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Non-Invasive Intermittent Positive Pressure Ventilation: Addressing the "Achilles Heel" of Systematic Reviews on Non-Invasive Ventilation in Premature Infants – An Argument for More Contemporaneous, Well-Conducted Trials

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Most premature infants <32 weeks' gestation will experience respiratory distress at birth and require respiratory support [1]. Current guidelines advise non-invasive ventilation (NIV) as the first line treatment. The most widely used NIV mode is continuous positive airways pressure (CPAP) [2], though clinicians have a range of modalities to choose from [3]. Of these, nasal intermittent positive pressure ventilation (NIPPV) has received much interest over recent years. With NIPPV, a ventilator delivers a rate of inflations at a set positive inspiratory pressure (PiP) over a defined positive end-expiratory airway pressure (PEEP) at the nasal interface, which, mechanistically, contributes to the mean airway pressure (MAP) [4]. The MAP generated with NIPPV can be significantly higher than commonly applied CPAP levels. NIPPV is thought to improve alveolar distension and chest wall stability, and, through continuous delivery of inflation breaths, reduce the risk of apnoea, compared to other forms of NIV [5–7]. NIPPV can be delivered either non-synchronised or synchronised with the infant's breathing efforts. Due to lack of comprehensive guidance, the PiP and PEEP are commonly set at the clinician's discretion. Clinical trials have found NIPPV (synchronised and non-synchronised) to be more successful than other forms of NIV both for avoiding primary respiratory failure, leading to endotracheal intubation and ventilation, and for secondary respiratory failure, following mechanical ventilation [5–7]. In most trials, NIPPV was predominantly tested against CPAP, with the outcome of avoiding endotracheal intubation [6, 7].

We believe that the above warrants some scrutiny. A recent Cochrane review [7] compared early NIPPV to early CPAP as initial respiratory support, with the aim of preventing intubation. Sixteen studies were included with the number of infants randomised ranging from 42 to 284. A minimum of 10 different ventilators were used in these studies, with 4 studies not specifying their ventilator(s). In the review's conclusion, there was similar optimism for NIPPV possibly reducing the rate of respiratory failure (and hence need for intubation).

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Table 1. Studies included in 2023 Cochrane reviews [6, 7] on NIPPV in preterm infants and their NIPPV settings

	Number of studies included	Settings not provided/given as changes to pre-extubation pressures, *n*	Respiratory rate, breaths/min	PiP, cmH_2O	PEEP, cmH_2O	IT, s
Post-extubation Cochrane review	19	6	12–40	8–25	3–8	0.6–1.0
Early NIPPV Cochrane review	16	3	10–50	8–22	4–7	0.3–1.0

Another Cochrane review by Lemyre et al. [6] (2023) compares NIPPV to CPAP as post-extubation support for preterm infants who had previously been intubated and ventilated. Nineteen trials with a primary outcome of respiratory failure were included. The overall findings were that use of NIPPV likely reduces the risk of respiratory failure and need for re-intubation. No clear differences were seen in secondary outcomes, including gastrointestinal perforation, bronchopulmonary dysplasia, and mortality before discharge. While these findings would encourage the adoption of NIPPV as the core respiratory support post-extubation for very preterm infants, we believe it is worth highlighting the significant heterogeneity of included studies, which includes that studies were performed with a minimum of 17 different ventilators (three did not specify which ventilator(s) were used). In addition, the wide range of sample sizes is worth noting – the number of participants ranged from 40 to 845 (median 64).

The reviews are, indeed, highly credible; however, we believe a more critical appraisal of the included studies and the conclusions drawn from combining their data warrants further discussion: pressure settings are key to success or failure of NIV. To replicate study results in the real-world, clinicians need to know what settings were used in studies. On review of the included studies, we noted that this information was missing in many. Where data were provided, we found wide variations (Table 1), for instance, PEEP ranged from 3 to 8 cmH_2O, PiP from 8 to 25 cmH_2O, and respiratory rate from 12 to 40 breaths/min [6, 7]. Unfortunately, this meant we were often unable to calculate the MAP for several trial interventions. Where MAP could be calculated, we found a notable range (5 to 12 cmH_2O), again demonstrating significant heterogeneity. Further, the definition of the primary outcome, especially respiratory failure, varied significantly. Time for assessing failure ranged from 48 h to 1 week or was at times not specified. Cut-off values of parameters defining failure also varied significantly, e.g., fractional inspired oxygen from 0.59 to 0.70 and partial pressure of CO_2 from >59 mm Hg to >70 mm Hg. The studies are spread over a long time (with publication dates from 1999 to 2022) [6, 7] during which respiratory management of preterm infants has changed. There is now an increasing evidence base for and acceptance of higher MAPs during NIV. Both CPAP and NIPPV in the included studies were often provided at pressures lower than used in contemporaneous practice [6, 7]. Other details such as how, when, and why NIV settings were modified are not provided in many studies. In addition to this, the reviews include both synchronised and non-synchronised NIPPV. While both have been shown as superior to other forms of NIV for avoiding primary respiratory failure and as post-extubation support [5–7], studies are needed whether either of these modalities is superior in providing respiratory support to the neonate [8]. Synchronicity of ventilation or lack thereof is one additional variable that should be further assessed in future reviews. Reports came from multiple countries with wide differences in resources and clinical practice and thresholds of viability [5–7]. As an example, in the UK and in other similar settings, survival-oriented care is now offered to infants born from 22 weeks' gestation with increasing numbers of the most preterm infants surviving to admission to NICU [9], with widespread coverage of antenatal steroids. The trend towards providing survival-focused care to the most premature is a relatively recent clinical change, and these infants would likely not have been included in earlier studies [10].

This heterogeneity among available trials, with the many anachronous practices included, makes combining their results challenging [11]. While systematic reviews in general are highly valuable and these specific ones are welcome additions to the knowledge base on use of NIV for preterm infants, we believe that more robust and detailed evidence is needed to compare CPAP and NIPPV. Indeed, future clinical trials should ensure that they are forward thinking and strive to include newer modalities of non-invasive respiratory support, such as nasal high frequency oscillation and its variants. In

accordance with Lemyre et al. future trials comparing NIPPV to other forms of NIV should consider comparing the modalities at comparable MAP settings. Further, trial protocols with explicit inclusion and exclusion criteria should be included in the publications and specifically note the pressure settings, rate, and inspiratory times for NIPPV, together with escalation and de-escalation strategies for the trial interventions. Lastly, as we are moving towards increasingly offering survival-oriented care for the most premature infants, future trials must include infants born at or below 25 weeks' gestation. Any trial that does include these infants should stratify data by gestational age in addition to whole-cohort analysis to allow for the strikingly distinct physiology of the most preterm infants. Information should be presented in accessible protocols such that comparisons, replication, and translation into clinical practice are possible. Outcomes, aligned with pre-determined core outcome sets including survival and neurodevelopment to at least 2 years of age, should be uniformly reported. To allow better comparison of trials, we may need an international consensus definition on respiratory failure to allow streamlining research in this area.

In aggregate, we make a strong call for a concerted effort to further refine NIV in neonatology to improve outcomes of the most premature infants. Future clinical trials must continue to build on the efforts of past studies in creating an evidence base which builds on well-designed, collaboratively conducted studies with transparent protocols and are adequately powered for core clinical outcome sets. This will provide greater value than ongoing meta-analyses of studies that may not be ideal for aggregations and do not allow translation into contemporaneous clinical practice.

Conflict of Interest Statement

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Author Contributions

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