPAP has been used as primary respiratory support and as post-extubation support for several decades now and there is ample clinical data supporting its safety. The other modes of respiratory support have also not been associated with important adverse effects. In two systematic reviews comparing NIPPV with CPAP as primary respiratory support and as post-extubation support, no differences in rates of feeding intolerance, gastrointestinal perforation, necrotizing enterocolitis, or air leak were identified [30,35]. The recent NASONE trial also showed that nHFOV, NIPPV and CPAP were equally safe in a large population of very preterm infants [31]. Nasal trauma occurred slightly less often during high-flow therapy than with alternative means of respiratory support [24].

5. What's next for post-extubation support in preterm infants

While many respiratory support strategies before, during and after extubation have been investigated, there are still many open questions for clinicians and researchers. We suggest that future trials should answer the following questions in order to improve extubation outcomes of preterm infants:

Pre-extubation.

1) Pre-oxygenation in preterm infants to determine the optimal safe and effective SpO_2 target range
2) Evaluation of the ideal pre-extubation mean airway pressure (e.g. using higher MAPs to recruit the lung before extubation)

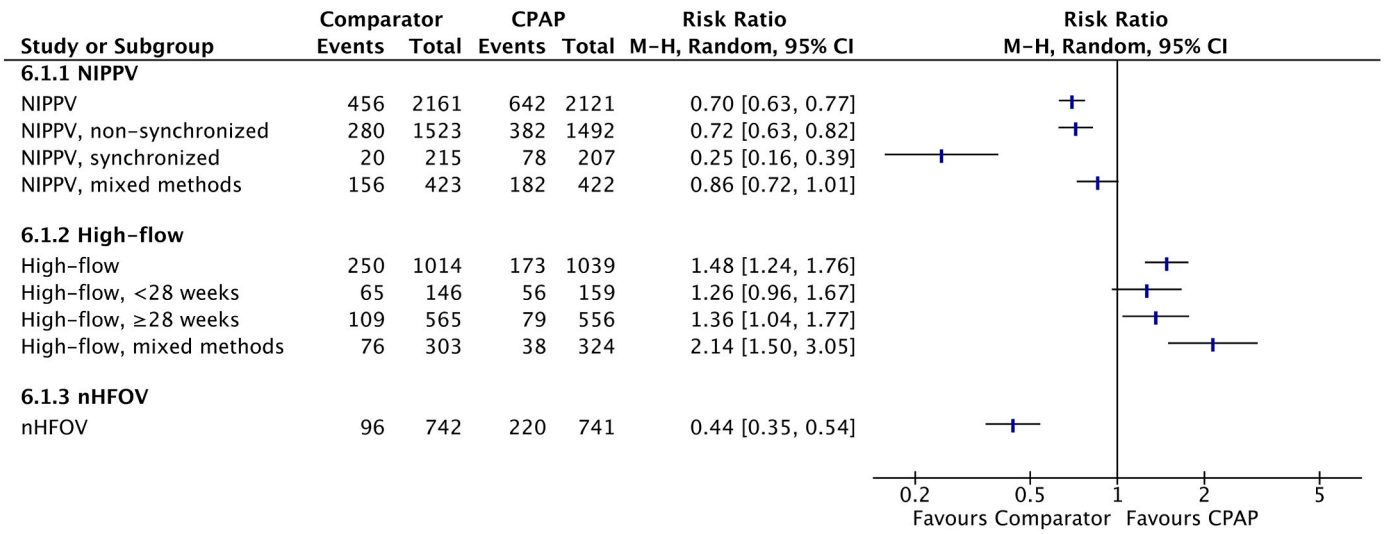

Fig. 6. Summary of meta-analyses comparing alternative non-invasive respiratory support strategies versus CPAP for preterm infants after extubation.

3) Extubation in prone vs supine position to improve cardiorespiratory stability during extubation

During extubation.

1) Use of *PrePAP*, i.e. continuous positive distending pressure during the extubation procedure in order to stabilize the nasopharynx and reduce handling during the critical extubation period.

Post-extubation.

1) Investigation of a higher CPAP vs NIPPV after extubation (to determine whether the increased MAP or the peak inspiratory pressures are crucial for extubation success)
2) Investigate NIV-NAVA as a method to synchronize non-invasive ventilation after extubation with spontaneous breaths
3) In the future, possibly investigate a synchronized nHFOV-NIPPV combination

6. Summary and recommendations

There are still many gaps in our knowledge regarding the ideal mode of respiratory support after extubation of newborn infants. However, based on the available data from RCTs, the following recommendations can be made.

1) Continuous positive airway pressure support (CPAP) remains the standard of care in the postextubation period. There is a considerable amount of evidence indicating its safety and effectiveness and most centres are experienced in its use. Thus, CPAP should be used for children ≥28 weeks' gestational age and without prior cardiorespiratory difficulties. If no alternative mode of respiratory support is available, CPAP may be used in smaller infants as well. Higher pressures of 9–11 cm H_2O appear safe and effective in the single trial testing their use in preterm infants <28 weeks' gestational age.
2) In our updated meta-analysis, high-flow therapy was associated with higher rates of respiratory failure than CPAP (Fig. 6). However, if backup CPAP is available, the reintubation rate was similar to CPAP in the last Cochrane review [24]. Thus, backup CPAP should always be available when high-flow therapy is used as post-extubation respiratory support in order to prevent reintubation. If CPAP is available, high-flow therapy can be chosen for more mature infants, particularly those >30 weeks with a fraction of inspired oxygen of less than 0.3 [36].
3) For high-risk infants <28 weeks' gestation or infants with expected cardiorespiratory instability, either NIPPV or nHFOV should be used as post-extubation respiratory support. Both modes showed an important reduction in reintubation rate when compared with CPAP in our updated meta-analysis (Fig. 6). The use of synchronized, ventilator-generated NIPPV may be the most effective mode to deliver positive pressure ventilation but there is only limited data from small studies and thus, results should be interpreted with caution. The use of nHFOV after extubation seems to confer the largest benefit for very preterm infants but clinical experience is limited in most centres.

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Declaration of competing interest

The authors have no conflicts of interest to declare.

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