DOI:
10.1016/j.chest.2024.05.012

Document Version
Peer reviewed version

[Critical Care Guideline and Consensus Statement]

CHEST

Framework for Research Gaps in Pediatric Ventilator Liberation

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BACKGROUND: The 2023 International Pediatric Ventilator Liberation Clinical Practice Guidelines provided evidence-based recommendations to guide pediatric critical care providers on how to perform daily aspects of ventilator liberation. However, because of the lack of high-quality pediatric studies, most recommendations were conditional based on very low to low certainty of evidence.

RESEARCH QUESTION: What are the research gaps related to pediatric ventilator liberation that can be studied to strengthen the evidence for future updates of the guidelines?

STUDY DESIGN AND METHODS: We conducted systematic reviews of the literature in eight predefined Population, Intervention, Comparator, Outcome (PICO) areas related to pediatric ventilator liberation to generate recommendations. Subgroups responsible for each PICO question subsequently identified major research gaps by synthesizing the literature. These gaps were presented at an international symposium at the Pediatric Acute Lung Injury and Sepsis Investigators meeting in spring 2022 for open discussion. Feedback was incorporated, and final evaluation of research gaps are summarized herein. Although randomized controlled trials (RCTs) represent the highest level of evidence, the panel sought to highlight areas where alternative study designs also may be appropriate, given challenges with conducting large multicenter RCTs in children.

RESULTS: Significant research gaps were identified in six broad areas related to pediatric ventilator liberation. Several of these areas necessitate multicenter RCTs to provide definitive results, whereas other gaps can be addressed with multicenter observational studies or quality improvement initiatives. Furthermore, a need for some physiologic studies in several areas remains, particularly regarding newer diagnostic methods to improve identification of patients at high risk of extubation failure.

INTERPRETATION: Although pediatric ventilator liberation guidelines have been created, the certainty of evidence remains low and multiple research gaps exist that should be filled through high-quality RCTs, multicenter observational studies, and quality improvement initiatives.

CHEST 2024; ■(■):■-■

KEY WORDS: airway extubation; clinical protocols; mechanical ventilators; pediatric ICUs; ventilator weaning

ABBREVIATIONS: ERT = extubation readiness testing; IMV = invasive mechanical ventilation; NRS = noninvasive respiratory support; PiMax = maximum inspiratory pressure during airway occlusion; POCUS = point-of-care ultrasound; PS = pressure support; QI = quality improvement; RCT = randomized controlled trial; SBT = spontaneous breathing trial; UAO = upper airway obstruction

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Liberation from invasive mechanical ventilation (IMV; ie, extubation) is a daily practice in PICUs and pediatric cardiac ICUs worldwide. The first international guidelines for pediatric ventilator liberation were published in 2023 and included 15 recommendations to guide pediatric critical care providers on how to perform different aspects of ventilator liberation.[1-4] Most recommendations were based on very low to low certainty of evidence largely because of the lack of high-quality studies. The aim of this article is to summarize systematically the research gaps related to pediatric ventilator liberation identified by literature review and the panel of experts. This can be used to set the agenda for future studies to strengthen the quality of evidence for future updates of the clinical practice guidelines.

Methods

As part of generation of the ventilator liberation guidelines,[1-4] eight Population, Intervention, Comparator, Outcome framework questions were identified related to important aspects of pediatric ventilator liberation. A group of 26 international multiprofessional experts were divided into five subgroups to perform a literature review in each subsection and to craft recommendations. During the synthesis of the evidence, the experts identified key research gaps in each of these subsections. Subsequently, each subsection presented what they believed were the most pressing research gaps to the pediatric critical care community during a symposium at the Pediatric Acute Lung Injury and Sepsis Investigators network spring 2022 meeting. The symposium was attended by 51 pediatric intensive care practitioners in person and 65 such practitioners who attended virtually, many with expertise in pediatric mechanical ventilation because the research priorities for the second Pediatric Acute Lung Injury Consensus Conference also were presented. Detailed transcription was performed for the entire meeting, and open discussion occurred for each of the priorities. The transcript was provided back to the section leads, who subsequently incorporated feedback from the audience as well as commentary from guidelines experts to identify top research gaps and potential study designs that could address the gaps. The purpose of this article is to provide a framework or outline to help investigators seeking to improve the knowledge base in pediatric ventilator liberation. No specific voting process was carried out to rank the gaps (ie, 1,2,3) because all were believed to be important, and the methods to answer the questions may vary.

To that end, panelists sought to provide practical guidance for how to answer some of these research questions. Although randomized controlled trials (RCTs) represent the highest level of evidence, they require substantial funding, regulatory structure, and collaboration with large multicenter networks. Certainly, each of the research gaps may be answered with a large multicenter RCT, but when appropriate, the panel sought to highlight areas where alternative study designs also may be considered, given the challenges with conducting large multicenter RCTs in children. Hence, the panelists sought to highlight the research gaps where very substantial investment in the form of multicenter RCTs were needed, while proposing alternative study designs such as observational studies or quality improvement initiatives for some of the other research gaps.

In addition, the panelists believed that when studying short-term and long-term outcomes related to pediatric ventilator liberation, pediatric critical care providers need to have a holistic view of the interventions throughout the IMV course starting from the decision to intubate the patient to the decision to attempt liberation. Although our focus is on circumstances around the ventilator liberation attempt, the outcomes are influenced by the entire

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*Collaborators from the Pediatric Ventilator Liberation Consensus Conference Expert Panel are listed in the Acknowledgments.

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DOI: https://doi.org/10.1016/j.chest.2024.05.012

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ventilator course. A conceptual map tying key elements or principles that are important for ventilator liberation to other phases of IMV initially was drafted by a subgroup of panelists including a representative from each of the Population, Intervention, Comparator, Outcome questions and subgroups, the lead and senior authors, and the methodologist. Then, this was presented and edited by all authors during manuscript review and revisions. As part of the main guidelines, a detailed literature review was conducted, and panelists extracted risk factors for extubation failure. These risk factors then were reviewed by the experts when crafting the guidelines and were used to help inform the conceptual mapping.[5,6]

Results

The final conceptual map is provided in Table 1. Five areas were identified as important concepts that were believed to increase the risk of extubation failure (upper airway obstruction, respiratory muscle strength, respiratory load, cardiac load, and neuropsychologic factors). We subsequently describe factors from peri-intubation, the IMV course, and ventilator liberation assessment that may impact short-term or long-term outcomes. These short-term and long-term outcomes can be used as core outcomes set for future studies. For example, subglottic supper airway (UAO) risk may be assessed by the air leak test at the time of ventilator liberation to determine the prescription of periextubation corticosteroids. However, the risk for UAO and the response to corticosteroids also may be affected by the size and type of endotracheal tube used, management of endotracheal cuff during the IMV course, sedation, and delirium management. Similarly, respiratory muscle strength can be affected by ventilator management, sedation, use of corticosteroids, use of neuromuscular blockade, and nutritional status. The pediatric ventilator liberation guidelines focus on evaluating the patient's readiness for an extubation attempt, including measures to quantify risk of complications such as UAO and respiratory muscle weakness as they relate to risk of extubation failure or longer duration of IMV. Thus, this conceptual map is meant to highlight the multitude of other elements that are not in the direct scope of the guidelines, but may influence short-term and long-term outcomes.

Research Gaps

Herein we summarize the research gaps and priorities related to different elements covered by the pediatric ventilator liberation guidelines.

Extubation Readiness Testing Screening and Bundle

Rationale 1A: The expert panel was in 100% agreement that extubation readiness testing (ERT) safety screening should be performed for children intubated for > 24 h. In most studies included in the guidelines, patients were screened for ERT eligibility daily.[7-14] More frequent evaluation of patients might reduce IMV duration, but also could increase the burden on bedside providers incrementally.[15] However, we found no RCTs comparing frequency of ERT screening (once daily vs more frequent evaluations). Simple checklists with training of the providers might help to avoid excessive burden on bedside providers and increase adherence,[8,10,11] because adherence can be quite low even among trained providers.[12] Alerts in electronic clinical records, computer-driven protocols, or both could improve the adherence to ERT safety screening.[9]

Research Gaps 1A: What is the optimal frequency of ERT safety screening that can improve extubation outcomes without significantly increasing the burden on critical care providers? Who are the optimal providers (ie, bedside respiratory therapist, nurse, physician) to perform ERT screening, and is this ICU or country specific? Would adding computerized decision support tools improve the adherence to ERT safety screening?

Suggested Studies 1A: Multicenter implementation and quality improvement (QI) studies can investigate multiple questions related to ERT screening and their effectiveness on patient-centered extubation outcomes like time to first successful spontaneous breathing trial (SBT), IMV duration, extubation failure, ICU length of stay, and hospital length of stay.[16] Examples of interventions that can be studied are screening frequency, personnel performing the ERT screening (bedside respiratory therapist vs nurse vs physician), and the use of computerized decision support tools for screening. Compliance rates to ERT safety screening and balancing measures like bedside provider workload should be followed and correlated to the primary outcomes.

Rationale 1B: Clinical evaluations included in the ERT safety screening vary from study to study (Table 2).[7-11,13,15] The optimal ventilator settings that trigger an ERT (ie, positive end-expiratory pressure,

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TABLE 1] Conceptual Map for Pediatric Ventilator Liberation

Intubation	IMV Course	Extubation Attempt	Short-term Outcomes	Long-term Outcomes
Subglottic upper airway obstruction				
• ETT size • ETT type (cuffed or uncuffed) • Intubation process and no. of attempts	• ETT cuff management • Agitation (sedation and delirium) • Fluid overload • Acquired vocal cord paralysis	• **Air leak test** • **Peri-extubation corticosteroids** • **NRS use after extubation**	• UAO • Extubation failure due to UAO • **NRS use after extubation** • New tracheostomy placement • VFDs-28 • ICU LOS • Hospital LOS • Mortality	• Subglottic stenosis or other airway anomalies • New tracheostomy placement • PICS-P
Respiratory muscle strength (respiratory capacity)				
• Use of NRS before intubation • Decision to intubate and timing of intubation • Preexisting respiratory muscle weakness	• VIDD • **Sedation assessment and management** • Delirium assessment and management • NMB use • Fluid overload • Nutrition and electrolytes • Ventilator management • Early mobilization • Acquired diaphragm paresis	• **PiMax** • Diaphragm ultrasound • NRS use after extubation • **ERT systematic screening** • **SBT method** • **SBT duration** • **Sedation assessment and management** • Delirium assessment and management	• Extubation failure because of respiratory muscle weakness • NRS use after extubation • VFDs-28 • ICU LOS • Hospital LOS • Mortality	• Prolonged NRS use • New tracheostomy placement • Long-term ventilation • PICS-P (especially muscle weakness and need for rehabilitation)
Respiratory load				
• Use of NRS before intubation • Decision to intubate and timing of intubation • Severity of initial respiratory disease	• Fluid overload • Timing of resolution of initial disease • VILI • VAE	• Fluid overload • **ERT systematic screening** • **SBT method** • **SBT duration** • SBT pass criteria • **NRS use after extubation**	• Extubation failure because of lung disease • **NRS use after extubation** • VFDs-28 • ICU LOS • Hospital LOS • Mortality	• Prolonged NRS use • New tracheostomy placement • Long-term ventilation • PICS-P

(Continued)

TABLE 1] *(Continued)*

Intubation	IMV Course	Extubation Attempt	Short-term Outcomes	Long-term Outcomes
Cardiac load				
• Use of NRS before intubation • Decision to intubate and timing of intubation • Degree of cardiac dysfunction	• Fluid overload • Vasoactive support • Cardiac function • Pulmonary hypertension management • Rhythm control • Surgical correction and residual cardiac lesions	• Monitoring of cardiac output during ERT (ie, perfusion, lactate, NIRS, CVP, echocardiography, dead space fraction) • **NRS after extubation**	• Extubation failure • **NRS use after extubation** • VFDs-28 • ICU LOS • Hospital LOS • Mortality	• Prolonged NRS use • New tracheostomy placement • Long-term ventilation • Heart transplantation • Ventricular assist device • PICS-P
Neuropsychological factors				
• Use of NRS before intubation • Decision to intubate and timing of intubation • Central drive • Neurologic control of the airway	• **Sedation assessment and management** • Delirium assessment and management	• **Sedation assessment and management** • Delirium assessment and management • Withdrawal assessment and management • **Ability to control oropharyngeal secretions** • Spasticity	• Extubation failure • **NRS use after extubation** • VFDs-28 • ICU LOS • Hospital LOS • Mortality	• Prolonged NRS use • New tracheostomy placement • Long-term ventilation • PICS-P

Topics covered by the pediatric ventilator liberation guidelines and research priorities appear in boldface. CVP = central venous pressure; ERT = extubation readiness testing; ETT = endotracheal tube; IMV = invasive mechanical ventilation; LOS = length of stay; NIRS = near infrared spectroscopy; NMB = neuromuscular blockade; NRS = noninvasive respiratory support; PICS-P = post-intensive care syndrome in pediatrics; PiMax = maximal inspiratory pressure during airway; SBT = spontaneous breathing trial; UAO = upper airway obstruction; VAE = ventilator-associated event; VFD = ventilator-free day; VIDD = ventilator induced diaphragmatic dysfunction; VILI = ventilator-induced lung injury.

TABLE 2] Examples of ERT Safety Screening Criteria Used in Pediatric Clinical Studies

Evaluation criteria	Randolph et al[7]	Foronda et al[8]	Jouvet et al[9]	Faustino et al[10]	Abu-Sultaneh et al[11]	Ferreira et al[13]	Loberger et al[15]
Clinical	• No increased ventilator support in the last 24 h • No planned operative procedures in the next 12 h	An absence of new infiltrates on the CXR		• A decrease or plateau in ventilator support, or both, over the previous 12 h • The acute phase of acute lung injury ends	• No increase of ventilator support in the last 24 h • No planned procedures in the next 12 h	• No signs of significant pulmonary congestion or pleural effusion on CXR • Excluded patients with preoperative mechanical ventilation and uncontrolled pulmonary hypertension	• No increase in ventilator settings ≤ 12 h • No planned sedated or surgical procedures in the next 24 h
IMV settings and gas exchange	• F_{IO_2} ≤ 0.6 • PEEP ≤ 7 • pH 7.32-7.47	• F_{IO_2} ≤ 0.5 • PEEP ≤ 8 • PIP ≤ 25	• F_{IO_2} 0.6 • SpO_2 ≥ 95% • PEEP ≤ 8 • Plateau pressure ≤ 25	• OI or OSI < 6	• F_{IO_2} ≤ 0.50 • SpO_2 ≥ 92% • PEEP ≤ 6 • PIP ≤ 25 • Vt 6-8 mL/kg	• F_{IO_2} ≤ 0.50 • SpO_2 > 90% after total corrections or 75%-85% after palliative operations • Positive PEEP ≤ 5 • PIP ≤ 20 • pH > 7.3	• F_{IO_2} ≤ 0.5 • PEEP ≤ 6 • PS ≤ 10 • PIP ≤ 30 • Vt > 5 mL/kg Q20
Oxygen availability and consumption	. . .	• Hemodynamic stability (doses of sodium nitroprusside, dopamine, or dobutamine < 10 μg/kg/min) • Hemoglobin ≥ 8 g/dL	• No vasopressor or inotrope medication (other than digoxin or low-dose dopamine [≤ 5 μg/kg/min])	. . .	• Hemodynamic stability • No increase of vasoactive drips for 12 h	• Hemodynamic stability (dopamine < 10 μg/kg/min or epinephrine < 0.1 μg/kg/min) • Absence of bleeding	• ≤ 1vasoactive infusions and no increases ≤ 12 h Q21
Airway protection	Gag or cough with suctioning	. . .	. . .	. . .	. . .	Intact cough and gag reflexes	. . .
Electrolytes	. . .	Correction of electrolyte changes (calcium, magnesium, phosphorus, and potassium)	. . .	. . .	. . .	Absence of electrolyte disturbance	. . .

(Continued)

TABLE 2] *(Continued)*

Evaluation criteria	Randolph et al[7]	Foronda et al[8]	Jouvet et al[9]	Faustino et al[10]	Abu-Sultaneh et al[11]	Ferreira et al[13]	Loberger et al[15]
Neurologic or sedation level	• Spontaneous breathing • Level of consciousness acceptable for extubation	• Spontaneous breathing • No continuous sedation • No use of neuromuscular blockers in the last 24 h	Spontaneous breathing	Spontaneous breathing	Spontaneous breathing	• Adequate respiratory drive • Appropriate level of consciousness	• No current neuromuscular blockade • SBS ≥ (−1) • GCS ≥ 8
Attending physician approval	Yes	No	No	No	No	Yes	Yes

CXR = chest radiography; ERT = extubation readiness testing; GCS = Glasgow coma scale; OI = oxygenation index; OSI = oxygenation saturation index; PEEP = positive end-expiratory pressure; PIP = peak inspiratory pressure; PS = pressure support; SBS = state behavioral scale; SpO_2 = oxygen saturation; Vt = tidal volume.

FIO_2, peak inspiratory pressure) are still unclear and warrant additional investigation. Furthermore, some studies include evaluations in a safety screen that might be considered elements of the ERT itself, like sedation level or the presence of gag or cough with suctioning. This makes it difficult to compare outcomes between studies because of a lack of common operational definitions.[7,8] Furthermore, most patients who are identified as high risk for extubation failure in the pediatric ventilator liberation guidelines (like patients with airway, pulmonary, cardiac, and neuromuscular diseases) are underrepresented in existing studies of ERT safety screening, yet these are the patients who are most likely to benefit from ERT safety screening.

Research Gaps 1B: What are the optimal thresholds for each of the ERT screening components that can improve ERT bundle performance (like time to first successful SBT) and extubation outcomes? Do these thresholds need to be modified for different patient populations?

Suggested Studies 1B: Although RCTs can be created to answer these questions, it is likely that optimal thresholds (aggressive vs conservative) for each of the ERT screening components can be investigated using contemporary observational data from multicenter QI collaborations (Fig 1). For example, different positive end-expiratory pressure thresholds (6 cm H_2O vs 8 cm H_2O vs 10 cm H_2O) and PIP thresholds (20 cm H_2O vs 25 cm H_2O vs 30 cm H_2O) can be tested in different centers comparing patient-centered extubation outcomes (ie, extubation failure and IMV duration).

Rationale 1C: ERT bundles have been shown to improve extubation outcomes, but important questions remain about which elements of the bundle are most important, or if the bundle should be expanded to include additional elements.

Research Gaps 1C: What elements of the ERT bundle are more predictive of extubation outcomes? Are these elements different for patients at high risk of extubation failure? What additional elements need to be added to ERT bundles to improve bundle performance and extubation outcomes? Does this differ in subpopulations at high risk of extubation failure?

Suggested Studies 1C: Given the complexity of conducting large RCTs and the challenges with implementation after an RCT has concluded, it is likely that elements of the ERT bundle suggested in the guidelines can be optimized using contemporary observational data from multicenter QI collaborations.

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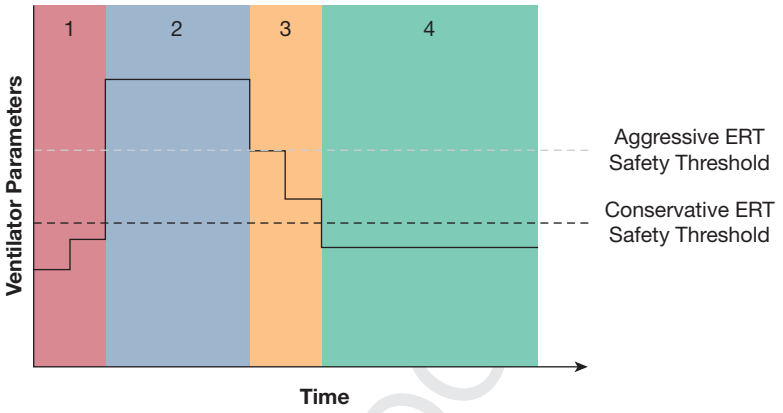

Figure 1 – *Conceptual framework showing invasive mechanical ventilation phases and ERT safety thresholds: (1) escalation phase, (2) plateau phase, (3) de-escalation phase, and (4) liberation phase. ERT = extubation readiness testing.*

For example, this can include different thresholds of respiratory muscle strength, other methods to assess the risk for UAO (like point-of-care ultrasound [POCUS]), assessment and management of delirium, and assessment and management of fluid overload. In addition, the most common reason for SBT failure in children relates to high work of breathing. Although this commonly is assessed clinically, variability exists in this assessment that is practitioner and patient dependent. Alternative methods to evaluate respiratory effort or work of breathing directly such as esophageal manometry (invasive), airway occlusion maneuvers (expiratory occlusion pressure, noninvasive), or diaphragm ultrasound (thickening fraction) should be investigated.[17]

SBT Method and Duration

Rationale 2A: The guidelines recommend including SBTs as an essential element of the ERT bundle.[1] The guidelines suggest using either pressure support (PS) augmentation with CPAP or CPAP alone during SBTs in mechanically ventilated children at standard risk of extubation failure. For those at high risk of extubation failure, the guidelines suggest using CPAP without PS augmentation SBTs for better assessment of extubation readiness.[1] This recommendation was based on one RCT that showed no significant difference between PS-augmented and T-piece SBTs.[18] The drawback of PS-augmented SBTs is the underestimation of postextubation work of breathing.[19-21] Conversely, perceived high work of breathing on CPAP alone compared with PS with CPAP may result in delayed extubation. A recent open-label, randomized, noninferiority trial that was published after the guidelines showed that a 2-h PS-augmented SBT was noninferior to CPAP alone SBT in predicting successful liberation from IMV, although the number of high-risk patients in this study is unclear.[22] Nonetheless, few studies have evaluated the effect of PS augmentation on extubation success in high-risk populations.

Research Gaps 2A: What is the optimal method to perform SBTs in children? Does the SBT method need to be adjusted depending on risk of extubation failure?

Rationale 2B: Regarding SBT duration, the guidelines suggest that the SBT should be conducted for either 30 min or 60 to 120 min, depending on the patient's risk of extubation failure. Obviously, a shorter SBT likely will result in more patients passing the SBT, but also likely a higher extubation failure rate. In contrast, a longer SBT likely will result in lower rates of extubation failure. Since the publication of the guidelines, a single-center observational study showed that a 30-min SBT might be too short in children recovering from pediatric ARDS because many go on to fail the SBT at between 30 and 120 min.[23] Another observational study showed similar extubation failure rates for 1-h and 2-h SBTs in a general PICU population.[24] However, no pediatric RCTs have evaluated SBT duration on extubation outcomes or SBT duration in patients at high risk of extubation failure.

Research Gaps 2B: What is the optimal duration of an SBT in pediatric population? Does SBT duration need to be adjusted depending on risk of extubation failure?

Suggested Studies 2A and 2B: Because the SBT method and duration are linked intimately, a potential design may include a two-by-two factorial RCT. Comparator groups could include (1) a PS-augmented SBT vs CPAP alone SBT and (2) a 30-min SBT vs a 120-min SBT focused on patient-centered clinical outcomes, that is, extubation failure and IMV duration. Enrollment can be stratified based on extubation failure risk (standard vs high risk). Corresponding Population, Intervention, Comparator, Outcome questions are summarized in Table 3.

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TABLE 3] Suggested Randomized Control Trials

SBT method and duration
In children receiving IMV for > 24 h, should SBTs be performed with PS augmentation?
P: Children who are intubated for > 24 h undergoing an extubation attempt (stratified into standard risk vs high risk of extubation failure)
I: SBT with CPAP of 5 cm H_2O without PS augmentation
C: SBT with CPAP of 5 cm H_2O and PS augmentation between 5 and 10 cm H_2O
O: Primary: IMV duration
Secondary: SBT success rate, extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU
In children receiving IMV for > 24 h, should SBTs be performed for 30 min or 120 min?
P: Children who are intubated for > 24 h undergoing an extubation attempt (stratified into standard risk vs high risk of extubation failure)
I: 30-min SBT
C: 120-min SBT
O: Primary: IMV duration
Secondary: SBT success rate, extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU
UAO risk assessment and prevention after extubation
In children receiving IMV for > 24 h with indeterminant risk of UAO after extubation (ie, uncuffed endotracheal tube), should corticosteroids be given before the extubation attempt?
P: Children who are intubated for > 24 h with indeterminant risk of UAO after extubation undergoing an extubation attempt (stratified using PiMax into standard risk vs high risk of extubation failure)
I: Dexamethasone 0.5mg/kg/dose for 4 doses (maximum, 10 mg) started at least 6 h before planned extubation attempt
C: Placebo
O: Primary: IMV duration
Secondary: UAO rate, extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU
NRS after extubation
In children receiving IMV for > 24 h who are considered at high risk of extubation failure, should planned BPAP be used immediately after extubation?
P: Children who are intubated for > 24 h and considered at high risk of extubation failure undergoing extubation attempt (stratified by age and PiMax)
I: Planned BPAP after extubation
C: Planned HFNC after extubation
O: Primary: IMV duration
Secondary: extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU

BPAP = bilevel positive airway pressure; CICU = cardiac ICU; HFNC = high-flow nasal cannula; IMV = invasive mechanical ventilation; LOS = length of stay; NRS = noninvasive respiratory support; PiMax = maximum inspiratory pressure during airway occlusion; PS = pressure support; SBT = spontaneous breathing trial; UAO = upper airway obstruction.

Rationale 2C: Finally, the guidelines did not specify objective criterion for passing an SBT and if this should be adjusted for certain high-risk populations (ie, patients with myocardial dysfunction, neurologic impairment, neuromuscular disease, or chronic critical illness disease).[25] A recent systematic review and meta-analysis showed that the published assessments have poor prediction of extubation failure in pediatric populations.[26]

Research Gaps 2C: What are the optimal criteria that can be used to assess the success of an SBT? What is the optimal threshold of each of these criteria?

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Suggested Studies 2C: An RCT to answer this question is likely impractical given the multitude of combinations of elements and thresholds. It is likely that high-fidelity data from electronic medical records with machine learning models from a multicenter QI collaboration can be used to study different sets of objective criteria and different thresholds and their effect on SBT and ERT success rate, extubation failure, and IMV duration. Modifications of items included in these criteria and thresholds subsequently can be tested in high-risk populations mentioned above with RCTs or QI interventions. However, it is also clear that passage of an SBT does not always lead to extubation, because clinicians also consider a multitude of other factors before extubation. Certainly, studies focused on clinical decision-making regarding timing of extubation and identifying barriers leading to the delay between passing SBTs and extubation are needed.[27]

Measures of Respiratory Muscle Strength and Function

Rationale 3A: The guidelines suggest the use of maximum inspiratory pressure during airway occlusion (PiMax) as an element of an ERT bundle in critically ill children with risk factors for muscle weakness, extubation failure, or both. The guidelines did not recommend a specific cutoff value for PiMax. Moreover, an international survey of pediatric critical care providers showed that PiMax is not commonly used.[28] No RCTs have shown the impact of using a PiMax threshold to inform extubation decisions. However, existing studies support that a dose-dependent relationship between PiMax and re-intubation risk likely exists, so PiMax should be considered together with other variables that may put the patient at high risk for extubation failure.[29] For example, a PiMax of 25 cm H_2O in a patient with no other risk factors for extubation failure may not prompt any change in behavior. But if this patient is also at high risk of UAO or has significant residual pulmonary disease, it may inform waiting for further resolution of the pulmonary disease or modulation of the risk for UAO. It may also inform whether the patient should be extubated to noninvasive respiratory support (NRS) prophylactically.

Research Gaps 3A: How should PiMax information, gathered as part of an ERT, be used to improve extubation decisions? Does a clear cutoff for PiMax exist that defines patients at high risk of extubation failure where prophylactic extubation to NRS would be helpful?

Suggested Studies 3A: Because PiMax is measured infrequently in routine clinical practice, the first step likely involves gathering multicenter observational data with routine use of PiMax that can be used to evaluate the independent effect that PiMax has on extubation outcomes. Furthermore, high-quality observational data also can be used to evaluate whether the combination of a low PiMax and other extubation risk factors (such as UAO) leads to even higher rates of extubation failure (ie, an interaction). This may lend itself well to large multicenter QI collaborations in which elements of the ventilator liberation bundle are implemented and PiMax is measured. Stratification of extubation outcomes as a function of PiMax and measurement of potential heterogeneity of treatment effect from implementation of ERT bundle elements (such as periextubation corticosteroids) as a function of various PiMax thresholds may provide more evidence to support using a specific PiMax threshold to inform decision-making or to test in an RCT.

Rationale 3B: Although the guidelines focus on assessing the respiratory muscle capacity using PiMax, other potential measures of respiratory muscle strength and function exist, such as diaphragm ultrasound or diaphragmatic electrical activity, that warrant further investigation.[17] Most of the existing data on these techniques have included a relatively small number of patients, and they have not been compared head-to-head with PiMax regarding extubation outcomes.

Research Gaps 3B: Would the use of alternative methods to assess respiratory muscle function like diaphragm ultrasound or diaphragmatic electrical activity instead of PiMax improve extubation outcomes?

Suggested Studies 3B: Observational studies with assessment of the relationship of both PiMax and diaphragm ultrasound (or electrical activity) against extubation outcomes are needed. Because both diaphragm ultrasound and electrical activity require use of specialized equipment, it is likely that these comparative studies would need to begin as smaller pilot projects, and certainly additional physiologic data evaluating the relationship among all these parameters if measured simultaneously also may be helpful.

UAO Risk Assessment and Prevention After Extubation

Rationale 4A: Identification of patients at high risk of subglottic UAO after extubation for whom the prophylactic administration of corticosteroids may be

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helpful is important because at least one-third of all extubation failures are attributed to UAO after extubation.[30] The guidelines suggest the use of the air leak test in pediatric patients with cuffed endotracheal tubes to assess the risk of subglottic UAO after extubation.[1] However, the air leak test has limitations related to interrater reliability and was not shown to be predictive of UAO after extubation if the endotracheal tube is uncuffed. Other methods of assessment such as upper airway POCUS measuring the difference in laryngeal air column width between an inflated and deflated cuff are being studied, although a relative paucity of pediatric data remains, and this method similarly is meant for cuffed endotracheal tubes.[31-33] Also concerns exist regarding interrater reliability that may be more significant than with the air leak test.

Research Gaps 4A: Is upper airway POCUS more accurate than the air leak test at identifying patients at high risk of subglottic UAO after extubation and extubation failure related to UAO?

Suggested Studies 4A: Physiologic studies directly comparing these methods against objective measures of UAO after extubation (given that about half of the cases of UAO after extubation are supraglottic) could be an important way to evaluate the initial diagnostic accuracy of POCUS. Larger studies against clinical outcomes such as UAO after extubation will still be limited by lack of an objective marker to differentiate supraglottic from subglottic disease. Outcomes such as reintubation ultimately carry the most clinical impact, but such a study may be impractical given the very large number of patients that would be needed and the limited number of potentially trained practitioners. Ultimately, if upper airway POCUS methods are shown to have more diagnostic accuracy than the air leak test, implementation studies would be crucial to ensure that the technique could be applied broadly for all patients, with adequate training of a large number of practitioners to perform the procedure in each ICU.

Rationale 4B: Proper identification of patients at risk of subglottic UAO after extubation allows administration of systemic corticosteroids to prevent subglottic UAO after extubation, potentially reducing the risk of extubation failure. The guidelines suggest that dexamethasone administration initiated at least 6 h before elective extubation may be beneficial in decreasing subglottic UAO after extubation, particularly in high-risk patients.[1,2]

The clinical guidelines identified eight RCTs that served as the basis for a subsequent pairwise and network metanalysis.[2] The data demonstrate that timing of administration likely is most important (at least 6 h but optimally 12 h) before extubation. If such a time window is not available, then higher-dose corticosteroids likely are preferable than low-dose corticosteroids. Of note, the meta-analysis did show benefit for the outcome of UAO, but not directly for reintubation. Because corticosteroids should be started at least 6 h before extubation, an unintended consequence can be unnecessary delay in extubation, which prompted the guideline committee specifically to suggest targeted use in patients at high risk of UAO. Given the lack of diagnostic accuracy for the air leak test with uncuffed endotracheal tubes, uncertainty remains regarding whether to prescribe corticosteroids for patients with uncuffed endotracheal tubes.

Research Gaps 4B: For patients with uncuffed endotracheal tubes, should corticosteroids be prescribed if no other risk factors for UAO after extubation are identified (ie, airway trauma, inappropriately large endotracheal tube)? For patients at high risk of extubation failure resulting from causes other than UAO (ie, respiratory muscle weakness) who have an indeterminant risk of UAO after extubation (ie, uncuffed endotracheal tube), should corticosteroids be used to lower the risk of reintubation?

Suggested Studies 4B: An RCT of patients at high risk of UAO after extubation focused on the outcome of reintubation may be clinically important, although multiple RCTs have confirmed that it is useful to reduce the rates of UAO after extubation. Reducing UAO after extubation in itself is important clinically, given that UAO is distressing to the patient and their family, may lead to additional therapeutics and longer ICU stay, and may be associated with long-term adverse outcomes.[34] Hence, this RCT may be a lower priority, given the results of the network meta-analyses.

Significantly more uncertainty in what to do about corticosteroids in patients with indeterminant risk of UAO after extubation remains (ie, uncuffed endotracheal tubes). Here an RCT is likely warranted, with comparison of corticosteroids started at least 6 h before extubation against placebo in children with uncuffed endotracheal tubes. Additional stratification based on risk factors for extubation failure (ie, using PiMax) is important to evaluate potential heterogeneity in treatment effect, particularly for the outcome of reintubation (Table 3).

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NRS After Extubation

Rationale 5A: Planned NRS (NRS started immediately after extubation) frequently is used in children to reduce the risk of extubation failure. The guidelines suggest using planned NRS over conventional oxygen therapy in children considered at high risk of extubation failure.[1] The list of risk factors of extubation failure was based on previously published studies and expert opinion; one key risk factor identified in previous literature is prolonged IMV before extubation.[35] However, a paucity of contemporary multicenter observational studies is available to describe the risk of extubation failure accurately in different patient groups and to identify specific causes of extubation failure. This is particularly relevant because the PICU population has changed over the past decade, with a rising prevalence of patients with complex chronic conditions, in whom the risk of extubation failure may be greater.[36]

Research Gaps 5A: What factors should be used to identify patients who are at high risk of extubation failure for whom prophylactic extubation to NRS may be warranted?

Suggested Studies 5A: Given many potential risk factors for extubation failure, individual RCTs in subpopulations are not really feasible. In this case, large observational studies with causal inference techniques or quasirandomized trials with QI methodology may be able to answer this question. In contemporary practice, the use of prophylactic NRS is practitioner and institution dependent, with very few protocols in place to define the population likely to benefit. Analysis of observational data may be helpful to identify the population at high risk of extubation failure, while capitalizing on the variability in treatment decisions by using causal inference methods to identify who benefited from prophylactic extubation to NRS. Furthermore, studying a protocol to use prophylactic NRS before and after implementation in a population deemed high risk can evaluate which subsets of patients (ie, which risk factors) benefited the most from prophylactic NRS. PiMax may be an important element to stratify patients into standard vs high risk of extubation failure, given that patients with impaired respiratory muscle capacity are at higher risk of extubation failure.[29] An additional important element of such a study includes protocols for de-escalating NRS or weaning patients from it, because prophylactic use of NRS in fact may prolong ICU stay if it is not discontinued or patients weaned from it in a timely fashion.

Rationale 5B: Different methods of NRS are available, with high-flow nasal cannula and CPAP being the most frequently used.[3] Bilevel positive airway pressure is used less frequently, but offers ventilatory assistance, which may be important in children with neuromuscular disease or ICU-associated muscle weakness. Only one large RCT has compared high-flow nasal cannula with CPAP after extubation so far[37] and showed that the time to liberation from respiratory support was shorter in the CPAP group, with a subgroup analysis indicating that this was most notable in infants. This informed the guideline recommendation that CPAP is suggested to be used as the first-line NRS method for children younger than 1 year. However, half of the children recruited in that RCT were infants, and only small numbers of children had cardiac disease or immunosuppression. The relative risk to benefit ratio of CPAP as the first NRS method in specific subgroups remains unclear, especially in children who require ventilatory assistance. The increasing prevalence of children with complex comorbid conditions, including neurologic and neuromuscular diseases, makes this even more important.

Research Gaps 5B: What method of NRS should be used as the first-line therapy and how does this differ based on risk factors of extubation failure (ie, respiratory muscle weakness, residual pulmonary disease, upper airway obstruction).

Suggested Studies 5B: An RCT should be conducted in children considered at high risk of extubation failure comparing the initiation of planned high-flow nasal cannula vs bilevel positive airway pressure on extubation outcomes. Stratification of these patients can be carried out using the list published in the guidelines and data can be obtained from multicenter QI collaborations, in addition to using PiMax obtained before extubation. Planned subgroup analysis can look at different patient populations (eg, those who have undergone cardiac surgery, those who are immunocompromised, those with neuromuscular disease), ages, and centers (Table 3).

Sedation Assessment

Rationale 6A: Evaluation of the level of sedation, cough effectiveness, and capacity to manage oropharyngeal secretions before extubation was suggested as part of ERT bundle by the guidelines, and evaluation of level of sedation in the periextubation period also was suggested by the 2022 Society of Critical Care Medicine PANDEM guidelines.[38]

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Two large well-conducted RCTs studied the impact of sedation assessment on pediatric ventilator liberation (namely, IMV duration).[14,39] Although sedation level was a key component of both trials, complexity between sedation assessment or titration and other human factor components of ventilator weaning and extubation in children remains. Both RCTs used bundled interventions (including sedation assessment and management in addition to an ERT component), so it is unclear which one of the bundle components are more important to decrease IMV duration, and neither trial showed a large effect on IMV duration for the intervention. Neither trial examined the impact of delirium, partly because of a lack of validated assessment tools being used at that time.

Research Gaps 6A: What is the effect of delirium on pediatric ventilator liberation outcomes?

Suggested Studies 6A: Observational studies focused on extubation outcomes should incorporate delirium assessment tools in the periextubation period to identify if delirium has an independent effect on extubation outcomes (IMV duration and extubation failure).

Conclusions

Substantial research gaps exist in the field of pediatric ventilator liberation, and although RCTs certainly are needed in many areas, high-quality observational studies and quasirandomized trials also are important to improve the level of certainty behind some of the recommendations and to establish firmer guidelines for what truly constitutes high-risk patients in whom different therapies or strategies may be warranted around the time of ventilator liberation.

Furthermore, for the interventions that are ready for an RCT, a platform trial focused on pediatric patients who have been receiving ventilation for $>$ 24 h may be ideal. In pediatric critical care, many challenges exist to conducting well-powered multicenter RCTs, including heterogeneity of patient populations, relative paucity of patients available to study, and recreation of clinical trial infrastructure for each study, greatly increasing costs. A multicenter platform trial would increase efficiency and would enable simultaneous testing of multiple interconnected elements of pediatric ventilator liberation, iterative cycling through promising interventions in each domain area of ventilator liberation, and risk-based enrollment strata with borrowing techniques between groups to estimate treatment effects better.[40] Although platform trials certainly are an attractive option to improve efficiency, to increase patient recruitment, and to decrease cost, they do add an extra layer of complexity during study design, need alternative methods for funding, and require unique expertise for adaptation and data analysis.[41]

We hope these guidelines can set the stage for research in pediatric ventilator liberation, but acknowledge important limitations with our approach. Fundamentally, a great deal of expert opinion remains in this article, particularly related to potential study designs and methods to answer these questions. In addition, the priorities initially were identified by a small group of international experts, and we had limited patient and family representation in the process. We have tried to add rigor to this document and process by basing the gaps on systematic review, presentation of gaps to an international community of pediatric intensive care practitioners and investigators for feedback, and iterative refinement based on feedback the larger community.

In conclusion, we have presented several crucial research gaps in pediatric ventilator liberation and have proposed a conceptual map for how to think about these gaps. This is coupled with suggested methods and study designs to address these gaps, taking into consideration the use of study designs outside of traditional RCTs when they may be applicable. Nevertheless, several crucial areas should be a focus for multicenter RCTS.

Funding/Support

The project was funded by Eunice Kennedy Shriver National Institute of Child Health and Human Development National Heart, Lung, and Blood Institute of the National Institutes of Health [Grant R13HD102137], in addition to funds from the Department of Pediatrics at Indiana University School of Medicine.

Financial/Nonfinancial Disclosures

None declared.

Acknowledgments

Author contributions: All authors contributed to the conception or design of the work or in the acquisition, analysis, or interpretation of data for the work. All authors participated in drafting the work or revising it critically for important intellectual content, approved the work, and are responsible for the final version submitted for publication.

Role of sponsors: The sponsor had no role in the design of the study, the collection and analysis of the data, or the preparation of the manuscript.

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