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On behalf of Pediatric Ventilator Liberation Consensus Conference Expert Panel and the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network

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Abbreviation List

BPAP	Bi-level positive airway pressure
CICU	Cardiac intensive care unit
CPAP	Continuous positive airway pressure
Pocc	Expiratory occlusion pressure
ERT	Extubation readiness testing
FiO2	Faction of inspired oxygen
GCS	Glasgow coma scale
HFNC	High flow nasal cannula
ICU	Intensive care unit
IMV	Invasive mechanical ventilation
LOS	Length of stay
NRS	Non-invasive respiratory support
OI	Oxygenation index
OSI	Oxygenation saturation index
PALICC-2	Second Pediatric Acute Lung Injury Consensus Conference
PALISI	Pediatric Acute Lung Injury and Sepsis Investigators
PEEP	Positive end expiratory pressure
PICO	Population, Intervention, Comparator, Outcome
PICU	Pediatric intensive care unit
PiMax	Maximal inspiratory pressure during airway occlusion
PIP	Peak inspiratory pressure
POCUS	Point of care ultrasound
PS	Pressure support
QI	Quality improvement
RCT	Randomized controlled trial
SBS	State behavioral scale
SBT	Spontaneous breathing trial
SpO2	oxygen saturation
UAO	Upper airway obstruction
Vt	Tidal volume

Abstract (292/300 words):

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, due to 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 8 pre-defined 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 (PALISI) meeting in Spring 2022 for open discussion, feedback was incorporated, and final evaluation of research gaps are summarized in this document. While randomized trials trials (RCTs) represent the highest level of evidence, the panel sought to highlight areas where alternative study designs may also be appropriate, given challenges with conducting large multi-center RCTs in children.

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

Interpretation:
While pediatric ventilator liberation guidelines have been created, the certainty of evidence remains low and there are multiple research gaps which should be filled through high quality RCTs, and multi-center observational studies and quality improvement initiatives.

Introduction:
Liberation from invasive mechanical ventilation (IMV) (i.e. extubation) is a daily practice in pediatric intensive care units (PICUs) and pediatric cardiac intensive care units (CICUs) worldwide. The first international guidelines for pediatric ventilator liberation were published in 2023 and had 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 due, in large part, to the lack of high-quality studies. The aim of this manuscript is to systematically summarize 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 (PICO) questions were identified related to important aspects of pediatric ventilator liberation. A group of 26 international multi-professional experts were divided into five subgroups to perform literature review in each sub-section and craft recommendations. During the synthesis of the evidence, the experts identified key research gaps in each of these sub-sections. Subsequently, each subsection presented what they felt were the most pressing research gaps to the pediatric critical care community during a symposium at the Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network Spring 2022 Meeting. The symposium was attended by 51 pediatric intensive care practitioners in person, and 65 who attended virtually, many with expertise in pediatric mechanical ventilation because the research priorities for the second Pediatric Acute Lung Injury Consensus Conference (PALICC-2) were also presented. Detailed transcription was performed for the entire meeting, and there was open discussion about 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 which could address the gaps. The purpose of this document is to provide a framework or outline to help investigators seeking to improve the knowledge base in pediatric ventilator liberation. There was no specific voting process to rank the gaps (i.e. 1,2,3) because all were felt 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. While randomized controlled trials (RTCs) represent the highest level of evidence, they require substantial funding, regulatory structure, and collaboration with large multi-center networks. Certainly, each of the research gaps may be answered with a large multi-center RCT, but, when appropriate, the panel sought to highlight areas where alternative study designs may also be considered, given challenges with conducting large multi-center RCTs in children. Hence, the panelists sought to highlight the research gaps where very substantial investment in the form of multi-center 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 felt that when studying short- 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. While our focus is on circumstances around the ventilator liberation attempt, the outcomes are influenced by the entire ventilator course. A conceptual map tying key elements or principles which are important for ventilator liberation to other phases of IMV was initially drafted by a subgroup of panelists including a representative from each of the PICO questions/ subgroups, the lead and senior

author, and methodologist. This was then presented and edited by all authors during manuscript review and revisions. As part of the main guidelines, detailed literature review was conducted and panelists extracted risk factors for extubation failure. These risk factors were then 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 which were felt 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 which may impact short- or long-term outcomes. These short- 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 peri-extubation corticosteroids. However, the risk for UAO and the response to corticosteroids may also 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 which are not in the direct scope of the guidelines but may influence short- and long-term outcomes.

Research Gaps:
In the following sections we will summarize the research gaps and priorities related to different elements covered by the pediatric ventilator liberation guidelines.

1. Extubation Readiness Testing (ERT) Screening and Bundle

Rationale 1a:
The expert panel had 100% agreement that ERT safety screening should be performed for children intubated for more than 24 hours. 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 could also incrementally increase the burden on bedside providers [15]. However, we found no RCTs comparing frequency of ERT screening (once a day vs more frequent evaluations). Simple checklists with training of the providers might help avoid excessive burden on bedside providers and increase adherence [8,10,11], as adherence can be quite low even amongst trained providers [12]. Alerts in electronic clinical records and/or computer driven protocols 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 (i.e. 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:
Multi-center 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

(LOS) and hospital LOS [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**). The optimal ventilator settings that trigger an ERT [i.e. positive end expiratory pressure (PEEP), fraction of inspired oxygen (FiO2), peak inspiratory pressure (PIP)] 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:
While 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 (**Figure 1**). For example, different PEEP thresholds (6 vs 8 vs 10 cmH2O) and PIP thresholds (20 vs 25 vs 30 cmH2O) can be tested in different centers comparing patients-centered extubation outcomes (i.e. extubation failure and IMV duration).

Rationale 1c:
ERT bundles have been shown to improve extubation outcomes, but there are remaining important questions 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 sub-populations at high-risk of extubation failure?

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

this is commonly assessed clinically, there is variability in this assessment which is practitioner and patient dependent. Alternative methods to directly evaluate respiratory effort or work of breathing such as esophageal manometry (invasive) or airway occlusion maneuvers (Pocc, non-invasive) or diaphragm ultrasound (thickening fraction) should be investigated [17].

2. 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 continuous positive airway pressure (CPAP) or CPAP alone during SBTs in mechanically ventilated children at standard risk of extubation failure. For those at high-risk of extubation failure, it suggests 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 post-extubation 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 non-inferiority trial that was published after the guidelines showed that a two hours PS augmented SBT was non-inferior to CPAP alone SBT in predicting successful liberation from IMV, although the number of "high-risk" patients in this study is unclear [22]. Nonetheless, there are few studies evaluating 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 minutes or 60–120 minutes depending on the patient's risk of extubation failure. Obviously, a shorter SBT will likely result in more patients passing the SBT but likely a higher extubation failure rate. In contrast, a longer SBT will likely result in lower rates of extubation failure. Since the publication of the guidelines, a single center observational study showed that a 30-minute SBT might be too short in children recovering from pediatric acute respiratory distress syndrome as many go on to fail between 30 and 120 minutes [23]. Another observational study showed similar extubation failure rates for one hour and two hours SBTs in a general PICU population [24]. However, there are no pediatric RCTs that 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 2 a & b:

Since the SBT method and duration are intimately linked, a potential design may include a two-by-two factorial RCT. Comparator groups could include (1) a PS-augmented to CPAP alone SBT and (2) a 30 minute SBT to a 120 minute SBT focused on patient- centered clinical outcomes; i.e extubation failure and IMV duration. Enrollment can be stratified based on extubation failure risk (standard vs high-risk). Corresponding PICO questions are summarized in **Table 3**.

Rationale 2c:
Lastly, the guidelines did not specify objective criterion for passing a SBT and if this should be adjusted for certain high-risk populations (i.e. patients with myocardial dysfunction, neurologic impairment, neuromuscular disease, 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? And what is the optimal threshold of each of these criteria?

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/ERT success rate, extubation failure and IMV duration. Modifications of items included in these criteria and thresholds can be subsequently 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, as there are also a multitude of other factors which clinicians consider 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].

3. Measures of Respiratory Muscle Strength/Function

Rationale 3a:
The guidelines suggest the use of maximal inspiratory pressure during airway occlusion (PiMax) as an element of an ERT bundle in critically ill children with risk factors for muscle weakness and/or extubation failure. The guidelines did not recommend a specific cut-off value of PiMax. Moreover, an international survey of pediatric critical care providers showed that PiMax is not commonly utilized [28]. There are no RCTs which have shown the impact of using a PiMax threshold to inform extubation decisions. However, existing studies support there is likely a dose dependent relationship of PiMax and re-intubation risk, so PiMax should be considered together with other variables which may make the patient at high-risk for extubation failure [29]. For example, a PiMax of 25 cmH2O 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 for 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 non-invasive respiratory support (NRS) prophylactically.

Research Gaps 3a:
How should PiMax information, gathered as part of an ERT, be used to improve extubation decisions? Is there a clear cut-off PiMax that defines patients at high-risk of extubation failure where prophylactic extubation to NRS would be helpful?

Suggested Studies 3a:
Because PiMax is infrequently measured in routine clinical practice, the first step likely involves gathering multi-center observational data with routine use of PiMax which can be used to evaluate the independent effect that PiMax has on extubation outcomes. Furthermore, high quality observational

data can also 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 (i.e. an interaction). This may lend itself well to large multicenter QI collaborations where 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 peri-extubation 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:
While the guidelines focus on assessing the respiratory muscle capacity using PiMax, there are other potential measures of respiratory muscle strength/function 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 between all these parameters if measured simultaneously may also be helpful.

4. Post-extubation UAO Risk Assessment and Prevention
Rationale 4a:
Identification of patients at high-risk of post-extubation subglottic UAO for whom the prophylactic administration of corticosteroids may be helpful is important because at least one third of all extubation failures are attributed to post-extubation UAO [30]. The guidelines suggest the use of the air leak test in pediatric patients with cuffed endotracheal tubes to assess the risk of post-extubation subglottic UAO [1]. However, the air leak test has limitations related to inter-rater reliability and was not shown to be predictive of post-extubation UAO 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 there remains a relative paucity of pediatric data, and this method similarly is meant for cuffed endotracheal tubes [31-33]. There are also concerns with inter-rater reliability which 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 for post-extubation subglottic UAO and extubation failure related to UAO?

Suggested Studies 4a:
Physiologic studies directly comparing these methods against objective measures of post-extubation UAO (given that about half of the cases of post-extubation UAO are supraglottic) could be an important way to evaluate the initial diagnostic accuracy of POCUS. Larger studies against clinical outcomes such as

post-extubation UAO will still be limited by lack of an objective marker to differentiate supraglottic from subglottic disease. Outcomes such as re-intubation are ultimately the most clinically impactful, 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 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 post-extubation subglottic UAO allows administration of systemic corticosteroids to prevent post-extubation subglottic UAO, potentially reducing the risk of extubation failure. The guidelines suggest that dexamethasone administration initiated at least 6 hours before elective extubation may be beneficial in decreasing post-extubation subglottic UAO, particularly in high-risk patients [1,2].

The clinical guidelines identified eight RCTs, which served as the basis for a subsequent pairwise and network metanalysis [2]. The data demonstrate that timing of administration is likely most important (at least 6 but optimally 12 hours) prior to extubation. If such a time window is not available, then higher dose corticosteroids are likely preferable than low dose. Of note, the meta-analysis did show benefit for the outcome of UAO, but not directly for re-intubation. Because corticosteroids should be started at least 6 hours prior to extubation, an unintended consequence can be unnecessary delay in extubation, which prompted the guideline committee to specifically suggest targeted use in patients at high-risk for UAO. Given the lack of diagnostic accuracy for the air leak test with uncuffed endotracheal tubes, there remains uncertainty 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 there are no other identified risk factors for post-extubation UAO (i.e. airway trauma, inappropriately large endotracheal tube)? For patients at high-risk of extubation failure from causes other than UAO (i.e. respiratory muscle weakness) who have an indeterminant risk for post-extubation UAO (i.e. uncuffed endotracheal tube), should corticosteroids be used to lower the risk of re-intubation?

Suggested Studies 4b:
An RCT in patients at high-risk of post-extubation UAO focused on the outcome of re-intubation may be clinically important, although multiple RCTs have confirmed it is useful to reduce the rates of post-extubation UAO. Reducing post-extubation UAO is in itself clinically important 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 outcome [34]. Hence this RCT may be lower priority, given the results of the network meta-analyses.

There remains significantly more uncertainty in what to do about corticosteroids in patients with indeterminant risk of post-extubation UAO (i.e. uncuffed endotracheal tubes). Here an RCT is likely warranted, with comparison of corticosteroids started at least 6 hours prior to extubation against placebo in children with uncuffed endotracheal tubes. Additional stratification based on risk factors for extubation failure (i.e. using PiMax) would be important to evaluate potential heterogeneity in treatment effect, particularly for the outcome of re-intubation (**Table 3**).

5. Post-extubation NRS

Rationale 5a:

Planned NRS (NRS started immediately after extubation) is frequently 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 prior to extubation [35]. However, there is a paucity of contemporary multicenter observational studies to accurately describe the risk of extubation failure in different patient groups and to identify specific causes of extubation failure. This is particularly relevant since 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. Here large observational studies with causal inference techniques, or quasi-randomized 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 pre- post-implementation of a protocol to use prophylactic NRS in a population deemed high-risk can evaluate which subsets of patients (i.e. 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 or weaning NRS, as prophylactic use of NRS may in fact prolong ICU stay if it is not weaned or discontinued in a timely fashion.

Rationale 5b:

There are different modalities of NRS, high flow nasal cannula (HFNC) and CPAP being the most frequently used [3]. Bi-level positive airway pressure (BPAP) is used less frequently but offers ventilatory assistance, which may be important in children with neuromuscular disease or ICU-associated muscle weakness. There has only been one large RCT comparing HFNC with CPAP following extubation so far [37], which showed that the time to liberation from respiratory support was shorter in the CPAP group, with a subgroup analysis indicating that this was most noticeable in infants. This informed the guideline recommendation that CPAP is suggested to be used as the first line NRS mode for children less than one year of age. 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-benefit ratio of CPAP as the first NRS mode in specific subgroups is still unclear, especially in children who require ventilatory assistance. The increasing prevalence of children with complex co-morbid conditions including neurological and neuromuscular diseases makes this even more important.

Research Gaps 5b:
What mode of NRS should be used as the first line therapy, and how does this differ based upon risk factors of extubation failure (i.e. 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 HFNC vs BPAP on extubation outcomes. Stratification of these patients can be done using the list published in the guidelines and data obtained from multicenter QI collaborations, in addition to using pre-extubation PiMax. Planned subgroup analysis can look at different patient populations (e.g., post-cardiac surgery, immunocompromised, neuromuscular disease), age and center (**Table 3**).

6. Sedation Assessment

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

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, there is still a complexity between sedation assessment/titration and other human factor components of ventilator weaning and extubation in children. 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 due to 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 peri-extubation period to identify if delirium has an independent effect on extubation outcomes (IMV duration and extubation failure).

Conclusions:
There are substantial research gaps in the field of pediatric ventilator liberation, and while RCTs are certainly needed in many areas, high quality observational studies and quasi-randomized trials are also important to improve the level of certainty behind some of the recommendations and 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 which are ready for an RCT, a platform trial focused on pediatric patients who have been ventilated for more than 24 hours may be ideal. In pediatric critical care, there are many challenges to conducting well powered multi-center RCTs including heterogeneity of patient populations, relative paucity of patients available to study, and re-creation of clinical trial infrastructure

for each study, greatly increasing costs. A multi-center platform trial would increase efficiency and 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 better estimate treatment effects [40]. While platform trials are certainly an attractive option to improve efficiency, increase patient recruitment and 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 this document can set the stage for research in pediatric ventilator liberation but acknowledge important limitations with our approach. Fundamentally, there remains a great deal of "expert opinion" in this manuscript, particularly related to potential study designs and methods to answer these questions. In addition, the priorities were initially 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 on 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, there are several crucial areas which should be a focus for multi-center RCTS.

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Figure legends

Figure 1: Conceptual Framework of Invasive Mechanical Ventilation Phases and ERT Safety Thresholds

(1) Escalation Phase, (2) Plateau Phase, (3) De-escalation Phase, (4) Liberation Phase

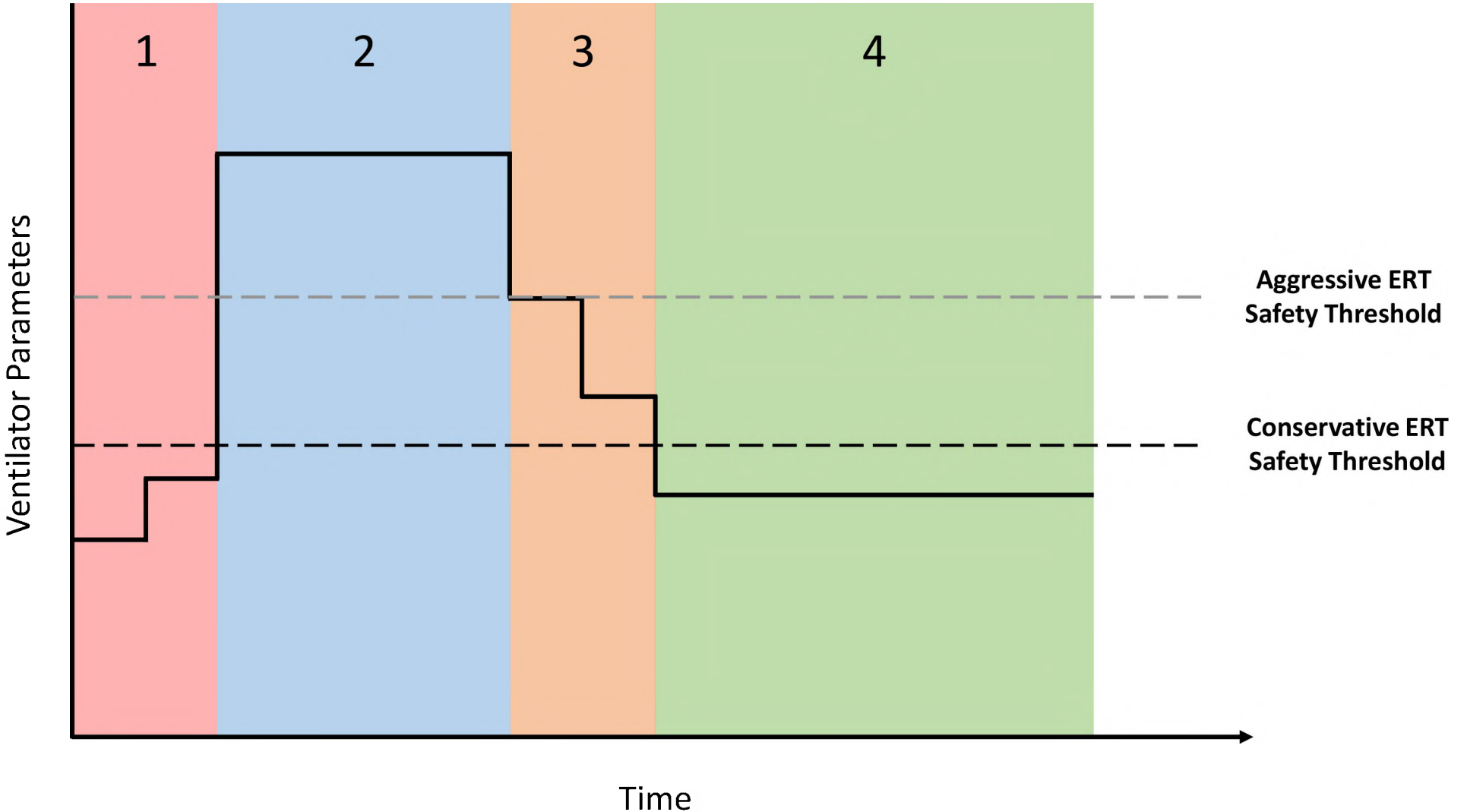
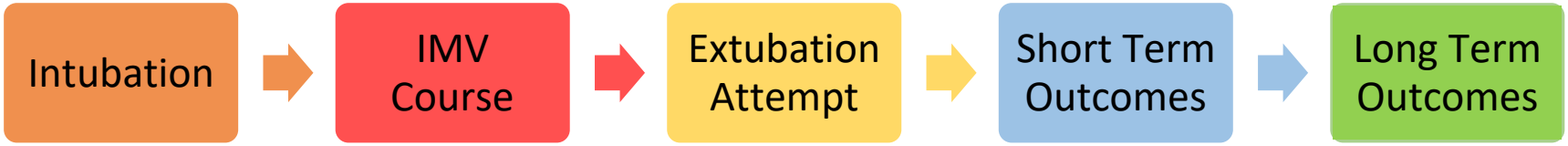

1
2
3
4
Ventilator Parameters
Aggressive ERT
Safety Threshold
Conservative ERT
Safety Threshold
Time

Table 1: Conceptual Map for Pediatric Ventilator Liberation*



A. Subglottic Upper Airway Obstruction

ETT size ETT type (cuffed/uncuffed) Intubation process and number of attempts	ETT cuff management Agitation (**sedation** & delirium) Fluid overload Acquired vocal cord paralysis	**Air leak test** **Peri-extubation corticosteroids** **Post-extubation NRS use**	UAO Extubation failure due to UAO **Post-extubation NRS use** New tracheostomy placement VFDs-28 ICU LOS Hospital LOS Mortality	Subglottic stenosis or other airway anomalies New tracheostomy placement PICS-P

B. Respiratory Muscle Strength (Respiratory Capacity)

Use of NRS prior to intubation Decision to intubate and timing of intubation Pre-existing respiratory muscle weakness	VIDD **Sedation assessment/ management** Delirium assessment/ management NMB use Fluid overload Nutrition and electrolytes Ventilator management Early mobilization Acquired diaphragm paresis	**PiMax** Diaphragm ultrasound **Post-extubation NRS use** **ERT systematic screening** **SBT method** **SBT duration** **Sedation assessment/ management** Delirium assessment/ management	Extubation failure due to respiratory muscle weakness **Post-extubation NRS use** 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)

C. Respiratory Load

Use of NRS prior to 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 **Post-extubation NRS use**	Extubation failure due to lung disease **Post-extubation NRS use** VFDs-28 ICU LOS Hospital LOS Mortality	Prolonged NRS use New tracheostomy placement Long term ventilation PICS-P

D. Cardiac Load:

Use of NRS prior to 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 (i.e. perfusion, lactate, NIRS, CVP, echocardiogram, dead space fraction) **Post-extubation NRS**	Extubation failure **Post-extubation NRS use** VFDs-28 ICU LOS Hospital LOS Mortality	Prolonged NRS use New tracheostomy placement Long term ventilation Heart transplantation Ventricular assist device PICS-P

E. Neuropsychological Factors:

Use of NRS prior to intubation Decision to intubate and timing of intubation Central drive Neurologic control of the airway	**Sedation assessment/ management** Delirium assessment/ management	**Sedation assessment/ management** Delirium assessment/ management Withdrawal assessment/ management **Ability to control oropharyngeal secretions** Spasticity	Extubation failure **Post-extubation NRS use** VFDs-28 ICU LOS Hospital LOS Mortality	Prolonged NRS use New tracheostomy placement Long term ventilation PICS-P

***Topic covered by the pediatric ventilator liberation guidelines and research priorities are written in Bold.**

CVP: central venous pressure; ERT: extubation readiness testing; ETT: endotracheal tube; ICU: intensive care unit; LOS: length of stay; NIRS: near infrared spectroscopy; NMB: neuromuscular blockade; NRS: non-invasive respiratory support; PICS-P: post intensive care syndrome in pediatrics; PiMax: maximal inspiratory pressure during airway; SBT: spontaneous breathing trial; VAE: ventilator-associated event; VFDs: ventilator free days; 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[7]	Foronda[8]	Jouvet[9]	Faustino[10]	Abu-Sultaneh[11]	Ferreira[13]	Loberger[15]
Clinical	No increased ventilator support in the last 24 hrs No planned operative procedures in the next 12 hrs	An absence of new infiltrates on the chest radiograph		A decrease and/or plateau in ventilator support over the previous 12 hrs The acute phase of acute lung injury ends	No increase of ventilator support in the last 24 hrs No planned procedures in the next 12 hrs	CXR no signs of significant pulmonary congestion or pleural effusion Excluded patients with preoperative mechanical ventilation, and uncontrolled pulmonary hypertension	No increase in ventilator settings ≤ 12 hrs No planned sedated/surgical procedures In the next 24 hrs
IMV settings & gas exchange	FiO2 ≤ 0.6 PEEP ≤ 7 pH 7.32-7.47	FiO2 ≤ 0.5 PEEP ≤ 8 PIP ≤ 25	FiO2 0.6 SpO2 ≥ 95 % PEEP ≤ 8 Plateau pressure ≤ 25	OI or OSI < 6	FiO2 ≤ 0.50 SpO2 ≥ 92% PEEP ≤ 6 PIP ≤ 25 Vt 6-8 ml/kg	FiO2 ≤ 0.50 SpO2 > 90% after total corrections or 75% - 85% after palliative operations positive PEEP ≤ 5 PIP ≤ 20 pH >7.3	FiO2 ≤ 0.5 PEEP ≤ 6 PS ≤ 10 PIP ≤ 30 Vt > 5 ml/kg
Oxygen availability /consumption		Hemodynamic stability (doses of sodium nitroprusside,	No vasopressor or inotrope medication [other than		Hemodynamic stability	Hemodynamic stability (dopamine < 10 µg/kg/min	One or less vasoactive infusions and no increases ≤ 12 hrs

		dopamine, or dobutamine < 10 µg/kg/min) Hemoglobin ≥ 8 g/dL	digoxin or low-dose dopamine (≤5 µg/kg/min)]		No increase of vasoactive drips for 12 hrs	or epinephrine < 0.1 µg/kg/min) Absence of bleeding	
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	
Neurologic/sedation level	Spontaneous breathing Level of consciousness acceptable for extubation	Spontaneous breathing No continuous Sedation No use of neuromuscular blockers in the last 24 hrs	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

FiO2 Fraction of inspired oxygen; GCS: Glasgow coma scale; OI oxygenation index; OSI: oxygenation saturation index; PEEP: positive end expiratory pressure; PIP: peak inspiratory pressure; SBS: state behavioral scale; SpO2: oxygen saturation; Vt: tidal volume.

Table 3: Suggested Randomized Control Trials:

A. SBT Method and Duration

a. In children receiving IMV for more than 24 hours should SBTs be performed with PS augmentation?
P: Children who are intubated for more than 24 hours undergoing an extubation attempt (stratified into standard risk vs high-risk of extubation failure)
I: SBT with CPAP of 5 cmH_2O without PS augmentation
C: SBT with CPAP of 5 cmH_2O and PS augmentation between 5-10 cmH_2O
O: Primary: IMV duration
Secondary: SBT success rate, extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU

b. In children receiving IMV for more than 24 hours should SBTs be performed for 30 minutes or 120 minutes?
P: Children who are intubated for more than 24 hours undergoing an extubation attempt (stratified into standard risk vs high-risk of extubation failure)
I: 30 minutes SBT
C: 120 minutes SBT
O: Primary: IMV duration
Secondary: SBT success rate, extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU

B. Post-extubation UAO Risk Assessment and Prevention

- In children receiving IMV for more than 24 hours with indeterminant risk of post-extubation UAO (i.e. uncuffed endotracheal tube), should corticosteroids be given prior to the extubation attempt?
P: Children who are intubated for more than 24 hours with indeterminant risk of post-extubation UAO 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 (max of 10 mg) started at least 6 hours prior to planned extubation attempt.
C: Placebo
O: Primary: IMV duration
Secondary: UAO rate, extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU

C. Post-extubation NRS

- In children receiving IMV for more than 24 hours who are considered at high-risk of extubation failure, should planned BiPAP be used immediately after extubation?
P: Children who are intubated for more than 24 hours and considered at high-risk of extubation failure undergoing extubation attempt (stratified by age and PiMax)
I: Planned post-extubation BiPAP
C: Planned post-extubation HFNC
O: Primary: IMV duration
Secondary: extubation failure, ICU LOS, hospital LOS
Setting: PICU, CICU