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Clinical Challenges in Pediatric Ventilation Liberation: A Meta-Narrative Review

Jefta van Dijk, MD[1]

Robert G. T. Blokpoel, MD[1]

Samer Abu-Sultaneh, MD, FAAP, FCCM[2]

Christopher J. L. Newth, MD, FRCPC, FRACP[3]

Robinder G. Khemani, MD, MScI[3]

Martin C. J. Kneyber, MD, PhD, FCCM[1,4]

OBJECTIVES: To map the evidence for ventilation liberation practices in pediatric respiratory failure using the Realist And MEta-narrative Evidence Syntheses: Evolving Standards publication standards.

DATA SOURCES: CINAHL, MEDLINE, COCHRANE, and EMBASE. Trial registers included the following: ClinicalTrials.gov, European Union clinical trials register, International Standardized Randomized Controlled Trial Number register.

STUDY SELECTION: Abstracts were screened followed by review of full text. Articles published in English language incorporating a heterogeneous population of both infants and older children were assessed.

DATA EXTRACTION: None.

DATA SYNTHESIS: Weaning can be considered as the process by which positive pressure is decreased and the patient becomes increasingly responsible for generating the energy necessary for effective gas exchange. With the growing use of noninvasive respiratory support, extubation can lie in the middle of the weaning process if some additional positive pressure is used after extubation, while for some extubation may constitute the end of weaning. Testing for extubation readiness is a key component of the weaning process as it allows the critical care practitioner to assess the capability and endurance of the patient's respiratory system to resume unassisted ventilation. Spontaneous breathing trials (SBTs) are often seen as extubation readiness testing (ERT), but the SBT is used to determine if the patient can maintain adequate spontaneous ventilation with minimal ventilatory support, whereas ERT implies the patient is ready for extubation.

CONCLUSIONS: Current literature suggests using a structured approach that includes a daily assessment of patient's readiness to extubate may reduce total ventilation time. Increasing evidence indicates that such daily assessments needs to include SBTs without added pressure support. Measures of elevated load as well as measures of impaired respiratory muscle capacity are independently associated with extubation failure in children, indicating that these should also be assessed as part of ERT.

KEY WORDS: extubation failure; extubation readiness testing; mechanical ventilation; pressure support; spontaneous breathing trials; weaning

Invasive mechanical ventilation (MV) is ubiquitous in PICUs. Unmistakably lifesaving, MV is also associated with serious adverse events including ventilation-induced lung injury, ventilation-induced diaphragmatic dysfunction, nosocomial pneumonia, cardiovascular instability, endotracheal tube (ETT) related upper airway injury, and need for sedatives and/or analgesics drugs associated with inherent side-effects such as withdrawal syndrome or delirium (1–3). MV weaning and ventilation liberation should therefore be targeted as soon as the patient's clinical condition has improved sufficiently enough that the patient is able to maintain gas exchange without excessive

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work of breathing (WOB), to decrease the likelihood of MV-related complications (4, 5).

The definition of weaning is in and of itself challenging. Conceptually, weaning can be considered as the process by which positive pressure is decreased and the patient becomes increasingly responsible for generating the energy necessary for effective gas exchange. With the growing use of noninvasive modes of respiratory support, extubation can lie in the middle of the weaning process, if some additional positive pressure is used after extubation, while for some extubation may constitute the end of weaning. This has further complicated definitions of weaning and extubation success (5). Ventilator liberation is conceptually the time that the ETT is successfully removed, but this may not constitute the end of weaning if noninvasive modalities of positive pressure are used after extubation.

To date, both weaning, and ventilator liberation have been understudied in children, with few controlled trials testing weaning or extubation strategies. This lack of evidence may be explained by a relatively short duration of ventilation for most children, and a relatively low failed extubation (FE) rate, varying between 2% and 20% (6–9). Nonetheless, this does not mean that the practice of weaning MV in children is not important. Increasing evidence indicates that failure to consider weaning early in the ventilation course may cause harm, particularly the development of respiratory muscle weakness. This meta-narrative review summarizes current practices and understanding of pediatric ventilator weaning and liberation by discussing various steps in the weaning process, including onset of and approach to weaning, and ERT (**Fig. 1**). Meta-narrative review is a relatively new method of systematic review designed for topics that have been differently conceptualized and studied by different groups of researchers (10).

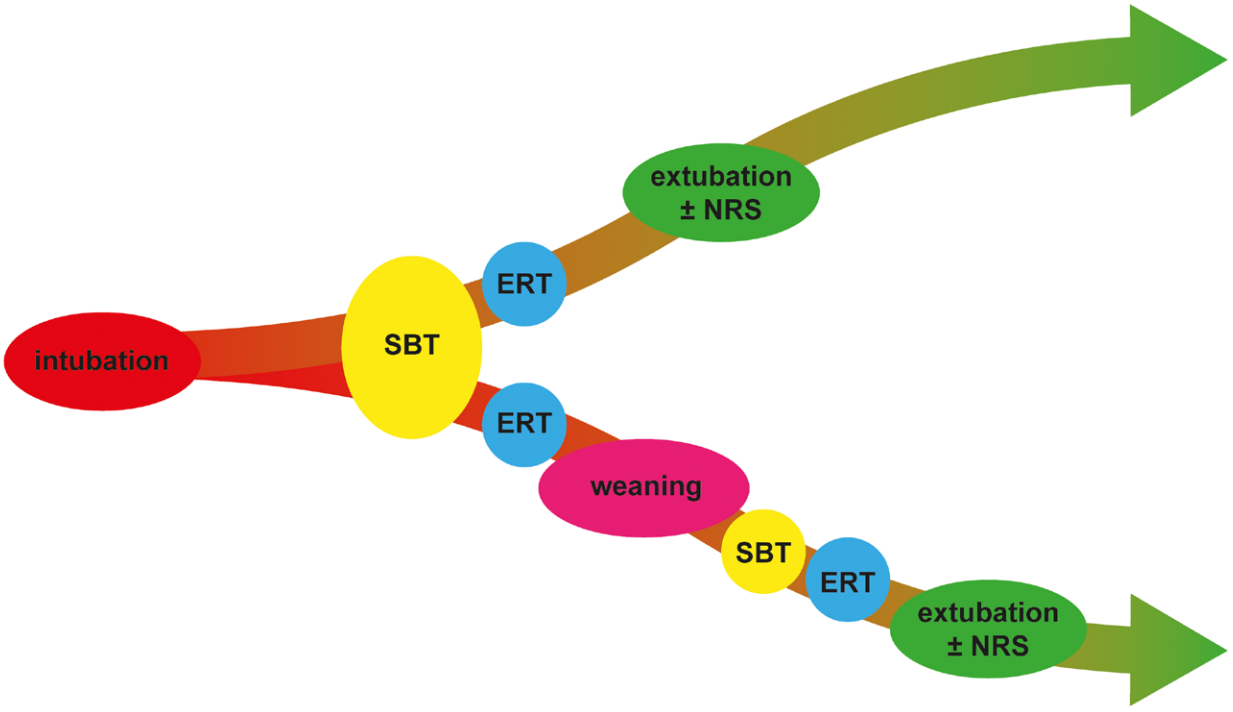
METHODS

We used an adaptation of meta-narrative review based on Kuhn's notion of the scientific paradigm (a coherent body of work that shares a common set of concepts, theories, methods, and instruments) (10). Publications were included if they included subjects greater than 36 weeks gestation and less than 18 years old, requiring MV via an ETT for acute respiratory failure, and admitted to PICU. Publications were excluded if they included only adults or only preterm infants less than 36 weeks or discussed noninvasive MV as primary ventilation mode. The search was not limited by publication year, country, or methodology. Articles were limited to those in the English language. All published and unpublished studies, related articles, and conference abstracts were considered for review.

The search strategy included the following databases: CINAHL, MEDLINE, COCHRANE, and EMBASE using a combination of the (medical subject headings [MESH]) search terms: ((((((((((((weaning[MeSH Terms])) OR (mechanical ventilator weaning[MeSH Terms])) OR (respirator weaning[MeSH Terms])) OR (ventilator weaning[MeSH Terms])) OR (ventilator weaning, mechanical[MeSH Terms])) OR (spontaneous breathing trial[MeSH Terms])) OR (airway extubation[MeSH Terms])) OR (airway extubations[MeSH Terms])) OR (endotracheal extubation[MeSH Terms])) OR (endotracheal extubations[MeSH Terms])) OR (extubation, airway[MeSH Terms])) OR (extubation failure[MeSH Terms])) OR (failed extubation[MeSH Terms])) OR (extubation readiness testing[MeSH Terms]). Trial registers searched included the following: ClinicalTrials.gov, European Union clinical trials register, and International Standardized Randomized Controlled Trial Number register. The search included all studies up to May 2022. A search of databases and hand sift was performed. Titles and abstracts were reviewed. Full-text articles were reviewed by two reviewers (J.v.D., M.C.J.K.). Included articles were synthesized via three main themes: start of weaning, technique of weaning, extubation readiness and spontaneous breathing trials (SBTs), indices identifying weaning and extubation success, and use of noninvasive ventilation postextubation.

START OF WEANING

Conceptually, one can think of two phases of MV: acute and weaning phases. During the acute phase, the goals of ventilation often surround maintenance of gas exchange, decreasing high effort of breathing (EOB), and providing lung protective ventilation. The level of MV is continuously titrated both up and down during the acute phase and is typically dictated by the underlying disease trajectory and a variety of clinical factors. In usual practice, once the patient has stabilized and begins to show sustained signs of clinical improvement, practitioners more consistently decrease the level of ventilatory support, typically marking



	SBT	Weaning	Extubation ± NRS
WHAT WE KNOW	Reduced ventilation time with SBT use SBT can be done without added PS	Not all patients need to be weaned; many can be successfully extubated once the underlying disease is resolving Respiratory muscle strength	
WHAT WE DON'T KNOW	Minimum and maximum time of SBT?	Weaning definition? Onset of weaning? Who should lead weaning? Weaning technique? Which parameters predict weaning success?	Should post-extubation NRS be used empirically? What mode of NRS is preferable? What best defines extubation failure? Which element(s) best predicts extubation outcome?

Figure 1. Knowns and unknowns in pediatric ventilation liberation. This figure graphically summarizes the disease trajectory of mechanically ventilated children. At some point, when their underlying disorder is resolving, patients meet predefined criteria for them to be assessed with a spontaneous breathing test (SBT), and if they pass this test according to specific criteria, they can be assessed for extubation readiness (extubation readiness testing [ERT]). Such as test takes other factors into account, including level of sedation, neurologic status, and other factors that might be predictive for failed extubation. Patients can then be extubated to postextubation nonrespiratory support (NRS) or no support. Most patients most likely do not need a weaning strategy, except for those who fail the SBT. In these patients, a certain weaning strategy might be indicated before they undergo another SBT. However, there are more unknowns than knowns when it comes to pediatric ventilation liberation, as outlined in the table. PS = pressure support.

the onset of weaning. This starting point differs from patient to patient but also from practitioner to practitioner. Advocates of ventilator protocols often use standardized criteria to mark the start of weaning, which at a minimum requires spontaneous breathing, and sometimes incorporates maintaining pH in a physiologic range and oxygenation with certain criteria for maximum permitted F_{IO_2} and/or positive end-expiratory pressure (PEEP). However, in clinical practice this starting point is less consistently defined and often based on nonspecific clinical assessments of patient improvement. The pediatric critical care community would benefit from more consistent definitions marking the start of weaning. However, not all patients need to be weaned as they can be successfully extubated once the acute phase has improved. FE rates

after planned extubation are usually below 10%; thus, most patients can be successfully extubated on their first attempt (5). Among patients who pass a spontaneous breathing test and are subjected to an extubation readiness test, 50–75% of the patients were deemed ready to extubate and will do so successfully (11, 12). Interestingly, reintubation rates after unplanned extubation have in a systematic review been reported to vary between 14% and 65% of pediatric patients, suggesting that earlier extubation is possible for at least of group of patients (13). Only one study included in this systematic review identified risk factors for reintubation after unplanned extubation, with duration of MV greater than 28 days being one of the risk factors (14).

TECHNIQUE OF WEANING

There is no pediatric data supporting or refuting any weaning technique over the other. So, it remains to be determined if weaning should be led by physicians, nurses, or respiratory therapists (15–17). This means that the way children are weaned from the ventilator is heavily influenced by institutional preferences and personal experiences rather than scientific evidence (18).

There are multiple approaches to weaning. A gradual reduction in ventilatory support by reducing the number of mandatory breaths during (synchronized) intermittent mandatory ventilation ((S)IMV) with or without pressure support (PS represents the most common weaning mode (19, 20). Once the patient meets some preset criteria, they either receive extubation readiness testing (ERT) on a supported mode of ventilation only (i.e., continuous positive airway pressure [CPAP] with or without PS) or are extubated directly from a low rate. Interestingly, many adult ICUs have moved away from using SIMV ± PS after it became clear that these ventilator modes when used for weaning actually delayed extubation (21). This practice change followed the outcomes of two randomized controlled trials (RCTs), showing prolonged weaning with a ventilator weaning strategy making use of SIMV (or PS in one trial) compared with a daily SBT (22, 23).

Others advocate incorporating daily scheduled assessments of extubation readiness once the acute phase has stabilized. This typically involves a SBT, and if the patient passes, then weaning is unnecessary, and the patient can be extubated if other criteria for extubation readiness are met. If the patient fails, then any variety of approaches are entertained including continued gradual reduction in ventilatory support in an SIMV mode, switch to a supported mode of ventilation (i.e., PS or volume support), or alternating periods of more fully supported time-cycled ventilation with shorter periods of supported ventilation with, for example, CPAP with or without PS. Some refer to this latter approach as "sprinting" and is perceived as a method to "train the patient" who has acquired respiratory muscle weakness early during MV (24, 25).

Neurally adjusted ventilatory assist is a mode of ventilation where the level of the delivered respiratory support is proportional to the electrical activity of the diaphragm, which is reflective of the neural respiratory drive. To date, pediatric data are inconclusive about its usefulness in weaning (26).

There are no clear data supporting one or the other weaning techniques in patients who fail an SBT, and it may be that incorporating daily scheduled assessments of weaning and extubation readiness might be of greater importance than any weaning mode or criteria. Foronda et al (27) reported a reduced duration of MV among children randomized to a 2-hour trial of breathing with PS 10 cm H_2O (with 5 cm H_2O PEEP) compared with standard care (28). It requires increased awareness among critical care practitioners to identify patients who meet screening criteria and are ready for a SBT, something that can be achieved by means of a protocolized weaning algorithm or closed-loop systems (29–34). However, to date, weaning protocols or closed-loop systems are infrequently used probably because a beneficial effect on patient outcome has not been unequivocally demonstrated (18, 35–38). Randolph et al (11) tested three different approaches to weaning in 182 mechanically ventilated children in a RCT: an automated approach that consisted of volume support achieved by a continuous automated adjustment by the ventilator (n = 60), a manual, paper protocol-driven adjustment of PS (n = 62), or no protocol at all (n = 60). The protocols were designed to set the PS level targeting an expiratory tidal volume (Vt) of 5–7 mL/kg. SBTs were done daily, using a minimum level of PS. Patients failed the SBT if they experienced tachypnea and/or transcutaneous oxygen saturation (Spo_2) less than 95%. The study was stopped because it showed that duration of weaning and rates of FE were comparable between the

three randomization arms. However, poor protocol compliance observed in this study (only 66%) may partially explain these negative findings. In contrast, an RCT conducted in 223 pediatric general and post-cardiac surgery intensive care patients randomized to physician-directed weaning or a predetermined weaning algorithm (39) showed some potential clinical benefit. Although there was no reduction in total duration of MV, protocol-guided weaning did result in a significantly shorter weaning time and time between onset of weaning and extubation compared with physician-guided weaning and comparable FE rates. The difficulty of this study was the inclusion of postsurgery patients—especially in the protocol-guided weaning group—which may limit translation to more difficult to wean patients.

EXTUBATION READINESS TESTING AND SPONTANEOUS BREATHING TRIALS

ERT is a key component of the weaning process as it allows the critical care practitioner to assess the capability and endurance of the patient's respiratory system to resume unassisted ventilation. The literature is messy in differentiating ERTs from SBTs, with inconsistent definitions. Conceptually, passage of a SBT is used to determine if the patient can maintain adequate spontaneous ventilation with minimal ventilatory support. In contrast, an ERT includes not only the SBT but also other elements to determine if the patient is ready for extubation. ERTs typically incorporate factors such as presence of airway protective reflexes, degree of sedation, measures of respiratory muscle strength, assessment of risk of upper airway obstruction, planned procedures that may delay extubation, etc.

The optimal method and duration of SBTs in children continue to be subject of debate. Many use an SBT as described in the post hoc analysis of the Randomized Evaluation of Sedation Titration for Respiratory Failure (RESTORE) trial, that is, a standardized 2-hour SBT with the level of PS dictated by ETT size and 5 cm H_2O PEEP (40). Similar SBTs have been described in a number of pediatric studies, although the length and level of inspiratory pressure augmentation varies from study to study. It is unclear whether SBTs should include inspriatory pressure augmentation with PS or Automatic Tube Compensation. Chavez et al (41) reported that children tolerated a 15-minute SBT when the ETT was connected to a flow-inflating bag set to provide 5 cm H_2O CPAP. Farias et al (42) did not observe a difference in reintubation rate (15.1% vs 12.7%) among 257 children ventilated for at least 48 hours randomized to undergo a 2-hour trial of breathing when they compared two types of SBT, being PS 10 cm H_2O with 5 cm H_2O PEEP versus T-piece that only provides flow. PS is often added during an SBT as it is presumed that especially with smaller ETT sizes, there is an increased imposed WOB due to a higher artificial airway resistance ("breathing through a straw"). Of course, the ETT bypasses the natural resistance of the upper airway, which may offset any perceived increase in resistance. Various studies reported that the WOB during CPAP alone was comparable to the WOB postextubation, while using PS significantly leads to a significant underestimated postextubation WOB (43–46). It is important to remember that resistance is a function of flow, so when peak inspiratory flow rates stay within age-related limits for a given ETT size, there are minimal effects of increased artificial airway resistance (5, 47). At the time of extubation, flow rates for children are generally in a predicted physiologic range (43). Obviously, objective criteria are needed when the SBT outcome is evaluated, thereby reducing practice variability and subjective assessment of patient effort.

Another unanswered question surrounds the optimal duration of the SBT. There are no comparative trials in pediatrics, and observational data highlights SBTs, which range from 10 to 120 minutes. It appears that most PICUs perform the SBT for at least 30 minutes, with longer SBTs potentially in patients who are deemed to have an increased likelihood of FE.

INDICES IDENTIFYING WEANING AND EXTUBATION SUCCESS

The reasons for FE are often multifactorial. Ultimately, FE can be thought of as an imbalance between respiratory load (i.e., factors that affect resistance and compliance) and respiratory muscle capacity (i.e., respiratory muscle weakness). In fact, measures of elevated load as well as measures of impaired respiratory muscle capacity are independently associated with pediatric FE (48). As such, it becomes important to assess these factors as part of the ERT to help predict the outcome of the weaning process. Passage of an ERT typically assures the patient

has achieved adequate resolution of respiratory disease at a minimum support gas exchange. Nevertheless, gas exchange abnormalities contribute to FE, and in particular, measures of physiologic dead space can be predictive especially in certain subsets of children. However, more specific monitoring during ERTs can be helpful to assess respiratory load and respiratory capacity. Respiratory load can be assessed directly with indices such as a variable composed of compliance, resistance, oxygenation, and pressure index, or direct measures of patient effort such as WOB calculated using the Campbell diagram, or EOB metrics such as pressure-rate product or pressure-time product (49). However, these measures of work or effort are dependent upon an estimate of pleural pressure, such as esophageal manometer, and are therefore rarely available in routine clinical practice. For this reason, surrogate markers such as spontaneous V_T or rapid shallow breathing index (i.e., the ratio of frequency over V_T), are often used to estimate residual elevations in respiratory load. Respiratory muscle capacity can be assessed during airway occlusion maneuvers by measuring the maximal inspiratory pressure at the airway or using an esophageal manometer or the airway pressure after 0.1 seconds. Some combination measures of respiratory load and capacity are sometimes used, such as the tension time index (TTi), or TTi of the diaphragm are a measure of the load capacity ratio of the diaphragm. It is derived by relating the mean transdiaphragmatic pressure per breath to the maximal inspiratory transdiaphragmatic pressure and the inspiratory time to the total respiratory cycle time. Phase angle from Respiratory Inductance Plethysmography is another nonspecific measure, which can point to either increased respiratory load or decreased capacity. Ultrasound has gained in popularity as a diagnostic tool in clinical management and research in the PICU (50). The thickening fraction of the diaphragm (TFdi) in the zone of apposition during inspiration can be used as a measure of contractile activity (49). Of the various parameters measured, TFdi has been identified as a strong parameter for predicting extubation success (51).

Upper airway obstruction after MV often complicates ERTs, as it is thought to contribute to 40% of extubation failures in pediatrics. While it may be possible to identify some children at high risk for postextubation upper airway obstruction (UAO), prevention strategies have not definitively been tested (52). As recently demonstrated, the UAO is most strongly associated with reintubation in children with impaired respiratory muscle capacity, who cannot tolerate even short periods of increased respiratory load from the UAO. Hence, it is important to carefully consider extubation in a patient with diminished respiratory muscle capacity who is at high risk for UAO (48).

Finally, a variety of general factors has been considered in extubation readiness assessments. These include age, nutritional status, neurologic functioning, Pediatric Risk of Mortality score, mean airway pressure, oxygenation index, spontaneous respiratory rate, and hemodynamic status (7, 12, 28, 42, 45, 46, 48, 52–68). Limited studies have been performed in pediatric cardiac patients (69). This group of patients might be studied separately as extubation failure in these patients underlying cardiac dysfunction can be unmasked during ventilator weaning, although the concept and approach to ventilation liberation may in fact not be different from noncardiac patients (70, 71).

USE OF NIV AFTER EXTUBATION

A recent systematic review and network meta-analysis including 36 RCTs in adults showed a lower reintubation rate with noninvasive respiratory support compared with usual care, although no mode of noninvasive respiratory support proved superior (72). In pediatrics, there is very little data supporting or refuting the use of noninvasive ventilation to prevent reintubation (73, 74). Nonetheless, use of postextubation NIV either routinely or as a rescue therapy is common (75). This signifies the need for better patient identification in whom postextubation NIV may be beneficial. Pediatric patients with neuromuscular disease may be at particular risk for postextubation failure. In these patients, a combination of postextubation noninvasive ventilation in combination with cough-assist techniques may be beneficial, although this has not been confirmed in clinical trials (76–79). The recently published FIRST-line support for assistance in breathing in children First-ABC trial addressed the question what type of postextubation noninvasive respiratory support would be preferable (80). This pragmatic trial showed that high-flow nasal cannula compared with CPAP following extubation failed to meet the criterion for noninferiority for time to liberation from respiratory support, thereby not providing no definitive answer to this question.

NONRESPIRATORY RISK FACTORS THAT INFLUENCE WEANING AND EXTUBATION

Weaning a patient from the ventilator is influenced by many factors seemingly unrelated to the patient's respiratory disease, such as fluid balance and level of sedation (4, 81). Alobaidi et al (81) performed a systematic review of all prospective and retrospective studies including 7,507 patients examining the effect of any fluid overload (FO) on patient outcome. FO was associated with fewer ventilator-free days or prolonged ventilation greater than 48 hours (odds ratio, 2.14 hr; 25–75 interquartile range, 1.25–3.166 hr), suggesting that FO is certainly a confounder in ventilator weaning and extubation readiness.

Furthermore, sedation has been implicated as a frequent cause of FE and complicates ventilator weaning and ERT. Hence, targeting minimal but effective sedation by means of a sedation protocol may shorten the ventilatory trajectory and improve extubation outcome (82). Curley et al (40) randomized 2,449 mechanically ventilated children with acute respiratory failure to a protocol including targeted sedation, arousal assessments, ERT, sedation adjustment every 8 hours, and sedation weaning versus usual care. Remarkably, the duration of MV was not different between two treatment arms and complex relationships among wakefulness, pain, and agitation were identified. The recently completed Sedation AND Weaning In Children trial reported that a structured approach consisting of sedation level assessment, daily screening for readiness to undertake a SBT, a SBT to test ventilator liberation potential, daily rounds to review sedation and readiness screening, and set patient-relevant targets in critically ill children resulted in a significant reduction in ventilation time compared with usual care (64.8 vs 66.2 hr), although the clinical impact of a 2-hour reduction in length of ventilation is debatable. Nevertheless, this study did demonstrate the feasibility of a standardized approach (83). Thus, the role of sedation as modifiable factor during weaning and ERT warrants further exploration.

CLINICAL IMPLICATIONS AND DIRECTIONS FOR FURTHER RESEARCH

At present, there are no recommendations related to weaning children from the ventilator that can be supported by rigorous evidence, and our review does not provide any definitive answers (84). There is a need to generate more evidence related to pediatric ventilator liberation so that any recommendations can have stronger certainty (85, 86). Many patients do not need a weaning strategy, as they are likely to pass a SBT on the first attempt and can successfully be extubated if other ERT criteria are met. SBTs should be implemented in the daily assessment for extubation readiness. This can be done safely without adding PS as there is no increased resistance when age-appropriate ETTs are used. In those patients failing the SBT, there likely should be a strategy to encourage spontaneous breathing and prevent respiratory muscle weakness. The ultimate decision to extubate should not only include an SBT but should so consider other factors related to FE, such as respiratory muscle strength (5).

We propose that future studies should be designed to address important knowledge gaps, including how to promote more timely weaning from ventilation, and how to wean children who fail SBTs. These investigations should not only examine the weaning technique itself but also if this weaning needs to be protocolized. Recently completed studies highlight the potential benefits of protocolized weaning to reduce time on ventilation and prevent respiratory muscle weakness and a larger clinical trial is ongoing (Real-time Effort Driven VENTilator Management [https://clinicaltrials.gov/show/NCT03266016]) (87, 88).

1 *Department of Paediatrics, Division of Paediatric Critical Care Medicine, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.*

2 *Indiana University School of Medicine and Riley Children Hospital at Indiana University Health, Indianapolis, IN.*

3 *Anesthesiology and Critical Care Medicine, University of Southern California, Children's Hospital Los Angeles, Los Angeles, CA.*

4 *Critical care, Anaesthesiology, Peri-operative & Emergency medicine (CAPE), University of Groningen, Groningen, The Netherlands.*

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For information regarding this article, E-mail: m.c.j.kneyber@umcg.nl

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