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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.

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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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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,

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 suppur 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.

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}

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 Q18

Intubation	IMV Course	Extubation Attempt	Short-term Outcomes	Long-term Outcomes
<p>Subglottic upper airway obstruction</p> <ul style="list-style-type: none"> • ETT size • ETT type (cuffed or uncuffed) • Intubation process and no. of attempts 	<ul style="list-style-type: none"> • ETT cuff management • Agitation (sedation and delirium) • Fluid overload • Acquired vocal cord paralysis 	<ul style="list-style-type: none"> • Air leak test • Peri-extubation corticosteroids • NRS use after extubation 	<ul style="list-style-type: none"> • UAO • Extubation failure due to UAO • NRS use after extubation • New tracheostomy placement • VFDs-28 • ICU LOS • Hospital LOS • Mortality 	<ul style="list-style-type: none"> • Subglottic stenosis or other airway anomalies • New tracheostomy placement • PICS-P
<p>Respiratory muscle strength (respiratory capacity)</p> <ul style="list-style-type: none"> • Use of NRS before intubation • Decision to intubate and timing of intubation • Preexisting respiratory muscle weakness 	<ul style="list-style-type: none"> • VIDD • Sedation assessment and management • Delirium assessment and management • NMB use • Fluid overload • Nutrition and electrolytes • Ventilator management • Early mobilization • Acquired diaphragm paresis 	<ul style="list-style-type: none"> • PiMax • Diaphragm ultrasound • NRS use after extubation • ERT systematic screening • SBT method • SBT duration • Sedation assessment and management • Delirium assessment and management 	<ul style="list-style-type: none"> • Extubation failure because of respiratory muscle weakness • NRS use after extubation • VFDs-28 • ICU LOS • Hospital LOS • Mortality 	<ul style="list-style-type: none"> • Prolonged NRS use • New tracheostomy placement • Long-term ventilation • PICS-P (especially muscle weakness and need for rehabilitation)
<p>Respiratory load</p> <ul style="list-style-type: none"> • Use of NRS before intubation • Decision to intubate and timing of intubation • Severity of initial respiratory disease 	<ul style="list-style-type: none"> • Fluid overload • Timing of resolution of initial disease • VILI • VAE 	<ul style="list-style-type: none"> • Fluid overload • ERT systematic screening • SBT method • SBT duration • SBT pass criteria • NRS use after extubation 	<ul style="list-style-type: none"> • Extubation failure because of lung disease • NRS use after extubation • VFDs-28 • ICU LOS • Hospital LOS • Mortality 	<ul style="list-style-type: none"> • Prolonged NRS use • New tracheostomy placement • Long-term ventilation • PICS-P

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TABLE 1] (Continued)

Intubation	IMV Course	Extubation Attempt	Short-term Outcomes	Long-term Outcomes
Cardiac load <ul style="list-style-type: none"> • Use of NRS before intubation • Decision to intubate and timing of intubation • Degree of cardiac dysfunction 	<ul style="list-style-type: none"> • Fluid overload • Vasoactive support • Cardiac function • Pulmonary hypertension management • Rhythm control • Surgical correction and residual cardiac lesions 	<ul style="list-style-type: none"> • Monitoring of cardiac output during ERT (ie, perfusion, lactate, NIRS, CVP, echocardiography, dead space fraction) • NRS after extubation 	<ul style="list-style-type: none"> • Extubation failure • NRS use after extubation • VFDs-28 • ICU LOS • Hospital LOS • Mortality 	<ul style="list-style-type: none"> • Prolonged NRS use • New tracheostomy placement • Long-term ventilation • Heart transplantation • Ventricular assist device • PICS-P
Neuropsychological factors <ul style="list-style-type: none"> • Use of NRS before intubation • Decision to intubate and timing of intubation • Central drive • Neurologic control of the airway 	<ul style="list-style-type: none"> • Sedation assessment and management • Delirium assessment and management 	<ul style="list-style-type: none"> • Sedation assessment and management • Delirium assessment and management • Withdrawal assessment and management • Ability to control oropharyngeal secretions • Spasticity 	<ul style="list-style-type: none"> • Extubation failure • NRS use after extubation • VFDs-28 • ICU LOS • Hospital LOS • Mortality 	<ul style="list-style-type: none"> • 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; VIIDD = ventilator induced diaphragmatic dysfunction; VILI = ventilator-induced lung injury.

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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	<ul style="list-style-type: none"> 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		<ul style="list-style-type: none"> A decrease or plateau in ventilator support, or both, over the previous 12 h The acute phase of acute lung injury ends 	<ul style="list-style-type: none"> No increase of ventilator support in the last 24 h No planned procedures in the next 12 h 	<ul style="list-style-type: none"> No signs of significant pulmonary congestion or pleural effusion on CXR Excluded patients with preoperative mechanical ventilation and uncontrolled pulmonary hypertension 	<ul style="list-style-type: none"> No increase in ventilator settings \leq 12 h No planned sedated or surgical procedures in the next 24 h
IMV settings and gas exchange	<ul style="list-style-type: none"> $FiO_2 \leq 0.6$ $PEEP \leq 7$ pH 7.32-7.47 	<ul style="list-style-type: none"> $FiO_2 \leq 0.5$ $PEEP \leq 8$ $PIP \leq 25$ 	<ul style="list-style-type: none"> $FiO_2 0.6$ $SpO_2 \geq 95\%$ $PEEP \leq 8$ Plateau pressure ≤ 25 	<ul style="list-style-type: none"> OI or OSI < 6 	<ul style="list-style-type: none"> $FiO_2 \leq 0.50$ $SpO_2 \geq 92\%$ $PEEP \leq 6$ $PIP \leq 25$ Vt 6-8 mL/kg 	<ul style="list-style-type: none"> $FiO_2 \leq 0.50$ $SpO_2 > 90\%$ after total corrections or 75%-85% after palliative operations Positive PEEP ≤ 5 $PIP \leq 20$ pH > 7.3 	<ul style="list-style-type: none"> $FiO_2 \leq 0.5$ $PEEP \leq 6$ $PS \leq 10$ $PIP \leq 30$ Vt > 5 mL/kg
Oxygen availability and consumption	...	<ul style="list-style-type: none"> Hemodynamic stability (doses of sodium nitropruside, dopamine, or dobutamine < 10 μg/kg/min) Hemoglobin ≥ 8 g/dL 	<ul style="list-style-type: none"> No vasopressor or inotrope medication (other than digoxin or low-dose dopamine [≤ 5 μg/kg/min]) 	...	<ul style="list-style-type: none"> Hemodynamic stability No increase of vasoactive drips for 12 h 	<ul style="list-style-type: none"> Hemodynamic stability (dopamine < 10 μg/kg/min or epinephrine < 0.1 μg/kg/min) Absence of bleeding 	<ul style="list-style-type: none"> ≤ 1 vasoactive infusions and no increases ≤ 12 h
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	...

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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	<ul style="list-style-type: none"> Spontaneous breathing Level of consciousness acceptable for extubation 	<ul style="list-style-type: none"> Spontaneous breathing No continuous sedation No use of neuro-muscular blockers in the last 24 h 	Spontaneous breathing	Spontaneous breathing	Spontaneous breathing	<ul style="list-style-type: none"> Adequate respiratory drive Appropriate level of consciousness 	<ul style="list-style-type: none"> No current neuromuscular blockade SBS \geq (-1) GCS \geq 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; SpO₂ = oxygen saturation; Vt = tidal volume.

FiO₂, 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?

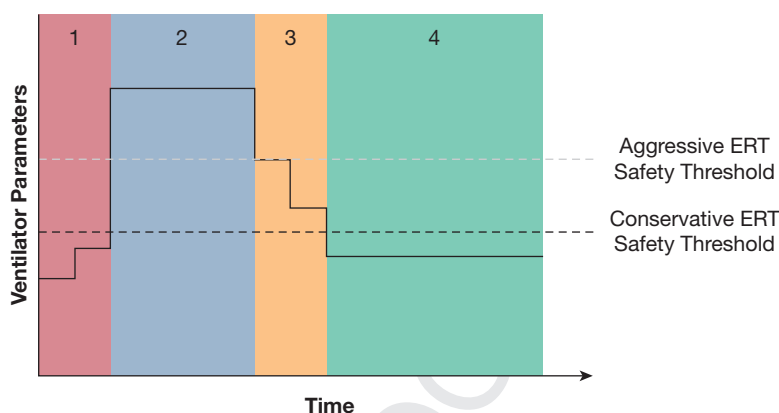
Suggested Studies 1B: Although RCTs can be created to answer these questions, it is likely that optimal thresholds (aggressive vs conservative) for each of the ERT screening components can be investigated using contemporary observational data from multicenter QI collaborations (Fig 1). For example, different positive end-expiratory pressure thresholds (6 cm H₂O vs 8 cm H₂O vs 10 cm H₂O) and PIP thresholds (20 cm H₂O vs 25 cm H₂O vs 30 cm H₂O) 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.

771 ^{Q17} Figure 1 – Conceptual framework showing invasive
 772 mechanical ventilation phases and ERT safety
 773 thresholds: (1) escalation phase, (2) plateau phase, (3)
 774 ^{Q24} de-escalation phase, and (4) liberation phase. ERT =
 775 extubation readiness testing.



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

803 *SBT Method and Duration*

804 **Rationale 2A:** The guidelines recommend including
 805 SBTs as an essential element of the ERT bundle.¹ The
 806 guidelines suggest using either pressure support (PS)
 807 augmentation with CPAP or CPAP alone during SBTs in
 808 mechanically ventilated children at standard risk of
 809 extubation failure. For those at high risk of extubation
 810 failure, the guidelines suggest using CPAP without PS
 811 augmentation SBTs for better assessment of extubation
 812 readiness.¹ This recommendation was based on one RCT
 813 that showed no significant difference between PS-
 814 augmented and T-piece SBTs.¹⁸ The drawback of PS-
 815 augmented SBTs is the underestimation of
 816 postextubation work of breathing.¹⁹⁻²¹ Conversely,
 817 perceived high work of breathing on CPAP alone
 818 compared with PS with CPAP may result in delayed
 819 extubation. A recent open-label, randomized,
 820 noninferiority trial that was published after the guidelines
 821 showed that a 2-h PS-augmented SBT was noninferior to
 822 CPAP alone SBT in predicting successful liberation from
 823 IMV, although the number of high-risk patients in this

824 study is unclear.²² Nonetheless, few studies have
 825 evaluated the effect of PS augmentation on extubation
 826 success in high-risk populations.

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

830 **Rationale 2B:** Regarding SBT duration, the guidelines
 831 suggest that the SBT should be conducted for either
 832 30 min or 60 to 120 min, depending on the patient's risk
 833 of extubation failure. Obviously, a shorter SBT likely will
 834 result in more patients passing the SBT, but also likely a
 835 higher extubation failure rate. In contrast, a longer SBT
 836 likely will result in lower rates of extubation failure. Since
 837 the publication of the guidelines, a single-center
 838 observational study showed that a 30-min SBT might be
 839 too short in children recovering from pediatric ARDS
 840 because many go on to fail the SBT at between 30 and
 841 120 min.²³ Another observational study showed similar
 842 extubation failure rates for 1-h and 2-h SBTs in a general
 843 PICU population.²⁴ However, no pediatric RCTs have
 844 evaluated SBT duration on extubation outcomes or SBT
 845 duration in patients at high risk of extubation failure.

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

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

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TABLE 3] Suggested Randomized Control Trials

881	SBT method and duration	936
882		937
883	In children receiving IMV for > 24 h, should SBTs be performed with PS augmentation?	938
884		939
885	P: Children who are intubated for > 24 h undergoing an extubation attempt (stratified into standard risk vs high risk of extubation failure)	940
886		941
887	I: SBT with CPAP of 5 cm H ₂ O without PS augmentation	942
888	C: SBT with CPAP of 5 cm H ₂ O and PS augmentation between 5 and 10 cm H ₂ O	943
889	O: Primary: IMV duration	944
890	Secondary: SBT success rate, extubation failure, ICU LOS, hospital LOS	945
891	Setting: PICU, CICU	946
892		947
893	In children receiving IMV for > 24 h, should SBTs be performed for 30 min or 120 min?	948
894		949
895	P: Children who are intubated for > 24 h undergoing an extubation attempt (stratified into standard risk vs high risk of extubation failure)	950
896		951
897	I: 30-min SBT	952
898	C: 120-min SBT	953
899	O: Primary: IMV duration	954
900	Secondary: SBT success rate, extubation failure, ICU LOS, hospital LOS	955
901	Setting: PICU, CICU	956
902		957
903	UAO risk assessment and prevention after extubation	958
904		959
905	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?	960
906		961
907	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)	962
908		963
909	I: Dexamethasone 0.5mg/kg/dose for 4 doses (maximum, 10 mg) started at least 6 h before planned extubation attempt	964
910		965
911	C: Placebo	966
912	O: Primary: IMV duration	967
913	Secondary: UAO rate, extubation failure, ICU LOS, hospital LOS	968
914	Setting: PICU, CICU	969
915		970
916	NRS after extubation	971
917		972
918	In children receiving IMV for > 24 h who are considered at high risk of extubation failure, should planned BPAP be used immediately after extubation?	973
919		974
920	P: Children who are intubated for > 24 h and considered at high risk of extubation failure undergoing extubation attempt (stratified by age and PiMax)	975
921		976
922	I: Planned BPAP after extubation	977
923		978
924	C: Planned HFNC after extubation	979
925	O: Primary: IMV duration	980
926	Secondary: extubation failure, ICU LOS, hospital LOS	981
927	Setting: PICU, CICU	982
928		983

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?

991 **Suggested Studies 2C:** An RCT to answer this question
 992 is likely impractical given the multitude of combinations
 993 of elements and thresholds. It is likely that high-fidelity
 994 data from electronic medical records with machine
 995 learning models from a multicenter QI collaboration can
 996 be used to study different sets of objective criteria and
 997 different thresholds and their effect on SBT and ERT
 998 success rate, extubation failure, and IMV duration.
 999 Modifications of items included in these criteria and
 1000 thresholds subsequently can be tested in high-risk
 1001 populations mentioned above with RCTs or QI
 1002 interventions. However, it is also clear that passage of an
 1003 SBT does not always lead to extubation, because
 1004 clinicians also consider a multitude of other factors
 1005 before extubation. Certainly, studies focused on clinical
 1006 decision-making regarding timing of extubation and
 1007 identifying barriers leading to the delay between passing
 1008 SBTs and extubation are needed.²⁷

1012 *Measures of Respiratory Muscle Strength and* 1013 *Function*

1014 **Rationale 3A:** The guidelines suggest the use of
 1015 maximum inspiratory pressure during airway occlusion
 1016 (PiMax) as an element of an ERT bundle in critically ill
 1017 children with risk factors for muscle weakness,
 1018 extubation failure, or both. The guidelines did not
 1019 recommend a specific cutoff value for PiMax.
 1020 Moreover, an international survey of pediatric critical
 1021 care providers showed that PiMax is not commonly
 1022 used.²⁸ No RCTs have shown the impact of using a
 1023 PiMax threshold to inform extubation decisions.
 1024 However, existing studies support that a dose-
 1025 dependent relationship between PiMax and re-
 1026 intubation risk likely exists, so PiMax should be
 1027 considered together with other variables that may put
 1028 the patient at high risk for extubation failure.²⁹ For
 1029 example, a PiMax of 25 cm H₂O in a patient with no
 1030 other risk factors for extubation failure may not prompt
 1031 any change in behavior. But if this patient is also at
 1032 high risk of UAO or has significant residual pulmonary
 1033 disease, it may inform waiting for further resolution of
 1034 the pulmonary disease or modulation of the risk for
 1035 UAO. It may also inform whether the patient should be
 1036 extubated to noninvasive respiratory support (NRS)
 1037 prophylactically.

1040 **Research Gaps 3A:** How should PiMax information,
 1041 gathered as part of an ERT, be used to improve
 1042 extubation decisions? Does a clear cutoff for PiMax exist
 1043 that defines patients at high risk of extubation failure
 1044 where prophylactic extubation to NRS would be helpful?
 1045

Suggested Studies 3A: Because PiMax is measured
 1046 infrequently in routine clinical practice, the first step
 1047 likely involves gathering multicenter observational data
 1048 with routine use of PiMax that can be used to evaluate
 1049 the independent effect that PiMax has on extubation
 1050 outcomes. Furthermore, high-quality observational data
 1051 also can be used to evaluate whether the combination of
 1052 a low PiMax and other extubation risk factors (such as
 1053 UAO) leads to even higher rates of extubation failure (ie,
 1054 an interaction). This may lend itself well to large
 1055 multicenter QI collaborations in which elements of the
 1056 ventilator liberation bundle are implemented and PiMax
 1057 is measured. Stratification of extubation outcomes as a
 1058 function of PiMax and measurement of potential
 1059 heterogeneity of treatment effect from implementation
 1060 of ERT bundle elements (such as periextubation
 1061 corticosteroids) as a function of various PiMax
 1062 thresholds may provide more evidence to support using
 1063 a specific PiMax threshold to inform decision-making or
 1064 to test in an RCT.

Rationale 3B: Although the guidelines focus on
 1065 assessing the respiratory muscle capacity using PiMax,
 1066 other potential measures of respiratory muscle strength
 1067 and function exist, such as diaphragm ultrasound or
 1068 diaphragmatic electrical activity, that warrant further
 1069 investigation.¹⁷ Most of the existing data on these
 1070 techniques have included a relatively small number of
 1071 patients, and they have not been compared head-to-head
 1072 with PiMax regarding extubation outcomes.

Research Gaps 3B: Would the use of alternative
 1073 methods to assess respiratory muscle function like
 1074 diaphragm ultrasound or diaphragmatic electrical
 1075 activity instead of PiMax improve extubation outcomes?
 1076

Suggested Studies 3B: Observational studies with
 1077 assessment of the relationship of both PiMax and
 1078 diaphragm ultrasound (or electrical activity) against
 1079 extubation outcomes are needed. Because both
 1080 diaphragm ultrasound and electrical activity require use
 1081 of specialized equipment, it is likely that these
 1082 comparative studies would need to begin as smaller pilot
 1083 projects, and certainly additional physiologic data
 1084 evaluating the relationship among all these parameters if
 1085 measured simultaneously also may be helpful.
 1086

1094 *UAO Risk Assessment and Prevention After* 1095 *Extubation*

Rationale 4A: Identification of patients at high risk of
 1096 subglottic UAO after extubation for whom the
 1097 prophylactic administration of corticosteroids may be
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 1100

1101 helpful is important because at least one-third of all
 1102 extubation failures are attributed to UAO after
 1103 extubation.³⁰ The guidelines suggest the use of the air
 1104 leak test in pediatric patients with cuffed endotracheal
 1105 tubes to assess the risk of subglottic UAO after
 1106 extubation.¹ However, the air leak test has limitations
 1107 related to interrater reliability and was not shown to
 1108 be predictive of UAO after extubation if the
 1109 endotracheal tube is uncuffed. Other methods of
 1110 assessment such as upper airway POCUS measuring
 1111 the difference in laryngeal air column width between
 1112 an inflated and deflated cuff are being studied,
 1113 although a relative paucity of pediatric data remains,
 1114 and this method similarly is meant for cuffed
 1115 endotracheal tubes.³¹⁻³³ Also concerns exist regarding
 1116 interrater reliability that may be more significant than
 1117 with the air leak test.
 1118
 1119

1120 **Research Gaps 4A:** Is upper airway POCUS more
 1121 accurate than the air leak test at identifying patients at
 1122 high risk of subglottic UAO after extubation and
 1123 extubation failure related to UAO?
 1124

1125 **Suggested Studies 4A:** Physiologic studies directly
 1126 comparing these methods against objective measures of
 1127 UAO after extubation (given that about half of the cases
 1128 of UAO after extubation are supraglottic) could be an
 1129 important way to evaluate the initial diagnostic accuracy
 1130 of POCUS. Larger studies against clinical outcomes such
 1131 as UAO after extubation will still be limited by lack of an
 1132 objective marker to differentiate supraglottic from
 1133 subglottic disease. Outcomes such as reintubation
 1134 ultimately carry the most clinical impact, but such a
 1135 study may be impractical given the very large number of
 1136 patients that would be needed and the limited number of
 1137 potentially trained practitioners. Ultimately, if upper
 1138 airway POCUS methods are shown to have more
 1139 diagnostic accuracy than the air leak test,
 1140 implementation studies would be crucial to ensure that
 1141 the technique could be applied broadly for all patients,
 1142 with adequate training of a large number of practitioners
 1143 to perform the procedure in each ICU.
 1144
 1145

1146 **Rationale 4B:** Proper identification of patients at risk of
 1147 subglottic UAO after extubation allows administration
 1148 of systemic corticosteroids to prevent subglottic UAO
 1149 after extubation, potentially reducing the risk of
 1150 extubation failure. The guidelines suggest that
 1151 dexamethasone administration initiated at least 6 h
 1152 before elective extubation may be beneficial in
 1153 decreasing subglottic UAO after extubation, particularly
 1154 in high-risk patients.^{1,2}
 1155

The clinical guidelines identified eight RCTs that served
 as the basis for a subsequent pairwise and network
 meta-analysis.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.
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1175 **Research Gaps 4B:** For patients with uncuffed
 1176 endotracheal tubes, should corticosteroids be prescribed
 1177 if no other risk factors for UAO after extubation are
 1178 identified (ie, airway trauma, inappropriately large
 1179 endotracheal tube)? For patients at high risk of
 1180 extubation failure resulting from causes other than UAO
 1181 (ie, respiratory muscle weakness) who have an
 1182 indeterminant risk of UAO after extubation (ie,
 1183 uncuffed endotracheal tube), should corticosteroids be
 1184 used to lower the risk of reintubation?
 1185

1186 **Suggested Studies 4B:** An RCT of patients at high risk
 1187 of UAO after extubation focused on the outcome of
 1188 reintubation may be clinically important, although
 1189 multiple RCTs have confirmed that it is useful to reduce
 1190 the rates of UAO after extubation. Reducing UAO after
 1191 extubation in itself is important clinically, given that
 1192 UAO is distressing to the patient and their family, may
 1193 lead to additional therapeutics and longer ICU stay, and
 1194 may be associated with long-term adverse outcomes.³⁴
 1195 Hence, this RCT may be a lower priority, given the
 1196 results of the network meta-analyses.
 1197
 1198

1199 Significantly more uncertainty in what to do about
 1200 corticosteroids in patients with indeterminant risk of
 1201 UAO after extubation remains (ie, uncuffed
 1202 endotracheal tubes). Here an RCT is likely warranted,
 1203 with comparison of corticosteroids started at least 6 h
 1204 before extubation against placebo in children with
 1205 uncuffed endotracheal tubes. Additional stratification
 1206 based on risk factors for extubation failure (ie, using
 1207 PiMax) is important to evaluate potential heterogeneity
 1208 in treatment effect, particularly for the outcome of
 1209 reintubation (Table 3).
 1210

1211 *NRS After Extubation*

1212 **Rationale 5A:** Planned NRS (NRS started immediately
1213 after extubation) frequently is used in children to reduce
1214 the risk of extubation failure. The guidelines suggest
1215 using planned NRS over conventional oxygen therapy in
1216 children considered at high risk of extubation failure.¹
1217 The list of risk factors of extubation failure was based on
1218 previously published studies and expert opinion; one key
1219 risk factor identified in previous literature is prolonged
1220 IMV before extubation.³⁵ However, a paucity of
1221 contemporary multicenter observational studies is
1222 available to describe the risk of extubation failure
1223 accurately in different patient groups and to identify
1224 specific causes of extubation failure. This is particularly
1225 relevant because the PICU population has changed over
1226 the past decade, with a rising prevalence of patients with
1227 complex chronic conditions, in whom the risk of
1228 extubation failure may be greater.³⁶

1232 **Research Gaps 5A:** What factors should be used to
1233 identify patients who are at high risk of extubation
1234 failure for whom prophylactic extubation to NRS may be
1235 warranted?
1236

1237 **Suggested Studies 5A:** Given many potential risk factors
1238 for extubation failure, individual RCTs in
1239 subpopulations are not really feasible. In this case, large
1240 observational studies with causal inference techniques or
1241 quasirandomized trials with QI methodology may be
1242 able to answer this question. In contemporary practice,
1243 the use of prophylactic NRS is practitioner and
1244 institution dependent, with very few protocols in place
1245 to define the population likely to benefit. Analysis of
1246 observational data may be helpful to identify the
1247 population at high risk of extubation failure, while
1248 capitalizing on the variability in treatment decisions by
1249 using causal inference methods to identify who benefited
1250 from prophylactic extubation to NRS. Furthermore,
1251 studying a protocol to use prophylactic NRS before and
1252 after implementation in a population deemed high risk
1253 can evaluate which subsets of patients (ie, which risk
1254 factors) benefited the most from prophylactic NRS.
1255 PiMax may be an important element to stratify patients
1256 into standard vs high risk of extubation failure, given
1257 that patients with impaired respiratory muscle capacity
1258 are at higher risk of extubation failure.²⁹ An additional
1259 important element of such a study includes protocols for
1260 de-escalating NRS or weaning patients from it, because
1261 prophylactic use of NRS in fact may prolong ICU stay if
1262 it is not discontinued or patients weaned from it in a
1263 timely fashion.
1264
1265

Rationale 5B: Different methods of NRS are available, 1266
with high-flow nasal cannula and CPAP being the most 1267
frequently used.³ Bilevel positive airway pressure is used 1268
less frequently, but offers ventilatory assistance, which 1269
may be important in children with neuromuscular 1270
disease or ICU-associated muscle weakness. Only one 1271
large RCT has compared high-flow nasal cannula with 1272
CPAP after extubation so far³⁷ and showed that the time 1273
to liberation from respiratory support was shorter in the 1274
CPAP group, with a subgroup analysis indicating that 1275
this was most notable in infants. This informed the 1276
guideline recommendation that CPAP is suggested to be 1277
used as the first-line NRS method for children younger 1278
than 1 year. However, half of the children recruited in 1279
that RCT were infants, and only small numbers of 1280
children had cardiac disease or immunosuppression. 1281
The relative risk to benefit ratio of CPAP as the first NRS 1282
method in specific subgroups remains unclear, especially 1283
in children who require ventilatory assistance. The 1284
increasing prevalence of children with complex 1285
comorbid conditions, including neurologic and 1286
neuromuscular diseases, makes this even more 1287
important. 1288
1289
1290

Research Gaps 5B: What method of NRS should be 1291
used as the first-line therapy and how does this differ 1292
based on risk factors of extubation failure (ie, respiratory 1293
muscle weakness, residual pulmonary disease, upper 1294
airway obstruction). 1295
1296

Suggested Studies 5B: An RCT should be conducted in 1297
children considered at high risk of extubation failure 1298
comparing the initiation of planned high-flow nasal 1299
cannula vs bilevel positive airway pressure on extubation 1300
outcomes. Stratification of these patients can be carried 1301
out using the list published in the guidelines and data 1302
can be obtained from multicenter QI collaborations, in 1303
addition to using PiMax obtained before extubation. 1304
Planned subgroup analysis can look at different patient 1305
populations (eg, those who have undergone cardiac 1306
surgery, those who are immunocompromised, those 1307
with neuromuscular disease), ages, and centers 1308
(Table 3). 1309
1310
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1312 *Sedation Assessment*

Rationale 6A: Evaluation of the level of sedation, cough 1313
effectiveness, and capacity to manage oropharyngeal 1314
secretions before extubation was suggested as part of 1315
ERT bundle by the guidelines, and evaluation of level of 1316
sedation in the periextubation period also was suggested 1317
by the 2022 Society of Critical Care Medicine PANDEM 1318
guidelines.³⁸ 1319
1320

1321 Two large well-conducted RCTs studied the impact of
 1322 sedation assessment on pediatric ventilator liberation
 1323 (namely, IMV duration).^{14,39} Although sedation level
 1324 was a key component of both trials, complexity between
 1325 sedation assessment or titration and other human factor
 1326 components of ventilator weaning and extubation in
 1327 children remains. Both RCTs used bundled
 1328 interventions (including sedation assessment and
 1329 management in addition to an ERT component), so it is
 1330 unclear which one of the bundle components are more
 1331 important to decrease IMV duration, and neither trial
 1332 showed a large effect on IMV duration for the
 1333 intervention. Neither trial examined the impact of
 1334 delirium, partly because of a lack of validated assessment
 1335 tools being used at that time.

1337 **Research Gaps 6A:** What is the effect of delirium on
 1338 pediatric ventilator liberation outcomes?

1339 **Suggested Studies 6A:** Observational studies focused on
 1340 extubation outcomes should incorporate delirium
 1341 assessment tools in the periextubation period to identify
 1342 if delirium has an independent effect on extubation
 1343 outcomes (IMV duration and extubation failure).

1344 Conclusions

1345 Substantial research gaps exist in the field of pediatric
 1346 ventilator liberation, and although RCTs certainly are
 1347 needed in many areas, high-quality observational studies
 1348 and quasirandomized trials also are important to
 1349 improve the level of certainty behind some of the
 1350 recommendations and to establish firmer guidelines for
 1351 what truly constitutes high-risk patients in whom
 1352 different therapies or strategies may be warranted
 1353 around the time of ventilator liberation.

1354 Furthermore, for the interventions that are ready for an
 1355 RCT, a platform trial focused on pediatric patients who
 1356 have been receiving ventilation for > 24 h may be ideal.
 1357 In pediatric critical care, many challenges exist to
 1358 conducting well-powered multicenter RCTs, including
 1359 heterogeneity of patient populations, relative paucity of
 1360 patients available to study, and recreation of clinical trial
 1361 infrastructure for each study, greatly increasing costs. A
 1362 multicenter platform trial would increase efficiency and
 1363 would enable simultaneous testing of multiple
 1364 interconnected elements of pediatric ventilator
 1365 liberation, iterative cycling through promising
 1366 interventions in each domain area of ventilator
 1367 liberation, and risk-based enrollment strata with
 1368 borrowing techniques between groups to estimate
 1369 treatment effects better.⁴⁰ Although platform trials

1370 certainly are an attractive option to improve efficiency,
 1371 to increase patient recruitment, and to decrease cost,
 1372 they do add an extra layer of complexity during study
 1373 design, need alternative methods for funding, and
 1374 require unique expertise for adaptation and data
 1375 analysis.⁴¹

1376 We hope these guidelines can set the stage for research
 1377 in pediatric ventilator liberation, but acknowledge
 1378 important limitations with our approach.

1379 Fundamentally, a great deal of expert opinion remains in
 1380 this article, particularly related to potential study designs
 1381 and methods to answer these questions. In addition, the
 1382 priorities initially were identified by a small group of
 1383 international experts, and we had limited patient and
 1384 family representation in the process. We have tried to
 1385 add rigor to this document and process by basing the
 1386 gaps on systematic review, presentation of gaps to an
 1387 international community of pediatric intensive care
 1388 practitioners and investigators for feedback, and iterative
 1389 refinement based on feedback the larger community.

1390 In conclusion, we have presented several crucial research
 1391 gaps in pediatric ventilator liberation and have proposed
 1392 a conceptual map for how to think about these gaps.
 1393 This is coupled with suggested methods and study
 1394 designs to address these gaps, taking into consideration
 1395 the use of study designs outside of traditional RCTs
 1396 when they may be applicable. Nevertheless, several
 1397 crucial areas should be a focus for multicenter RCTs.

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