Executive Summary: International Clinical Practice Guidelines for Pediatric Ventilator liberation, A PALISI Network Document

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1

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Running title: Pediatric ventilator liberation guidelines

At a Glance Commentary:

Scientific Knowledge on the Subject

While there have been several studies focused on aspects of pediatric ventilator liberation, there are no clear clinical practice guidelines, which contributes to unnecessary variability in practice.

What this study adds to the field

These evidence-based guidelines provide a framework to use when evaluating a pediatric patient for ventilator liberation. Evidence has been synthesized in nine key topics, with 15 recommendations surrounding screening and conduct of spontaneous breathing trials and extubation readiness tests, measurements of respiratory muscle strength, evaluating for risk of

post-extubation upper airway obstruction and its prevention, use of post-extubation

noninvasive respiratory support, and sedation assessment.

Author Contributions:

All authors contributed to the conception or design of the work, or the acquisition, analysis, or

interpretation of data for the work. All authors participated in drafting the work or revising it

critically for important intellectual content and have approved and are responsible for the final

version submitted for publication.

**This clinical practice guideline was endorsed by the American Thoracic Society on July 27,
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This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org

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Abstract: (249/250 words)

Rationale:

Pediatric specific ventilator liberation guidelines are lacking despite the many studies exploring elements of extubation readiness testing. The lack of clinical practice guidelines has led to significant and unnecessary variation in methods used to assess pediatric patients' readiness for extubation.

Methods:

Twenty-six international experts comprised a multi-professional panel to establish pediatric specific ventilator liberation clinical practice guidelines, focusing on acutely hospitalized children receiving invasive mechanical ventilation for more than 24 hours. Eleven key questions were identified and first prioritized using the Modified Convergence of Opinion on Recommendations and Evidence. Systematic review was conducted for questions which did not meet an a-priori threshold of ≥80% agreement, with Grading of Recommendations, Assessment, Development, and Evaluation methodologies applied to develop the guidelines. The panel evaluated the evidence, drafted, and voted on the recommendations.

Measurements and Main Results:

Three questions related to systematic screening, using an extubation readiness testing bundle and use of a spontaneous breathing trial as part of the bundle met Modified Convergence of Opinion on Recommendations criteria of ≥80% agreement. For the remaining 8 questions, 5 systematic reviews yielded 12 recommendations related to the methods and duration of

spontaneous breathing trials; measures of respiratory muscle strength; assessment of risk of

post-extubation upper airway obstruction and its prevention; use of post-extubation non-

invasive respiratory support; and sedation. Most recommendations were conditional and based

on low to very low certainty of evidence.

Conclusion:

This clinical practice guideline provides a conceptual framework with evidence-based

recommendations for best practices related to pediatric ventilator liberation.

Abstract word count: 249

Introduction:

Pediatric critical care providers balance minimizing invasive mechanical ventilation (IMV)

duration against the risk of extubation failure and its associated morbidities (1-3). Adult clinical

practice guidelines for IMV liberation have been published (4). While there have been several

observational and interventional studies related to aspects of pediatric ventilator liberation,

most of the pediatric literature is limited to narrative reviews and meta-analyses (5-9). There is

also significant practice variation and limited adoption of ventilator liberation protocols in

children.(10) We sought to develop the first international pediatric specific ventilator liberation

clinical practice guidelines, focused on acutely hospitalized children receiving IMV for more

than 24 hours.

Methods:

Please refer to the online justification supplement for detailed methods and extensive

justifications for all recommendations in this Executive Summary.   The guidelines panel was a

multi-professional international group, including two co-chairs (SAS and RGK), a lead (NI) and

assistant methodologist (SKK), and 2 medical librarians (ECW, HJC). The panel included 19

pediatric intensive care specialists, 2 respiratory therapists, 4 nurses, and 1 expert in human

and translational physiology (14 from North America, 3 from South America, 7 from Europe,

and 2 from Asia). Panelists were chosen based on their publications in the area of pediatric

ventilator liberation in last 10 years. Panelists were divided into sub-groups in charge of

literature review, data extraction, and preparing draft recommendations and manuscripts for

each clinical question. The committee identified clinical questions and outcomes of importance.

As suggested by Grading of Recommendations Assessment, Development, and Evaluation (GRADE), only outcomes that were 'critical' or 'important' were used to formulate recommendations (11). Abbreviations and nomenclature are defined in detail in Table 1. As part of the modified Convergence of Opinion on Recommendations and Evidence (CORE) process, panelists were asked to select a recommendation for the intervention in each of the clinical questions: a) in favor; b) neither for nor against; c) against. Three questions had ≥80% agreement on the direction of the recommendation, which were accepted as CORE recommendations, without a formal systematic review (Figure 1) (12). For questions where consensus was not reached, we used the GRADE approach (13, 14) to identify and summarize relevant evidence, and develop recommendations for clinical practice (Figure 1).

Eight Population Intervention Comparator Outcome (PICO) questions, encompassing five comprehensive literature searches were run in MEDLINE (Ovid), Embase (Elsevier), and CINAHL Complete (EBSCOhost) in March 2021 and re-run in January 2022. Risk of bias was assessed using the Cochrane's risk of bias-2 tool for randomized trials and ROBINS-I tool for observational studies (15, 16). We used GRADEpro Guideline Development Tool online software to develop evidence profiles for each PICO question (13, 17, 18). To pool quantitative data, we performed meta-analysis using random effects models and Review Manager software (RevMan). For recommendations 9-12, we performed a random effects model network meta-analysis in Bayesian framework (19).

11

When randomized controlled trials (RCT) were available, only these were used to create the evidence profiles. Observational studies were used only when relevant outcome data was not available from RCTs (20). We used the GRADE framework to determine the certainty of evidence (21). For one question (Recommendation 6), there was no direct or indirect evidence to inform the recommendation. To provide expert opinion using a systematic process, we used the RAND-UCLA Appropriateness tool to ascertain the panel's judgment on different spontaneous breathing trial (SBT) durations for different extubation contexts (22). Recommendations were described as '**strong**' or '**conditional**' and the categorization was based on the GRADE's evidence to decision framework (11). Recommendations developed using the CORE process were considered conditional since this method does not include the rating of certainty of evidence. The implication of the strength of recommendations for different stakeholders is provided in Table 3. We offered good practice statements in the absence of direct evidence, using guidelines provided by GRADE, when it was clear that implementing the recommendation will result in large net positive effect (23). These guidelines apply to all children (age 1 day to 18 years). While many of these principles extend to pre-term neonates and young adults, ventilator liberation in those populations were not specifically covered in these guidelines. This clinical practice guideline was endorsed by the Society of Critical Care Medicine (SCCM) on June 27, 2022 and by the American Thoracic Society (ATS) on July 27, 2022.

12

Results

CORE Recommendations (Recommendations 1-3)

Recommendation 1

We suggest the use of protocolized screening compared to no screening to assess eligibility for extubation readiness testing (ERT) (CORE statement, ungraded, 100% agreement).

Remarks

Protocolized screening for eligibility for ERT should be conducted at regular intervals to identify when a patient has met pre-specified targets for physiologic parameters, ventilator settings, or pathology-specific milestones to safely conduct an ERT.

Rationale: Panelists based this recommendation using data from five RCTs (24-28), and three quality improvement (QI) studies (29-31). Most studies identified a reduction in IMV duration or time of weaning for those undergoing systematic ERT screening, ranging from several hours to several days (24, 25, 28, 31). In addition, several studies identified lower rates of extubation failure (27, 29), although many studies do not specifically separate protocolized screening from other elements of the ERT bundle. There are likely no patient-related undesirable effects with judicious screening criteria. There are potential undesirable effects related to staff burden and screening fatigue which may contribute to low rates of compliance (30), although these effects can be minimized when screening is integrated into the clinical workflow (29, 31). Some studies have observed increased use of post-extubation high flow nasal cannula (HFNC) (29-31) and non-invasive ventilation (NIV) (28, 30). Protocolized screening should include a series of physiologic parameters, ventilator targets, or pathology-specific milestones that are applied to

13

all eligible patients at regular, periodic intervals to determine whether they have reached an

appropriate point to proceed with an ERT. Examples of ERT safety screening criteria is shown in

supplemental Table E1. Screening can be conducted by any qualified member of the care team.

Recommendation 2

We suggest using a protocolized ERT bundle compared to clinical assessment of extubation

readiness (CORE statement, ungraded, 88% agreement)

Remarks

This ERT bundle includes elements that are used to assess if the patient is ready to be liberated

from IMV. In addition to a SBT, this may include factors such as assessment of sedation level,

adequacy of neurologic control of the airway (i.e. cough and gag), likelihood of post-extubation

upper airway obstruction, assessment of respiratory muscle strength, magnitude of airway

secretions, hemodynamic status, and a plan for post-extubation respiratory support.

Rationale: Panelists based this recommendation using data from three QI studies (29-31). The

implementation of a protocolized ERT bundle resulted in lower extubation failure rates

(absolute risk reduction between 3.3%-11.7%) (29, 31), with sensitivity and positive predictive

value for extubation success with the use of an ERT bundle of 90% and 94%, respectively (31).

No study demonstrated a significant difference with respect to IMV duration, but one study

observed a significant reduction in PICU length of stay (LOS) (31). Very few adverse effects were

reported following the implementation of an ERT bundle (29), with similar rates of unplanned

extubation between those subjects managed with and without extubation readiness protocols.

14

There may be a risk of higher post-extubation NIV use after ERT bundles are implemented (30). ERT bundles provide a systematic approach within the process of evaluating whether a pediatric patient is ready to be successfully liberated from IMV: a daily screening followed by an SBT and a series of pulmonary and non-pulmonary criteria to help with decision-making.

Recommendation 3

We suggest performing a SBT, as part of an ERT bundle, to objectively assess the patient's ability to independently maintain adequate minute ventilation and gas exchange without excessive respiratory effort if liberated from IMV. (CORE statement, ungraded, 96% agreement)

Rationale: Panelists based this recommendation using data from three RCTs (24, 28, 32), three QI studies (29-31), and two observational studies (27, 33). The use of SBTs was associated with lower extubation failure rates in several studies (28, 29, 32, 33), although others showed no difference in extubation failure rates (24, 30, 31). No studies showed higher extubation failure rates with the use of SBTs. The diagnostic accuracy of SBTs in predicting extubation success is high, with positive predictive value above 90% (27, 33). Almost all studies have shown that IMV duration or length of the weaning phase is either shorter or no different in patients who receive a SBT compared to patients not subjected to a SBT. Reductions in IMV duration were as large as 30% (hazard ratio 0.70; 95% confidence interval (CI), 0.53–0.9) (median of 1.2 days) (24) in some studies, although other studies report smaller differences [i.e. median of 6.1 hours (28) or no difference (29, 31, 32)]. No studies showed longer IMV duration with SBTs. There is no clear signal of increased harm with the use of SBTs identified in these studies. An additional risk relates to potential higher use of post-extubation NIV or HFNC, although this finding is not

15

consistent (24, 28, 29). Conduct of the SBT should include a procedure to reduce ventilator settings to pre-specified values (see recommendations 4 and 5) with systematic evaluation by bedside providers of the patient's ability to maintain adequate minute ventilation and gas exchange without excessive respiratory effort.

Systematic Review Recommendations (Recommendations 4-15)

Recommendation 4, 5

- We 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 for extubation failure (Table 4). (Conditional recommendation, very low certainty of evidence).

- For children at higher risk of extubation failure (Table 4), we suggest using CPAP without PS augmentation during SBTs for better assessment of extubation readiness. (Conditional recommendation, very low certainty of evidence).

Rationale: One RCT evaluated critical outcomes related to extubation failure, mortality, or LOS (34) and showed no significant difference between PS augmented and T-piece SBT. Three observational studies have shown that work/effort of breathing was significantly lower during PS augmented SBTs versus CPAP alone, and that PS augmentation significantly underestimates post-extubation work/effort of breathing (35-37). Underestimation of effort of breathing may result in premature extubation and an increased extubation failure rate. Conversely, perceived high work of breathing on CPAP alone compared to PS with CPAP may result in delayed

extubation for several patients who potentially could be extubated successfully, leading to longer IMV duration. This effect was not demonstrated in the only pediatric RCT. We considered avoidance of extubation failure and its associated sequelae as the most critical outcome for patients, and therefore gave it the highest weight. Based on the available evidence, we are unable to state an overall benefit of one approach to SBTs over the other. In patients who may be at higher risk of extubation failure the panel valued a higher degree of accuracy in predicting extubation failure (i.e., positive predictive value), and therefore recommended the use of CPAP only for SBTs in these sub-populations.

Recommendation 6

We suggest the SBT be conducted for either 30 minutes or 60-120 minutes depending on the patient's risk for extubation failure (Conditional recommendation, very low certainty of evidence).

Remarks:

For children at high-risk of extubation failure (Table 4), the panel considered a longer SBT of 60-120 minutes as more appropriate.

Rationale: There were no studies directly comparing different SBT durations. Data from 7 RCTs (24, 26, 28, 32, 34, 38, 39) and 11 observational cohort studies (29, 31, 33, 40-47) were used to provide indirect evidence about SBT duration. A shorter SBT (i.e. 30 minutes) is likely to result in more patients passing the SBT, potentially shortening the IMV duration. In contrast, a longer SBT (i.e. 60-120 minutes) is likely to result in a lower rate of extubation failure, although none

17

of the studies were able to confirm these theoretical benefits. It is likely that a 60–120 minutes

SBT, when compared to 30-minute SBT, can better approximate the effort of breathing post-

extubation, especially in patients at higher risk of extubation failure (e.g., cardiac disease,

neuromuscular condition, prolonged IMV). We considered avoidance of extubation failure and

its associated sequelae as the most critical outcome for patients, and therefore weighted this

outcome more importantly for patients at higher risk for extubation failure. Most panelists

considered a SBT <30 minutes inappropriate for any mechanically ventilated child who has been

ventilated for more than 24 hours. For standard risk patients, SBT durations between 30 and 60

minutes were considered the most appropriate because lowering the already low risk of

extubation failure does not clearly outweigh the benefit of a potentially more accurate SBT. For

high-risk patients, SBT durations between 60 to120 minutes were considered the most

appropriate given that preventing extubation failure is a higher priority, and a 60-120 minutes

SBT was considered to have higher diagnostic accuracy. Risk factors considered for high-risk are

summarized in Table 4.

Recommendation 7

We suggest using measurement of maximal inspiratory pressure during airway occlusion

(PiMax) as an element of ERT bundle for critically ill children at risk for muscle weakness or at

risk for extubation failure (Conditional recommendation, very low certainty of evidence).

Remarks

Based on existing evidence, the optimal cutoff for PiMax cannot be recommended. A PiMax

<20cmH$_2$O suggests increased risk of extubation failure due to inspiratory muscle weakness

18

while a PiMax >50 cmH$_2$O suggests preserved inspiratory muscle strength, and therefore

reduced risk of extubation failure because of poor inspiratory muscle function.

Rationale: Nineteen studies assessing associations between respiratory muscle function before

extubation and extubation outcomes were identified. Nine studies evaluated maximal

inspiratory pressure (PiMax or equivalent measure) (40, 48-55), 7 studies evaluated

diaphragmatic ultrasound (56-62); and 3 studies evaluated respiratory muscle

electromyography (63-65). Compared to PiMax, studies of diaphragmatic ultrasound and

respiratory muscle electromyography recruited fewer participants, were more heterogeneous,

and required technologies and expertise that are not readily available or easily implementable

at most institutions. All but one of the included studies assessing PiMax showed an association

between PiMax and extubation success. Studies report various PiMax thresholds (20-50 cmH$_2$O)

with wide ranges for sensitivity for extubation success (12.5%-100%) and specificity (50%-96%)

(40, 48, 49, 51-55). In one study, PiMax threshold of 20 cmH$_2$O was associated with lowest

sensitivity but highest specificity for extubation success (40); while other studies have shown

that a PiMax of 50 cm H$_2$O had higher sensitivities (50%-100%) but variable specificities (50%-

94%) (51, 53, 55). Hence PiMax measurement can be beneficial to improve the diagnostic

accuracy of extubation failure risk and may be particularly important in children who have a

higher baseline risk of extubation failure (Supplemental Table E7). No studies reported any

adverse events from PiMax measurement. Because the diagnostic accuracy of PiMax for

predicting extubation success is variable, there is a potential that systematic measurement of

respiratory muscle function may result in delayed extubation if PiMax is considered inadequate.

19

Furthermore, we cannot recommend a specific PiMax threshold for discriminating children with respiratory muscle weakness. Although pediatric evidence is limited, risk factors of respiratory muscle weakness include prolonged IMV, neuromuscular disease, prolonged use of corticosteroids or neuromuscular blocking agents, sepsis, malnutrition, and chronic illnesses. Identification of respiratory muscle weakness was considered to be important for patients and clinicians because it could identify patients at higher risk of extubation failure and may prompt additional preventive or therapeutic strategies.

Recommendation 8

We suggest using the air leak test in children with **cuffed** endotracheal tube (ETT) as part of ERT bundle to assess the risk for the development of post-extubation upper airway obstruction (UAO). (Conditional recommendation, very low certainty evidence).

Remarks

For children with an **uncuffed** ETT, an air leak test is an unreliable method to assess the risk for the development of post-extubation UAO.

Rationale: We identified 8 observational studies (66-73) utilizing air leak at the time of extubation. The diagnostic accuracy of air leak testing varies depending on whether the ETT is cuffed or uncuffed. For children with **cuffed** ETTs, the presence of an air leak at the time of extubation (below 25-30 cmH$_2$O) did not have a clear relationship with extubation failure [pooled sensitivity 0.33 (95%CI 0.13-0.60), pooled specificity 0.80 (95%CI 0.54-0.93)]. For the outcome of post-extubation UAO, the presence of an air leak at the time of extubation had some diagnostic accuracy [pooled sensitivity 0.57 (95% CI 0.39- 0.73), pooled specificity 0.91

20

(95%CI 0.32-1.00)] (67, 70-72) (Supplemental Table E11). For children with **uncuffed** ETTs, the presence of an air leak (below 25-30 cmH$_2$O) at the time of extubation has no clear relationship with extubation failure [pooled sensitivity 0.44 (95%CI, 0.27-0.62), pooled specificity 0.58 (95%CI, 0.32-0.80)] (69). Results were similar for the outcome of post-extubation UAO [pooled sensitivity 0.37 (95%CI 0.23-0.54), pooled specificity 0.56 (95%CI 0.40-0.71)] (66-68, 70, 73) (Supplemental Table E11). The potential benefits of identifying patients at higher risk of post-extubation UAO include administering dexamethasone (see recommendation 9) to prevent subglottic post-extubation UAO. While the risk of performing an air leak test itself at the time of extubation is negligible, the actions that may follow because of the air leak test could have unintended negative consequences. Given the low sensitivity, identifying patients who do not have an air leak could result in a delay in extubation to administer dexamethasone, which may prolong IMV duration.

Recommendation 9

We suggest using dexamethasone at least six hours prior to extubation in children at high-risk of developing post-extubation UAO (Conditional recommendation, very low certainty of evidence).

Remarks:

While data from our network meta-analysis estimated a benefit with the use of dexamethasone to prevent UAO in all subgroups, there was unclear benefit in decreasing extubation failure due to UAO. As such, the panel considered that extubation should not be delayed by administering a course of dexamethasone, particularly in standard risk children.

Rationale:

Data from 8 RCTs (74-81) were used for pairwise and network meta-analysis (82). In the pairwise analysis, in comparison to placebo, prophylactic dexamethasone did not result in a statistically significant reduction in extubation failure rates, odds ratio (OR) 0.55 (95%CI, 0.21-1.46); absolute risk reduction 73 fewer per 1000 patients (95%CI, 137 fewer re-intubations to 63 more re-intubations) (Supplemental Table E12). However, prophylactic dexamethasone did result in a decrease in the incidence of UAO; OR 0.40 (95%CI, 0.21-0.73); absolute risk reduction, 205 fewer per 1000 patients (95%CI, 306 to 76 fewer) (Supplemental Table E12).

In network meta-analysis, we identified that early use of dexamethasone ($\geq$12 hours prior to extubation) was likely the most important factor to consider, and when started early, high, or low dose regimens were associated with similar likelihood of UAO prevention and were likely better than either high or low dose regimens which are started later. Similar results were seen when using >6 hours prior to extubation as the definition of early use, although the effect size was slightly smaller and credible intervals wider. When dexamethasone was administered within 6 hours of extubation, use of higher dose dexamethasone ($\geq$0.5 mg/kg/dose) was likely to have some benefit for prevention of post-extubation UAO, while lower dose dexamethasone (<0.5 mg/kg/dose) within 6 hours of extubation appeared to have minimal impact on preventing extubation failure or post-extubation UAO. Given the preference for early administration of dexamethasone, there is therefore a theoretical concern for delayed extubation when clinicians wait for dexamethasone administration prior to extubation.

For patients at high-risk for post-extubation UAO (Table 5), the benefits of prophylactic dexamethasone administered at least 6 hours prior to extubation for preventing extubation subglottic post-extubation UAO and failure outweigh potential risks, including delaying extubation by up to 6 hours. However, the panel believed that in patients at standard risk for post-extubation UAO incremental benefits of dexamethasone are not outweighed by potential delays in extubation.

Recommendation 10, 11, 12

- For children at high-risk for extubation failure, we suggest using non-invasive respiratory support (NRS which includes HFNC, CPAP or NIV) over conventional oxygen therapy immediately after extubation (Table 4) (Conditional recommendation, very low certainty of evidence).

- For children developing respiratory distress while on conventional oxygen therapy post-extubation, we suggest using NRS over continued use of conventional oxygen therapy (Conditional recommendation, very low certainty of evidence).

- For children <1 year of age who are being started on NRS (either planned or rescue), we suggest the use of CPAP over HFNC. (Conditional recommendation, low certainty of evidence).

Remarks:

- For children >1 year of age who are started on NRS; CPAP, HFNC, or NIV are appropriate first line therapies and the choice will depend on the clinical setting and patient circumstances.

23

- NIV can be considered if CPAP or HFNC does not relieve post-extubation respiratory distress, or for children who receive NIV for other chronic conditions.

Rationale: We identified 2 RCT comparing the effectiveness of HFNC to CPAP following extubation as planned or rescue treatment (83, 84) and 5 RCTs comparing HFNC (85-87), CPAP (88) or NIV (89) against conventional oxygen therapy. Treatment with NRS versus conventional oxygen therapy had an odds ratio for reducing extubation failure of 0.6 (95%CI, 0.31-1.14) (Supplemental Figure E15). Treatment with NRS support post-extubation would result in 30 fewer extubation failures per 1000 patients in a control population with an expected extubation failure rate of 8% and 83 fewer extubation failures in higher-risk populations where the expected failure rate is 25%. To try to understand which NRS therapy was most effective (i.e. HFNC vs. CPAP/NIV), we conducted a network meta-analysis where both HFNC (OR 0.53; 95% credible interval, 0.23-1.2) and NIV/CPAP (OR 0.49; 95% credible interval, 0.19-1.2) had better odds of preventing extubation failure compared to conventional oxygen therapy (Supplemental Table 15). For preventing extubation failure, NIV/CPAP had the highest probability of being ranked the most effective therapy (60%), followed by HFNC (38%) (Supplemental Table E15). For the combined outcome of treatment failure, NIV/CPAP also had the highest probability of being ranked the most effective therapy (69%), followed by HFNC (31%) (Supplemental Table E15). In pairwise meta-analysis comparing HFNC to CPAP in mostly patients <1 year of age, CPAP had 5% fewer reintubations at any time after the first extubation (OR 0.7; 95%CI, 0.47-1.04) and lower in-hospital mortality compared to HFNC (OR 0.38; 95%CI, 0.15-0.97). In terms of risks, the use of NRS could result in a prolonged PICU and hospital LOS. In the few studies

24

where these outcomes were reported, conventional oxygen therapy was associated with a 0.74

days (95%CI, -0.72-2.19] reduction in PICU LOS and 9 day (95% CI, -0.97-18.9) reduction in

hospital LOS, although there is significant imprecision in these estimates (87). Treatment with

NIV/CPAP may be poorly tolerated in some children, but this outcome is rarely reported (84,

89).

Recommendation 13, 14, 15

- We recommend that the level of sedation, cough effectiveness, and capacity to manage

    oropharyngeal secretions be evaluated prior to extubation (Ungraded, good practice

    statement).

- We recommend a targeted sedation management strategy using a validated, reliable

    tool to set sedation targets (Ungraded, good practice statement).

- We suggest either the use of a standardized sedation titration protocol or no

    standardized protocol to guide targeted sedation management during IMV and ERT

    (Conditional recommendation, moderate certainty of evidence).

Remarks

There were no studies specifically focused on sedation management in the peri-extubation

period; the panel thus voted to examine the clinical impact of protocolized sedation over the

entire course of IMV.

Rationale: We identified two RCTs (n=11,292) (28, 90) which randomized by PICU. One study

included mechanically ventilated children with acute respiratory failure with an expected length

25

of IMV >24 hours (RESTORE) (90). The other RCT included all patients receiving IMV but reported a pre-specified analysis of patients with expected duration of IMV >24 hours at the time of admission based on diagnosis (SANDWICH) (28). Both RCTs compared usual PICU care to an intervention consisting of protocolized sedation assessment, targeted sedation goals and extubation readiness testing. Both studies used validated sedation tools to assess level of consciousness and the patient's ability to comfortably accept ventilation, breathe spontaneously, respond to stimulation and console. The SANDWICH trial demonstrated a statistically significant 0.25 day reduction in IMV duration (95%CI, -0.34 to -0.22 days) for patients receiving the intervention (Supplemental Figure E18) (28), although this difference did not meet the panel's a priori threshold for clinical significance, which was 12 hours. The RESTORE trial demonstrated no difference in IMV duration (90). Absolute extubation failure rates were 0.5-0.6% lower in patients in the intervention groups in both RCTs, but neither were statistically different from the usual care groups. The SANDWICH trial demonstrated a significantly shorter hospital LOS for the usual care group (median 0.91 days shorter, interquartile range 0.84-0.97) (28), increased use of NIV post-extubation among intervention patients (adjusted relative risk 1.22, 1.01-1.49), and a higher frequency of unplanned extubation (adjusted relative risk 1.62, 1.05-2.51) (28). The RESTORE trial showed a higher rate of post-extubation stridor among the intervention group (adjusted relative risk 1.6, 1.15-2.22) (90). In addition to these potential harms, there is a potential burden on PICUs to incorporate protocolized sedation management which may increase human costs and personnel. While the benefits of a sedation titration protocol are not clear, critical care providers should work on

strategies of incorporating the use of valid and reliable sedation assessment scales with a

targeted goal in their daily workflow.

Conclusions: Synthesizing these recommendations into clinical practice

As has been shown in several pediatric studies, extubation failure is often multifactorial. For

this reason, extubation evaluation should consider multiple factors and requires clinical

judgment. A systematic approach to evaluate parameters which characterize risk for extubation

failure should be used and can be operationalized into an ERT bundle. The elements proposed

as part of this guideline, we believe, characterize the most important factors to consider prior

to ventilator liberation in children. We synthesized these concepts into a flowchart (Figure 2)

and provide more guidance on implementation considerations in the online justification

manuscript. Unfortunately, the certainty of evidence was low or very low for nearly all our

recommendations, highlighting the need for high-quality research in each of these domains.

27

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Figure legends

Figure 1: Guidelines development process

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Wilson KC, Schoenberg NC, Raghu G. Idiopathic Pulmonary Fibrosis Guideline

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Figure 2: Extubation Readiness Testing Conceptual Framework and Bundle Elements

CPAP: continuous positive airway pressure; ERT: extubation readiness testing; ETT: endotracheal tube; HFNC: high flow nasal cannula, NIV: non-invasive respiratory support (HFNC, CPAP or NIV); PiMax: maximal inspiratory pressure during airway occlusion; PS: pressure support; SBT: spontaneous breathing trial; UAO: upper airway obstruction

35

Table 1: Nomenclature used During the Guideline Development Process

Term	Definition
Continuous positive airway pressure (CPAP)	Positive pressure with a single continuous distending pressure delivered through endotracheal tube, tracheostomy, or non-invasive interface (e.g. nasal mask, nasal pillows/prongs, full face mask or helmet).
Extubation failure (EF)	Need for reintubation typically within 72 hours of extubation.
Extubation readiness test (ERT)	A bundle of items elements that are used to assess the patient's eligibility to be liberated from invasive mechanical ventilation.
High flow nasal cannula (HFNC)	Flow that is delivered through a heated humidified nasal cannula circuit and interface.
Non-invasive ventilation (NIV)	Positive pressure with variable levels of pressure delivered without an artificial airway (e.g. nasal mask, nasal pillows/prongs, full face mask or helmet)
Non-invasive respiratory support (NRS)	HFNC, CPAP, or NIV
Spontaneous breathing trial (SBT)	A systematic method of reduction of ventilator support to assess patient's ability to independently maintain gas exchange without excessive respiratory effort.

Table 2: Guidelines PICO Questions and Summary of Recommendations

PICO Question	Recommendations	Strength of Recommendation	Certainty of evidence
Should acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours have protocolized screening to assess eligibility for ERT?	1. We suggest the use of protocolized screening compared to no screening to assess eligibility for ERT	CORE statement	N/A

Should acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours have a protocolized extubation readiness bundle performed?	2. We suggest using a protocolized ERT bundle compared to clinical assessment of extubation readiness	CORE statement	N/A
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should a SBT be included in determining extubation readiness?	3. We suggest performing a SBT, as part of an ERT bundle, to objectively assess the patient's ability to independently maintain adequate minute ventilation and gas exchange without excessive respiratory effort if liberated from IMV	CORE statement	N/A
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours who are undergoing a SBT as part of extubation readiness assessments, should inspiratory pressure augmentation [i.e. PS or automatic tube compensation] be used?	4. We suggest using either PS augmentation with CPAP or CPAP alone during SBTs in mechanically ventilated children at standard risk of extubation failure	Conditional	Very low
	5. For children at higher risk of extubation failure, we suggest using CPAP without PS augmentation during SBTs for better assessment of extubation readiness.	Conditional	Very low

In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours who are undergoing a spontaneous breathing trial to assess for extubation readiness, should the SBT be conducted for 30 minutes or 60-120 minutes?	6. We suggest the SBT be conducted for either 30 minutes or 60-120 minutes.	Conditional	Very low
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should a measure of respiratory muscle strength during airway occlusion (i.e. NIF or PiMax) or function be included in determining extubation readiness?	7. We suggest using PiMax as an element of ERT bundle for critically ill children at risk for muscle weakness or at risk for extubation failure	Conditional	Very low
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should an endotracheal tube air leak test be measured prior to extubation to predict post-extubation UAO?	8. We suggest using the air leak test, in children with **cuffed** ETT, as part of ERT bundle to assess the risk for the development of post-extubation UAO.	Conditional	Very low

In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should systemic corticosteroids be administered prior to extubation to prevent post-extubation UAO?	9. We suggest using dexamethasone at least six hours prior to extubation in children at high-risk of developing post-extubation UAO	Conditional	Very low
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should planned non-invasive respiratory support (HFNC, CPAP, or NIV) be used after extubation?	10. For children at high-risk for extubation failure, we suggest using NRS (which includes HFNC, CPAP or NIV) over conventional oxygen therapy immediately after extubation	Conditional	Very low

In acutely hospitalized children being extubated to planned non-invasive respiratory support (HFNC, CPAP, or NIV), would NIV/CPAP be superior to HFNC?	11. For children developing respiratory distress while on conventional oxygen therapy post-extubation, we suggest using NRS over continued use of conventional oxygen therapy	Conditional	Very low
	12. For children <1 year of age who are being started on NRS (either planned or rescue), we suggest the use of CPAP over HFNC	Conditional	Low
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours, should a goal-directed sedation protocol be used compared to non-protocolized sedation management to guide sedation management during mechanical ventilation and endotracheal extubation?	13. We recommend that the level of sedation, cough effectiveness, and capacity to manage oropharyngeal secretions be evaluated prior to extubation	Good practice statement	N/A
	14. We recommend a targeted sedation management strategy using a validated, reliable tool to set sedation targets	Good practice statement	N/A

	15. We suggest either the use of a standardized sedation titration protocol or no standardized protocol to guide targeted sedation management during IMV and ERT	Conditional	Moderate

CPAP: continuous positive airway pressure; ERT: extubation readiness testing; ETT: endotracheal tube; HFNC: high flow nasal cannula, IMV: invasive mechanical ventilation; NIF: negative inspiratory force; NIV: non-invasive ventilation; NIV: non-invasive ventilation; NRS: non-invasive respiratory support (HFNC, CPAP or NIV); PiMax: maximal inspiratory pressure during airway occlusion; PS: pressure support; SBT: spontaneous breathing trial; UAO: upper airway obstruction

Table 3: Implications of strength of recommendations to stakeholders

Stakeholder	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the **recommended** course of action and only a small proportion would not.	The majority of individuals in this situation would want the **suggested** course of action, but many would not.
Clinicians	Most individuals should receive the **recommended** course of action.	Recognize that different choices will be appropriate for different patients, and that you must help each patient arrive at a management decision consistent with her or his values and preferences.
Policy makers	The recommendation can be adapted as policy in most situations including for the use as performance indicators.	Policy making will require substantial debates and involvement of many stakeholders. Policies are also more likely to vary between regions.

Table 4: Populations to consider as potentially high-risk for extubation failure

Younger age
Prolonged invasive mechanical ventilation (>14 days)
Chronic lung disease
Chronic critical illness
Pre-existing NIV/CPAP use for any reason
Myocardial dysfunction
Neurologic impairment
Neuromuscular disease
Upper airway anomalies/surgical interventions
Trisomy 21 and other genetic syndromes
Previously failed extubation
Borderline passing SBT

CPAP: continuous positive airway pressure; NIV: Non-invasive ventilation; SBT: spontaneous breathing trial

8

Table 5: Populations to consider as potentially high-risk for upper airway obstruction

Multiple intubation attempts
Traumatic intubation
Use of large for age ETT
ETT air leak pressure >25 cmH2O for cuffed ETT
Anatomical anomaly of upper airways

ETT: endotracheal tube

9

Figure 1: Guidelines development processAdapted with permission of the American Thoracic Society. Copyright © 2022 American Thoracic Society. All rights reserved. Wilson KC, Schoenberg NC, Raghu G. Idiopathic Pulmonary Fibrosis Guideline Recommendations. Need for Adherence to Institute of Medicine Methodology? Ann Am Thorac Soc. 2019 Jun;16(6):681-686. Annals of the American Thoracic Society is an official journal of the American Thoracic Society. Readers are encouraged to read the entire article for the correct context at https://www.atsjournals.org/doi/10.1513/AnnalsATS.201812-871OCThe authors, editors, and The American Thoracic Society are not responsible for errors or omissions in adaptations.

387x207mm (118 x 118 DPI)
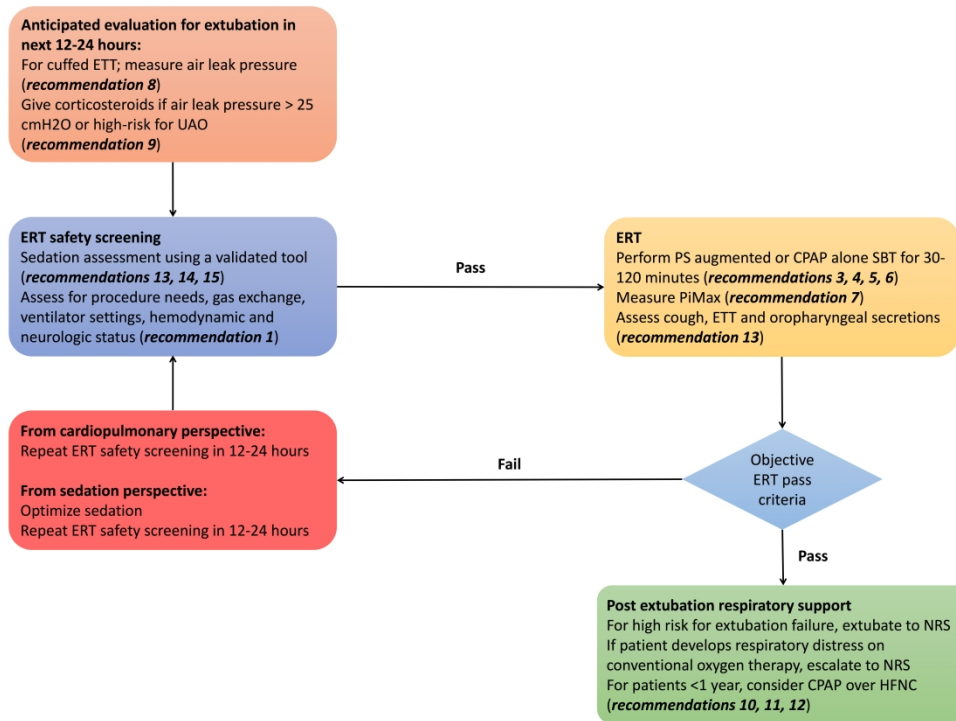
Figure 2: Extubation Readiness Testing Conceptual Framework and Bundle ElementsCPAP: continuous positive airway pressure; ERT: extubation readiness testing; ETT: endotracheal tube; HFNC: high flow nasal cannula, NIV: non-invasive respiratory support (HFNC, CPAP or NIV); PiMax: maximal inspiratory pressure during airway occlusion; PS: pressure support; SBT: spontaneous breathing trial; UAO: upper airway obstruction

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International Clinical Practice Guidelines for Pediatric Ventilator liberation, A PALISI Network Document

ONLINE SUPPLEMENTARY DATA

International Clinical Practice Guidelines for Pediatric Ventilator Liberation, A PALISI Network

Document: Detailed Justification

Introduction:

Each day on invasive mechanical ventilation (IMV) carries the risk of exposure to sedative medications, ventilator associated events, ventilator induced lung injury and increasing healthcare costs (1-4). Pediatric critical care providers balance minimizing the IMV duration against the risk of extubation failure and its associated morbidities (5-7). Adult clinical practice guidelines for IMV liberation have been published (8). While there have been several observational and interventional studies related to aspects of pediatric ventilator liberation, most of the pediatric literature is limited to narrative reviews and meta-analyses (9-13).

The lack of pediatric-specific ventilator liberation guidelines and crucial differences between adult and pediatric practice and physiology as it relates to ventilator liberation has led to significant variation in practice (14-17). Most Pediatric ICUs lack standardized ventilator liberation strategies or protocols.(17) Furthermore, some topic areas of pediatric ventilator liberation have had a wealth of investigations, while others have had very few. We sought to develop the first ever international pediatric-specific ventilator liberation clinical practice guidelines, focused on acutely hospitalized children receiving IMV for more than 24 hours.

Methods:

To improve efficiency in guideline development, we used the modified Convergence of Opinion on Recommendations and Evidence (CORE) process to identify Population Intervention Comparator Outcome (PICO) questions with consensus (18). Wilson et al have previously shown that when panelists reach ≥70% consensus on a recommendation, the recommendation is nearly identical to that generated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) process in a systematic review. Since this is the first guideline which has used the CORE process, we chose a higher consensus threshold (≥80%). For questions where consensus was not reached, we conducted a systematic review and used the GRADE approach (19, 20) to identify and summarize relevant evidence, and develop recommendations for clinical practice (Figure 1).

Committee composition
The guidelines panel was a multi-professional international group, including two co-chairs (SAS and RGK), a lead (NI) and assistant methodologist (SKK), and 2 medical librarians (ECW, HJC). The panel included 19 pediatric intensive care specialists, 2 respiratory therapists, 4 nurses, and 1 expert in human and translational physiology (14 from North America, 3 from South America, 7 from Europe, and 2 from Asia). Panelists were chosen based on their publications in the area of pediatric ventilator liberation in last 10 years. Panelists were divided into sub-groups in charge of literature review, data extraction and preparing draft recommendations and

1

manuscript content for each clinical question. Committee members disclosed all potential conflicts of interest using Indiana University's conflict of interest policy.

Formulating clinical questions

The committee used expert opinion to identify clinical questions and outcomes of importance for mechanically ventilated children in pediatric intensive care units (PICU), their caregivers, and clinicians who care for such children. As suggested by GRADE, only outcomes that were 'critical' or 'important' to the decision making were used to formulate recommendations. These outcomes are also considered high priority for caregivers of children treated in pediatric critical care units (21). Abbreviations and nomenclature are defined in detail in Table 1.

CORE process

The panel members received training in the modified CORE process and the evidence to decision framework described by GRADE (22). As part of the modified CORE process, panelists were asked to select a recommendation for the intervention in each of the clinical questions: a) in favor; b) neither for or against; c) against. Twelve questions were originally considered based on nomination from panel members, but one related to using fluid balance as an element of assessing extubation readiness was excluded due to low priority. The panel sought to limit the number of questions to those with highest priority, to ensure the project could be completed in a reasonable timeframe. During the CORE process, 11 questions were presented to the panelists as a survey using RedCap (Table 2) (23). Three questions had ≥80% agreement on the direction of the recommendation and were accepted as CORE recommendations, without the need for a systematic review (Figure 1).

Literature search

We grouped the remaining 8 questions into 5 literature searches. Comprehensive search strategies were run in MEDLINE (Ovid), Embase (Elsevier), and CINAHL Complete (EBSCOhost) in March 2021 and re-run in January 2022. There were no language or date limitations. For each PICO question, one panelist independently conducted title/abstract review, and 2 panelists conducted full text review and data extraction using the web-based program Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia). Risk of bias was assessed using the Cochrane's risk of bias-2 tool for randomized trials and ROBINS-I tool for observational studies (24, 25). The complete search strategies and PRISMA flowcharts can be found in supplemental material.

Evidence reviews and development of clinical recommendations

We used GRADEpro Guideline Development Tool online software (McMaster University, Hamilton, ON, Canada) to develop evidence profiles for each PICO question (19, 26, 27). To pool quantitative data, where applicable, we performed meta-analysis using random effects models and Review Manager software (RevMan) version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). For recommendations 9-12, we performed a

2

random effects model network meta-analysis in Bayesian framework using GEMTC package of R version 3.5.3 (RStudio, Boston, MA) (28).

When randomized controlled trials (RCT) were available, only these were used to create the evidence profiles. Observational studies were used only when relevant outcome data was not available from RCTs (29).

We used the GRADE framework to determine the certainty of evidence, defined as the degree of confidence that an estimate of the effect is correct, for each outcome (30). The overall certainty of evidence was determined across all outcomes considered critical for decision making. We considered the minimal clinically meaningful thresholds for the outcomes; these were selected based on the panel's perceptions of what differences might change clinician behavior. We also identified the following thresholds (all favoring intervention): IMV duration 12-hour reduction, PICU length of stay (LOS) 1-day reduction, post-extubation upper airway obstruction (UAO) 5% reduction, and extubation failure rate 1% reduction. We used the 'evidence to decision' (EtD) framework proposed by GRADE to weigh the trade-offs involved between competing outcomes, patient centeredness of outcomes, feasibility and acceptability of proposed recommendations and the impact of recommendations on health equity and cost to health system and patients.

For one question (Recommendation 6), there was no direct or indirect evidence to inform the recommendation. To provide expert opinion using a systematic process, we used the RAND-UCLA appropriateness tool to ascertain the panel's judgment on different spontaneous breathing trial (SBT) durations for different extubation contexts (31). We used this process not to develop the recommendation, rather to elaborate the panel's opinion for a question where no pediatric evidence existed.

Recommendations were described as 'strong' or 'conditional' and the categorization was based on the GRADE's evidence to decision framework (22). "**We recommend**" was used for "**strong**" recommendation and "**we suggest**" was used for "**conditional**" recommendation. Recommendations developed using the CORE process were considered conditional since this method does not include the rating of certainty of evidence. Evidence tables and evidence to decision tables can be found in supplemental material.

These guidelines are intended to apply to all children (age 1 day to 18 years). While many of these principles extend to pre-term neonates and young adults, ventilator liberation in those populations were not specifically covered in these guidelines. The implication of the strength of recommendations for different stakeholders is provided in Table 3. We offered good practice statements in the absence of direct evidence, using guidelines provided by GRADE, when it was clear that implementing the recommendation will result in large net positive effect (32).

Endorsement:
This clinical practice guidelines was endorsed by the Society of Critical Care Medicine (SCCM) on June 27, 2022 and by the American Thoracic Society (ATS) on July 27, 2022.

3

Results:

CORE Recommendations (Recommendations 1-3)

The timing of when to begin assessing a patient for extubation readiness, and what parameters to use for extubation readiness assessment can vary substantially based on provider preference. This may lead to unnecessary prolongation of IMV, and higher rates of extubation failure.

Recommendation 1
We suggest the use of protocolized screening compared to no screening to assess eligibility for extubation readiness testing (ERT) (CORE statement, ungraded, 100% agreement).

Remarks
Protocolized screening for eligibility for ERT should be conducted at regular intervals to identify when a patient has met pre-specified targets for physiologic parameters, ventilator settings, or pathology-specific milestones to safely conduct an ERT.

Literature Considered
Panelists based this recommendation using data from 5 RCTs (16, 33-36), and 3 quality improvement (QI) studies (14, 37, 38). Elements of the ERT screening protocols included: plans for procedures, targets of gas exchange and ventilator settings (positive end expiratory pressure, FiO_2, SpO_2, tidal volume, inspiratory pressure, escalation of ventilator support in previous 12 to 24 hours, blood gas), sedation (spontaneously breathing, target sedation score using a validated sedation tool), hemodynamic status (heart rate, blood pressure, inotropes and vasopressors) and neurologic status (level of consciousness, control of seizures, intracranial pressure). Increasingly screening for ERTs is respiratory therapist-driven (14, 37, 38) or nurse-driven, (16) sometimes using computer-driven protocols (34). ERT screening is most frequently done daily (14, 16, 33-37), although screening as frequently as every 3 hours has been reported (38). Compliance with ERT screening and initiation varies between studies (40-92%) (14, 16, 33, 37, 38).

Benefits
The potential benefits of ERT protocolization include a reduction in IMV duration by reducing unnecessary practice variation, improving consistency of care, and reducing morbidity and resource utilization related to IMV. Most studies have identified a reduction in IMV duration or time of weaning for those undergoing systematic ERT screening, ranging from several hours to several days (16, 33, 34, 38). In addition, several studies identified lower rates of extubation

4

failure (36, 37). However, many studies do not specifically separate protocolized screening from other elements of the ERT bundle, making it difficult to quantify the specific impact of protocolized screening on outcomes, although ERT screening is a key element in nearly every trial.

Harms and burden

There are likely no patient-related undesirable effects with judicious screening criteria. There are potential undesirable effects related to staff burden and screening fatigue which may contribute to low compliance rates (14). However, if screening is well-integrated into workflows and carried out efficiently, these harms are expected to be minimal (37, 38). Some studies have observed increased use of post-extubation high flow nasal cannula (HFNC) (14, 37, 38) and non-invasive ventilation (NIV) (14, 16) when passage of an ERT with extubation occurs sooner than clinicians expected. This could have a negative impact on resource utilization but is unlikely to have negative patient-related effects as the harms of extra time on IMV generally outweigh the harms of HFNC or NIV use.

Considerations for stakeholders

Clinicians and patients value extubation failure, IMV duration, and IMV-related morbidity as critical outcomes. Reducing resource utilization related to IMV is also important to clinicians and policymakers. Cost effectiveness favors protocolized screening because resource use with additional time on IMV and/or extubation failure is high. Acceptability and feasibility of protocolized screening is dependent on various factors that will vary between care models but is not unlike many other protocolized interventions in the PICU, which are generally acceptable.

Implementation considerations

Protocolized screening should include a series of physiologic parameters, ventilator targets, or pathology-specific milestones that are applied to all eligible patients at regular, periodic intervals to determine whether they have reached an appropriate point to proceed with an ERT. Examples of ERT safety screening criteria are shown in supplemental Table E1. Screening can be conducted by any qualified member of the care team such as physicians, nurses, or respiratory therapists, including tools using data from the electronic medical record or patient monitors. Protocols should be developed to integrate with local workflow and practice, including what to do when patients pass the screen. Protocolized screening should be developed locally because patients with conditions such as complex airway issues, irreversible neurological injury, pulmonary hypertension, pre-existing tracheostomy, or neuromuscular or cardiac disease may require special considerations for ERT screening criteria and conduct.

What others are saying

Our recommendation aligns with American Thoracic Society's (ATS)/ American College of Chest Physicians (ACCP) ventilator liberation guidelines for adults which suggest that acutely hospitalized adults who have been mechanically ventilated for more than 24 hours be managed with a ventilator liberation protocol, rather than no protocol (8).

5

Conclusions

Protocolized screening compared to non-protocolized screening is likely to result in improved outcomes related to extubation failure and IMV duration among critically ill children with few harms. A multi-professional approach to implementation is needed to make this intervention acceptable and feasible.

Recommendation 2
We suggest using a protocolized ERT bundle compared to clinical assessment of extubation readiness (CORE statement, ungraded, 88% agreement)

Remarks
This ERT bundle includes elements that are used to assess if the patient is ready to be liberated from IMV. In addition to a SBT, this may include factors such as assessment of sedation level, adequacy of neurologic control of the airway (i.e. cough and gag), likelihood of post-extubation upper airway obstruction, assessment of respiratory muscle strength, magnitude of airway secretions, hemodynamic status, and a plan for post-extubation respiratory support.

Literature Considered

Panelists based this recommendation using data from three QI studies (14, 37, 38). Each semi-experimental study incorporated pre-intervention and intervention comparison using a systematic approach for assessing for extubation readiness which included a screening test for extubation readiness which included an SBT and had other elements of an ERT. In all studies, ERT assessments were performed by a respiratory therapist, although the final decision to extubate was approved by physicians. Extubation failure rates and IMV duration were reported in all studies, with secondary outcomes related to length of stay and adverse events reported in some of the studies. Compliance with the ERT bundle ranged from 56% (14) to 92% (37, 38).

Benefits

The implementation of a protocolized ERT resulted in lower extubation failure rates (absolute risk reduction between 3.3-11.7%) (37, 38). When reported, the sensitivity and positive predictive value for extubation success with the use of an ERT bundle was 90 and 94%, respectively (38). None of the studies demonstrated a statistically significant difference with respect to IMV duration. One study also observed a reduction in PICU LOS (196.59 hours pre-intervention group vs 177.19 hours intervention group, p=0.05) (38).

Harms and burden

Very few adverse effects were reported following the implementation of an ERT bundle (37), with similar rates of unplanned extubation between those subjects managed with and without extubation readiness protocols. There appears to be a risk of higher post-extubation NIV use after ERT bundles are implemented, 1 hour (odds ratio [OR] 2.29; 95% confidence interval [CI], 1.1-4.8) and 12 hours (OR 2.53; 95%CI, 1.2-5.2) post-extubation (14).

Considerations for stakeholders

6

For patients, a protocolized ERT might be considered valuable to increase the likelihood of extubation success without increasing IMV duration. Clinicians would similarly value these outcomes, and a protocolized ERT bundle can spread the workload across the entire critical care team and reduce variability in practice related to subjective assessment of extubation readiness (14, 37, 38). For policymakers, implementation of a protocolized ERT bundle is a complex process influenced by factors such resource availability, interprofessional relationships, and education of healthcare professionals (11), but reducing extubation failure would likely be a critical outcome. Furthermore, there may be cost savings with protocolized ERT bundles, but we did not find any studies to evaluate this outcome.

Implementation considerations
This recommendation comprises a systematic approach within the process of evaluating whether a pediatric patient is ready to be successfully liberated from IMV: a frequent screening (most often daily based on reported studies) followed by an SBT and a series of pulmonary and non-pulmonary criteria to help with decision-making. This recommendation does not inform which specific assessment criteria (physiological, etc.) are most appropriate within an ERT, and that will be addressed in other sections of this guideline. Furthermore, as detailed in other sections, elements of the bundle should be catered for special populations (i.e. chronic critical illness, congenital cardiac disease, neuromuscular disease, etc.). Within each local environment, promoters and barriers for protocolized ERT bundle implementation should be identified and used as part of process improvement.

Conclusions
Implementation of a protocolized ERT bundle is likely to result in lower rates of extubation failure with very few risks of harm.

Recommendation 3
We suggest performing a SBT, as part of an ERT bundle, to objectively assess the patient's ability to independently maintain adequate minute ventilation and gas exchange without excessive respiratory effort if liberated from IMV. (CORE statement, ungraded, 96% agreement)

Literature Considered
Panelists based this recommendation using data from three RCTs (16, 33, 39), three QI studies (14, 37, 38) and two observational studies (36, 40). These studies evaluated outcomes focused on extubation failure and IMV duration, both of which were deemed critical outcomes, as well as adverse events. All SBTs involved evaluating the patient on a spontaneous mode of ventilation with pressure support (PS) augmentation with continuous positive airway pressure (CPAP), CPAP alone, or a T-piece. The duration of the SBTs ranged from 15-120 minutes.

Benefits
The use of SBTs was associated with lower extubation failure rates in several studies (16, 37, 39, 40), although several other studies showed no difference in extubation failure rates (14, 33, 38). No studies showed higher extubation failure rates with the use of SBTs. In general, the

7

diagnostic accuracy of SBTs in predicting extubation success is high, with positive predictive value above 90% (36, 40).

Almost all studies, regardless of the study design, have shown that IMV duration or the length of IMV weaning phase is either shorter or no different in patients who receive SBTs versus those that do not. In one study, the reductions in IMV duration were as large as 30% (hazard ratio 0.70; 95%CI, 0.53–0.93) (median of 1.2 days) (33), although other studies report smaller differences (i.e. median of 6.1 hours) (16) or no difference (37-39). Typically, the benefits on IMV duration are seen in the weaning phase (38). No studies showed longer IMV duration with SBTs.

Harms and burden
There is no clear signal of increased harm with the use of SBTs identified in these studies. Theoretical harms include higher rates of unplanned extubation, which has not consistently been identified (33, 37) although a clinically insignificant increase was reported in a recent RCT (3.0% vs. 2.6%. Adjusted hazard ratio 1.62; 95%CI, 1.05-2.51) (16). This trial however was also testing sedation targets, which may have had a larger impact on unplanned extubation than the SBT. An additional risk relates to potential higher use of post-extubation NIV or HFNC, although this finding is not consistent. Foronda reported a trend for lower post-extubation NIV use in the group which received the SBT (21.6 vs 31%, p =0.088) (33), Abu-Sultaneh reported no change (7.7% vs 7.1%; p=0.82) (37), while Blackwood found moderate increase of NIV use (18.9% vs 14.4%; p<0.001) (16) in the group which received the SBT.

Considerations for stakeholders
Clinicians, patients, and policymakers all value implementing a procedure which may lower extubation failure and the IMV duration. Furthermore, epidemiologic studies have confirmed that SBTs are increasingly being used as standard of care in children (41-47), and many clinical trials on mechanically ventilated children require an SBT for both intervention and control arms (35, 48-54).

Implementation considerations
Conduct of the SBT should include a procedure to reduce ventilator settings to pre-specified values (see recommendations 4 and 5) with systematic evaluation by bedside providers of the patient's ability to maintain adequate minute ventilation and gas exchange without excessive respiratory effort. The optimal criteria to gauge passage of the SBT remains an area of investigation and has not been specifically addressed as part of this guideline. However, we suggest the use of standardized criteria, whenever possible, in addition to clinical judgment.

There are generally few barriers implementing SBTs because the necessary resources are usually available in most PICUs. Use of a sedation scoring tool during ventilation with daily targets can improve the implementation of SBTs (see recommendations 13-15). Furthermore, processes should be put in place to prevent significant delays in extubation after a successful SBT, presuming other criteria in the ERT have been met (55).

8

Conclusions

Use of an SBT as an element of the ERT bundle is likely to result in lower extubation failure rates and shorter IMV duration, without significant risk of harm.

Systematic Review Recommendations (Recommendations 4-15)

Recommendation 4, 5
- We suggest using either PS augmentation with CPAP or CPAP alone during SBTs in mechanically ventilated children at standard risk for extubation failure (Table 4). (Conditional recommendation, very low certainty of evidence).
- For children at higher risk of extubation failure (Table 4), we suggest using CPAP without PS augmentation during SBTs for better assessment of extubation readiness. (Conditional recommendation, very low certainty of evidence).

Rationale: There is considerable practice variation in PICUs regarding how much PS to use or whether any PS augmentation should be used during SBTs.

Summary of the Evidence

We identified one RCT (56) evaluating clinical outcomes of extubation failure and three observational studies reporting effort of breathing during SBTs with PS augmentation versus SBTs without PS augmentation in a cross-over design (52, 57, 58). Farias et al enrolled infants and children receiving IMV for at least 48 hours and deemed ready by treating physician to undergo SBT. Patients were randomized to PS of 10 cmH_2O or T-piece SBT. The observational studies measured work/effort of breathing in children undergoing SBTs with PS augmentation (10 cmH_2O) versus CPAP alone (5 cmH_2O). Two of these trials also measured work of breathing after extubation (52, 57). Subgroup-analyses of higher risk sub-populations were not performed in any studies.

Benefits

Only one study evaluated critical outcomes related to extubation failure, mortality, or length of stay (56) and showed no significant difference between the groups. Extubation failure was 12.7% with PS augmentation and 15.2% with T-piece (relative risk reduction of 0.85; 95%CI, 0.42-1.72). PICU mortality was 12% in the group with PS augmentation and 12.1% in the T-piece group (relative risk reduction of 0.99; 95%CI, 0.50-1.90). PICU and hospital LOS did not differ significantly between groups. Several studies have shown that work/effort of breathing was significantly lower during PS augmented SBTs versus CPAP alone, and that PS augmentation significantly underestimates post-extubation work/effort of breathing (52, 57, 58).

Harms and burden

PS augmented SBTs may significantly underestimate the effort of breathing post-extubation. Underestimation of effort of breathing may result in premature extubation and an increased

9

extubation failure rate, although this was not demonstrated in the only pediatric RCT. Conversely, perceived high work of breathing on CPAP alone compared to PS with CPAP may result in delayed extubation for several patients who potentially could be extubated successfully, leading to longer IMV duration. This also was not demonstrated in the only pediatric RCT.

Certainty of the Evidence
The certainty of the evidence was judged to be very low. The single RCT showed no important difference in measured clinical outcomes between groups. Observational studies did not assess critical outcomes, and findings related to effort/work of breathing provide only indirect evidence.

Other evidence to decision criteria and considerations for stakeholders
We considered avoidance of extubation failure and its associated sequelae as the most critical outcome for patients, and therefore gave it the highest weight. Some, however, may be concerned that requiring a CPAP only SBT would potentially delay extubation unnecessarily for many patients, which will prolong PICU and hospital LOS. There is likely significant individual variability with the relative importance of outcomes of extubation failure, IMV duration, PICU and hospital LOS amongst patients, clinicians, and hospital policymakers.

Based on the available evidence, we are unable to state an overall benefit of one approach to SBTs over the other. In sub-populations of patients, who may be at higher risk of extubation failure (e.g., underlying cardiac disease, neuromuscular weakness, prolonged IMV), the panel valued a higher degree of accuracy in predicting extubation failure (i.e., positive predictive value). We judge that in such patients, likelihood of extubation failure and its associated adverse events (e.g., cardiac arrest) are greater than in patients with standard risk of extubation failure. In these sub-populations, we valued preventing extubation failure more than the potential for an increase in IMV duration by 1 to 2 days. In these sub-populations, SBT with CPAP alone, therefore, is favored. Risk factors considered for high-risk are summarized in Table 4.

Implementation considerations
Data from the recently published SANDWICH trial (16) and a previously published survey of PICU physicians (43) shows SBT using CPAP with PS augmentation is preferred by most providers. These data suggest SBT with CPAP alone is unlikely to be broadly adopted for patients with standard risk of extubation failure, although this can be implemented, and is the standard in the PICUs for several of the reported studies. Further, though the panel recommends SBTs with CPAP alone for sub-populations at higher risk of extubation failure, further research supporting the practice is warranted, because the certainty of evidence is very low. A RCT of SBTs with CPAP alone versus CPAP with PS augmentation which includes standardized screening with an ERT bundle should be pursued.

What others are saying

10

ATS/ACCP adult ventilator liberation guidelines suggest conducting daily SBT with PS augmentation (5–8 cmH$_2$O), rather than without (T-piece or CPAP) based on 4 RCTs comparing PS augmented SBT to T-piece SBT which showed higher rate of successful extubation and a trend to lower ICU mortality in PS augmented SBT group (8, 59). Similar randomized trials do not exist in the pediatric population, and differences in physiology, diagnoses, and co-morbidities preclude extrapolation of adult data to children.

Conclusions
Either PS augmented SBT or a CPAP alone SBT can be used to assess a pediatric patient's readiness for extubation. Patients with higher risk of extubation failure may benefit from a CPAP only SBT.

Recommendation 6
We suggest the SBT be conducted for either 30 minutes or 60-120 minutes depending on the patient's risk for extubation failure (Conditional recommendation, very low certainty of evidence).

Remarks:
For children at high-risk of extubation failure (Table 4), the panel considered a longer SBT of 60-120 minutes as more appropriate.

Rationale: The duration of SBTs vary considerably in clinical practice, and the diagnostic accuracy of the SBT to predict extubation failure may be influenced by the length of the SBT.

Summary of the Evidence
There were no studies directly comparing different SBT durations. Data from 7 RCTs (16, 33, 35, 39, 56, 60, 61) and 11 observational cohort studies (37, 38, 40, 47, 55, 62-67) were used to provide indirect evidence about SBT duration. These studies included heterogeneous PICU populations with SBT durations ranging from 10 to 120 minutes, with a 120-minutes SBT being the most common (16, 33, 35, 37-39, 47, 55, 56, 60-63, 66). One study used a 10-minute SBT (67), one used a 15-minute SBT (40), one used a 30-minute SBT (64) and one used a 60-minute SBT (65). We were unable to evaluate the relationship between extubation failure rates or IMV duration and SBT duration given that few studies used shorter SBTs, in addition to significant heterogeneity related to patient population, SBT screening criteria, SBT methods, and SBT failure criteria.

Benefits
A shorter SBT (i.e. 30 minutes) is likely to result in more patients passing the SBT, potentially shortening the IMV duration. In contrast, a longer SBT (i.e. 60-120 minutes) is likely to result in a lower rate of extubation failure, although none of the studies were able to confirm these theoretical benefits. It is likely that a 60–120-minute SBT, when compared to 30-minute SBT, can better approximate the effort of breathing post-extubation, especially in patients at higher risk of extubation failure (e.g., cardiac disease, neuromuscular condition, prolonged IMV). Adult studies have shown similar rates of extubation failure with 30 vs 120-minutes SBTs (68, 69).

11

Harms and burden
A shorter SBT (i.e. 30 minutes) is likely to result in a higher extubation failure rate, while a longer SBT (i.e. 60-120 minutes) is likely to result in a longer IMV duration, although none of the studies were able to confirm these theoretical harms.

Certainty of Evidence
The certainty of the evidence was judged to be very low. There are no pediatric studies comparing SBT duration. Pooling observational data was not possible because of significant heterogeneity. Extracted data from observational studies provided indirect evidence.

Other evidence to decision criteria and considerations for stakeholders
We considered avoidance of extubation failure and its associated sequelae as the most critical outcome for patients, and therefore weighted this more importantly for patients at higher risk for extubation failure. Some, however, may be concerned that a longer SBT would potentially delay extubation unnecessarily for many patients, which will prolong PICU and hospital LOS. There is likely significant individual variability with the relative importance of outcomes of extubation failure, IMV duration, PICU and hospital LOS amongst patients, clinicians, and hospital policymakers.

The panel voted on the appropriateness of different lengths for SBTs (<30 minutes, 30 minutes, 60 minutes, 120 minutes) in sub-populations of critically ill children. Data are summarized in supplemental Figure E3. Most panelists considered that an SBT <30 minutes inappropriate for any mechanically ventilated child who has been ventilated for more than 24 hours. For standard risk patients, SBT durations between 30 and 60 minutes were considered the most appropriate because lowering the already low risk of extubation failure does not clearly outweigh the benefit of a potentially more accurate SBT. For high-risk patients (Table 4), SBT durations between 60-120 minutes was considered the most appropriate given that preventing extubation failure is a higher priority, and a 60-120 minutes SBT, when compared to a 30-minute SBT, is likely to have higher diagnostic accuracy.

Implementation considerations
Critical care providers should identify patients at high-risk for extubation failure that would benefit from a longer SBT. ERT protocols should focus on early extubation soon after patients pass SBTs to avoid further prolongation of IMV duration (47). The panel recognized that there may be special populations, such as those with chronic or progressive neuromuscular conditions, in which the risk of prolonged IMV may further compromise neuromuscular function. For these patients, practitioners and patients may value weaning strategies which target more rapid extubation to non-invasive ventilation. On balance, however, the panel felt that a longer SBT (60-120 minutes) performed on CPAP alone (without PS augmentation) was still most appropriate to gauge whether the acute illness leading to IMV had adequately resolved for liberation from IMV.

12

Conclusions

SBT duration should be customized based on the risk for extubation failure. Standard risk patients could receive a shorter SBT (i.e. 30-60 minutes), while higher risk patients a longer SBT (60-120 minutes) may be more appropriate.

Recommendation 7

We suggest using measurement of maximal inspiratory pressure during airway occlusion (PiMax) as an element of ERT bundle for critically ill children at risk for muscle weakness or at risk for extubation failure (Conditional recommendation, very low certainty of evidence).

Remarks

Based on existing evidence, the optimal cutoff for PiMax cannot be recommended. A PiMax <20cmH$_2$O suggests increased risk of extubation failure due to inspiratory muscle weakness while a PiMax >50 cmH$_2$O suggests preserved inspiratory muscle strength, and therefore reduced risk of extubation failure because of poor inspiratory muscle function.

Rationale: Respiratory muscle weakness may be an important risk factor for both extubation failure and difficult ventilator weaning, with different tools used at the bedside to assess respiratory muscle strength.

Summary of the evidence

No studies evaluating the impact on extubation outcomes of systematic measurement of respiratory muscle function, compared to no measurement were identified. Nineteen studies assessing associations between pre-extubation respiratory muscle function and extubation outcomes were identified. Nine studies (n= 1791) evaluated maximal inspiratory pressure (PiMax or equivalent measure) (48, 53, 62, 70-75), 7 studies (n= 349) evaluated diaphragmatic ultrasound (76-82); and 3 studies (n= 192) respiratory muscle electromyography (83-85). Compared to PiMax, studies of diaphragmatic ultrasound and respiratory muscle electromyography recruited fewer participants, were more heterogeneous, and required technologies and expertise that are not readily available or easily implementable. Justification of our recommendation is therefore based on evidence related to PiMax only. Further details on ultrasound and electromyography related measures are provided in the online supplemental Table E7.

Benefits

All included studies but one showed an association between PiMax and extubation success. Studies report various PiMax thresholds (20-50 cmH$_2$O) with wide ranges for sensitivity (12.5-100%) and specificity (50-96%) for extubation success (48, 53, 62, 70, 71, 73-75). In one study, a PiMax of 20 cmH$_2$O was associated with lowest sensitivity but highest specificity for extubation success (62); while other studies have shown that a PiMax of 50 cmH$_2$O had higher sensitivities (50%-100%), but variable specificities (50-94%) for extubation success (48, 74, 75). Hence PiMax measurement can be beneficial to improve the diagnostic accuracy of the extubation failure risk

13

and may be particularly important in children who have a baseline higher risk of extubation failure.

Harms and burden

No studies reported any adverse events from PiMax measurement. Risks from airway occlusion include brief discomfort, cough, or desaturation. Because the diagnostic accuracy of PiMax for predicting extubation success is variable, there is a potential that systematic measurement of respiratory muscle function may result in delayed extubation if a PiMax is considered inadequate.

Certainty in the evidence of effects

We judged the certainty of evidence to be very low as only observational studies were identified. No study evaluated the clinical impact of systematically including respiratory muscle strength assessment in an ERT. Furthermore, variable thresholds of PiMax and a wide range of sensitivities and specificities were reported. Therefore, we cannot recommend a specific PiMax threshold for discriminating children with respiratory muscle weakness that would precipitate extubation failure.

Other evidence to decision criteria and considerations for stakeholders

Although pediatric evidence is limited, risk factors of respiratory muscle weakness include prolonged IMV, neuromuscular disease, prolonged use of corticosteroids or neuromuscular blocking agents, sepsis, malnutrition, and chronic illnesses. Identification of respiratory muscle weakness was considered to be important for patients and clinicians because it could identify patients at higher risk of extubation failure and may prompt additional preventive or therapeutic strategies Extubation may be attempted, especially if other risk factors of extubation failure are absent. Prophylactic use of non-invasive respiratory support such as HFNC, CPAP or NIV might be considered. Alternatively, extubation may be delayed allowing for more respiratory muscle conditioning and/or resolution of other risk factors. Decision making should be individualized, balancing risks associated with extubation failure with risks of unnecessary prolongation of IMV, also considering patient and caregivers comfort and values.

Implementation considerations

Unlike in adults, PiMax cannot be measured using the ventilator due to ventilator circuit compliance. The additional technology (manometer or pressure line) required are commonly available, do not require additional personnel, and are low cost. When considered against the costs of extubation failure, there could be considerable healthcare savings. Savings may be balanced by costs associated with prolonging IMV in the case of delayed extubation.

We suggest PiMax measurement is standardized. A manometer or other pressure monitoring system should be inserted between the endotracheal tube (ETT) and ventilator circuit. The maneuver should be explained to the child and parents. A sustained (5-8 breaths) end expiratory occlusion should be performed using a valve or gloved hand and the maximum negative inspiratory pressure recorded. The occlusion maneuver is repeated three times with

14

the maximum negative pressure achieved across all occlusions documented. Repeated occlusions are not required if a strong inspiratory effort (>50 cmH$_2$O) is observed.

Widespread adoption of PiMax seems reasonable, although identification of which patient populations will benefit the most from PiMax is required. Although pediatric evidence is limited, risk factors of respiratory muscle weakness include prolonged IMV, neuromuscular disease, prolonged use of corticosteroid or neuromuscular blocking agents, sepsis, malnutrition, and chronic illnesses.

Conclusions

Measurement of respiratory muscle strength may improve risk assessment of extubation failure due to respiratory muscle weakness and is particularly important for children at high-risk of respiratory muscle weakness or other risk factors for extubation failure. Children with PiMax <20 cmH$_2$O are at the highest risk for extubation failure related to respiratory muscle weakness, while children with PiMax >50 cmH$_2$O are unlikely to have extubation failure related to respiratory muscle weakness.

Recommendation 8

We suggest using air leak test in children with **cuffed** ETT as part of an ERT bundle to assess the risk for the development of post-extubation UAO. (Conditional recommendation, very low certainty evidence).

Remarks

For children with an **uncuffed** ETT, an air leak test is an unreliable method to assess the risk for the development of post-extubation UAO.

Rationale: At least one-third of all extubation failures are attributed to post-extubation UAO (5). Correct identification of a patient that is high-risk for post-extubation UAO can help prevent short and long-term airway morbidities (86).

Summary of the evidence

We identified 8 observational studies (87-94) utilizing the air leak test for various purposes at the time of extubation. Seven studies described the utility of the air leak test to predict post-extubation UAO (87-89, 91-94), four studies used the air leak test to predict extubation failure (88-90, 92) and only one study reported the association of the air leak test with the IMV duration (88). In all studies ETT type (cuffed versus uncuffed) were reported, but some studies used subjects who only or mostly had cuffed ETTs (92, 93) while other studies mainly had uncuffed ETTs (87, 89, 90, 94). Two studies performed comparisons of the diagnostic utility of the air leak test between cuffed and uncuffed ETTs (88, 91). There was heterogeneity in how the air leak test was performed with some studies using cuff leak volume or leak percentage (93, 94) and others reporting the pressure at which an audible leak occurred (25 to 30 cmH$_2$O) (87-92). Most studies had small sample sizes, used subjective auscultation of the upper airway to classify obstruction (i.e. clinical exam findings of stridor), and did not differentiate subglottic from supraglottic causes of UAO. One large physiologic study (N=409) used a combination of

15

esophageal manometry and respiratory inductance plethysmography to objectively determine subglottic UAO (91).

Benefits

The diagnostic accuracy of the air leak test varies depending on whether the ETT is cuffed or uncuffed.

For children with **cuffed** ETTs, the presence of an air leak at the time of extubation did not have a clear relationship with extubation failure [pooled sensitivity 0.33 (95%CI, 0.13-0.60), pooled specificity 0.80 (95%CI, 0.54-0.93). For post-extubation UAO, the presence of an air leak below 25-30 cmH$_2$O at the time of extubation had some diagnostic accuracy [pooled sensitivity 0.57 (95%CI, 0.39-0.73), pooled specificity 0.91 (95%CI, 0.32-1.00) (88, 91-93)] (Supplemental Table E10).

For children with **uncuffed** ETTs the presence of an air leak test (below 25-30 cmH$_2$O) at the time of extubation has no clear relationship with extubation failure [pooled sensitivity 0.44 (95%CI, 0.27-0.62), pooled specificity 0.58 (95%CI, 0.32-0.80)] (90). Results were similar for post-extubation UAO [pooled sensitivity 0.37 (95%CI, 0.23-0.54), pooled specificity 0.56 (95%CI, 0.40-0.71)] (87-89, 91, 94) (Supplemental Table E10).

The potential benefits of identifying patients at higher risk of post-extubation UAO include the potential to administer dexamethasone (see recommendation 9) to prevent post-extubation subglottic UAO and potentially lower the extubation failure risk.

Harms and Burdens

While the risk of performing the air leak test itself at the time of extubation is negligible, the actions that may follow because of the air leak test could have unintended negative consequences. Identifying patients who do not have an air leak could result in a delay in extubation to administer dexamethasone, which may prolong IMV duration.

Certainty in the evidence of effects

The overall certainty of evidence was deemed to be very low for all outcomes given that all studies were observational, had serious risk of bias, used different thresholds for the air leak test, and used different determinations for what was considered post-extubation UAO.

Other evidence to decision criteria and considerations for stakeholders

The increased IMV duration that comes with extubation failure likely contributes hundreds of millions of dollars in healthcare costs each year (95, 96). The air leak test is a fast, low-cost intervention using readily available equipment.

A patient that has a **cuffed** ETT and fails the air leak test prior to extubation may be considered high-risk for post-extubation subglottic UAO, and treatments aimed at reducing edema such as dexamethasone may be considered (see recommendation 9). The potential benefit of

16

correcting airway edema in a high-risk patient to prevent UAO likely outweighs the harm of potential delaying extubation to administer dexamethasone when the ETT is cuffed, or when the patient has other risk factors for UAO (Table 5). However, when the ETT is **uncuffed**, since the predictive ability of the air leak test is essentially a coin-flip, the potential benefits do not outweigh the potential harms and it should not be used to inform clinical decision making.

Implementation considerations

We propose that the air leak test is performed in the supine position with the patient's head midline. The cuff is deflated completely, allowing time for suctioning if required. Then the patient is manually ventilated to a maximal pressure of 30 cmH_2O, and if an audible air leak is not heard below 25-30 cmH2O, they have failed the test and are considered higher risk for post-extubation UAO. Further implementation studies should focus on timely assessment of air leak test to avoid prolongation of IMV in case systemic dexamethasone are being considered (see recommendation 9). Future research should employ objective measures to differentiate post-extubation subglottic UAO from supraglottic UAO (86, 91, 97).

What others are saying

Our recommendation aligns with ATS/ACCP adult ventilator liberation guidelines that suggest performing an air leak test in mechanically ventilated adults who meet extubation criteria and are deemed high-risk for post-extubation UAO (8). However, the adult guidelines do not suggest a specific threshold which constitutes failure of the air leak test.

Conclusions

The air leak test has utility in identifying children at high likelihood of developing post-extubation UAO when the ETT is **cuffed**. While this resulted in variable impact on extubation failure rates, the benefits of identifying these higher risk children to consider administration of dexamethasone outweigh the harms. However, the air leak test in **uncuffed** ETTs demonstrated no predictive ability and should not be used to guide clinical decision making.

Recommendation 9

We suggest using dexamethasone at least six hours prior to extubation in children at high-risk of developing post-extubation UAO (Conditional recommendation, very low certainty of evidence).

Remarks:

While data from our network meta-analysis estimated a benefit with the use of dexamethasone to prevent UAO in all subgroups, there was unclear benefit in decreasing extubation failure due to UAO. As such, the panel considered that extubation should not be delayed by administering a course of dexamethasone, particularly in standard risk children.

Rationale: The use of corticosteroids to prevent subglottic UAO is still debatable in the PICU community, with variation in timing, dosing, and duration.

Summary of the evidence:

17

Data from 8 RCTs (n= 903) (98-105) were used for pairwise and network meta-analysis (106). All studies compared intravenous dexamethasone to placebo. Dexamethasone dose ranged from 0.15 mg/kg to 1 mg/kg (with 0.25 and 0.5 mg/kg/dose the most used) and the timing ranged from 24 hours prior to extubation to within 1 hour of extubation. Included studies had relatively high UAO rates (28-87.5%) with extubation failure rates that ranged from 6.25-63% in the control group.

In the network meta-analysis (8 studies) we grouped studies as "early" if dexamethasone was initiated at least 12 hours prior to extubation and "high dose" if at least 0.5 mg/kg/dose was used (12-hour network meta-analysis). This way we had five groups of studies: Early high, early low, late high, late low and no dexamethasone. As a second analysis, we also performed a network meta-analysis where early initiation was defined as more than 6 hours prior to extubation (6-hour network meta-analysis).

Benefits:
In the pairwise analysis, in comparison to placebo, prophylactic dexamethasone did not result in a statistically significant reduction in extubation failure rates, OR 0.55 (95%CI, 0.21-1.46); absolute risk reduction, 73 fewer per 1000 patients (95%CI, 137 fewer reintubations to 63 more reintubations) (Supplemental Table E12). In the 12-hour network meta-analysis, we have very low certainty in the effect estimates for all comparisons. In comparison to 'no dexamethasone' the effect estimates (OR and 95% credible interval) for preventing extubation failure were: a) High early 0.24 (0.04, 1.17); b) High late 0.44 (0.10, 1.27); c) Low early 0.26 (0.02, 3.4) and d) Low late 1.1 (0.15, 7.77). In the 6-hour network meta-analysis we have very low certainty in the effect estimates for all comparisons. In comparison to 'no dexamethasone' the effect estimates for preventing extubation failure in the 6-hour network meta-analysis were: a) High early 0.41 (0.10 1.21); b) High late 0.44 (0.06, 2.4); c) Low early 0.63 (0.10, 3.78) and d) Low late 0.99 (0.02, 69) (Supplemental Table E12).

In the pairwise analysis comparison to placebo, prophylactic dexamethasone did result in a decrease in the incidence of UAO; OR 0.40 (95%CI, 0.21-0.73); absolute risk reduction, 205 fewer per 1000 patients (95%CI, 306 fewer to 76 fewer cases of UAO) (Supplemental Table E12). In the 12-hour network meta-analysis, in comparison to no dexamethasone we have low certainty in the OR (95% credible interval) of benefit: a) High early 0.13 (0.04-0.36); b) High late 0.39 (0.19-0.74); c) Low early 0.15 (0.04-0.59) and d) Low late 0.58 (0.22-1.52) (Supplemental Table E12). The two most effective strategies probably are high early and low early, while high late is also likely to be effective in preventing UAO. In the 6-hour network meta-analysis, only the high early strategy had evidence of clear benefit with OR 0.30 (0.13-0.55, low certainty) (Supplemental Table E12). The effect estimates for low early had a trend towards benefit with OR 0.42 (0.17-1.0, low certainty). High late OR 0.72 (0.24-1.9, low certainty) and low late OR 0.53 (0.08-3.2, very low certainty) had some possibility of being effective but had very wide credible intervals (Supplemental Table E12).

To summarize, in the network meta-analysis, we identified that early use of dexamethasone (≥12 hours prior to extubation) was likely the most important factor to consider. When started

18

early, high or low dose regimens were associated with similar likelihood of UAO prevention and were likely better than regimens started later. Similar results were seen when using >6 hours prior to extubation as the definition of early, although the effect size was slightly smaller and credible intervals were wider. When dexamethasone was administered within 6 hours of extubation, use of higher dose dexamethasone (≥0.5 mg/kg/dose) was likely to have some benefit for prevention of post-extubation UAO, while lower dose dexamethasone (<0.5 mg/kg/dose) within 6 hours of extubation appeared to have minimal impact on preventing extubation failure or post-extubation UAO.

In the pairwise analysis, there appears to be a small reduction in IMV duration (median difference of 0.2 days), reported in 4 studies (98, 99, 103, 104), although this duration may not be clinically significant.

Harms and burden
Very few adverse effects were reported in RCTs included in the pairwise analysis. Two studies reported gastrointestinal bleeding (OR 3.09; 95%CI, 0.12-78) (99, 104). Three studies reported hypertension (OR 1; 95%CI, 0.06-16.6) (99, 103, 104). Median PICU LOS was reported to be higher in the dexamethasone group in 2 studies (mean difference 0.44 days higher; 95%CI,-0.66 to 1.55) (101, 103). There is a theoretical concern for delayed extubation when clinicians wait for dexamethasone administration prior to extubation, although this could not be specifically tested in these randomized trials.

Certainty in the evidence
For UAO there is low certainty of evidence due to inconsistency and indirectness due to dose and timing differences of pairwise comparison among the analyzed RCTs. For the extubation failure, the evidence was judged as very low because of inconsistency and imprecision of pairwise comparison. The 12-hour and 6-hour network meta-analyses were mainly downgraded for imprecision in the direct and indirect comparisons.

Other evidence to decision criteria and considerations for stakeholders
For patients, families and practitioners, the value of prevention of UAO and extubation failure, the potential reduction in IMV duration and hospital LOS must be balanced against the risk of adverse events and potentially delayed extubation associated with dexamethasone administration. It is likely that these stakeholders value their prevention of UAO and extubation failure more than a slightly increased risk of gastrointestinal bleeding and temporary hypertension. Dexamethasone is a widely available and affordable drug which probably would have no impact on health equity.

For patients at high-risk for post-extubation UAO (Table 5), the benefits of prophylactic dexamethasone administered at least 6 hours prior to extubation on preventing subglottic post-extubation UAO and extubation failure outweigh any potential risks, including delaying extubation by up to 6 hours. However, the panel believed that in patients at standard risk for post-extubation UAO any incremental benefits of dexamethasone are not outweighed by any potential delays in extubation.

19

Implementation considerations

It is crucial to identify children at high-risk of post-extubation UAO at least 6 hours prior to extubation, and ideally at least 12 hours prior to extubation, to prevent potential delays in extubation to administer dexamethasone. Assessment of risk factors for UAO should be conducted on the day prior to potential extubation, so that prophylactic dexamethasone can be administered without delaying extubation. The optimal dosing is not entirely clear, but network meta-analysis would suggest using regimens between 0.15-0.5 mg/kg/dose, starting a minimum of 6 hours prior to extubation (ideally 12-24 hours), with repeated doses (between 4-6 doses) which can be completed after extubation. If administration is considered within 6 hours of extubation, higher dose regimens (0.5 mg/kg/dose) should be used, with a maximum of 10 mg.

What others are saying

Our recommendation aligns with AST/ACCP adult ventilator liberation guidelines that suggest administering systemic corticosteroids for at least 4 hours before extubation for adults who have failed an air leak test but are otherwise ready for extubation (8).

Conclusions

Dexamethasone started at least 6 hours prior to elective extubation may be beneficial in decreasing post-extubation subglottic UAO, particularly in patients at high-risk for post-extubation UAO.

Recommendation 10, 11, 12

- For children at high-risk for extubation failure, we suggest using non-invasive respiratory support (NRS which includes HFNC, CPAP or NIV) over conventional oxygen therapy immediately after extubation (Table 4) (Conditional recommendation, very low certainty of evidence).
- For children developing respiratory distress while on conventional oxygen therapy post-extubation, we suggest using NRS over continued use of conventional oxygen therapy (Conditional recommendation, very low certainty of evidence).
- For children <1 year of age who are being started on NRS (either planned or rescue), we suggest the use of CPAP over HFNC. (Conditional recommendation, low certainty of evidence).

Remarks:

- For children >1 year of age who are started on NRS; CPAP, HFNC, or NIV are appropriate first line therapies and the choice will depend on the clinical setting and patient circumstances.
- NIV can be considered if CPAP or HFNC does not relieve post-extubation respiratory distress, or for children who receive NIV for other chronic conditions.

Rationale: Post-extubation NRS (i.e., HFNC, CPAP, NIV) is increasingly used in PICUs, although it is unclear which patients are likely to benefit, whether the therapies should be used

20

prophylactically or as rescue, and how their use impacts critical outcomes such as extubation failure, IMV duration, PICU LOS and hospital LOS.

Summary of the evidence

We identified 2 RCTs (n = 637) comparing the effectiveness of HFNC to CPAP following extubation as planned or rescue treatment (107, 108) and 5 RCTs (n = 474) comparing HFNC (109-111), CPAP (112) or NIV (50) against conventional oxygen therapy. We performed pairwise meta-analysis where NRS (i.e, HFNC, CPAP, NIV) were combined as one intervention and compared to conventional oxygen therapy. We also performed pairwise meta-analysis comparing HFNC to CPAP for outcomes which were only available in two trials. Finally, we performed a network meta-analysis where HFNC, NIV/CPAP, and conventional oxygen therapy were assessed using both direct and indirect comparisons (106). In all but 2 of the 7 studies (including the 2 studies which compared HFNC to CPAP), the majority of patients were infants.

Benefits

NRS had an OR for reducing extubation failure of 0.6 (95%CI, 0.31-1.14) versus conventional oxygen therapy (Supplemental Table E15) in pairwise meta-analysis. Compared to conventional oxygen, treatment with NRS post-extubation would result in 30 fewer extubation failures per 1000 patients in a context where the control population has an extubation failure rate of 8% (number needed to treat= 33). The effect size will be larger in scenarios where the risk of extubation failure is expected to be higher (e.g., 83 fewer extubation failures, number needed to treat = 12 when the expected extubation failure rate is 25%).

To try to understand which NRS therapy was most effective (i.e., HFNC vs. CPAP/NIV), we conducted a network meta-analysis where all three interventions were assessed separately. We found that both HFNC (OR 0.53; 95% credible interval, 0.23-1.2) and NIV/CPAP (OR 0.49; 95% credible interval, 0.19-1.2) had better odds of preventing extubation failure compared to conventional oxygen therapy (Supplemental Table 15). For preventing extubation failure, NIV/CPAP had the highest probability of being ranked the most effective therapy (60%), followed by HFNC (38%), and then conventional oxygen therapy (2%) (Supplemental Table E15). When considering reintubation at any time after the first extubation, pairwise meta-analysis suggested CPAP resulted approximately 5% fewer reintubations (baseline reintubation rate 22%) compared to HFNC (OR 0.7; 95%CI, 0.47-1.04).

For the outcome of treatment failure, defined as the need for reintubation, cross-over to another NRS mode, or escalation to NIV, NRS resulted in significantly lower odds of treatment failure compared to conventional oxygen therapy (OR 0.33; 95%CI, 0.13-0.84) (Supplemental Table E15) in pairwise meta-analysis. NRS post-extubation would result in 52 fewer treatment failures per 1000 patients treated in a context where the control population has a treatment failure rate of 8%. In network meta-analysis, both HFNC (OR 0.35; 95% credible interval, 0.14-0.73) and NIV/CPAP (OR 0.3; 95% credible interval 0.11-0.7) showed better odds of preventing treatment failure than conventional oxygen therapy. NIV/CPAP had the highest probability of being ranked the most effective therapy (69%), followed by HFNC (31%), for the combined outcome of treatment failure (Supplemental Table E15). Finally, patients who received CPAP

21

post-extubation had lower in-hospital mortality compared to HFNC (OR 0.38; 95%CI, 0.15-0.97) when pooling the two randomized controlled trials which reported this outcome.

Harms and burden

Treatment with NRS could result in a prolonged PICU and hospital LOS, compared to conventional oxygen therapy. Treatment with conventional oxygen therapy led to a statistically and clinically insignificant reduction of 0.74 days (95%CI, -0.72-2.19) in PICU LOS compared to HFNC (109, 111) and a potentially clinically significant but statistically insignificant reduction of 9 days (95%CI, -0.97-18.9) in hospital LOS (111). Patients extubated to CPAP had a 9.5% treatment crossover to HFNC due to discomfort compared to 2.6% in patients extubated to HFNC (108). Intolerance to NIV was reported in 13% of children in one study (50).

Certainty in the evidence of effects

The network meta-analysis comparisons for conventional oxygen therapy versus HFNC versus NIV/CPAP both had low certainty of evidence based on serious risk of bias and imprecision. The certainty of evidence for NIV/CPAP versus HFNC was judged to be low. Certainty of evidence was judged to be low in the comparison of HFNC and NIV/CPAP as one intervention versus conventional oxygen therapy. In the pairwise analysis including two RCTs comparing HFNC and CPAP, there was low certainty of evidence in the comparison of CPAP to HFNC for most outcomes, with moderate certainty of evidence for the outcome of mortality.

Other evidence to decision criteria and considerations for stakeholders

We considered avoidance of treatment failure (cross-over to another NRS mode, escalation to NIV or re-intubation) as a critical outcome for patients following extubation. However, the decrease in treatment failure in patients treated with NRS compared to conventional oxygen therapy must be weighed against other factors, including resource utilization, feasibility, acceptability, cost, equity, and undesirable effects.

Data on undesirable effects were not consistently reported in all studies, so the panel was unable to compare the competing outcomes with certainty. While NRS resulted in lower rates of treatment failure compared to conventional oxygen therapy, we recognize that their planned use after all extubation may not be acceptable to clinicians or patients and should perhaps be reserved for use in children at high-risk of failure (e.g., children with respiratory muscle weakness, prior failed extubation, equivocal SBT) (Table 4) and for those experiencing post-extubation respiratory distress.

Furthermore, although the cost of NRS is lower than that of IMV, any savings from avoidance of extubation failure may be offset by costs associated with these treatments. Examples include additional clinical burden on nursing and respiratory therapists, and the scenario where a child requires prolonged NRS to avoid extubation failure with an attendant increase in PICU and hospital LOS. There is inconsistency in the comparative costs of CPAP versus HFNC, as there are significant regional differences in availability of devices, interfaces, and disposables.

Implementation considerations

22

Treatment failure and its associated complications might be mitigated by adopting strategies to optimize NRS settings and early recognition of treatment failure. Protocols for early weaning of NRS when a patient's respiratory status stabilizes might help decrease NRS duration and PICU LOS. Furthermore, availability of technology and cost may be additional barriers for the adoption of NRS in resource limited settings (113-115). Finally, the majority of studies are conducted in patients <1 year of age, so extrapolation of findings to older children, particularly in comparative studies between HFNC and CPAP, should be done with caution given a number of differences in respiratory physiology between patients <1 year of age and older children.

What others are saying

The ATS/ACCP adult ventilator liberation guidelines strongly recommend planned extubation to NIV for patients at high-risk for extubation failure who have been receiving IMV for more than 24 hours and who have passed a SBT (8).

Conclusion

The overall benefit of NRS (compared to conventional oxygen therapy) is possibly larger in children at high-risk of extubation failure and for those experiencing respiratory distress post-extubation. In this situation, the panel valued prevention of extubation failure over the possible increased PICU and hospital LOS.

Recommendation 13, 14, 15
- We recommend that the level of sedation, cough effectiveness, and capacity to manage oropharyngeal secretions be evaluated prior to extubation (Ungraded, good practice statement).
- We recommend a targeted sedation management strategy using a validated, reliable tool to set sedation targets (Ungraded, good practice statement).
- We suggest either the use of a standardized sedation titration protocol or no standardized protocol to guide targeted sedation management during IMV and ERT (Conditional recommendation, moderate certainty of evidence).

Remarks

There were no studies specifically focused on sedation management in the peri-extubation period; the panel thus voted to examine the clinical impact of protocolized sedation over the entire course of IMV.

Rationale: Level of sedation, cough effectiveness, and capacity to manage oropharyngeal secretions can affect ERT results and extubation outcomes.

Summary of the evidence

We identified two RCTs (n=11,292) (16, 51) which were randomized by cluster (i.e PICU), and enrolled children from infancy through adolescence who were mechanically ventilated for acute conditions. One study included mechanically ventilated children intubated for acute respiratory failure with an expected length of IMV >24 hours (RESTORE) (51). The other RCT included all patients receiving IMV but reported a pre-specified analysis of patients with expected duration of IMV >24 hours at the time of admission based on diagnosis (SANDWICH

(16). Both RCTs compared usual PICU care to an intervention consisting of protocolized sedation assessment, targeted sedation goals and extubation readiness testing. The RESTORE trial used State Behavioral Scale (116), while SANDWICH used COMFORT-behavior scale (117). IMV Duration until first successful extubation was the main outcome measure in both RCTs. Each reported extubation failure rates after attempted extubation, post-extubation stridor, PICU and hospital LOS and PICU mortality. Based on differences in study inclusion criteria and presentation of outcome data we did not pool the data from both RCTs. Protocol adherence was >80-83% on sedation assessment and target setting, but much lower for initiating a SBT when safety screening criteria were met (40%) in SANDWICH trial (16).

Benefits

The SANDWICH trial (16) demonstrated a statistically significant 0.25 day reduction in IMV duration (95%CI, -0.34 to -0.22 days) for patients receiving the intervention arm (Supplemental Table E18), although this difference did not meet the panel's a priori threshold for clinical significance, which was 12 hours. The RESTORE trial (51) demonstrated no difference in IMV duration in patients ventilated for acute respiratory failure. Absolute extubation failure rates were lower in patients in the intervention groups in both RCTs but neither were statistically different from the usual care groups (7.9% in intervention group vs 8.4% in usual care group, p=0.56) (51) and (11.6% in intervention group vs 12.2% in usual care group, absolute risk reduction 0.83 (95%CI, −1.70 to 3.37) (16).

Regarding hospital LOS, the RESTORE trial showed a statistically significant 2-day (Interquartile range, 0.96-3.04 days) median reduction for the intervention group compared to usual care, however this difference was not significant on adjusted analysis (51). Conversely, SANDWICH trial demonstrated a significantly shorter hospital LOS for the usual care group (median 0.91 days shorter, interquartile range 0.84-0.97) (16). Other findings favoring the intervention from RESTORE trial include a lower risk of stage 2 pressure ulcer (relative risk 0.21, 95%CI, 0.08-0.530; absolute risk reduction 1.3%) and a lower risk of tracheostomy in unadjusted analysis (relative risk 0.48; 95%CI, 0.27-0.88) that was not significant in adjusted analysis (51).

Harms and burden

Both RCTs demonstrated potential harm from the intervention: in addition to the findings on hospital LOS above, SANDWICH trial found increase post-extubation NIV use among intervention patients (18.9% vs. 14.4%; adjusted relative risk 1.22, 95%CI 1.01-1.49), and a higher frequency of unplanned extubation (3.0% vs. 2.6%; adjusted relative risk 1.62, 95%CI 1.05-2.51) (16). The RESTORE trial showed a higher rate of post-extubation stridor among the intervention group (7.1% vs. 4.4%; adjusted relative risk 1.6, 95%CI, 1.15-2.22) (51). In addition to these potential harms, there is a potential burden on PICUs to incorporate protocolized sedation management which may increase personnel costs.

Certainty in the evidence of effects

We judged the certainty of evidence to be moderate from these RCTs, due to imprecision on critical outcomes (IMV duration).

24

Other evidence to decision criteria and considerations for stakeholders
Two other good practice statements were constructed for patients who are mechanically ventilated for acute conditions. First, should level of sedation, cough effectiveness, and capacity to manage oropharyngeal secretions be evaluated prior to endotracheal extubation? We recommend this practice because the benefits clearly outweigh any risks associated with such assessments. Second, should a targeted sedation level using a valid and reliable sedation assessment scale be used near the time of ventilator liberation compared to no tool or no specific target even if a standardized tool is implemented? On this we recommend the use of a validated tool as this offers the obvious benefit of improving team communication and focusing therapy to specific goals. Beyond the level of consciousness these scales target multiple elements of the patient's ability to comfortably accept ventilation, breathe spontaneously, respond to stimulation and console (116-118). In addition, these sedation scales are recommended by the 2022 SCCM Clinical Practice Guidelines on Prevention and Management of Pain, Agitation, Neuromuscular Blockade, and Delirium in Critically Ill Pediatric Patients (PANDEM) (119).

Implementation considerations
Critical care providers should work on strategies of incorporating the use of valid and reliable sedation assessment scales with a targeted goal in their daily workflow. The sedation level goal should be adjusted based on the patient's clinical condition and sedation should be optimized to allow the patient to spontaneously breathe when possible. Sedation targets should be adjusted when extubation evaluation and SBTs are being considered. Monitoring and educational efforts should focus on maintaining compliance with sedation assessment and reliability.

What others are saying
The ATS/ACCP adult ventilator liberation guidelines suggest using protocols to attempt minimizing sedation (8). A similar recommendation was made by SCCM PANDEM sedation guidelines specifically for children (119). The PANDEM guidelines included the RESTORE RCT and nine before-after protocol implementation studies. The SANDWICH trial was not included in the PANDEM review. Synthesis of critical clinical outcomes such as IMV duration and LOS showed no difference between protocol versus non protocol groups, but they identified that use of sedation protocols was associated with more days awake and calm while intubated. While our group also evaluated these outcomes, given the potential harms seen in the trials above, we believe the neutral recommendation to either use or not use sedations protocols in children best fit with the evidence to the decision framework.

Conclusion
We recommend using a reliable validated tool to set sedation targets during IMV and ERT. The balance of effects from two RCTs is not in favor or against the use of a standardized sedation titration protocol; none of the outcomes met a priori determined clinical significance thresholds in adjusted analysis.

Synthesizing these recommendations into clinical practice

25

The decision on when to attempt to liberate a child from mechanical ventilation must consider a multitude of factors which affect the likelihood of successful liberation. As has been shown in several pediatric studies, extubation failure is often multifactorial. For example, a child with neuromuscular weakness who develops UAO is more likely to fail extubation than a child who develops UAO but does not have neuromuscular weakness (53). For this reason, extubation evaluation should consider multiple factors and requires clinical judgment. A systematic approach to evaluate parameters which characterize risk for extubation failure should be used and can be operationalized into an ERT bundle. The elements proposed as part of this guideline, we believe, characterize the most important factors to consider prior to ventilator liberation in children. We synthesized these concepts into a flowchart (Figure 2). Of note, these guidelines are intended to apply to children who are ventilated for > 24 hours where the systematic assessment of the multi-factorial elements which contribute to extubation failure are likely most important. These elements may not be equally important in lower-risk patients, such as those who are ventilated for < 24 hours.

Given our recommendation for the use of dexamethasone to prevent UAO, evaluation for extubation should begin 12-24 hours before planned extubation, so the air leak test can be measured for children with a cuffed ETT. In addition, all children should be evaluated for other potential risk factors for subglottic UAO (Table 5), allowing timely administration of dexamethasone (0.15-0.5 mg/kg/dose) (maximum of 10 mg) at least 6 hours prior to extubation and repeated every 6 hours for total of 4-6 doses.

The ERT safety screening begins by assessing the patient's sedation level using a validated tool with titration of sedation to ensure the patient is in the desired range. This implies, at a minimum, the patient consistently triggers the ventilator with adequate minute ventilation. Other eligibility criteria include physiologic parameters, ventilator targets, hemodynamic and neurological criteria as outlined in recommendation 1. The actual criteria in each of these domains was not a focus of this guideline and should be individualized to fit with local practices. Examples of ERT safety screening criteria is shown in supplemental Table E1. This screening can be done by any member of the critical care team (physician, advance care provider, nurse, or respiratory therapist) and can be augmented by integration into electronic medical records or bedside decision support tools. The screening should be done at least daily but can be done more often if workflow allows.

If a patient is eligible, an SBT should be conducted with prespecified settings (PS augmentation or CPAP alone) for the specified duration (30-120 minutes) based on the patient's risk for extubation failure (Table 4). Either just prior to or upon completion of the SBT, PiMax, cough effectiveness, and capacity to manage ETT and oropharyngeal secretions should be assessed to better characterize the patient's risk for extubation failure. Of note, the decision to extubate should be based on the synthesis of all elements of the ERT bundle and is based on clinical judgment of patient-specific risk factors, trajectory of illness, and patient and family values on the tradeoff between extubation failure and IMV/NRS duration.

26

Prior to extubation, the critical care team should discuss the post-extubation respiratory support plan, based on the patient's risk for extubation failure (Table 4). For patients at higher risk for extubation failure, the use of HFNC or CPAP or NIV immediately after extubation should be considered.

For patients who are not extubated, re-evaluation for extubation using the ERT bundle should occur within 12 to 24 hours, ensuring that sedation is optimized in anticipation of subsequent ERT.

Limitations:

We have proposed clinical practice guidelines for pediatric ventilator liberation using transparent and objective methodology, as recommended by GRADE. However, there are important limitations. First, most topic areas lacked randomized controlled trials, which makes most recommendations conditional. This implies that practitioners must evaluate the individual risks and benefits for a recommendation for a given patient, although conditional recommendations are still applicable to most children who are ventilated for > 24 hours. The evidence to decision framework clearly delineates the benefits and harms for a particular recommendation, to enable practitioners to make educated decisions for individual patients. Second, we tried to remove subjectivity and personal opinion from the guideline process. We used the GRADE process and the evidence to decision to minimize risk of bias, included a diverse group of panelists who have published in pediatric ventilator liberation, had clear criteria for conflict of interest, included pre-specified inclusion/exclusion criteria, used outcome prioritization and standardized data extraction, and had anonymous voting. Third, we limited the number of topic areas for feasibility. There are certainly additional elements to consider with pediatric ventilator liberation, which should be considered in future guidelines. Finally, many of these recommendations are already in line with clinical practice in many PICUs, which some may consider as a limitation since the information may not be considered "novel". Ultimately, there is significant practice variation and uptake of standardized protocols regarding ventilator liberation in most PICUs, which underscores the importance of having clinical practice guidelines to elaborate best practices.(17) Furthermore, the fact that most recommendations would be considered standard practice in many ICUs adds face validity to the guidelines. If recommendations were substantially different than what is believed to be appropriate for clinical practice, they would be unlikely to be followed.

Conclusions:

We have provided a conceptual framework and clinical practice guidelines focused on pediatric ventilator liberation. We have addressed topic areas in pediatric ventilator liberation which the panel believes are most important to consider prior to ventilator liberation. Unfortunately, the certainty of evidence was low or very low for nearly all our recommendations, highlighting the need for high-quality research in each of these domains.

27

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35

Supplemental Material for Pediatric Ventilator Liberation Guidelines, A PALISI Network Document

A. ERT Safety Screening Criteria

Supplemental Table E1: Examples of Published ERT Safety Screening Criteria

1. No scheduled operating room trips in next 12-24 hours

2. Respiratory parameters:
- No significant escalation of ventilator support in the last 12 hours
- PEEP ≤6-8
- FiO2 ≤ 0.4-0.5 to keep SpO2 ≥ 90% (SpO2 in goal range for patients with cyanotic congenital heart disease)
- PIP ≤ 22-25 for tidal volume 5-8 ml/kg

3. Hemodynamic parameters:
- No escalation of vasoactive support in last 12 hours
- Blood pressure and heart rate within normal range for age

4. Sedation assessment:
- Patient spontaneously breathing
- Has cough/gag
- SBS 0 to -1, RASS 0 to -2, COMFORT-B 11-22

5. Central nervous system:
- No abnormal intracranial pressure
- No active seizures
- No use of paralytics

Remarks: These criteria are meant to be used as examples of ERT safety criteria based on most used criteria in the literature. Each pediatric critical care unit should customize these criteria based on their experience and discussions between multi-professional team members.

COMFORT-B: COMFORT behavior; FiO2: fraction of inspired oxygen; PEEP: positive end-expiratory pressure; PIP: peak inspiratory pressure; RASS: Richmond agitation sedation scale; SBS: state behavioral scale; SpO2: Oxygen saturation

B. SBT method and duration

Supplemental Table E2: Search strategies for SBT method and duration

SBT method question

In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours who are undergoing a SBT as part of extubation readiness assessments, should inspiratory pressure augmentation (i.e. PS or automatic tube compensation) be used?

P Pediatric patients receiving conventional mechanical ventilation >24 hours undergoing a spontaneous breathing trial

I Spontaneous breathing trial using any level of inspiratory pressure augmentation (PS or automatic tube compensation)

C Spontaneous breathing trial done without any level of inspiratory pressure augmentation (i.e CPAP or T-tube)

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), ventilator free days (VFDs), pediatric ICU (PICU) length of stay, hospital length of stay, effort/work of breathing, mortality

SBT duration question

In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours who are undergoing a spontaneous breathing trial to assess for extubation readiness, should the SBT be conducted for 30 minutes or 60-120 minutes?

P Pediatric patients receiving conventional mechanical ventilation >24 hours undergoing a spontaneous breathing trial

I Spontaneous breathing trial conducted for 30 minutes

C Spontaneous breathing trial conducted for 60-120 minutes

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), VFDs, PICU length of stay, hospital length of stay, mortality

I. MEDLINE (Ovid)

Databases selected: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)

Line	Query
1	(Adaptive adj2 Support Ventilat*).mp.
2	Airway Extubation/
3	Airway extubat*.mp.
4	Artificial Respirati*.mp.

5	((intubation or extubation*) adj3 (airway or tracheal or intratracheal or endotracheal)).mp.
6	exp Intermittent Positive-Pressure Breathing/
7	Intermittent Positive-Pressure Breathing.mp.
8	exp Intermittent Positive-Pressure Ventilation/
9	Intermittent Positive-Pressure Ventilat*.mp.
10	Intubation, Intratracheal/
11	Mechanical Ventilat*.mp.
12	Neurally Adjusted Ventilatory Assist*.mp.
13	open lung ventilat*.mp.
14	Peep.mp.
15	Positive End Expiratory Pressure*.mp.
16	exp Positive-Pressure Respiration/
17	Positive-Pressure Ventilat*.mp.
18	pressure controlled ventilat*.mp.
19	Proportional Assist Ventilat*.mp.
20	Reintubat*.mp.
21	Respiration, Artificial/
22	Respirator Weaning*.mp.
23	Ventilator*.mp.
24	(Ventilat* adj3 Liberation*).mp.
25	exp Ventilators, Mechanical/
26	exp Ventilator Weaning/
27	Ventilator* Weaning*.mp.
28	Ventilation Weaning*.mp.
29	Adolescent/
30	Adolescen*.mp.
31	Teen*.mp.
32	Youth*.mp.
33	exp Child/
34	Child*.mp.
35	Infant/
36	Infant, Newborn/
37	Infant*.mp.
38	Infanc*.mp.
39	Newborn*.mp.
40	Neonat*.mp.
41	Pediatrics/
42	P?ediatric*.mp.
43	Hospitals, Pediatric/
44	Intensive Care Units, Pediatric/
45	PICU*.mp.
46	(Kid or kids).mp.
47	Toddler*.mp.
48	Continuous Positive Airway Pressure/
49	Continuous Positive Airway Pressure*.mp.
50	CPAP.mp.
51	Spontaneous breathing.mp.
52	SBT.mp.
53	Automatic tube compensation*.mp.
54	T-piece*.mp.

55	T-tube*.mp.
56	(ventilat* adj3 liberation).mp.
57	Pressure support*.mp.
58	(extubation* adj2 (readiness or failure* or outcome*)).mp.
59	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
60	29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47
61	48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
62	59 and 60 and 61

II. Embase (Elsevier)

Line	Query
#1	'continuous positive airway pressure'/de
#2	'continuous positive airway pressure*'
#3	cpap
#4	'spontaneous breathing trial'/exp
#5	'spontaneous breathing'/exp
#6	'spontaneous breathing'
#7	sbt
#8	extubation* NEAR/2 (readiness OR failure* OR outcome*)
#9	'automatic tube compensation'/exp
#10	'automatic tube compensation'
#11	't piece'/exp
#12	't piece*' OR 't tube*'
#13	ventilat* NEAR/3 liberation
#14	'pressure support ventilation'/exp
#15	'pressure support ventilator'/exp
#16	'pressure support*'
#17	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16
#18	adaptive NEAR/2 support NEXT/1 ventilat*
#19	'extubation'/de
#20	'airway extubat*'
#21	(intubation* OR extubation*) NEAR/3 (airway OR tracheal OR intratracheal OR endotracheal)
#22	'intermittent mandatory ventilation'/exp
#23	'intermittent positive-pressure breathing'
#24	'intermittent positive pressure ventilation'/exp
#25	'intermittent positive-pressure ventilat*'
#26	'endotracheal intubation'/exp
#27	'invasive ventilation'/exp
#28	'inverse ratio ventilation'/de
#29	'mechanical ventilat*'
#30	'neurally adjusted ventilatory assist*'
#31	'noninvasive positive pressure ventilation'/exp
#32	'open lung ventilat*'
#33	peep
#34	'positive end expiratory pressure ventilation'/exp
#35	'positive end expiratory pressure*'
#36	'positive pressure ventilation'/de

P a g e 5 | 150

#37	'positive-pressure ventilat*'
#38	'pressure controlled ventilation'/de
#39	'pressure controlled ventilat*'
#40	'pressure support ventilation'/de
#41	'proportional assist ventilat*'
#42	'protective ventilation'/exp
#43	reintubat*
#44	'artificial ventilation'/de
#45	'respirator weaning*'
#46	'tracheal extubation'/de
#47	'ventilator'/de
#48	ventilator*
#49	ventilat* NEAR/3 liberation*
#50	'mechanical ventilator'/de
#51	'ventilator weaning'/de
#52	'ventilator* weaning*'
#53	'ventilation weaning*'
#54	'volume controlled ventilation'/exp
#55	'artificial respirati*'
#56	#18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
#57	'adolescent'/exp
#58	'adolescence'/de
#59	adolescen*
#60	teen*
#61	youth*
#62	'child'/exp
#63	child*
#64	'infant'/exp
#65	'infancy'/exp
#66	'newborn'/exp
#67	infant*
#68	infanc*
#69	newborn*
#70	neonat*
#71	'pediatrics'/de
#72	p$ediatric*
#73	'pediatric intensive care unit'/de
#74	picu*
#75	kid OR kids
#76	'toddler'/exp
#77	toddler*
#78	#57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77
#79	#17 AND #56 AND #78

III.   CINAHL Complete (EBSCO)

Line	Query
S1	(MH "Continuous Positive Airway Pressure")
S2	continuous positive airway pressure*
S3	CPAP
S4	Spontaneous breathing
S5	SBT
S6	Extubation* N2 (readiness OR failure* OR outcome*)
S7	Automatic tube compensation
S8	(MH "T-Piece")
S9	T-piece* or t-tube*
S10	Ventilat* N3 liberation
S11	(MH "Pressure Support Ventilation")
S12	Pressure support*
S13	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12
S14	Ventilation Weaning*
S15	ventilator* weaning*
S16	(MH "Ventilator Weaning")
S17	(MH "Ventilators, Mechanical")
S18	ventilat* N3 liberation*
S19	ventilator*
S20	'respirator weaning*'
S21	(MH "Respiration, Artificial")
S22	reintubat*
S24	(MH "Pressure Support Ventilation")
S25	pressure controlled ventilat*
S26	positive-pressure ventilat*
S27	(MH "Positive Pressure Ventilation")
S28	Positive End Expiratory Pressure*
S29	(MH "Positive End- Expiratory Pressure")
S30	peep
S31	open lung ventilat*
S32	neurally adjusted ventilatory assist*
S33	mechanical ventilat*
S34	(MH "Mandatory Minute Volume Ventilation")
S35	(MH "Inverse Ratio Ventilation")
S36	(MH "Intubation, Intratracheal")
S37	Intermittent Positive- Pressure Ventilat*
S38	(MH "Intermittent Positive Pressure Ventilation")
S39	Intermittent Positive-Pressure Breathing
S40	(MH "Intermittent Positive Pressure Breathing")
S41	(intubation* OR extubation*) N3 (airway OR tracheal OR intratracheal OR endotracheal)
S42	artificial respirati*
S43	airway extubat*
S44	(MH "Extubation")
S45	adaptive N2 support ventilat*
S46	Toddler*
S47	Kid OR kids
S48	PICU*
S49	(MH "Intensive Care Units, Pediatric")

P a g e 7 | 150

S50	P#ediatric*
S51	(MH "Pediatrics")
S52	Neonat*
S53	Newborn*
S54	Infanc*
S55	Infant*
S56	(MH "Infant, Newborn")
S57	(MH "Infant") OR (MH "Infant, Hospitalized") OR (MH "Infant, High Risk")
S58	Child*
S59	(MH "Child") OR (MH "Child, Hospitalized") OR (MH "Child, Medically Fragile") OR (MH "Child, Preschool")
S60	Youth*
S61	Teen*
S62	Adolescen*
S63	(MH "Adolescence+")
S64	S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45
S65	S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63
S66	S13 AND S64 AND S65

Supplemental Figure E1: PRSIMA chart for SBT method

Identification of new studies via databases and registers

Identification

Records identified from:
Databases (n = 14,811)
Registers (n = 0)

→ Records removed before screening:
Duplicate records (n = 5,220)

Screening

Records screened
(n = 9,591)

→ Records excluded
(n = 9,350)

Reports sought for retrieval
(n = 241)

→ Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 241)

→ Reports excluded:
Wrong study design (n = 81)
Conference abstract (n = 65)
Wrong intervention (n = 20)
Adult population (n = 14)
NICU population (n = 13)
Review paper (n = 13)
Letter/comment (n = 9)
Wrong study design (n = 1)
Wrong comparator (n = 8)
Wrong outcomes (n = 7)
Wrong setting (n = 5)
Wrong indication (n = 1)

Included

New studies included in review
(n = 4)
Reports of new included studies
(n = 4)

Supplemental Figure E2: PRSIMA chart for SBT duration

Identification of new studies via databases and registers	
Records identified from: Databases (n = 14,811) Registers (n = 0)	Records removed before screening: Duplicate records (n = 5,220)
Records screened (n = 9,591)	Records excluded (n = 9,350)
Reports sought for retrieval (n = 241)	Reports not retrieved (n = 0)
Reports assessed for eligibility (n = 241)	Reports excluded: Wrong study design (n = 81) Conference abstract (n = 65) Wrong intervention (n = 24) Adult population (n = 14) NICU population (n = 13) Review paper (n = 13) Letter/comment (n = 9) Wrong study design (n = 1) Wrong comparator (n = 8) Wrong outcomes (n = 7) Wrong setting (n = 5) Wrong indication (n = 1)
New studies included in review (n = 0) Reports of new included studies (n = 0)	

Identification · Screening · Included

Supplemental Table E3: Evidence table for SBT method

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pressure Support with CPAP	CPAP	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
							№ of patients		**Effect**			
In-unit Mortality												
1[1]	randomized trials	not serious	not serious	serious[a]	very serious[b]	none	15/125 (12.0%)	16/132 (12.1%)	**RR 0.99** (0.50 to 1.90)	**1 fewer per 1,000** (from 61 fewer to 109 more)	⊕◯◯◯ VERY LOW	CRITICAL
Failed liberation from invasive mechanical ventilator												
1[1]	randomized trials	not serious	not serious	serious[a]	very serious[b]	none	13/102 (12.7%)	15/99 (15.2%)	**RR 0.85** (0.42 to 1.72)	**23 fewer per 1,000** (from 88 fewer to 109 more)	⊕◯◯◯ VERY LOW	CRITICAL
ICU length of stay												
1[1]	randomized trials	not serious	not serious	serious[a]	very serious[c]	none	125	132	-	median **1 day more**	⊕◯◯◯ VERY LOW	IMPORTANT
Hospital length of stay												
1[1]	randomized trials	not serious	not serious	serious[a]	very serious[c]	none	125	132	-	median **1 day more**	⊕◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pressure Support with CPAP	CPAP	Relative (95% CI)	Absolute (95% CI)		

Effort of breathing

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Pressure Support with CPAP	CPAP	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
3[2,3,4,d]	randomized trials	serious[e]	not serious	serious[f]	not serious	none	**Khemani et al:** Median pressure rate product was 100 (IQR 60,175) on pressure support 10/ CPAP 5 cmH2O; and 200 (IQR 120, 300) on CPAP 5 cmH2O alone; 300 (IQR 150, 500) 5 min after extubation. 5 min after extubation an individual patient's pressure rate product was a median 25 % (IQR −5, 72 %) higher than CPAP values and a median 147 % (67, 267 %) higher than pressure support values. **van Djik et al:** Median work of breathing was 0.00 (0-0.11) J/L on pressure support 10/ CPAP 5 cmH2O; 0.27 (0.2-0.5)J/L during CPAP 5cm H2O alone. **Willis et al:** Mean (standard deviation) pressure rate product pressure support 198(31), continuous positive airway pressure 237(30), T-piece 323(47), T-piece/ heliox 308(61), and extubation 378(43) cmH2O/min.				⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **RR:** Risk ratio

Explanations
a. Control was T-piece SBT rather than CPAP
b. Confidence interval around absolute estimates does not rule out substantial benefit or substantial harm.
c. Confidence interval not reported
d. Cross-over randomized trials
e. Different measurement techniques
f. Different measures of effort of breathing were used

References

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2. Willis BC, Graham AS,Yoon E,Wetzel RC,Newth CJ. Pressure-rate products and phase angles in children on minimal support ventilation and after extubation. Intensive Care Med; 2005.

3. Khemani RG, Hotz J,Morzov R,Flink RC,Kamerkar A,LaFortune M,Rafferty GF,Ross PA,Newth CJ.. Pediatric extubation readiness tests should not use pressure support.. Intensive Care Med; 2016.

4. J, van,Dijk, RGT, Blokpoel, AA, Koopman, S, Dijkstra, JGM, Burgerhof, MCJ, Kneyber, RG, Khemani, J, Hotz, R, Morzov, RC, Flink, A, Kamerkar, M, LaFortune, GF, Rafferty, PA, Ross, CJ, Newth, BC, Willis, AS, Graham, E, Yoon, RC, Wetzel, CJ, Newth, JA, Farias, A, Retta, I, Alía, F, Olazarri, A, Esteban, A, Golubicki, D, Allende, O, Maliarchuk, C, Peltzer, ME, Ratto, R, Zalazar, M, Garea, EG, Moreno. The effect of pressure support on imposed work of breathing during paediatric . Annals of intensive care; 2019.

Supplemental Table E4: Evidence to decision table for SBT method

Should Pressure Support with CPAP vs. CPAP be used for spontaneous breathing trial in mechanically ventilated children being considered for extubation?	
POPULATION:	Pediatric patients receiving conventional mechanical ventilation >24 hours undergoing a spontaneous breathing trial
INTERVENTION:	Pressure Support with CPAP
COMPARISON:	CPAP only
MAIN OUTCOMES:	In-unit Mortality; Failed liberation from invasive mechanical ventilator; ICU length of stay; Hospital length of stay; Effort of breathing;
SETTING:	PICU, Pediatric Cardiac ICU

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	SBTs are routinely used during extubation readiness trials. There is considerable practice variation in the pediatric ICUs in how SBTs are conducted specifically whether pressure augmentation is used along with CPAP during the conduct of a SBT.	

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ● **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	Much of the data on effort of breathing comes from **Khemani 2016** study where approximately half of the patients were intubated for cardiac pathologies. | Outcomes	With CPAP	With Pressure Support with CPAP	Difference	Relative effect (95% CI) | |---|---|---|---|---| | In-unit Mortality | 121 per 1,000 | **120 per 1,000** (61 to 230) | 1 fewer per | RR 0.99 |	SBT is used to accurately predict extubation outcomes. Clinical decisions based on SBT (whether to extubate or not) can affect patient centered outcomes: in-hospital mortality, reintubation, length of mechanical ventilation and hospital length of stay. SBT provides an estimate of the effort of breathing that the patient is likely to experience post-extubation. Accurate estimation of post-extubation effort of breathing using SBT will allow better selection of patients for extubation. It is possible, patients who show minimal/mild increase in effort during SBT with CPAP have higher likelihood to remain extubated

				1,000 (61 fewer to 109 more)	(0.50 to 1.90)	compared to patients who show minimal/mild increase in effort during SBT with Pressure augmentation plus CPAP.
Failed liberation from invasive mechanical ventilator	152 per 1,000	**129 per 1,000** (64 to 261)	**23 fewer per 1,000** (88 fewer to 109 more)	RR **0.85** (0.42 to 1.72)	
Hospital length of stay	The mean hospital length of stay was **0** day	The mean hospital length of stay in the intervention group was 1 day more	median **1 day more**	-	
Effort of breathing	**Khemani et al:** Median pressure rate product was 100 (IQR 60,175) on pressure support 10/ CPAP 5 cmH2O; and 200 (IQR 120, 300) on CPAP 5 cmH2O alone; 300 (IQR 150, 500) 5 min after extubation. 5 min after extubation an individual patient's pressure rate product was a median 25 % (IQR −5, 72 %) higher than CPAP values and a median 147 % (67, 267 %) higher than pressure support values. **van Djik et al:** Median work of breathing was 0.00 (0-0.11) J/L on pressure support 10/ CPAP 5 cmH2O; 0.27 (0.2-0.5)J/L during CPAP 5cm H2O alone. **Willis et al:** Mean (standard deviation) pressure rate product pressure support 198(31), continuous positive airway pressure 237(30), T-piece 323(47), T-piece/ heliox 308(61), and extubation 378(43) cmH2O/min.				

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know		Pressure augmentation during SBT may significantly underestimate effort of breathing. Underestimation of effort of breathing may result in earlier extubation, potentially leading to increased rates of extubation failure. Using CPAP alone during SBT may show excessive effort of breathing in some who may actually breath without increased effort post-extubation. In such situations, extubation may potentially be delayed.

Outcomes	With CPAP	With Pressure Support with CPAP	Difference	Relative effect (95% CI)
ICU length of stay	The mean ICU length of stay was **0** day	The mean ICU length of stay in the intervention group was 1 day more	median **1 day more**	-

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● **Low** ○ Moderate ○ High ○ No included studies		Only one randomized controlled trial reporting patient centered outcome. Total sample size was 257- probably much below the optimal information size needed to develop higher certainty of effect estimate.

Outcomes	Importance	Certainty of the evidence (GRADE)
In-unit Mortality	CRITICAL	⊕○○○ VERY LOW[a,b]
Failed liberation from invasive mechanical ventilator	CRITICAL	⊕○○○ VERY LOW[a,b]
ICU length of stay	IMPORTANT	⊕○○○ VERY LOW[a,c]
Hospital length of stay	IMPORTANT	⊕○○○ VERY LOW[a,c]
Effort of breathing	IMPORTANT	⊕⊕○○ LOW[d,e]

| | Control was T-piece SBT rather than CPAP
Confidence interval around absolute estimates does not rule out substantial benefit or substantial harm.
Confidence interval not reported
Different measures of effort of breathing were used
Different measurement techniques | |

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability** ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	Relative values of extubation failure, length of mechanical ventilation, hospital length of stay and PICU length of stay are likely valued differently by different patients and clinicians. Further, policy makers may give more prominence to resources used associated with PICU and hospital length of stay. Need for non-invasive respiratory support post-extubation is also important to clinicians and policy makers.	

Balance of effects Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ● **Does not favor either the intervention or the comparison** ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	Based on the available evidence, we are unable to state an overall benefit of one approach over the other. However, a subpopulation of patients who are considered to be at high risk of extubation failure ~>20% may have a different risk benefit profile Example- cardiac conditions, neuromuscular weakness, prolonged mechanical ventilation), a higher degree of accuracy, specifically positive predictive value, has been given emphasis by the panel. We judge that in such patients, harms associated with extubation failure (significant physiologic derangements including cardio-pulmonary arrest) is worse than in patients with average risk of extubation failure. In this sub-population, we valued preventing extubation failure more than a potentially unnecessary 1-2 days of mechanical ventilation. In this sub-population, SBT with CPAP, therefore, is favored.	

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs
○ Moderate costs
○ Negligible costs and savings
○ Moderate savings
○ Large savings
○ Varies
● **Don't know**

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low
○ Low
○ Moderate
○ High
● **No included studies**

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison
○ Probably favors the comparison
○ Does not favor either the intervention or the comparison
○ Probably favors the intervention
○ Favors the intervention
● **Varies**
○ No included studies

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Reduced
○ Probably reduced
● **Probably no impact**
○ Probably increased
○ Increased

○ Varies ○ Don't know		

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● **Varies** ○ Don't know	Practice patterns around the world, as reported by different studies and panelists, suggests SBT with CPAP is unlikely to be adopted for patients with average risk of extubation failure. The recently published SANDWICH trial and a previously published survey of pediatric ICU physicians shows SBT with Pressure Support with CPAP is preferred by the majority of providers.	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know		

Summary of judgements

	Judgement						
Problem	No	Probably no	**Probably yes**	Yes		Varies	Don't know
Desirable Effects	Trivial	**Small**	Moderate	Large		Varies	Don't know
Undesirable Effects	Large	Moderate	**Small**	Trivial		Varies	Don't know
Certainty of evidence	Very low	**Low**	Moderate	High			No included studies
Values	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important	No important uncertainty or variability			

Judgement							
			uncertainty or variability				
Balance of effects	Favors the comparison	Probably favors the comparison	<mark>Does not favor either the intervention or the comparison</mark>	Probably favors the intervention	Favors the intervention	Varies	Don't know
Resources required	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	<mark>Don't know</mark>
Certainty of evidence of required resources	Very low	Low	Moderate	High			<mark>No included studies</mark>
Cost effectiveness	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	<mark>Varies</mark>	No included studies
Equity	Reduced	Probably reduced	<mark>Probably no impact</mark>	Probably increased	Increased	Varies	Don't know
Acceptability	No	Probably no	Probably yes	Yes		<mark>Varies</mark>	Don't know
Feasibility	No	Probably no	<mark>Probably yes</mark>	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention
o	o	●	o	o

Conclusions

Recommendation

● We 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 for extubation failure. (Conditional recommendation, very low certainty of evidence).

● For children at higher risk of extubation failure, we suggest using CPAP without PS augmentation during SBTs for better assessment of extubation readiness. (Conditional recommendation, very low certainty of evidence).

Justification

Current literature comparing use of pressure support augmentation with CPAP versus CPAP alone during SBTs in general PICU populations do not show significant differences in patient-centered outcomes including extubation failure, hospital length-of-stay, and hospital mortality.

Subgroup considerations

For children at higher risk of extubation failure and its associated complications, we suggest using CPAP without pressure support augmentation, which more closely approximates the work of breathing after extubation based on current literature which we believe will provide a better assessment of extubation readiness and the likelihood of successful extubation.

Implementation considerations

Use of pressure support augmentation with CPAP versus CPAP alone in general PICU patient populations and higher-risk subpopulations should be protocolized at individual centers and be consistent among providers. Variations in these types of practices among providers causes confusion among other team members (e.g., nurses, respiratory therapists, trainees) and patients and their families.

Monitoring and evaluation

Standard PICU monitoring including continuous telemetry, pulse oximetry, and vital sign monitoring including respiratory rate and blood pressure should be in place during SBTs for all patients. Other adjunctive monitoring devices such as end-tidal carbon dioxide monitors and somatic and cerebral near-infrared spectroscopy monitors should also be considered. Criteria for passing and failing SBTs should also be protocolized and consistent among providers.

Research priorities

Supplemental Table E5: Evidence to decision table for SBT duration

In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours who are undergoing a spontaneous breathing trial to assess for extubation readiness, should the spontaneous breathing trial be conducted for 30 minutes or 60-120 minutes?	
Population:	Pediatric patients receiving conventional mechanical ventilation >24 hours undergoing a spontaneous breathing trial
Intervention:	Spontaneous breathing trial for 30 minutes
Comparison:	Spontaneous breathing trial for 60-120 minutes
Main outcomes:	Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation, VFDs, PICU length of stay, hospital length of stay, mortality
Setting:	PICU, Pediatric Cardiac ICU
Conflict of interests:	None

Assessment

Problem Is the problem a priority?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	Implementing SBTs in the ventilator liberation process reduces total ventilation time and thereby improves patient outcomes. However, there is no pediatric data supporting a specific minimum duration of SBTs to aid in the decision-making process of whether to extubate a patient. SBT duration varied between 30–120 minutes in various pediatric studies, although 120 minutes was most often reported. We could not identify a relationship between SBT duration and extubation failure rate when these studies were pooled.	

Desirable Effects How substantial are the desirable anticipated effects?		
Judgement	Research evidence	Additional considerations
○ Trivial ● **Small** ○ Moderate ○ Large	The rationale behind the SBT is that the bedside team assesses the patient's extubation readiness in a structured manner. This requires a certain time in which the patient is observed, allowing for justified decision-making, and reducing the likelihood of reintubation	It is possible that patients who 'pass' a 60-120 minutes SBT are more likely to have successful extubation than those who pass an SBT of 30 minutes duration. However, given the lack of evidence to address this issue, we are

○ Varies ○ Don't know	(extubation failure). Given the lack of a relationship between SBT duration, and the absence of studies comparing different SBT durations, the desirable effect (i.e., a lower risk of extubation failure), is probably not affected by SBT duration.	uncertain if there is a significant difference in the predictive ability of a SBT 60-120 minutes compared to a 30-minute SBT. However, the panel believed the likely additional diagnostic accuracy provided by the longer SBT was more important in children at higher risk of extubation failure (children with cardiac disease, neuromuscular condition, prolonged mechanical ventilation etc).

Undesirable Effects
How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ● **Trivial** ○ Varies ○ Don't know	There was an absence of studies comparing different SBT durations. Potential undesirable effects include premature extubation and higher risk of extubation failure if the SBT is of inadequate length (too short). Furthermore, if the patient passes a shorter SBT but fails a longer SBT and the provider chooses not to extubate, this may contribute to longer length of ventilation, without a significant impact on extubation failure.	

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	No direct evidence comparing SBT durations were identified.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability		It may be surmised that clinicians and patients/families similarly appreciate the importance of preventing reintubation. It is unclear how the tradeoff between longer length of ventilation and reintubation is valued, and whether duration of SBT will significantly impact these outcomes.

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **Don't know**		There are no pediatric data supporting a recommendation on the optimal duration of SBTs. A minimum of 30 minutes appears justified. However, the duration of SBT should be individualized, considering the risk for extubation failure. Higher risk patients may warrant a longer SBT, while low risk, a shorter SBT may be appropriate.

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ● **Negligible costs and savings** ○ Moderate savings ○ Large savings ○ Varies ○ Don't know		There are minimal differences in resources required for a 30 minute versus a 60-120 minutes SBT.

Equity
What would be the impact on health equity?

Judgement	Research evidence	Additional considerations

○ Reduced ○ Probably reduced ● **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		Implementing SBTs are feasible and the duration of 30 minutes to 60-120 minutes is unlikely to have a major impact on feasibility

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	**Conditional recommendation for either the intervention or the comparison**	Conditional recommendation for the intervention	Strong recommendation for the intervention

Conclusions

Recommendation

- We suggest the SBT be conducted for either 30 minutes or 60-120 minutes depending on the patient's risk for extubation failure (Conditional recommendation, very low certainty of evidence).

Justification

There are no pediatric data supporting the optimal duration of SBTs. A minimum of 30 minutes appears justified. However, the duration of SBT should be individualized, considering the risk for extubation failure. Higher risk patients may warrant a longer SBT, while in low-risk patients, a shorter SBT may be appropriate.

Subgroup considerations

Supplemental Figure 3: RAND-UCLA Voting for Appropriateness of Different Spontaneous Breathing Trial (SBT) Durations Based on Risk For Extubation Failure

	<30 min	30 min	60 min	120 min
A. Standard risk for extubation failure	5.0	7.0	7.0	5.0
B1. Prolonged invasive mechanical ventilation (> 14 days)	1.5	5.0	6.5	7.0
B2. Chronic lung disease	3.0	5.0	7.0	7.0
B3. Chronic critical illness	3.0	5.5	6.0	7.0
B4. Chronic noninvasive positive pressure use for any reason	3.0	4.0	6.5	7.0
B5. Myocardial dysfunction	3.0	3.5	6.5	7.0
B6. Neurologic impairment	3.0	5.0	7.0	7.0
B7. Neuromuscular disease	2.0	3.0	6.5	7.0
B8. Upper airway anomalies/surgical interventions	3.0	5.5	7.0	5.0
B9. Age less than 24 months	5.0	6.0	7.0	7.0
B10. Previously failed extubation	2.0	5.0	7.0	7.0
B11. Based on clinical evaluation during SBT	1.5	5.0	6.5	7.0

RAND UCLA median score of 1-3 range is classified as inappropriate, 4-6 range is classified as equipoise, and 7-9 range is classified as appropriate.

C. Measures of respiratory muscle strength/function

Supplemental Table E6: Search strategies for measures of respiratory muscle strength/function

Measures of respiratory muscle strength/function question
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should a measure of respiratory muscle strength during airway occlusion (i.e. NIF or PiMax) be included in determining extubation readiness?

P Acutely hospitalized children receiving conventional mechanical ventilation for at least 24 hours, and deemed ready for an extubation readiness trial

I A measure of respiratory muscle strength (NIF or PiMax) as part of extubation readiness assessment

C No assessment of respiratory muscle strength prior to extubation

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), VFDs, PICU length of stay, hospital length of stay, mortality

Search strategies for MEDLINE, Embase, and CINAHL

I. MEDLINE (Ovid)
Databases selected: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)

Line	Query
1	(diaphragm* adj3 electrical adj3 activit*).mp.
2	(diaphragm* adj3 EMG).mp.
3	(diaphragm* adj (function* or strength*)).mp.
4	diaphragm* paralys#s.mp.
5	eadi.mp.
6	EDI.mp.
7	Electromyogram*.mp.
8	Electromyography/
9	electromyograph*.mp.
10	EMGdi.mp.
11	?esophageal pressure*.mp.

12	?esophagus pressure*.mp.
13	(Expiratory muscle* adj (function* or strength*)).mp.
14	Extubation readiness test*.mp.
15	(Inspiratory muscle adj (function* or strength*)).mp.
16	Maximal airway pressure*.mp.
17	Maximal breathing capacit*.mp.
18	(maximal adj2 inspiratory adj (force* or pressure*)).mp.
19	Maximal Respiratory Pressures/
20	Maximal Respiratory Pressure*.mp.
21	negative inspiratory force*.mp.
22	Pdimax.mp.
23	Peak cough* flow*.mp.
24	(Phrenic nerve adj3 stimulat*).mp.
25	Pimax.mp.
26	(Respiratory muscle* adj (function* or strength*)).mp.
27	Tension Time Index.mp.
28	transdiaphragmatic pressure*.mp.
29	(twitch adj4 pressure*).mp.
30	Ventilat* muscle*.mp.
31	Diaphragm/
32	diaphragm*.mp.
33	Ultrasonography/
34	ultrasonograph*.mp.
35	ultrasound*.mp.
36	31 or 32
37	33 or 34 or 35
38	36 and 37
39	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 38
40	Adolescent/
41	Adolescen*.mp.
42	Teen*.mp.
43	Youth*.mp.
44	exp Child/
45	Child*.mp.
46	Infant/

47	Infant, Newborn/
48	Infant*.mp.
49	Infanc*.mp.
50	Newborn*.mp.
51	Neonat*.mp.
52	Pediatrics/
53	P?ediatric*.mp.
54	Hospitals, Pediatric/
55	Intensive Care Units, Pediatric/
56	PICU*.mp.
57	(Kid or kids).mp.
58	Toddler*.mp.
59	40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58
60	(Adaptive adj2 Support Ventilat*).mp.
61	Airway Extubation/
62	Airway extubat*.mp.
63	Artificial Respirati*.mp.
64	((intubation or extubation*) adj3 (airway or tracheal or intratracheal or endotracheal)).mp.
65	exp Intermittent Positive-Pressure Breathing/
66	Intermittent Positive-Pressure Breathing.mp.
67	exp Intermittent Positive-Pressure Ventilation/
68	Intermittent Positive-Pressure Ventilat*.mp.
69	Intubation, Intratracheal/
70	Mechanical Ventilat*.mp.
71	Neurally Adjusted Ventilatory Assist*.mp.
72	open lung ventilat*.mp.
73	Peep.mp.
74	Positive End Expiratory Pressure*.mp.
75	exp Positive-Pressure Respiration/
76	Positive-Pressure Ventilat*.mp.
77	pressure controlled ventilat*.mp.
78	Proportional Assist Ventilat*.mp.
79	Reintubat*.mp.
80	Respiration, Artificial/
81	Respirator Weaning*.mp.

82	Ventilator*.mp.
83	(Ventilat* adj3 Liberation*).mp.
84	exp Ventilators, Mechanical/
85	exp Ventilator Weaning/
86	Ventilator* Weaning*.mp.
87	Ventilation Weaning*.mp.
88	60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87
89	39 and 59 and 88

II. Embase (Elsevier)

Line	Query
#1	diaphragm* NEAR/3 electrical NEAR/3 activit*
#2	diaphragm* NEAR/3 emg
#3	diaphragm* NEAR/2 (function* OR strength*)
#4	'diaphragm* paralys?s'
#5	eadi
#6	edi
#7	'electromyogram'/de
#8	electromyogram*
#9	'electromyography'/exp
#10	electromyograph*
#11	emgdi
#12	'$esophageal pressure*'
#13	'esophagus pressure'/exp
#14	'$esophagus pressure*'
#15	'expiratory muscle*' NEAR/2 (function* OR strength*)
#16	'extubation readiness test*'
#17	'inspiratory muscle*' NEAR/2 (function* OR strength*)
#18	maximal NEXT/3 airway NEXT/3 pressure*
#19	'maximal breathing capacit*'
#20	'maximal expiratory pressure'/de
#21	'maximal expiratory pressure*'

#22	'maximal inspiratory pressure'/de
#23	maximal NEAR/3 inspiratory NEAR/2 (force* OR pressure*)
#24	'maximal respiratory pressure'/de
#25	'maximal respiratory pressure*'
#26	'negative inspiratory force*'
#27	pdimax
#28	'peak cough flow'/de
#29	'peak cough* flow*'
#30	'phrenic nerve' NEAR/3 stimulat*
#31	pimax
#32	'respiratory muscle*' NEAR/2 (function* OR strength*)
#33	'tension time index'
#34	'transdiaphragmatic pressure*'
#35	twitch NEAR/4 pressure*
#36	'ventilat* muscle*'
#37	'diaphragm'/de
#38	diaphragm*
#39	'ultrasound'/de
#40	ultrasonograph*
#41	ultrasound*
#42	#37 OR #38
#43	#39 OR #40 OR #41
#44	#42 AND #43
#45	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #44
#46	'adolescent'/exp
#47	'adolescence'/de
#48	adolescen*
#49	teen*
#50	youth*
#51	'child'/exp

#52	child*
#53	'infant'/exp
#54	'infancy'/exp
#55	'newborn'/exp
#56	infant*
#57	infanc*
#58	newborn*
#59	neonat*
#60	'pediatrics'/de
#61	p$ediatric*
#62	'pediatric intensive care unit'/de
#63	picu*
#64	kid OR kids
#65	'toddler'/exp
#66	toddler*
#67	#46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66
#68	adaptive NEAR/2 support NEXT/1 ventilat*
#69	'extubation'/de
#70	'airway extubat*'
#71	(intubation* OR extubation*) NEAR/3 (airway OR tracheal OR intratracheal OR endotracheal)
#72	'intermittent mandatory ventilation'/exp
#73	'intermittent positive-pressure breathing'
#74	'intermittent positive pressure ventilation'/exp
#75	'intermittent positive-pressure ventilat*'
#76	'endotracheal intubation'/exp
#77	'invasive ventilation'/exp
#78	'inverse ratio ventilation'/de
#79	'mechanical ventilat*'
#80	'neurally adjusted ventilatory assist*'
#81	'noninvasive positive pressure ventilation'/exp
#82	'open lung ventilat*'

#83	peep
#84	'positive end expiratory pressure ventilation'/exp
#85	'positive end expiratory pressure*'
#86	'positive pressure ventilation'/de
#87	'positive-pressure ventilat*'
#88	'pressure controlled ventilation'/de
#89	'pressure controlled ventilat*'
#90	'pressure support ventilation'/de
#91	'proportional assist ventilat*'
#92	'protective ventilation'/exp
#93	reintubat*
#94	'artificial ventilation'/de
#95	'respirator weaning*'
#96	'tracheal extubation'/de
#97	'ventilator'/de
#98	ventilator*
#99	ventilat* NEAR/3 liberation*
#100	'mechanical ventilator'/de
#101	'ventilator weaning'/de
#102	'ventilator* weaning*'
#103	'ventilation weaning*'
#104	'volume controlled ventilation'/exp
#105	'artificial respirati*'
#106	#68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105
#107	#45 AND #67 AND #106

III.   CINAHL Complete (EBSCO)

Line	Query
S1	diaphragm* N3 electrical N3 activit*
S2	diaphragm* N3 emg
S3	diaphragm* N2 (function* OR strength*)
S4	'diaphragm* paralys?s'
S5	eadi
S6	edi
S7	electromyogram*
S8	(MH "Electromyography")
S9	electromyograph*
S10	emgdi
S11	'#esophageal pressure*'
S12	'#esophagus pressure*'
S13	'expiratory muscle*' N2 (function* OR strength*)
S14	'extubation readiness test*'
S15	'inspiratory muscle*' N2 (function* OR strength*)
S16	maximal N3 airway N3 pressure*
S17	'maximal breathing capacit*'
S18	'maximal expiratory pressure*'
S19	maximal N3 inspiratory N2 (force* OR pressure*)
S20	'maximal respiratory pressure*'
S21	'negative inspiratory force*'
S22	pdimax
S23	'peak cough* flow*'
S24	phrenic nerve stimulat*
S25	pimax
S26	'respiratory muscle*' N2 (function* OR strength*)
S27	'tension time index'
S28	'transdiaphragmatic pressure*'
S29	twitch N4 pressure*
S30	'ventilat* muscle*'
S31	(MH "Diaphragm")
S32	diaphragm*
S33	(MH "Ultrasonography")
S34	ultrasonograph*

S35	ultrasound*
S36	S31 OR S32
S37	S33 OR S34 OR S35
S38	S36 AND S37
S39	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S38
S40	Toddler*
S41	Kid OR kids
S42	PICU*
S43	(MH "Intensive Care Units, Pediatric")
S44	P#ediatric*
S45	(MH "Pediatrics")
S46	Neonat*
S47	Newborn*
S48	Infanc*
S49	Infant*
S50	(MH "Infant, Newborn")
S51	(MH "Infant") OR (MH "Infant, Hospitalized") OR (MH "Infant, High Risk")
S52	Child*
S53	(MH "Child") OR (MH "Child, Hospitalized") OR (MH "Child, Medically Fragile") OR (MH "Child, Preschool")
S54	Youth*
S55	Teen*
S56	Adolescen*
S57	(MH "Adolescence+")
S58	Ventilation Weaning*
S59	ventilator* weaning*
S60	(MH "Ventilator Weaning")
S61	(MH "Ventilators, Mechanical")
S62	ventilat* N3 liberation*
S63	ventilator*
S64	'respirator weaning*'
S65	(MH "Respiration, Artificial")
S66	reintubat*
S67	proportional assist ventilat*

S68	(MH "Pressure Support Ventilation")
S69	pressure controlled ventilat*
S70	positive-pressure ventilat*
S71	(MH "Positive Pressure Ventilation")
S72	Positive End Expiratory Pressure*
S73	(MH "Positive End-Expiratory Pressure")
S74	peep
S75	open lung ventilat*
S76	neurally adjusted ventilatory assist*
S77	mechanical ventilat*
S78	(MH "Mandatory Minute Volume Ventilation")
S79	(MH "Inverse Ratio Ventilation")
S80	(MH "Intubation, Intratracheal")
S81	Intermittent Positive-Pressure Ventilat*
S82	(MH "Intermittent Positive Pressure Ventilation")
S83	Intermittent Positive-Pressure Breathing
S84	(MH "Intermittent Positive Pressure Breathing")
S85	(intubation* OR extubation*) N3 (airway OR tracheal OR intratracheal OR endotracheal)
S86	artificial respirati*
S87	airway extubat*
S88	(MH "Extubation")
S89	adaptive N2 support ventilat*
S90	S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69 OR S70 OR S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89
S91	S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53 OR S54 OR S55 OR S56 OR S57
S92	S39 AND S90 AND S91

Supplemental Figure E4: PRSIMA chart for measures respiratory muscle strength/function

Identification of new studies via databases and registers

Identification

Records identified from:
Databases (n = 3,708)
Registers (n = 0)

→ Records removed before screening:
Duplicate records (n = 937)

Screening

Records screened
(n = 2,771)

→ Records excluded
(n = 2,622)

Reports sought for retrieval
(n = 149)

→ Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 149)

→ Reports excluded:
Conference Abstract (n = 34)
Wrong intervention (n = 16)
NICU population (n = 21)
Wrong outcomes (n = 18)
Wrong study design (n = 10)
Wrong intervention (n = 2)
Adult population (n = 1)
Wrong indication (n = 8)
Adult population (n = 5)
Letter/comment (n = 6)
Wrong comparator (n = 2)
Wrong setting (n = 2)
Review Paper (n = 5)

Included

New studies included in review
(n = 19)
Reports of new included studies
(n = 19)

Supplemental Table E7: Evidence table for measures of respiratory muscle strength/function

Pi/PiMax

Certainty assessment							Data on predictive ability	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Extubation failure									
2[1,2]	observational studies	serious[a]	serious[e]	not serious	not serious	none	Range of thresholds: 0.30-0.33 Range of sensitivities: 33-87.5% Range of specificities: 87.5-91% Range of extubation failure rate: 10.7- 22% **El-Khatib, 1996** (n=50): Mean ratio (SD) in extubation success was 0.36 (0.14); in extubation failure was 0.45 (0.1)- not statistically significant. Pi/PiMax ≤ 0.3 had a sensitivity of 33% and a specificity of 91% in predicting extubation failure. **Harikumar, 2009** (n=80): Median (range) Pi/Pimax:Extubation success 0.23 (0.07-0.63); extubation failure 0.39 (0.3-0.57). Pi/Pimax <0.33 had sensitivity 87.5 and specificity 87.5%.	⊕◯◯◯ VERY LOW	CRITICAL

PiMax

Certainty assessment							Data on predictive ability	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			

Extubation failure

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Data on predictive ability	Certainty	Importance
8[2-9]	observational studies	serious[a]	serious[e]	not serious	not serious	none	Range of thresholds: 20- 50cmH2O Range of sensitivities: 12.5%-100% Range of specificities: 50-95% Range of extubation failure rate: 8.3- 22.2% **Harikumar 2009** (n=80): Pimax in cmH2O (median, Range): extubation success 46.1 (20,98); extubation failure: 30.45 (21,58). **Johnston 2010** (n=40): Pimax in cmH2O (median, IQR): extubation success 65 (64,72); extubation failure: 40 (34,50). Pimax <=50: sensitivity 100%, specificity 94%. **Farias 2002** (n=323): Median (IQR) Pimax (in cmH2O) in extubation success 35cmH2O (30,40); extubation failure 30 (25,47), p=0.10. Pimax ≤20 had sensitivity 12.5% and specificity 95.6%. **Khemani 2017** (n=409): Median (IQR) Pimax (in cmH2O): Extubation success was 40 (30,50); extubation failure was 30 (25,40) p=0.03. Pimax Odds ratio: 0.94 (0.9, 0.98) p<0.01 **Noziet 2005** (n=54): Pimax>50 cmH2O area under the curve 0.56 (0.35, 0.77). **Shimada 1979** (n=25): Mean (SD) Crying Pimax (cm H2O): Extubation success was 56 (16.6); extubation failure was 37 (10.2). **Thiagarajan 1999** (n=254): Negative inspiratory force (cm H2O). Average (SD) in extubation success 41.8 (15.4); extubation failure was 35.1 (12.6). **Toida 2017** (n=294): Pimax in cmH2O >50 had a sensitivity of 55.7%, and specificity of 50%.	⊕◯◯◯ VERY LOW	CRITICAL

Diaphragm thickness fraction (DTF)

Certainty assessment							Data on predictive ability	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			

Extubation failure

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Data on predictive ability	Certainty	Importance
5[10-13]	observational studies	serious[a,b]	serious[e]	not serious	not serious	none	Range of thresholds: 21%- 35% Range of sensitivities: 82% -100% Range of specificities: 81%-100% Range of extubation failure rate: 8.8%-39.6% **Abdel Rehman 2019:** DTF≤ 23.1% had a sensitivity of 100%, specificity of 100% in predicting extubation failure Dionisio, 2019: DTF ≤ 35% was noted in the 2/17 subjects who experienced extubation failure in the study. **Ijland 2020:** Sensitivity, specificity for DTF threshold not reported. Median (IQR) DTF for successful extubation group: 15.2% (9.6, 19.1); DTF for failed extubation 4% (0,4) **Xue 2019:** DTF <21% had a sensitivity of 82%, specificity of 81%. DTF (mean, SD) for extubation success was 30.9% (11) and for extubation failure was 15.9% (6.6) **Xue 2020:** Sensitivity, specificity for DTF threshold not reported. Extubation failure was noted more often in the diaphragm dysfunction (DTF<20%) group (8/24) compared to non-diaphragm dysfunction: 4/46 p<0.01	⊕◯◯◯ VERY LOW	CRITICAL

Mortality

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Data on predictive ability	Certainty	Importance
1[12]	observational studies	serious[a,b]	not serious	not serious	not serious	none	**Xue 2020:** Mortality in diaphragm dysfunction (DTF<20) group: 5/24; mortality in non-diaphragmatic dysfunction (DTF>20): 1/46. p<0.01	⊕◯◯◯ VERY LOW	CRITICAL

PICU Length of stay

Certainty assessment							Data on predictive ability	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
1[12]	observational studies	serious[a,b]	not serious	not serious	not serious	none	**Xue 2020:** Median (IQR) in diaphragm dysfunction (DTF<20%) group (n=24) : 26.5 (15,35) days; in non-diaphragm dysfunction (DTF>20%) group (n=46): 13 (10,18) days. p<0.01	⊕◯◯◯ VERY LOW	CRITICAL

Electric activity of diaphragm (Edi)

Certainty assessment							Data on predictive ability	Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Extubation readiness trial failure									
3[14-16]	observational studies	not serious	not serious	serious[c]	serious[d]	none	Range of extubation failure rate: 13.6-40% Wolf, 2011 (n=20): Tidal volume/ delta Edi (Mean, SD): ERT success 24.8 (20.9); ERT failure 67.2 (27) ml/mv, p=0.02. Wolf, 2011 (n=20): Tidal volume/weight/delta Edi: 1.1 (0.8)ml/kg/mv v 3.3 (5.1) ml/kg/mv p=0.06. **Van Leuteren 2021** (n= 147): Pre-extubation peak diaphragm activity was higher in children with extubation failure compared to those with extubation success (5.6 vs 7.0 µV; p = 0.04). Tonic diaphragmatic activity was also higher in children with extubation failure compared with children with extubation success (2.8 vs 4.1 µV; p = 0.04). Receiver operator curve analysis showed the highest area under the curve for tonic (end-inspiratory) diaphragm activity (0.65), with a tonic (end-inspiratory) diaphragm activity greater than 3.4 µV having a combined sensitivity and specificity of 55% and 77%, respectively, to predict extubation outcome. **MacBean 2016** (n=25): Three children had extubation failure. Area under the curve for predicting extubation failure during CPAP trial were: Neuroventilatory efficiency (<0.43ml/kg/mV) =0.94; EMGpara (parasternal intercostal electromyography)(>14.8 mV)= 0.91.	⊕◯◯◯ VERY LOW	CRITICAL

Footnotes:

[a] Bias due to confounding and missing data

[b] Selection bias

[c] Indirect measure of respiratory muscle strength

[d] Wide confidence intervals

[e] Wide range of sensitivities and specificities and wide range of thresholds and baseline extubation failure rate is likely to result in wide range of results.

1. el-Khatib MF, Baumeister B, Smith PG, Chatburn RL, Blumer JL. Inspiratory pressure/maximal inspiratory pressure: does it predict successful extubation in critically ill infants and children? Intensive Care Med 1996;22:264-8.

2. Harikumar G, Egberongbe Y, Nadel S, et al. Tension-time index as a predictor of extubation outcome in ventilated children. American journal of respiratory and critical care medicine 2009;180:982-8.

3. Johnston C, de Carvalho WB, Piva J, Garcia PC, Fonseca MC. Risk factors for extubation failure in infants with severe acute bronchiolitis. Respir Care 2010;55:328-33.

4. Farias JA, Alia I, Retta A, et al. An evaluation of extubation failure predictors in mechanically ventilated infants and children. Intensive Care Med 2002;28:752-7.

5. Khemani RG, Sekayan T, Hotz J, et al. Risk Factors for Pediatric Extubation Failure: The Importance of Respiratory Muscle Strength. Crit Care Med 2017;45:e798-e805.

6. Noizet O, Leclerc F, Sadik A, et al. Does taking endurance into account improve the prediction of weaning outcome in mechanically ventilated children? Crit Care 2005;9:R798-807.

7. Shimada Y, Yoshiya I, Tanaka K, Yamazaki T, Kumon K. Crying vital capacity and maximal inspiratory pressure as clinical indicators of readiness for weaning of infants less than a year of age. Anesthesiology 1979;51:456-9.

8.Thiagarajan RR, Bratton SL, Martin LD, Brogan TV, Taylor D. Predictors of successful extubation in children. American journal of respiratory and critical care medicine 1999;160:1562-6.

9. Toida C, Muguruma T, Miyamoto M. Detection and validation of predictors of successful extubation in critically ill children. PLoS One 2017;12:e0189787.

10. Dionisio MT, Rebelo A, Pinto C, Carvalho L, Neves JF. [Ultrasound Assessment of Ventilator-induced Diaphragmatic Dysfunction in Paediatrics]. Acta Med Port 2019;32:520-8.

11. MM IJ, Lemson J, van der Hoeven JG, Heunks LMA. The impact of critical illness on the expiratory muscles and the diaphragm assessed by ultrasound in mechanical ventilated children. Ann Intensive Care 2020;10:115.

12. Xue Y, Yang CF, Ao Y, Qi J, Jia FY. A prospective observational study on critically ill children with diaphragmatic dysfunction: clinical outcomes and risk factors. BMC Pediatr 2020;20:422.

13. Xue Y, Zhang Z, Sheng CQ, Li YM, Jia FY. The predictive value of diaphragm ultrasound for weaning outcomes in critically ill children. BMC Pulm Med 2019;19:270.

14. Wolf GK, Walsh BK, Green ML, Arnold JH. Electrical activity of the diaphragm during extubation readiness testing in critically ill children. Pediatr Crit Care Med 2011;12:e220-4.

15. van Leuteren RW, de Waal CG, de Jongh FH, Bem RA, van Kaam AH, Hutten G. Diaphragm Activity Pre and Post Extubation in Ventilated Critically Ill Infants and Children Measured With Transcutaneous Electromyography. Pediatr Crit Care Med 2021;22:950-9.

16. MacBean V, Jolley CJ, Sutton TG, et al. Parasternal intercostal electromyography: a novel tool to assess respiratory load in children. Pediatric research 2016;80:407-14.

Supplemental Table E8: Evidence to decision table for measuring of respiratory muscle strength

Should measure of respiratory muscle strength or function during airway occlusion vs. no measure of respiratory muscle strength or function be used for extubation readiness trials?	
POPULATION:	Acutely hospitalized children receiving conventional mechanical ventilation for at least 24 hours, and deemed ready for an extubation readiness trial
INTERVENTION:	Measure of respiratory muscle strength or function during airway occlusion
COMPARISON:	No measure of respiratory muscle strength or function
MAIN OUTCOMES:	Extubation failure rate, duration of mechanical ventilation, PICU length of stay, hospital length of stay, post-extubation respiratory support
SETTING:	PICU, Pediatric Cardiac ICU

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Respiratory muscle dysfunction is increasingly recognized as an important clinical problem in intensive care medicine. Studies conducted in adult critical care patients have shown that diaphragmatic function is frequently decreased, and this dysfunction is associated with adverse outcomes, including ventilation weaning failure, longer duration of IMV, prolonged ICU stay, and increased mortality. The respiratory muscle dysfunction is a multifactorial problem. It can be a complication of mechanical ventilation [ventilation induced diaphragmatic dysfunction (VIDD)], resulting from either insufficient support (muscle fatigue) or excessive support (muscle atrophy). The critical care illness and therapies also play an important role [ICU acquired diaphragmatic dysfunction (ICU-DD)]. Epidemiology of VIDD or ICU-DD in the PICU is less well known, but increasing data suggest that it is also a prevalent complication, and that respiratory muscle weakness can complicate the weaning process.	Respiratory muscle function is one component of extubation success. Respiratory weakness can therefore be a risk factor for extubation failure, and its role is probably particularly important when other risk factors (e.g upper airway obstruction, comorbidities, residual sedation, etc) are present.

Desirable Effects		
How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	Inspiratory force assessed using maximal airway pressure drop during an airway occlusion is the maneuver with the highest level of evidence in this setting. Authors report different acronyms for this concept (aPiMax, PiMax, MIP, MIF, NIF), and we will use PiMax in the rest of the document for simplicity. Seven observational studies that includes a wide age range- from infants to teenagers. Range of thresholds for PiMax: 20- 50cmH2O Range of sensitivities (ability to rule out patients without respiratory muscle strength weakness): 12.5%-100% Range of specificities (ability to identify patients with respiratory muscle strength weakness): 50-95% Range of extubation failure rate: 8.3- 22.2% The lowest sensitivity (12.5%) was in the study using a threshold of 20cmH2O, but this threshold had the highest specificity (95.6%). PiMax thresholds of 50cmH2O generally had higher but variable sensitivities (50%-100%) and variable specificities (50-94%). Of note, although the ranges of sensitivities and specificities are relatively wide, the studies consistently show an association between the level of PiMax and the extubation success rate.	Assessing respiratory muscle strength will improve the assessment of the risk of extubation failure. This knowledge may help to optimize the decision of extubation, in order to decrease the rate of extubation failure in high-risk patients. The muscle strength result is not sufficient to make a decision to extubate, but it should be taken into account and interpreted in the context of other potential risk factors. From a testing point of view, desirable consequences emanate from the test's high sensitivity (all those with weakness will be identified) and specificity (all those without weakness will be identified as not having weakness). Other methods have been used to assess the respiratory muscle function in pediatric ICU patients: diaphragm ultrasound (specifically the diaphragm thickening fraction), diaphragm electrical activity (either absolute values or related to muscle strength variables (neuro-muscular efficiency). The evidence supporting these maneuvers is more limited than for PiMax.

Study	Extubation failure	Extubation success
Farias, 2002	30 (25,47)	35 (30,40)
Harikumar, 2009	30 (21,58)	46 (20,98)
Johnston 2010	40 (34,50)	65 (64,72)
Khemani, 2-017	30 (25,40)	40 (30,50)
Shimada, 1979	37 (10)	56 (16)
Venkataraman, 2000	35 (12)	42 (15)

Undesirable Effects		
How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know	The measurement of PiMax was reported as safe in the studies. The airway occlusion can be associated with brief discomfort, cough, or desaturation. A potential undesirable effect could be a delayed extubation in patients who could have been successfully liberated but were kept intubated because their PiMax was deemed too low.	
Certainty of evidence		
What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Only observational studies have reported this measure. No studies have evaluated the clinical impact of systematically considering the respiratory muscle function in the extubation decision on clinical outcomes. The wide range of sensitivities and specificities does not allow us to have a higher level of confidence in the estimates of accuracy of the tests for PiMAx. Further, multiple thresholds were used in the studies, and we cannot be certain about which threshold is the most accurate in discriminating patients with weakness and those without weakness. When a patient is identified as weak, there is very limited evidence to support what should be done (extubation attempt in absence of other risk factors? Delaying extubation to allow respiratory muscle training or the disappearance of other risk factors? Extubation toward a non-invasive respiratory support?)	
Values		
Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ● **Possibly important uncertainty or variability**	Extubation failure and prolongation of invasive ventilation are considered important clinical outcomes by pediatric clinicians and	

○ Probably no important uncertainty or variability ○ No important uncertainty or variability	scientists, and probably by patients and parents although more research is clearly needed to explore their perception. If a patient is identified as at-risk because of respiratory muscle weakness, the risks/benefits balance of delaying extubation is extremely complex: what level of risk of failure should be accepted in order to minimize both the un-necessary prolongation of ventilation and the risks associated with extubation failure? Is an earlier extubation with non-invasive support preferable to a delayed extubation? Little evidence is available to support these decisions, which should therefore be individualized, considering the different benefits, risks, and the patient comfort and values.	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favors either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	The balance of effects favors the measurement of respiratory muscle strength to improve the assessment of the risk of extubation failure. There is insufficient evidence to determine the balance of effects of a systematic assessment of respiratory muscle function in all extubation readiness test.	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● **Varies** ○ Don't know		The costs of the test are negligible. There can be savings if the intervention could prevent extubation failure, which is associated with worse outcome and increased health care related cost. This savings may be balanced by cost related to prolonging IMV in case of delayed extubation.

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**		

Cost effectiveness Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**		

Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● **Probably increased** ○ Increased ○ Varies ○ Don't know		

Acceptability Is the intervention acceptable to key stakeholders?		

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know		The test is already currently available in clinical practice in a lot of pediatric ICUs, e.g. in the monitoring of patients with neuro-muscular disease. A wider use would probably be acceptable, although the identification of the population who will benefit is important. Some stakeholders or clinical teams may find it less justified in patients at very low risk of extubation failure, because of patient discomfort.

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		The intervention can be conducted with materials available in most PICUs (manometer or pressure line), by respiratory therapists or doctors who are part of the team, and it is fast, so it would not cause any delay.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	**Possibly important uncertainty or variability**	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the	**Probably favors the intervention**	Favors the intervention	Varies	Don't know

	JUDGEMENT						
			intervention or the comparison				
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
o	o	o	o	o

CONCLUSIONS

Recommendation

- We suggest using measurement of maximal inspiratory pressure during airway occlusion (PiMax) as an element of ERT bundle for critically ill children at risk for muscle weakness or at risk for extubation failure (Conditional recommendation, very low certainty of evidence).

Justification

PiMax measurement is relatively simple to do in the clinical workflow. It provides important information that is associated with the risk of extubation failure, as ascertained by consistent studies. As the evidence is supported by observational studies only, and the impact of a systematic use of this test has not been evaluated, it is unclear whether this test will be useful in all patients. However, the desirable effects likely outweigh the undesirable effects in patients who have other risks of extubation failure or muscle weakness.

Subgroup considerations

Although pediatric evidence is limited, some patients may be more prone to develop respiratory muscles dysfunction (e.g patients with prolonged ventilation, neuromuscular disease, prolonged steroid or neuro-muscular blocker agents, sepsis, nutrition, chronic illness). Assessing the respiratory strength in these patients appear therefore particularly important.

In patients with other risk factors of extubation failure, the additional impact of respiratory muscle weakness may be particularly important, as it has been observed in patients with upper airway obstruction.

Implementation considerations

The PiMax should be assessed in a standardized way.

The pressure should be monitored at the extremity of the endotracheal tube (before the Y piece), with a manometer or another pressure monitoring system.

The maneuver should be explained to the patient and the parents. An occlusion should be applied at the endotracheal tube extremity, during the expiration, for at least 3 to 5 breaths. The maximal inspiratory negative pressure over the occlusion should be noted.

Monitoring and evaluation

Research priorities

Identify optimal population who will benefit and optimal threshold
Improve feasibility (occlusion on the ventilator)
Other methods: diaphragm US, Edi data from NAVA

D. Air leak test and corticosteroids

Supplemental Table E9: Search strategies for air leak test and corticosteroids

Air leak test question
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should an endotracheal tube air leak test be measured prior to extubation to predict post-extubation upper airway obstruction?

P Pediatric patients receiving conventional mechanical ventilation more than 24 hours

I Measurement of endotracheal tube air leak test as part of extubation readiness assessment

C No endotracheal tube air leak test prior to extubation

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), VFDs, PICU length of stay, hospital length of stay, post-extubation upper airway obstruction (UAO), new tracheostomy rate, mortality

Corticosteroids question
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should systemic corticosteroids be administered prior to extubation to prevent post-extubation upper airway obstruction?

P Pediatric patients receiving conventional mechanical ventilation more than 24 hours

I Use of systemic corticosteroids prior to extubation to prevent post-extubation upper airway obstruction

C No use of systemic corticosteroids prior to extubation to prevent post-extubation upper airway obstruction

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), VFDs, PICU length of stay, hospital length of stay, post-extubation upper airway obstruction, new tracheostomy rate, GI bleeding, hyperglycemia, mortality.

I. **MEDLINE (Ovid)**
Databases selected: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)

Line	Query
1	Adolescent/
2	Adolescen*.mp.
3	Teen*.mp.
4	Youth*.mp.
5	exp Child/

6	Child*.mp.
7	Infant/
8	Infant, Newborn/
9	Infant*.mp.
10	Infanc*.mp.
11	Newborn*.mp.
12	Neonat*.mp.
13	Pediatrics/
14	P?ediatric*.mp.
15	Hospitals, Pediatric/
16	Intensive Care Units, Pediatric/
17	PICU*.mp.
18	(Kid or kids).mp.
19	Toddler*.mp.
20	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21	(Adaptive adj2 Support Ventilat*).mp.
22	Airway Extubation/
23	Airway extubat*.mp.
24	Artificial Respirati*.mp.
25	((intubation or extubation*) adj3 (airway or tracheal or intratracheal or endotracheal)).mp.
26	exp Intermittent Positive-Pressure Breathing/
27	Intermittent Positive-Pressure Breathing.mp.
28	exp Intermittent Positive-Pressure Ventilation/
29	Intermittent Positive-Pressure Ventilat*.mp.
30	Intubation, Intratracheal/
31	Mechanical Ventilat*.mp.
32	Neurally Adjusted Ventilatory Assist*.mp.
33	open lung ventilat*.mp.
34	Peep.mp.
35	Positive End Expiratory Pressure*.mp.
36	exp Positive-Pressure Respiration/
37	Positive-Pressure Ventilat*.mp.
38	pressure controlled ventilat*.mp.
39	Proportional Assist Ventilat*.mp.
40	Reintubat*.mp.
41	Respiration, Artificial/
42	Respirator Weaning*.mp.
43	Ventilator*.mp.
44	(Ventilat* adj3 Liberation*).mp.
45	exp Ventilators, Mechanical/
46	exp Ventilator Weaning/
47	Ventilator* Weaning*.mp.
48	Ventilation Weaning*.mp.
49	21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50	Dexamethasone/
51	Dexamethasone*.mp.
52	Adrenal Cortex Hormones/
53	((adrenal or adreno or adrenocortical or corticoadrenal) adj2 (steroid* or hormone*)).mp.
54	adrenocorticosteroid*.mp.

55	Corticoid*.mp.
56	Corticosteroid*.mp.
57	Cortico steroid*.mp.
58	Cortical steroid*.mp.
59	Glucocorticoids/
60	Glucocorticoid*.mp.
61	Hydrocortisone/
62	Hydrocortisone*.mp.
63	Cortisone/
64	Cortisone*.mp.
65	Prednisolone/
66	prednisolone*.mp.
67	Predonine*.mp.
68	Methylprednisolone/
69	Methylprednisolone*.mp.
70	Prednisone/
71	Prednison*.mp.
72	Anti-Inflammatory Agents/
73	Anti inflammator*.mp.
74	Antiinflamator*.mp.
75	Antiinflammation*.mp.
76	Anti inflammation*.mp.
77	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
78	airleak test*.mp.
79	leak test*.mp.
80	(leak adj5 extubation*).mp.
81	(leak adj3 endotracheal).mp.
82	tube leak*.mp.
83	cuff leak*.mp.
84	cuffleak*.mp.
85	leak pressure*.mp.
86	stridor*.mp.
87	inspiratory flow limitation*.mp.
88	(puls* adj2 paradox*).mp.
89	laryngeal ultrasound*.mp.
90	larynx ?edema*.mp.
91	laryngeal ?edema*.mp.
92	Racepinephrine/
93	Racepinefrine*.mp.
94	Racepinephrine*.mp.
95	racinephrine*.mp.
96	(racemic adj2 (epinephrine* or adrenaline*)).mp.
97	Racadrenalin*.mp.
98	vaponephrin*.mp.
99	Vaponefrin*.mp.
100	Micronefrin*.mp.
101	Micronephrine*.mp.
102	Mikronephrin*.mp.
103	78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102

104	77 or 103
105	20 and 49 and 104

II. Embase (Elsevier)

Line	Query
#1	'adolescent'/exp
#2	'adolescence'/de
#3	adolescen*
#4	teen*
#5	youth*
#6	'child'/exp
#7	child*
#8	'infant'/exp
#9	'infancy'/exp
#10	'newborn'/exp
#11	infant*
#12	infanc*
#13	newborn*
#14	neonat*
#15	'pediatrics'/de
#16	p$ediatric*
#17	'pediatric intensive care unit'/de
#18	picu*
#19	kid OR kids
#20	'toddler'/exp
#21	toddler*
#22	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23	adaptive NEAR/2 support NEXT/1 ventilat*
#24	'extubation'/de
#25	'airway extubat*'
#26	(intubation* OR extubation*) NEAR/3 (airway OR tracheal OR intratracheal OR endotracheal)
#27	'intermittent mandatory ventilation'/exp
#28	'intermittent positive-pressure breathing'
#29	'intermittent positive pressure ventilation'/exp
#30	'intermittent positive-pressure ventilat*'
#31	'endotracheal intubation'/exp
#32	'invasive ventilation'/exp
#33	'inverse ratio ventilation'/de
#34	'mechanical ventilat*'
#35	'neurally adjusted ventilatory assist*'
#36	'noninvasive positive pressure ventilation'/exp
#37	'open lung ventilat*'
#38	peep
#39	'positive end expiratory pressure ventilation'/exp
#40	'positive end expiratory pressure*'
#41	'positive pressure ventilation'/de
#42	'positive-pressure ventilat*'
#43	'pressure controlled ventilation'/de
#44	'pressure controlled ventilat*'

#45	'pressure support ventilation'/de
#46	'proportional assist ventilat*'
#47	'protective ventilation'/exp
#48	reintubat*
#49	'artificial ventilation'/de
#50	'respirator weaning*'
#51	'tracheal extubation'/de
#52	'ventilator'/de
#53	ventilator*
#54	ventilat* NEAR/3 liberation*
#55	'mechanical ventilator'/de
#56	'ventilator weaning'/de
#57	'ventilator* weaning*'
#58	'ventilation weaning*'
#59	'volume controlled ventilation'/exp
#60	'artificial respirati*'
#61	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
#62	'air leak'/exp
#63	'air leak test'/exp
#64	'airleak test*'
#65	'leak test*'
#66	leak NEAR/5 extubation*
#67	leak NEAR/3 endotracheal
#68	'tube leak*'
#69	'cuff leak test'/exp
#70	'cuff leak*' OR cuffleak*
#71	'leak pressure*'
#72	'stridor'/exp
#73	stridor*
#74	'inspiratory flow limitation*'
#75	'paradoxical pulse'/exp
#76	paradox* NEAR/2 puls*
#77	'laryngeal ultrasound*'
#78	'larynx edema'/exp
#79	'larynx $edema*'
#80	'laryngeal $edema*'
#81	'racepinefrine'/exp
#82	racepinefrine*
#83	racepinephrine*
#84	racinephrine*
#85	racemic NEAR/2 (epinephrine* OR adrenaline*)
#86	racadrenalin*
#87	vaponephrin*
#88	vaponefrin*
#89	micronefrin*
#90	micronephrine*
#91	mikronephrin*

#92	#62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91
#93	'dexamethasone'/de
#94	dexamethasone*
#95	(adrenal OR adreno OR adrenocortical OR corticoadrenal) NEAR/2 (steroid* OR hormone*)
#96	adrenocorticosteroid*
#97	corticoid*
#98	'corticosteroid'/de
#99	corticosteroid*
#100	'cortico steroid*'
#101	'cortical steroid*'
#102	'glucocorticoid'/de
#103	glucocorticoid*
#104	'hydrocortisone'/exp
#105	hydrocortisone*
#106	'cortisone'/exp
#107	cortisone*
#108	'prednisolone'/de
#109	prednisolone*
#110	predonine*
#111	'methylprednisolone'/exp
#112	methylprednisolone*
#113	'prednisone'/exp
#114	prednison*
#115	'antiinflammatory agent'/de
#116	'anti inflammator*'
#117	antiinflamator*
#118	antiinflammation*
#119	'anti inflammation*'
#120	#93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119
#121	#92 OR #120
#122	#22 AND #61 AND #121

III. CINAHL Complete (EBSCO)

Line	Query
S1	"airleak test*"
S2	"leak test*"
S3	leak N5 extubation*
S4	leak N3 endotracheal
S5	"tube leak*"
S6	"cuff leak*"
S7	Cuffleak*
S8	"leak pressure*"
S9	stridor*
S10	"inspiratory flow limitation*"
S11	paradox* N2 puls*
S12	"laryngeal ultrasound*"

S13	"larynx #edema*"
S14	(MH "Laryngeal Edema")
S15	"laryngeal #edema*"
S16	racepinefrine*
S17	racepinephrine*
S18	racinephrine*
S19	racemic N2 (epinephrine* OR adrenaline*)
S20	Racadrenalin*
S21	vaponephrin*
S22	vaponefrin*
S23	micronefrin*
S24	micronephrine*
S25	mikronephrin*
S26	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25
S27	"Anti inflammation*"
S28	Antiinflammation*
S29	Antiinflamator*
S30	"Anti inflammator*"
S31	(MH "Antiinflammatory Agents")
S32	Prednison*
S33	(MH "Prednisone")
S34	Methylprednisolone*
S35	Predonine*
S36	prednisolone*
S37	(MH "Prednisolone+")
S38	Cortisone*
S39	Hydrocortisone*
S40	Glucocorticoid*
S41	(MH "Glucocorticoids+")
S42	"Cortical steroid*"
S43	"Cortico steroid*"
S44	Corticosteroid*
S45	Corticoid*
S46	adrenocorticosteroid*
S47	(adrenal OR adreno OR adrenocortical OR corticoadrenal) N2 (steroid* OR hormone*)
S48	(MH "Adrenal Cortex Hormones")
S49	Dexamethasone*
S50	(MH "Dexamethasone")
S51	S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50
S52	Toddler*
S53	Kid OR kids
S54	PICU*
S55	(MH "Intensive Care Units, Pediatric")
S56	P#ediatric*
S57	(MH "Pediatrics")
S58	Neonat*
S59	Newborn*
S60	Infanc*
S61	Infant*

S62	(MH "Infant, Newborn")
S63	(MH "Infant") OR (MH "Infant, Hospitalized") OR (MH "Infant, High Risk")
S64	Child*
S65	(MH "Child") OR (MH "Child, Hospitalized") OR (MH "Child, Medically Fragile") OR (MH "Child, Preschool")
S66	Youth*
S67	Teen*
S68	Adolescen*
S69	(MH "Adolescence+")
S70	S52 OR S53 OR S54 OR S55 OR S56 OR S57 OR S58 OR S59 OR S60 OR S61 OR S62 OR S63 OR S64 OR S65 OR S66 OR S67 OR S68 OR S69
S71	Ventilation Weaning*
S72	ventilator* weaning*
S73	(MH "Ventilator Weaning")
S74	(MH "Ventilators, Mechanical")
S75	ventilat* N3 liberation*
S76	ventilator*
S77	'respirator weaning*'
S78	(MH "Respiration, Artificial")
S79	reintubat*
S80	proportional assist ventilat*
S81	(MH "Pressure Support Ventilation")
S82	pressure controlled ventilat*
S83	positive-pressure ventilat*
S84	(MH "Positive Pressure Ventilation")
S85	Positive End Expiratory Pressure*
S86	(MH "Positive End- Expiratory Pressure")
S87	peep
S88	open lung ventilat*
S89	neurally adjusted ventilatory assist*
S90	mechanical ventilat*
S91	(MH "Mandatory Minute Volume Ventilation")
S92	(MH "Inverse Ratio Ventilation")
S93	(MH "Intubation, Intratracheal")
S94	Intermittent Positive- Pressure Ventilat*
S95	(MH "Intermittent Positive Pressure Ventilation")
S96	Intermittent Positive- Pressure Breathing
S97	(MH "Intermittent Positive Pressure Breathing")
S98	(intubation* OR extubation*) N3 (airway OR tracheal OR intratracheal OR endotracheal)
S99	artificial respirati*
S100	airway extubat*
S101	(MH "Extubation")
S102	adaptive N2 support ventilat*
S103	S71 OR S72 OR S73 OR S74 OR S75 OR S76 OR S77 OR S78 OR S79 OR S80 OR S81 OR S82 OR S83 OR S84 OR S85 OR S86 OR S87 OR S88 OR S89 OR S90 OR S91 OR S92 OR S93 OR S94 OR S95 OR S96 OR S97 OR S98 OR S99 OR S100 OR S101 OR S102
S104	S26 OR S51
S105	S70 AND S103 AND S104

Supplemental Figure E5: PRSIMA chart for air leak test

Identification of new studies via databases and registers

Identification

Records identified from:
Databases (n = 14,285)
Registers (n = 0)

Records removed before screening:
Duplicate records (n = 3,050)

Screening

Records screened
(n = 11,235)

Records excluded
(n = 11,107)

Reports sought for retrieval
(n = 128)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 128)

Reports excluded:
Conference abstract (n = 26)
Letter/comment (n = 17)
Wrong intervention (n = 28)
Wrong study design (n = 13)
Narrative review (n = 9)
Wrong setting (n = 10)
NICU population (n = 7)
Adult population (n = 4)
Wrong indication (n = 2)
Wrong comparator (n = 1)
Wrong outcome (n = 3)

Included

New studies included in review
(n = 8)
Reports of new included studies
(n = 8)

Supplemental Figure E6: PRSIMA chart for corticosteroids

Identification of new studies via databases and registers		

Records identified from:
Databases (n = 14,285)
Registers (n = 0)

Records removed before screening:
Duplicate records (n = 3,050)

Records screened
(n = 11,235)

Records excluded
(n = 11,107)

Reports sought for retrieval
(n = 128)

Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 128)

Reports excluded:
Conference abstract (n = 26)
Letter/comment (n = 17)
Wrong intervention (n = 28)
Wrong study design (n = 13)
Narrative review (n = 9)
Wrong setting (n = 10)
NICU population (n = 7)
Adult population (n = 4)
Wrong indication (n = 2)
Wrong comparator (n = 1)
Metanalysis (n = 2)
Clinical guideline (n = 1)

New studies included in review
(n = 8)
Reports of new included studies
(n = 8)

Identification

Screening

Included

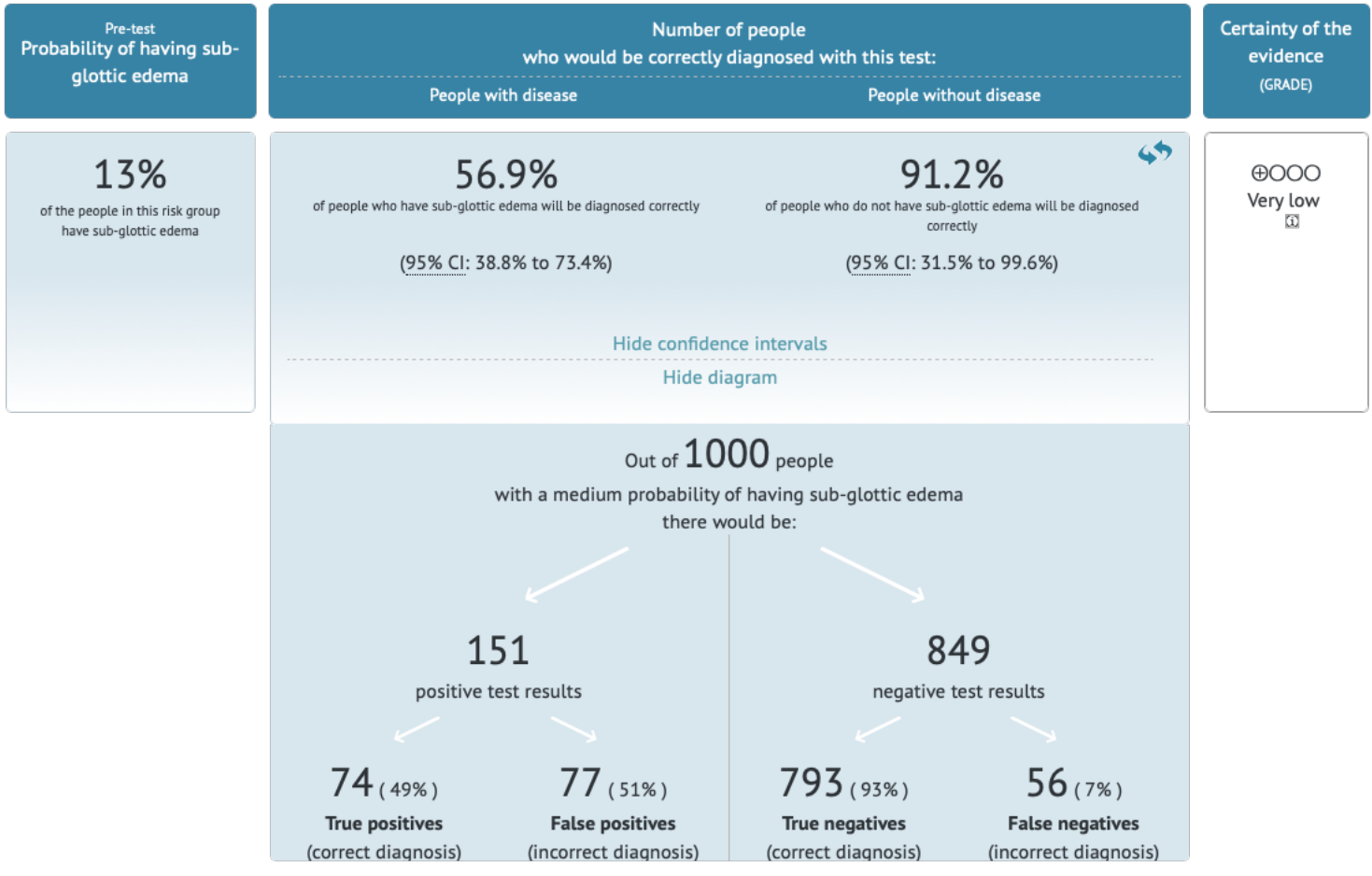## Supplemental Table E10: Evidence table for air leak test

I. Cuffed ETT

Question: Should the Air leak test be used to predicate upper airway obstruction (UAO) in intubated critically ill with cuffed ETT?

Sensitivity	0.57 (95% CI: 0.39 to 0.73)
Specificity	0.91 (95% CI: 0.32 to 1.00)

Prevalence	13%	25%	45%

| Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 13%	pre-test probability of 25%	pre-test probability of 45%	
True positives (patients with UAO)	2 studies 211 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	not serious	serious[c]	none	74 (50 to 95)	142 (97 to 184)	256 (175 to 330)	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having UAO)								56 (35 to 80)	108 (66 to 153)	194 (120 to 275)	
True negatives (patients without UAO)	2 studies 211 patients	cross-sectional (cohort type accuracy study)	serious[a]	serious[b]	serious[d]	serious[c]	none	793 (274 to 867)	684 (236 to 747)	502 (173 to 548)	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having UAO)								77 (3 to 596)	66 (3 to 514)	48 (2 to 377)	

Explanations

a. Lack of blinding for the assessment of stridor; subjective assessment of stridor

b. Cuffed and uncuffed ETT outcomes not reported separately in **Mhanna 2002**

c. Lower margin of confidence interval possibility of test has poor sensitivity/specificity

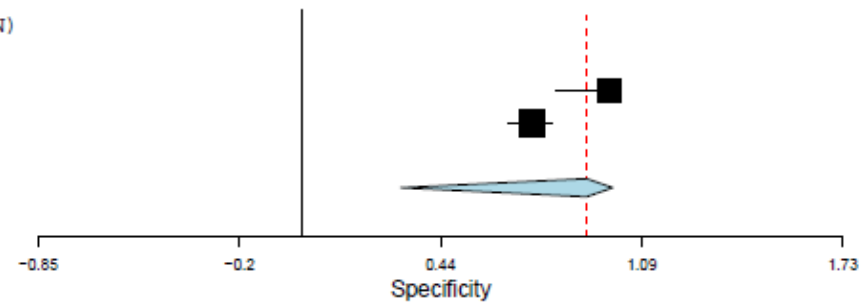d. Effect estimates and confidence intervals not overlapping much

Pre-test Probability of having sub-glottic edema	Number of people who would be correctly diagnosed with this test:		Certainty of the evidence (GRADE)
	People with disease	People without disease	
13% of the people in this risk group have sub-glottic edema	**56.9%** of people who have sub-glottic edema will be diagnosed correctly (95% CI: 38.8% to 73.4%)	**91.2%** of people who do not have sub-glottic edema will be diagnosed correctly (95% CI: 31.5% to 99.6%)	⊕○○○ Very low

Hide confidence intervals

Hide diagram

Out of **1000** people
with a medium probability of having sub-glottic edema
there would be:

151
positive test results

849
negative test results

74 (49%)
True positives
(correct diagnosis)

77 (51%)
False positives
(incorrect diagnosis)

793 (93%)
True negatives
(correct diagnosis)

56 (7%)
False negatives
(incorrect diagnosis)

Outcome: Upper airway obstruction. Forest plots for pooled sensitivities and specificities.

Sensitivity

Studies	Estimate (95% C.I.)	TP/(TP + FN)
Mhanna 2002	0.563 (0.241, 0.839)	4/7
Khemani 2016	0.571 (0.360, 0.760)	12/21
Overall (I^2=0 % , P=0.965)	0.569 (0.388, 0.734)	16/28
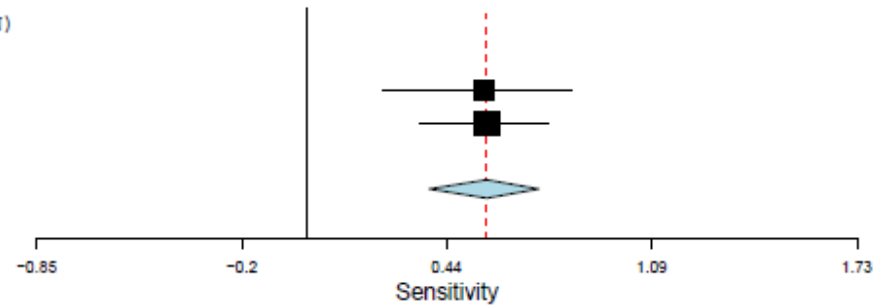
Specificity

Studies	Estimate (95% C.I.)	TN/(FP + TN)
Mhanna 2002	0.986 (0.813, 0.999)	35/35
Khemani 2016	0.736 (0.660, 0.801)	109/148
Overall (I^2=80.29 % , P=0.024)	0.912 (0.315, 0.996)	144/183

Outcome: Reintubation. Forest plots for pooled sensitivities and specificities.

Sensitivity

Studies	Estimate (95% C.I.)	TP/(TP + FN)
Mhanna 2002	0.167 (0.010, 0.806)	0/2
Khemani 2016	0.364 (0.143, 0.661)	4/11
Overall (I^2=0 % , P=0.530)	0.330 (0.136, 0.606)	4/13

Specificity

Studies	Estimate (95% C.I.)	TN/(FP + TN)
Mhanna 2002	0.893 (0.758, 0.957)	37/41
Khemani 2016	0.703 (0.627, 0.769)	111/158
Overall (I^2=82.44 % , P=0.017)	0.803 (0.545, 0.933)	148/199
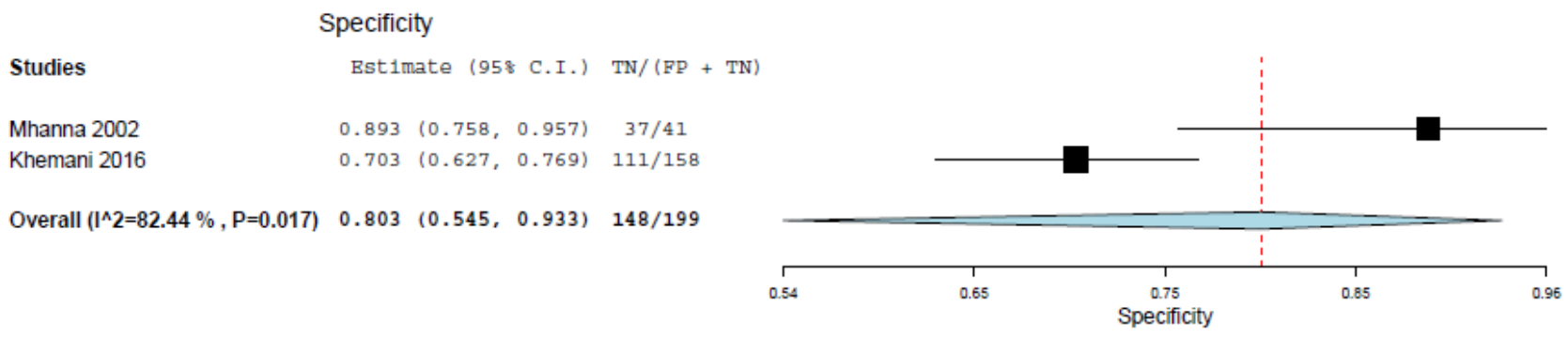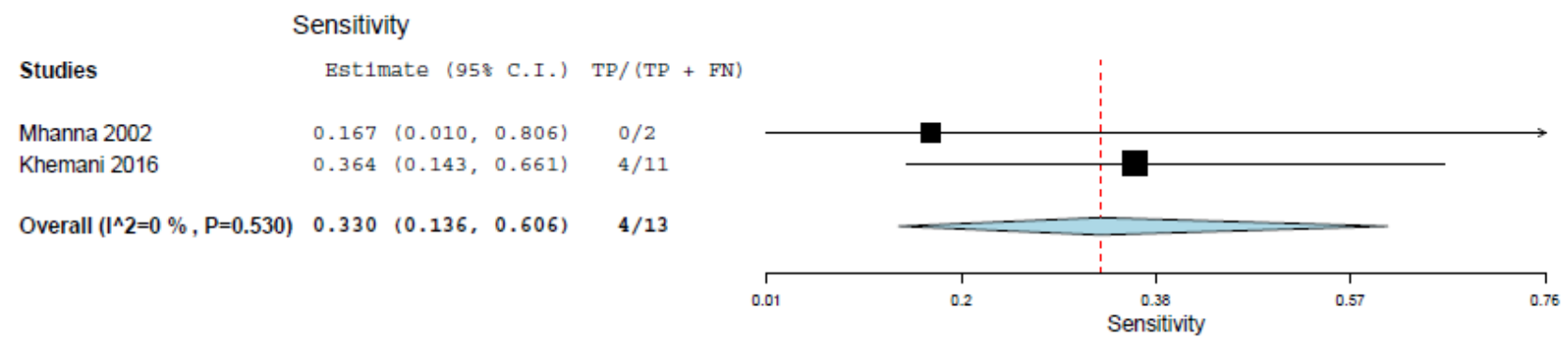
II. Uncuffed ETT

Question: Should Air leak test be used to predicate upper airway obstruction (UAO) in intubated critically ill with **uncuffed** ETT?

Sensitivity	0.37 (95% CI: 0.23 to 0.54)
Specificity	0.56 (95% CI: 0.40 to 0.71)

Prevalence	Low: 12%	Medium: 23%	High: 45%

Outcome	№ of studies (№ of patients)	Study design	Factors that may decrease certainty of evidence					Effect per 1,000 patients tested			Test accuracy CoE
			Risk of bias	Indirectness	Inconsistency	Imprecision	Publication bias	pre-test probability of 12%	pre-test probability of 23%	pre-test probability of 45%	
True positives (patients with UAO)	4 studies 451 patients	cross-sectional (cohort type accuracy study)	very serious[a]	serious[b]	very serious[c]	not serious	none	44 (27 to 64)	85 (52 to 123)	166 (102 to 241)	⊕◯◯◯ Very low
False negatives (patients incorrectly classified as not having UAO)								76 (56 to 93)	145 (107 to 178)	284 (209 to 348)	
True negatives (patients without UAO)	4 studies 451 patients	cross-sectional (cohort type accuracy study)	very serious[a]	serious[b]	very serious[c]	serious[d]	none	493 (349 to 626)	431 (306 to 547)	308 (218 to 391)	⊕◯◯◯ Very low
False positives (patients incorrectly classified as having UAO)								387 (254 to 531)	339 (223 to 464)	242 (159 to 332)	

Explanations

a. No blinding for assessment of UAO; pre-extubation steroids (confounding intervention) provided to some participants
b. Cuffed and uncuffed ETT status not reported separately in **Mhanna 2002** and **Suominen 2007**.
c. Point estimates and confidence intervals not overlapping much between studies.
d. Upper margin of confidence interval may suggest good specificity but lower margin of confidence interval suggests poor specificity

Pre-test Probability of having sub-glottic edema	Number of people who would be correctly diagnosed with this test:		Certainty of the evidence (GRADE)
	People with disease	People without disease	
23% of the people in this risk group have sub-glottic edema	**36.8%** of people who have sub-glottic edema will be diagnosed correctly (95% CI: 22.7% to 53.5%)	**56.0%** of people who do not have sub-glottic edema will be diagnosed correctly (95% CI: 39.7% to 71.1%)	⊕○○○ Very low

Hide confidence intervals

Hide diagram

Out of **1000** people with a medium probability of having sub-glottic edema there would be:

424 positive test results

576 negative test results

85 (20%) **True positives** (correct diagnosis)

339 (80%) **False positives** (incorrect diagnosis)

431 (75%) **True negatives** (correct diagnosis)

145 (25%) **False negatives** (incorrect diagnosis)

Outcome: Upper airway obstruction. Forest plots for pooled sensitivities and specificities.

Outcome: Reintubation. Forest plots for pooled sensitivities and specificities.

Sensitivity

Studies	Estimate (95% C.I.)	TP/(TP + FN)
Mhanna 2002	0.333 (0.043, 0.846)	1/3
Suomenin 2007	0.750 (0.109, 0.987)	1/1
Khemani 2016	0.435 (0.252, 0.637)	10/23
Overall (I^2=0 % , P=0.667)	0.443 (0.272, 0.629)	12/27
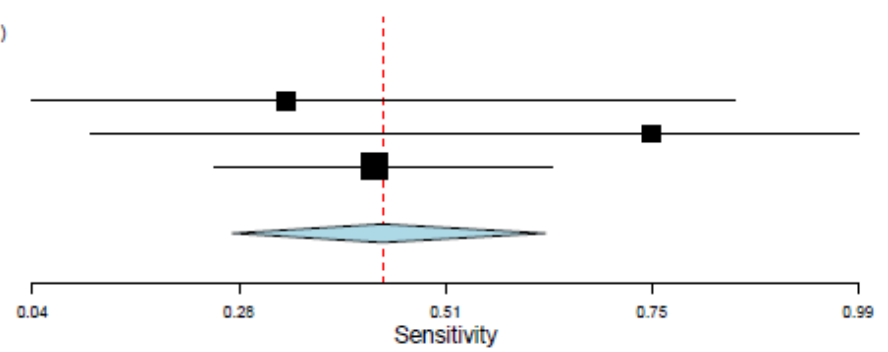
Specificity

Studies	Estimate (95% C.I.)	TN/(FP + TN)
Mhanna 2002	0.828 (0.716, 0.902)	53/64
Suomenin 2007	0.464 (0.321, 0.614)	19/41
Khemani 2016	0.424 (0.360, 0.491)	92/217
Overall (I^2=92.74 % , P< 0.001)	0.586 (0.327, 0.805)	164/322
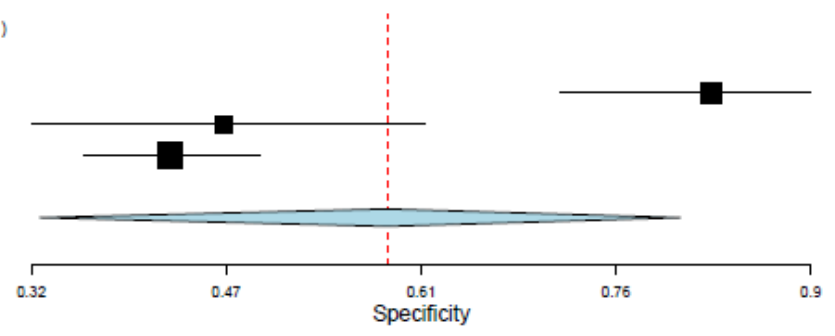
Supplemental Table E11: Evidence to decision table for air leak test

Should air leak test vs. no air leak test be used for extubation readiness trial?	
POPULATION:	Pediatric patients receiving conventional mechanical ventilation more than 24 hours
INTERVENTION:	Air leak test
COMPARISON:	No air leak test
MAIN OUTCOMES:	Upper airway obstruction; Extubation failure; Length of invasive mechanical ventilation;
SETTING:	PICU, Pediatric Cardiac ICU
CONFLICT OF INTERESTS:	None

Assessment

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o No o Probably no o Probably yes ● **Yes** o Varies o Don't know	Air leak tests are commonly performed at the bedside to predict the likelihood of post extubation stridor prior to extubation. There is high variability in the technique and interpretation of the results.	

Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Trivial o Small ● **Moderate** o Large o Varies o Don't know	<table><tr><th>Outcomes</th><th>Impact</th></tr><tr><td>Upper airway obstruction</td><td>**Range of thresholds:** a) Air leak (%): 10-11% b) 25-30cm H2O</td></tr></table>	Effects are highly dependent on whether the ETT is cuffed or uncuffed. In nearly every study and or sub-analysis, the air leak test had better accuracy to predict UAO when used with cuffed ETTs compared with when used with uncuffed ETTs.

		Range of sensitivities:
		Mostly cuffed ETTs: 57-88%
		Mostly uncuffed ETTs: 20-57%
		Range of specificities:
		Mostly cuffed ETTs – 53-100%; pooled sensitivity0.57, 95% CI 0.39, 0.73; pooled specificity 0.91, 95%CI 0.32, 1.00
		Mostly uncuffed ETTs – 67-84%; pooled sensitivity0.37, 95% CI 0.23, 0.54; pooled specificity 0.56, 9%CI 0.40, 0.71
		Range of UAO rate: 10-36%
		With a 25% UAO prevalence: a) 867 per 1000 are correctly diagnosed (true positive and true negative) with cuffed ETT; b) 516 per 1000 are correctly diagnosed (true positive and true negative) with uncuffed ETT.
	Extubation failure	**Range of thresholds:** 25- 30cm H2O
		Pooled sensitivities:
		Cuff ETT: 0.330 (95% CI 0.136, 0.606)
		Uncuffed ETT: 0.443 (95%CI 0.272, 0.629)
		Range of specificities:
		Cuff ETT: 0.803 (95% CI 0.545, 0.933)
		Uncuffed ETT: 0.586 (95%CI 0.327, 0.805)
		Range of extubation failure rate: 3.6% - 15.2%
	Length of invasive mechanical ventilation	Data mean (SD)
		For <7 yr old: (Mostly uncuffed) <30 mmHg: 7.4 (12.9), >=30 mmHg: 6.2 (6.6), NS.
		For >=7 yr old: (Mostly cuffed) <30mmHg 2.7 (2.9), >=30 mmHg: 20 (5.5), p=0.001

Being able to accurately predict UAO prior to extubation can help to identify a higher risk patient that may benefit from a course of steroids prior to extubation. Since UAO is an important cause of extubation

	failure, accurate prediction of UAO and use pre-extubation steroids will result in reduced incidence of extubation failure.	
Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know	Patients that are inaccurately identified as a high risk for UAO based on the results of this test may result in increased length of ventilation (few hours) if clinicians are waiting to administer steroids prior to extubation.	
Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	Most studies utilize a small sample size and subjective outcome of post extubation stridor as the outcome. In the **Khemani 2016** study an objective measure is used to classify upper airway obstruction with a very large sample size which increases certainty. Certainty of evidence was also reduced by serious risk of bias (subjective assessment of UAO, multifactorial causation of extubation failure, lack of blinding in many of the studies), indirectness due to some studies not reporting outcomes of cuffed and uncuffed ETT separately, imprecision due to low pooled sensitivities and specificities and wide 95% CIs.	
Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	Clinicians and patients both value the outcomes associated with an accurate diagnoses of UAO – recognition of a high-risk patient that may benefit from steroids to minimize risk of post extubation upper airway obstruction. A false positive would also be a cause of concern to both clinicians and patients as it may inadvertently lead to prolonged ventilation while waiting to complete a course of steroids. It is likely that patients and clinicians value the prediction of post-extubation UAO potentially leading to extubation failure more than an increase of a few hours of mechanical ventilation.	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ● **Probably favors the comparison** ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	With cuffed ETTs the higher predictive ability of the air leak test to identify patients at higher risk for post extubation stridor outweighs the harms as potential few hours increase in length of ventilation to receive steroids since a failed extubation caused by upper airway obstruction may result in an increase in length of ventilation by at least 2 or more days. With uncuffed ETTs the low predictive ability of the air leak test, which is essentially a coin flip, does not justify the potentially harms.	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● **Moderate savings** ○ Large savings ○ Varies ○ Don't know	Performing an air leak test is a low-cost intervention that takes less than two minutes by the care giver responsible for ventilator management with pressure manometer equipment that is readily available at most PICUs. Being able to avoid reintubation or prolonged non-invasive ventilation caused by upper airway obstruction can result in high-cost savings by reducing the length of ventilation and hospitalization.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No evidence	

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No evidence	

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Likely no impact	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know		

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	**Probably favors the comparison**	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**

	JUDGEMENT						
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

Conclusions

Recommendation

- We suggest using the air leak test in children with **cuffed** endotracheal tube (ETT) as part of ERT bundle to assess the risk for the development of post-extubation upper airway obstruction (UAO). (Conditional recommendation, very low certainty evidence).

Justification

Multiple studies have demonstrated predictive ability of the air leak test to predict the incidence of post extubation upper airway obstruction when using cuffed ETTs.
In studies using primarily uncuffed ETTs there appears to be no diagnostic utility of the air leak test.

Subgroup considerations

1. **Cuffed ETT** – suggest performing an air leak test prior to extubation.
2. **Uncuffed ETT** – suggest not performing an air leak test prior to extubation.

Implementation considerations

The air leak test should be performed in a standardized way. To complete the test the patient should be supine with the head in a midline position, then the cuff is deflated completely – allowing time for suctioning if required. The patient is then manually ventilated to a maximal pressure of 30 cmH2O – if an air leak that is audible to the naked ear with a pressure <25cmH2O they have passed the air leak test and is considered to be a low risk for developing post extubation stridor. If no air leak is heard at a pressure of >25 cmH2O they have failed the air leak test and are considered a higher risk of post extubation stridor and may benefit from a course of steroids prior to extubation.

Supplemental Table E12: Evidence table for corticosteroids

A. Forest plots for pairwise comparison: Reintubation

Study or Subgroup	Dexamethasone Events	Total	No Dexamethasone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Tellez 1991 (0.5mg/kg/dose)	9	76	4	77	21.5%	2.45 [0.72, 8.33]	1991
Anene 1996 (0.5mg/kg/dose)	0	31	7	32	8.4%	0.05 [0.00, 0.99]	1996
Malhotra 2009 (0.5mg/kg/dose)	9	30	19	30	23.3%	0.25 [0.08, 0.73]	2009
Cesar 2009 (0.2mg/kg/dose)	1	16	1	16	8.6%	1.00 [0.06, 17.51]	2009
de Carvalho 2020 (0.25mg/kg/dose)	3	41	8	44	19.4%	0.36 [0.09, 1.45]	2020
Ritu 2020 (0.15mg/kg/dose)	4	42	4	38	18.8%	0.89 [0.21, 3.86]	2020
Total (95% CI)		236		237	100.0%	0.55 [0.21, 1.46]	
Total events	26		43				

Heterogeneity: Tau² = 0.77; Chi² = 11.28, df = 5 (P = 0.05); I² = 56%
Test for overall effect: Z = 1.20 (P = 0.23)

Favours [Dexamethasone] Favours [No Dexamethason]
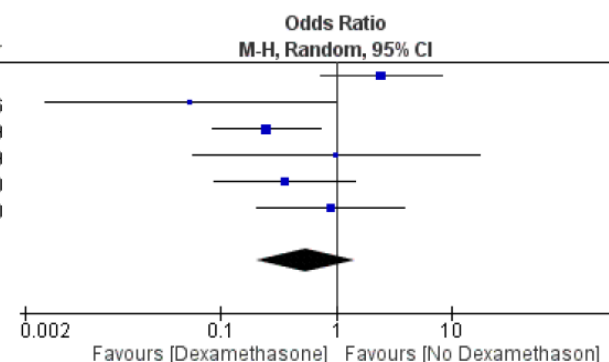
B. Forest plots for pairwise comparison: Upper airway obstruction

Study or Subgroup	Dexamethasone Events	Total	No Dexamethasone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Tellez 1991 (0.5mg/kg/dose)	16	76	23	77	24.6%	0.63 [0.30, 1.31]	1991
Anene 1996 (0.5mg/kg/dose)	14	31	28	32	14.6%	0.12 [0.03, 0.42]	1996
Cesar 2009 (0.2mg/kg/dose)	10	16	12	16	11.4%	0.56 [0.12, 2.54]	2009
Malhotra 2009 (0.5mg/kg/dose)	8	30	11	30	17.2%	0.63 [0.21, 1.88]	2009
Ritu 2020 (0.15mg/kg/dose)	18	42	21	38	21.2%	0.61 [0.25, 1.47]	2020
de Carvalho 2020 (0.25mg/kg/dose)	2	41	14	44	11.0%	0.11 [0.02, 0.52]	2020
Total (95% CI)		236		237	100.0%	0.40 [0.21, 0.73]	
Total events	68		109				

Heterogeneity: Tau² = 0.26; Chi² = 9.20, df = 5 (P = 0.10); I² = 46%
Test for overall effect: Z = 2.95 (P = 0.003)

Favours [Dexamethasone] Favours [No Dexamethason]
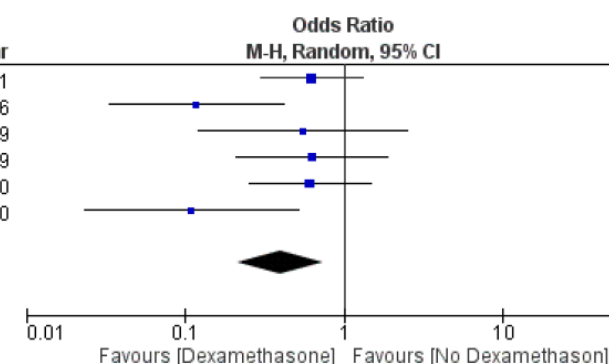
C. Forest plots for pairwise comparison: IMV duration

Study or Subgroup	Dexamethasone Mean	SD	Total	No Dexamethasone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
de Carvalho 2020 (0.25mg/kg/dose)	5.76	2.6	41	6.46	5.77	44	10.8%	-0.70 [-2.58, 1.18]
Malhotra 2009 (0.5mg/kg/dose)	5.9	2.76	30	5.43	2.01	30	25.7%	0.47 [-0.75, 1.69]
Tellez 1991 (0.5mg/kg/dose)	3.03	2.44	76	3.52	2.46	77	63.5%	-0.49 [-1.27, 0.29]
Total (95% CI)			147			151	100.0%	-0.27 [-0.89, 0.35]

Heterogeneity: Tau² = 0.00; Chi² = 1.92, df = 2 (P = 0.38); I² = 0%
Test for overall effect: Z = 0.84 (P = 0.40)
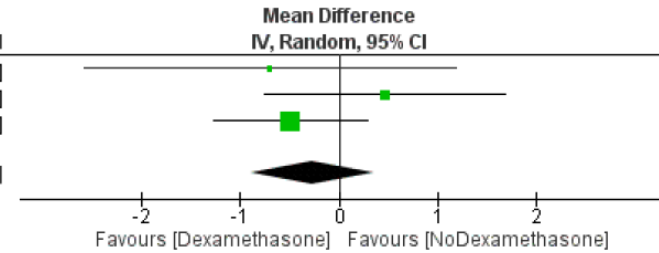
D. Forest plots for pairwise comparison: PICU LOS

Study or Subgroup	Dexamethasone Mean	SD	Total	No Dexamethasone Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI	Year
Malhotra 2009 (0.5mg/kg/dose)	5.9	2.7	30	5.4	2	30	84.7%	0.50 [-0.70, 1.70]	2009
de Carvalho 2020 (0.25mg/kg/dose)	7.83	6.7	41	7.71	6.57	44	15.3%	0.12 [-2.70, 2.94]	2020
Total (95% CI)			71			74	100.0%	0.44 [-0.66, 1.55]	

Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 0.78 (P = 0.43)
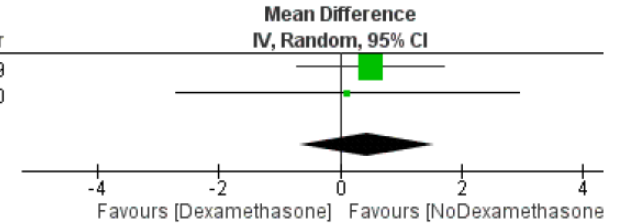
E. Forest plots for pairwise comparison: GI bleed

Study or Subgroup	Dexamethasone Events	Total	No Dexamethasone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Anene 1996 (0.5mg/kg/dose)	1	33	0	33	100.0%	3.09 [0.12, 78.70]	1996
Ritu 2020 (0.15mg/kg/dose)	0	42	0	38		Not estimable	2020
Total (95% CI)		75		71	100.0%	3.09 [0.12, 78.70]	
Total events	1		0				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.68 (P = 0.49)
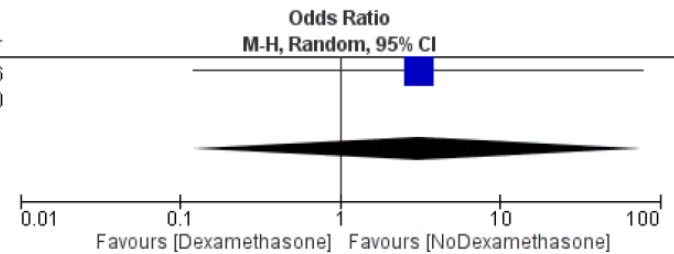
F. Forest plots for pairwise comparison: Hypertension

Study or Subgroup	Dexamethasone Events	Total	No Dexamethasone Events	Total	Weight	Odds Ratio M-H, Random, 95% CI	Year
Anene 1996 (0.5mg/kg/dose)	1	33	1	33	100.0%	1.00 [0.06, 16.69]	1996
de Carvalho 2020 (0.25mg/kg/dose)	0	41	0	44		Not estimable	2020
Ritu 2020 (0.15mg/kg/dose)	0	42	0	38		Not estimable	2020
Total (95% CI)		116		115	100.0%	1.00 [0.06, 16.69]	
Total events	1		1				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)

Odds Ratio M-H, Random, 95% CI

0.01 0.1 1 10
Favours [Dexamethasone] Favours [NoDexamethasone]
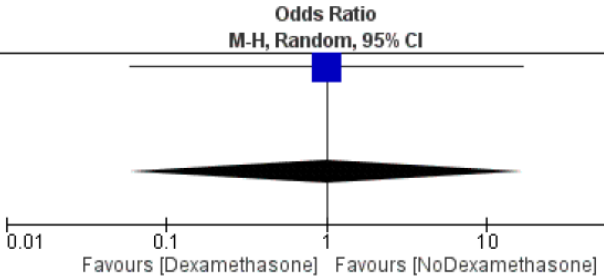
Network metanalysis forest plots: Reference treatment is 'No Dexamethasone'

    A. 12-hour model, Reintubation

Odds Ratio (95% CrI)

Compared with NoDex

HighEarly	0.24 (0.037, 1.2)
HighLate	0.43 (0.10, 1.3)
LowEarly	0.26 (0.015, 3.4)
LowLate	1.1 (0.15, 7.8)

0.01   1   8

    B. 12- hour model, upper airway obstruction

Odds Ratio (95% CrI)

Compared with NoDex

HighEarly	0.13 (0.044, 0.36)
HighLate	0.39 (0.19, 0.74)
LowEarly	0.15 (0.035, 0.58)
LowLate	0.58 (0.22, 1.5)

0.03   1 2

C. *6-hour model, Reintubation*

Odds Ratio (95% CrI)

Compared with NoDex

HighEarly	0.41 (0.093, 1.2)
HighLate	0.44 (0.068, 2.4)
LowEarly	0.63 (0.097, 3.8)
LowLate	0.99 (0.015, 69.)

0.01   1   70

D. *6-hour model, upper airway obstruction*

Odds Ratio (95% CrI)

Compared with NoDex

HighEarly	0.30 (0.14, 0.55)
HighLate	0.72 (0.24, 1.9)
LowEarly	0.42 (0.17, 1.0)
LowLate	0.53 (0.083, 3.2)

0.08   1   4

Supplemental Table E13: Evidence to decision table for corticosteroids

Should Dexamethasone vs. no Dexamethasone be used for preventing post extubation upper airway obstruction?	
POPULATION:	Pediatric patients receiving conventional mechanical ventilation more than 24 hours
INTERVENTION:	Dexamethasone
COMPARISON:	No dexamethasone
MAIN OUTCOMES:	Upper airway obstruction; Reintubation; Length of invasive mechanical ventilation; PICU Length of stay; GI Bleeding; Hypertension;
SETTING:	PICU, Pediatric Cardiac ICU
BACKGROUND:	Critically ill children requiring intensive care often require endotracheal intubation to maintain a patent airway. Despite its importance, endotracheal intubation is not without complications. Airway obstruction after extubation is a serious problem among pediatric patients, often requiring reintubation and prolonged intensive care. Dexamethasone is an anti-inflammatory drug that plays an important role in reducing laryngeal edema, although its prophylactic use to reduce the occurrence of post-extubation laryngeal edema remains controversial.

Assessment

Problem Is the problem a priority?		
Judgement	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	The presence of ETTs in the trachea during the period of mechanical ventilation has the potential for development of glottic and subglottic edema causing upper airway obstruction (UAO) resulting in stridor on extubation. UAO may occur in 2–73% of critically ill pediatric patients (**Tellez 1991, Baranwal 2014**). UAO is considered a serious complication of endotracheal intubation and one of the main causative factors of extubation failure. As a consequence, UAO may prolong the length of mechanical ventilation, length of stay in PICU and increase morbidity.	
Desirable Effects How substantial are the desirable anticipated effects?		

Judgement	Research evidence	Additional considerations
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	(see table below)	This analysis is based on 6 pediatric RCTs comparing the use of dexamethasone with no dexamethasone for the prevention of post-extubation stridor. The dose and interval of administration of dexamethasone was variable amongst the studies. The stridor rates in the control group varied from 28-87.5%. In general, these are high rates of stridor and potentially sub-glottic edema, which should be considered when generalizing these results to other settings. Similarly, reintubation rates ranged from 6.25% to 63% in the control group; again pointing to high event rates. Therefore, the benefits are representative of a population at high risk of UAO and reintubation. The network meta-analysis considered two additional trials focused on duration of treatment prior to extubation (**Baranwal 2014**) and dose (**Parajuli 2021**). Overall the network meta-analysis showed that the benefit on the outcome of UAO prevention comes from earlier delivery of the drug (6-12 hours) with multiple repeated dosing. Of note, none of the network meta-analysis estimates for the outcome of reintubation were statistically significant.

Outcomes	With no Dexamethasone	With Dexamethasone	Difference	Relative effect (95% CI)
Upper airway obstruction	456 per 1,000	**251 per 1,000** (150 to 380)	**205 fewer per 1,000** (306 fewer to 76 fewer)	**OR 0.40** (0.21 to 0.73)
Reintubation	181 per 1,000	**109 per 1,000** (44 to 244)	**73 fewer per 1,000** (137 fewer to 63 more)	**OR 0.55** (0.21 to 1.46)
Length of invasive mechanical ventilation	In the four studies (total sample of 384 subjects) pooled difference (in days) was 0.27 (-0.89, 0.35) days lower in the Dexamethasone group.			
PICU Length of stay	The mean PICU Length of stay was **0** days	The mean PICU Length of stay in the intervention group was 0.44 days higher (0.66 lower to 1.55 higher)	MD **0.44 days higher** (0.66 lower to 1.55 higher)	-

Prophylactic administration of glucocorticoids (dexamethasone) prior to extubation contributes to a decrease in the incidence of upper

airway obstruction (UAO), with a trend towards a reduction in reintubation rates. This beneficial effect also results in a reduction in the length of mechanical ventilation (IMV) or ICU length of stay (LOS) although not clinically relevant.

Undesirable Effects
How substantial are the undesirable anticipated effects?

Judgement	Research evidence	Additional considerations
○ Large ○ Moderate ○ Small ● **Trivial** ○ Varies ○ Don't know	(see table below)	Delayed extubation when clinicians wait for steroid administration prior to extubation should be considered an undesirable effect of the prophylactic administration of dexamethasone. Accordingly, patient subpopulations should be selected in which a high risk of UAO after extubation outweighs the risks of prolonging intubation while awaiting a course of prophylactic corticosteroids. Based on review of the available literature, high risk subpopulations for UAO post-extubation included at least one of the following: 1. Multiple intubation attempts 2. Traumatic intubation 3. Use of large for age ETT 4. ETT air leak pressure >25 cmH2O for cuffed ETT 5. Anatomical anomaly of upper airways In low-risk populations, the benefits of administering prophylactic dexamethasone are unclear, and any further delay in extubation to administer steroids should be avoided.

Outcomes	With no dexamethasone	With dexamethasone	Difference	Relative effect (95% CI)
GI Bleeding	0 per 1,000	**1 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**OR 3.09** (0.12 to 78.00)
Hypertension	8 per 1,000	**8 per 1,000** (1 to 123)	**0 fewer per 1,000** (8 fewer to 115 more)	**OR 1.00** (0.06 to 16.60)

Patients receiving dexamethasone to prevent UAO prior to extubation experience very few adverse events associated to glucocorticoids administration.

Certainty of evidence
What is the overall certainty of the evidence of effects?

Judgement	Research evidence	Additional considerations

● **Very low** ○ Low ○ Moderate ○ High ○ No included studies	(table below)	Certainty of evidence based on network metanalysis is 'very low' due to imprecision, serious risk of bias, inconsistency in direct comparisons.

Outcomes	Importance	Certainty of the evidence (GRADE)
Upper airway obstruction	IMPORTANT	⊕⊕⊕◯ MODERATE[a]
Reintubation	CRITICAL	⊕⊕◯◯ LOW[b,c]
Length of invasive mechanical ventilation	IMPORTANT	⊕⊕◯◯ LOW[d]
PICU Length of stay	IMPORTANT	⊕⊕⊕◯ MODERATE[c]
GI Bleeding	IMPORTANT	⊕⊕⊕◯ MODERATE[c]
Hypertension	IMPORTANT	⊕⊕⊕◯ MODERATE[c]

a. I2= 46%
b. I2=56%
c. Wide confidence limits
d. Results not statistically significant in individual studies

6 pediatric RCTs showed low certainty of evidence, downgraded by some inconsistency in important and critical outcomes such as UAO and reintubation, respectively. There was heterogeneity among studies in defining UAO, and different clinical scoring systems (most of them based on subjective assessment), dosing regimens and duration of treatment with dexamethasone were applied. There was also imprecision in the reintubation outcome.

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

Judgement	Research evidence	Additional considerations

○ Important uncertainty or variability ○ Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** ○ No important uncertainty or variability	For both patients/families and practitioners, the value of prevention of UAO and reintubation, and the potential reduction in IMV and PICU length of stay must be balanced against the risk of adverse events associated with dexamethasone administration prior to extubation. It is likely that patients, parents, or practitioners value the prevention of UAO and reintubation more than a slightly increased risk of gastrointestinal bleeding and temporary hypertension.	

Outcomes	Importance	Certainty of the evidence (GRADE)
Upper airway obstruction	IMPORTANT	⊕⊕⊕◯ MODERATE[a]
Reintubation	CRITICAL	⊕⊕◯◯ LOW[b,c]
Length of invasive mechanical ventilation	IMPORTANT	⊕⊕◯◯ LOW[d]
PICU Length of stay	IMPORTANT	⊕⊕⊕◯ MODERATE[c]
GI Bleeding	IMPORTANT	⊕⊕⊕◯ MODERATE[c]
Hypertension	IMPORTANT	⊕⊕⊕◯ MODERATE[c]

a. I2= 46%
b. I2=56%
c. Wide confidence limits
d. Results not statistically significant in individual studies

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ● **Favors the intervention** ○ Varies ○ Don't know	Systemic corticosteroids prior to elective extubation may be beneficial in decreasing post-extubation stridor particularly for cohorts with a high incidence of post extubation stridor, with a trend toward reduced reintubation rates for upper airway obstruction. UAO requires the use of anti-inflammatory therapy, noninvasive ventilatory support, and oftentimes reintubation, resulting in prolonged mechanical ventilation associated with a number of complications. The few reported adverse effects attributable to prophylactic administration of dexamethasone in the hours prior to extubation help determine the balance of effects.	

Resources required
How large are the resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Large costs ○ Moderate costs ○ Negligible costs and savings ● **Moderate savings** ○ Large savings ○ Varies ○ Don't know	Dexamethasone is a widely available, easy to use and affordable drug. Avoiding the occurrence of upper airway obstructions that may require noninvasive respiratory systems and/or reintubation will result in moderate savings by having a small effect on reducing the length of mechanical ventilation and thus the associated complications inherent to prolonged IMV.	

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

Judgement	Research evidence	Additional considerations
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

Judgement	Research evidence	Additional considerations

○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	Not applicable	

Equity What would be the impact on health equity?		
Judgement	Research evidence	Additional considerations
○ Reduced ○ Probably reduced ● **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know	Dexamethasone is a widely available and affordable drug. The use of prophylactic dexamethasone may prevent interventions that require a higher level of care.	

Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know		

Feasibility Is the intervention feasible to implement?		
Judgement	Research evidence	Additional considerations

○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		

SUMMARY OF JUDGEMENTS

	JUDGEMENT					
PROBLEM	No	Probably no	Probably yes	**Yes**	Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large	Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**	Varies	Don't know
CERTAINTY OF EVIDENCE	**Very low**	Low	Moderate	High		No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability		
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	**Favors the intervention**	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	**Moderate savings**	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High		**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

	JUDGEMENT						
FEASIBILITY	No	Probably no	Probably yes	**Yes**		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

- We suggest using dexamethasone at least six hours prior to extubation in children at high-risk of developing post-extubation UAO (Conditional recommendation, very low certainty of evidence).

Justification

Post-extubation UAO may prolong length of mechanical ventilation, particularly if airway obstruction is severe and reintubation proves necessary. Prolonged IMV is associated with morbidities and prolonged length of stay in PICU. Data from meta-analyses from randomized controlled trials in children suggests that prophylactic administration of dexamethasone prior to planned extubation contributes to a decrease in the incidence of upper airway obstruction, with a trend towards a reduction in reintubation rates, and with very few adverse events associated to dexamethasone administration. While prophylactic administration of dexamethasone could delay extubation in low-risk populations, prophylactic dexamethasone in high-risk populations was felt to balance the risks of unnecessarily prolonging IMV in the general pediatric patient population against the opposite risks of applying preventive therapies in populations which may be at risk of UAO. Data from the network meta-analysis estimates for prevention of UAO showed that the benefit comes from earlier delivery of the drug (at least 6 hours prior to extubation).

Subgroup considerations

1. High risk of UAO is defined by one of the following conditions: multiple intubation attempts, traumatic intubation, use of large for age ETT, ETT air leak pressure >25 cmH2O for cuffed ETT, and anatomical anomaly of upper airways.
For patients at high risk of UAO after extubation, the benefits of prophylactic dexamethasone outweigh the potential risks of prolonging IMV while awaiting a course of prophylactic dexamethasone.

2. Low risk for UAO is defined by those within the general pediatric population who do not meet any of the UAO risk criteria above-mentioned. In this low-risk population, administration of prophylactic dexamethasone has unclear benefit, and unless pre- planned, may result in unnecessarily prolonged of IMV while waiting to complete a course of dexamethasone.

Implementation considerations

Dexamethasone is widely available, affordable and easy to deliver, making its application feasible in most ICUs worldwide. Its administration by protocol (type of drug, specific dosage and intervals) within institutional guidelines for liberation of mechanical ventilation should follow the evidence as far as possible. Administration of a course of dexamethasone prior to extubation to patients meeting risk criteria is feasible if these risk criteria are properly identified. Contexts where UAO rates, and the resultant reintubation rates, are likely to higher- such as places where majority of intubations are uncontrolled or outside ICU settings or ICUs with high representation of airway abnormalities etc, may decide to institute prophylactic dexamethasone for all to facilitate better implementation especially when systems cannot be relied upon to identify patients at high risk of UAO.

Monitoring and evaluation

Objective clinical score systems and bedside applicable tools (ie, air leak test in patients with cuffed ETTs) should be used to implement a serial assessment of those patients who could benefit from corticosteroid prophylaxis prior to extubation.

Research priorities

Additional studies are warranted to identify high risk patients who might benefit from prophylactic dexamethasone administration prior to extubation, and future trials in children should explore if doses and intervals of doses prior to extubation improve critical outcomes (ie, reintubation rate) in populations where the incidence of post extubation stridor is high.

E. Non-invasive respiratory support

Supplemental Table E14: Search strategies for non-invasive respiratory support

Non-invasive respiratory support vs conventional oxygen therapy question
In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours should planned non-invasive respiratory support (HFNC, CPAP, or NIV) be used post-extubation?

P Pediatric patients receiving conventional mechanical ventilation >24 hours

I Planned use of non-invasive respiratory support (NIV, CPAP or HFNC) post-extubation

C Unplanned or no use of non-invasive respiratory support

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), VFDs, PICU length of stay, hospital length of stay, pressure injuries to the face, mortality

NIV/CPAP vs HFNC question
In acutely hospitalized children being extubated to planned non-invasive respiratory support (NIV, CPAP or HFNC), would NIV/CPAP be superior to HFNC?

P Pediatric patients receiving conventional mechanical ventilation >24 hours who are planned to be extubated to non-invasive respiratory support

I Planned use of NIV/CPAP post-extubation

C Planned use of HFNC post-extubation

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), VFDs, PICU length of stay, hospital length of stay, cross-over to other treatment, pressure injuries to the face, modality.

I. MEDLINE (Ovid)

Databases selected: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)

Line	Query
1	Continuous Positive Airway Pressure/
2	Continuous Positive Airway Pressure*.mp.
3	CPAP.mp.
4	1 or 2 or 3
5	exp Sleep Apnea Syndromes/
6	sleep apnea*.mp.
7	5 or 6
8	4 not 7
9	(extubation* adj2 (readiness or failure* or outcome*)).mp.

10	((face or nasal) adj mask ventilat*).mp.
11	helmet ventilat*.mp.
12	((High-flow or highflow) adj3 nasal cannula*).mp.
13	((high-flow or highflow or humidified) adj3 oxygen*).mp.
14	(negative pressure adj2 ventilator*).mp.
15	NIV.mp.
16	Noninvasive Ventilation/
17	Noninvasive Ventilation*.mp.
18	Non invasive Ventilation*.mp.
19	Oxygen Inhalation Therapy/
20	Oxygen inhalat* therap*.mp.
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22	Adolescent/
23	Adolescen*.mp.
24	Teen*.mp.
25	Youth*.mp.
26	exp Child/
27	Child*.mp.
28	Infant/
29	Infant, Newborn/
30	Infant*.mp.
31	Infanc*.mp.
32	Newborn*.mp.
33	Neonat*.mp.
34	Pediatrics/
35	P?ediatric*.mp.
36	Hospitals, Pediatric/
37	Intensive Care Units, Pediatric/
38	PICU*.mp.
39	(Kid or kids).mp.
40	Toddler*.mp.
41	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40
42	(Adaptive adj2 Support Ventilat*).mp.
43	Airway Extubation/
44	Airway extubat*.mp.
45	Artificial Respirati*.mp.
46	((intubation or extubation*) adj3 (airway or tracheal or intratracheal or endotracheal)).mp.
47	exp Intermittent Positive-Pressure Breathing/
48	Intermittent Positive-Pressure Breathing.mp.
49	exp Intermittent Positive-Pressure Ventilation/
50	Intermittent Positive-Pressure Ventilat*.mp.
51	Intubation, Intratracheal/
52	Mechanical Ventilat*.mp.
53	Neurally Adjusted Ventilatory Assist*.mp.
54	open lung ventilat*.mp.
55	Peep.mp.
56	Positive End Expiratory Pressure*.mp.
57	exp Positive-Pressure Respiration/
58	Positive-Pressure Ventilat*.mp.

59	pressure controlled ventilat*.mp.
60	Proportional Assist Ventilat*.mp.
61	Reintubat*.mp.
62	Respiration, Artificial/
63	Respirator Weaning*.mp.
64	Ventilator*.mp.
65	(Ventilat* adj3 Liberation*).mp.
66	exp Ventilators, Mechanical/
67	exp Ventilator Weaning/
68	Ventilator* Weaning*.mp.
69	Ventilation Weaning*.mp.
70	42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
71	21 and 41 and 70

II. Embase (Elsevier)

Line	Query
#1	'continuous positive airway pressure'/de
#2	'continuous positive airway pressure*'
#3	cpap
#4	extubation* NEAR/2 (readiness OR failure* OR outcome*)
#5	(face OR nasal) NEXT/1 'mask ventilat*'
#6	'heated humidifier'/de
#7	'helmet ventilat*'
#8	('high flow' OR highflow OR humidified) NEAR/3 'nasal cannula*'
#9	'high flow oxygen therapy'/de
#10	('high flow' OR highflow OR humidified) NEAR/3 oxygen*
#11	'negative pressure' NEAR/2 ventilat*
#12	niv
#13	'noninvasive ventilation'/de
#14	'noninvasive ventilat*'
#15	'non-invasive ventilat*'
#16	'oxygen inhalat* therap*'
#17	'sleep disordered breathing'/exp
#18	'sleep apnea*'
#19	#1 OR #2 OR #3
#20	#17 OR #18
#21	#19 NOT #20
#22	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #21
#23	'adolescent'/exp
#24	'adolescence'/de
#25	adolescen*
#26	teen*
#27	youth*
#28	'child'/exp

#29	child*
#30	'infant'/exp
#31	'infancy'/exp
#32	'newborn'/exp
#33	infant*
#34	infanc*
#35	newborn*
#36	neonat*
#37	'pediatrics'/de
#38	p$ediatric*
#39	'pediatric intensive care unit'/de
#40	picu*
#41	kid OR kids
#42	'toddler'/exp
#43	toddler*
#44	#23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43
#45	adaptive NEAR/2 support NEXT/1 ventilat*
#46	'extubation'/de
#47	'airway extubat*'
#48	(intubation* OR extubation*) NEAR/3 (airway OR tracheal OR intratracheal OR endotracheal)
#49	'intermittent mandatory ventilation'/exp
#50	'intermittent positive-pressure breathing'
#51	'intermittent positive pressure ventilation'/exp
#52	'intermittent positive-pressure ventilat*'
#53	'endotracheal intubation'/exp
#54	'invasive ventilation'/exp
#55	'inverse ratio ventilation'/de
#56	'mechanical ventilat*'
#57	'neurally adjusted ventilatory assist*'
#58	'noninvasive positive pressure ventilation'/exp
#59	'open lung ventilat*'
#60	peep
#61	'positive end expiratory pressure ventilation'/exp
#62	'positive end expiratory pressure*'
#63	'positive pressure ventilation'/de
#64	'positive-pressure ventilat*'
#65	'pressure controlled ventilation'/de
#66	'pressure controlled ventilat*'
#67	'pressure support ventilation'/de
#68	'proportional assist ventilat*'
#69	'protective ventilation'/exp
#70	reintubat*
#71	'artificial ventilation'/de

#72	'respirator weaning*'
#73	'tracheal extubation'/de
#74	'ventilator'/de
#75	ventilator*
#76	ventilat* NEAR/3 liberation*
#77	'mechanical ventilator'/de
#78	'ventilator weaning'/de
#79	'ventilator* weaning*'
#80	'ventilation weaning*'
#81	'volume controlled ventilation'/exp
#82	'artificial respirati*'
#83	#45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82
#84	#22 AND #44 AND #83

III.   CINAHL Complete (EBSCO)

Line	Query
S1	(MH "Continuous Positive Airway Pressure")
S2	"continuous positive airway pressure*"
S3	CPAP
S4	(MH "Sleep Apnea Syndromes+")
S5	"sleep apnea*"
S6	S1 OR S2 OR S3
S7	S4 OR S5
S8	S6 NOT S7
S9	Extubation* N2 (readiness OR failure* OR outcome*)
S10	(face OR nasal) N1 "mask ventilat*"
S11	"helmet ventilat*"
S12	("high flow" OR highflow OR humidified) N3 "nasal cannula*"
S13	("high flow" OR highflow OR humidified) N3 oxygen*
S14	"negative pressure" N2 ventilat*
S15	niv
S16	"noninvasive ventilat*"
S17	"non invasive ventilat*"
S18	"oxygen inhalat* therap*"
S19	(MH "Ventilation, Negative Pressure")
S20	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19
S21	Toddler*
S22	Kid OR kids
S23	PICU*
S24	(MH "Intensive Care Units, Pediatric")
S25	P#ediatric*
S26	(MH "Pediatrics")
S27	Neonat*
S28	Newborn*
S29	Infanc*

S30	Infant*
S31	(MH "Infant, Newborn")
S32	(MH "Infant") OR (MH "Infant, Hospitalized") OR (MH "Infant, High Risk")
S33	Child*
S34	(MH "Child") OR (MH "Child, Hospitalized") OR (MH "Child, Medically Fragile") OR (MH "Child, Preschool")
S35	Youth*
S36	Teen*
S37	Adolescen*
S38	(MH "Adolescence+")
S39	Ventilation Weaning*
S40	ventilator* weaning*
S41	(MH "Ventilator Weaning")
S42	(MH "Ventilators, Mechanical")
S43	ventilat* N3 liberation*
S44	ventilator*
S45	'respirator weaning*'
S46	(MH "Respiration, Artificial")
S47	reintubat*
S48	proportional assist ventilat*
S49	(MH "Pressure Support Ventilation")
S50	pressure controlled ventilat*
S51	positive-pressure ventilat*
S52	(MH "Positive Pressure Ventilation")
S53	Positive End Expiratory Pressure*
S54	(MH "Positive End-Expiratory Pressure")
S55	peep
S56	open lung ventilat*
S57	neurally adjusted ventilatory assist*
S58	mechanical ventilat*
S59	(MH "Mandatory Minute Volume Ventilation")
S60	(MH "Inverse Ratio Ventilation")
S61	(MH "Intubation, Intratracheal")
S62	Intermittent Positive-Pressure Ventilat*
S63	(MH "Intermittent Positive Pressure Ventilation")
S64	Intermittent Positive-Pressure Breathing
S65	(MH "Intermittent Positive Pressure Breathing")
S66	(intubation* OR extubation*) N3 (airway OR tracheal OR intratracheal OR endotracheal)
S67	artificial respirati*
S68	airway extubat*
S69	(MH "Extubation")
S70	adaptive N2 support ventilat*
S71	S38 OR S37 OR S36 OR S35 OR S34 OR S33 OR S32 OR S31 OR S30 OR S29 OR S28 OR S27 OR S26 OR S25 OR S24 OR S23 OR S22 OR S21
S72	S70 OR S69 OR S68 OR S67 OR S66 OR S65 OR S64 OR S63 OR S62 OR S61 OR S60 OR S59 OR S58 OR S57 OR S56 OR S55 OR S54 OR S53 OR S52 OR S51 OR S50 OR S49 OR S48 OR S47 OR S46 OR S45 OR S44 OR S43 OR S42 OR S41 OR S40 OR S39
S73	S20 AND S71 AND S72

Supplemental Figure E7: PRSIMA chart for non-invasive respiratory support

Identification of new studies via databases and registers		

Identification

Records identified from:
Databases (n = 15,992)
Registers (n = 0)

→ Records removed before screening:
Duplicate records (n = 4,919)
Records marked as ineligible by automation tools (n = 0)
Records removed for other reasons (n = 0)

Screening

Records screened
(n = 11,073)

→ Records excluded
(n = 10,902)

Reports sought for retrieval
(n = 171)

→ Reports not retrieved
(n = 0)

Reports assessed for eligibility
(n = 171)

→ Reports excluded:
Conference Abstract (n = 27)
Review Paper (n = 26)
Duplicate (n = 3)
Wrong comparator (n = 4)
Wrong intervention (n = 18)
Wrong outcomes (n = 13)
Wrong population (n = 1)
Adult population (n = 10)
Letter/comment (n = 11)
Wrong study design (n = 41)
Wrong indication (n = 8)
Wrong setting (n = 4)
NICU population (n = 2)
Master protocol paper (n = 1)
Article in chinese (n = 1)

Included

New studies included in review
(n = 7)
Reports of new included studies
(n = 7)

Supplemental Table E15: Evidence table for non-invasive respiratory support

Question: Noninvasive respiratory support (CPAP, NIV, HFNC) compared to conventional oxygen therapy for post-extubation support in critically ill children

Setting: PICU, CVICU

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRS	COT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Certainty assessment							№ of patients		Effect			

Reintubation

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRS	COT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
5 [1,2,3,4,5]	randomised trials	not serious	not serious	serious [a]	serious [b]	none	18/236 (7.6%)	31/238 (13.0%)	OR 0.60 (0.31 to 1.14)	48 fewer per 1,000 (from 86 fewer to 16 more)	⊕⊕◯◯ LOW	CRITICAL
								8.0%		30 fewer per 1,000 (from 54 fewer to 10 more)		
								25.0%		83 fewer per 1,000 (from 156 fewer to 25 more)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRS	COT	Relative (95% CI)	Absolute (95% CI)		

Extubation failure plus Treatment failure (Sensitivity)

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRS	COT	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
5 [1,2,3,4,5]	randomised trials	not serious	serious [c]	serious [a]	not serious	none	19/236 (8.1%)	45/238 (18.9%)	OR 0.33 (0.13 to 0.84)	**118 fewer per 1,000** (from 160 fewer to 25 fewer)	⊕⊕○○ LOW	CRITICAL
								8.0%		**52 fewer per 1,000** (from 69 fewer to 12 fewer)		
								25.0%		**151 fewer per 1,000** (from 208 fewer to 31 fewer)		

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NRS	COT	Relative (95% CI)	Absolute (95% CI)		

PICU length of stay (Only HFNC versus COT)

2 [1,3]	randomised trials	not serious	not serious	not serious	serious [b]	none	119	122	-	MD **0.74 days higher** (0.72 lower to 2.19 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Mortality

1 [1]	randomised trials	not serious	not serious	not serious	very serious [b]	none	4/76 (5.3%)	3/76 (3.9%)	**RR 1.35** (0.29 to 6.26)	**13 more per 1,000** (from 27 fewer to 188 more)	⊕⊕◯◯ LOW	CRITICAL

Hospital length of stay

1 [1]	randomised trials	not serious	not serious	not serious	very serious [b]	none	76	76	-	MD **9 days higher** (0.97 lower to 18.97 higher)	⊕⊕◯◯ LOW	IMPORTANT

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference; **RR:** Risk ratio

Explanations

a. NIV, HFNC and CPAP combined as non-invasive respiratory support

b. Wide 95%CI with confidence intervals not excluding plausible benefit or harm

c. Moderately high I2 on metnalysis

d. HFNC and CPAP combined as non-invasive respiratory support

References

1. Wijakprasert P, Chomchoey J. High flow nasal cannula versus conventional oxygen therpay in post-extubation pediatric patients: A randomized controlled trial.. Journal of Medical Association of Thailand; 2018.

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3. G, Testa, F, Iodice, Z, Ricci, V, Vitale, F, De,Razza, R, Haiberger, C, Iacoella, G, Conti, P, Cogo. Comparative evaluation of high-flow nasal cannula and conventional oxygen therapy in . Interactive cardiovascular and thoracic surgery; 2014.

4. JR, Fioretto, CF, Ribeiro, MF, Carpi, RC, Bonatto, MA, Moraes, EB, Fioretto, DJ, Fagundes. Comparison between noninvasive mechanical ventilation and standard oxygen therapy in . Pediatric critical care medicine : a journal of the Society of Critical Care ; 2015.

5. B, Akyıldız, S, Öztürk, N, Ülgen-Tekerek, S, Doğanay, SB, Görkem. Comparison between high-flow nasal oxygen cannula and conventional oxygen therapy . The Turkish journal of pediatrics; 2018.

Question: CPAP compared to HFNC for post-extubation non-invasive respiratory support

Setting: PICU, CVICU

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)		

Extubation failure (48-72 hours)

2	randomised trials	serious[a]	not serious	not serious	serious[b]	None	39/310 (12.6%)	46/322 (14.3%)	OR 0.86 (0.55 to 1.37)	17 fewer per 1,000 (from 59 fewer to 43 more)	⊕⊕○○ Low	CRITICAL
								25.0%		27 fewer per 1,000 (from 95 fewer to 64 more)		

Reintubation (Ever)

2	randomised trials	serious[a]	not serious	not serious	serious[b]	None	51/310 (16.5%)	71/322 (22.0%)	OR 0.70 (0.46 to 1.04)	57 fewer per 1,000 (from 105 fewer to 7 more)	⊕⊕○○ Low	CRITICAL
								10.0%		29 fewer per 1,000 (from 51 fewer to 4 more)		
								25.0%		44 fewer per 1,000 (from 79 fewer to 5 more)		

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
				Certainty assessment			№ of patients		Effect		Certainty	Importance

Crossover treatment

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2	randomised trials	serious[c]	not serious	not serious	not serious	None	36/313 (11.5%)	73/324 (22.5%)	OR 0.45 (0.29 to 0.69)	**110 fewer per 1,000** (from 148 fewer to 58 fewer)	⊕⊕⊕◯ Moderate	IMPORTANT

Crossover/Reintubation

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2	randomised trials	serious[a,c]	not serious	not serious	serious[b]	None	97/313 (31.0%)	115/324 (35.5%)	OR 0.82 (0.59 to 1.14)	**44 fewer per 1,000** (from 110 fewer to 31 more)	⊕⊕◯◯ Low	CRITICAL

Mortality

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
2	randomised trials	serious[a]	not serious	not serious	not serious	none	6/312 (1.9%)	16/323 (5.0%)	OR 0.38 (0.15 to 0.97)	**30 more per 1,000** (from 42 fewer to 1 fewer)	⊕⊕⊕◯ Moderate	CRITICAL

Time from randomization to liberation from respiratory support (hours)

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	CPAP	HFNC	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1	randomised trials	serious[a]	not serious	not serious	serious[d]	none	272	281	-	MD **7.9 hours lower** (4.4 lower to 20.2 higher)	⊕⊕◯◯ Low	CRITICAL

CI: confidence interval; **MD:** mean difference; **OR:** odds ratio

Explanations
a. Lack of blinding and allocation not blinded to some participants. Crossover to other intervention permitted.
b. Wide 95% CI that includes benefit to either intervention
c. Lack of blinding may have influenced crossover but unlikely to influence reintubation.
d. Adjusted Hazard ratio 0.83 (95%CI 0.72, 1.02) but mean difference estimate likely not clinically significant.

1. **NRS vs Conventional Oxygen Therapy Pairwise Meta-analysis**

   A. *Forest plot in pairwise analysis: Extubation failure*

Study or Subgroup	NRS Events	Total	COT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Akyldiz 2018	2	50	11	50	16.6%	0.15 [0.03, 0.71]
Fioretto 2015	5	55	6	53	25.6%	0.78 [0.22, 2.74]
Rodriguez 2002	0	12	1	13	3.8%	0.33 [0.01, 8.99]
Testa 2014	2	43	2	46	10.2%	1.07 [0.14, 7.97]
Wijakpraset 2018	9	76	11	76	43.8%	0.79 [0.31, 2.04]
Total (95% CI)		**236**		**238**	**100.0%**	**0.60 [0.31, 1.14]**
Total events	18		31			

Heterogeneity: Tau² = 0.02; Chi² = 4.10, df = 4 (P = 0.39); I² = 3%
Test for overall effect: Z = 1.57 (P = 0.12)

   B. *Forest plot in pairwise analysis: Extubation failure plus treatment failure*

Study or Subgroup	NRS Events	Total	COT Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Akyldiz 2018	2	50	11	50	18.7%	0.15 [0.03, 0.71]
Fioretto 2015	5	55	6	53	23.2%	0.78 [0.22, 2.74]
Rodriguez 2002	1	12	8	13	11.3%	0.06 [0.01, 0.59]
Testa 2014	2	43	9	46	18.3%	0.20 [0.04, 0.99]
Wijakpraset 2018	9	76	11	76	28.5%	0.79 [0.31, 2.04]
Total (95% CI)		**236**		**238**	**100.0%**	**0.33 [0.13, 0.84]**
Total events	19		45			

Heterogeneity: Tau² = 0.54; Chi² = 8.18, df = 4 (P = 0.09); I² = 51%
Test for overall effect: Z = 2.34 (P = 0.02)

C. *Forest plot in pairwise analysis: Hospital length of stay*

Study or Subgroup	NRS Mean	NRS SD	NRS Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI
Wijakpraset 2018	26.5	41.6	76	17.5	15.3	76	100.0%	9.00 [-0.97, 18.97]
Total (95% CI)			76			76	100.0%	9.00 [-0.97, 18.97]

Heterogeneity: Not applicable
Test for overall effect: Z = 1.77 (P = 0.08)

Mean Difference IV, Random, 95% CI — Favours [NRS] Favours [COT]
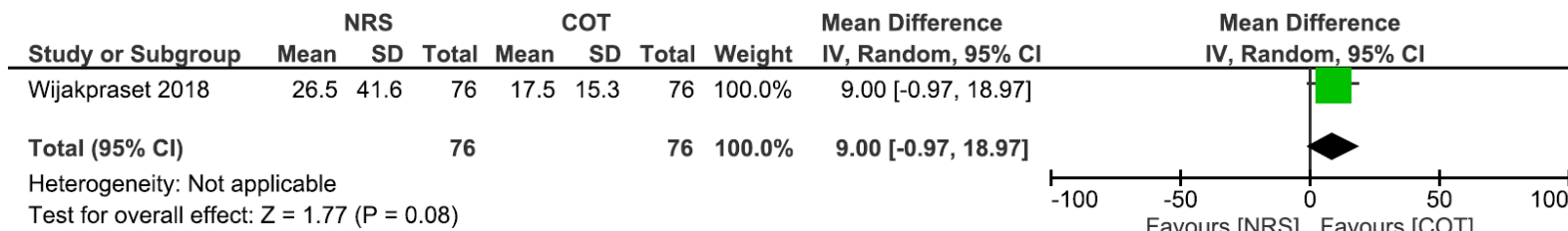
D. *Forest plot in pairwise analysis: PICU length of stay*

Study or Subgroup	NRS Mean	NRS SD	NRS Total	COT Mean	COT SD	COT Total	Weight	Mean Difference IV, Random, 95% CI
Testa 2014	5	4.4	43	4.5	3.7	46	73.5%	0.50 [-1.19, 2.19]
Wijakpraset 2018	8.1	10.3	76	6.7	7.2	76	26.5%	1.40 [-1.43, 4.23]
Total (95% CI)			119			122	100.0%	0.74 [-0.72, 2.19]

Heterogeneity: Tau² = 0.00; Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 1.00 (P = 0.32)

Mean Difference IV, Random, 95% CI — Favours [NRS] Favours [COT]

E. *Forest plot in pairwise analysis: Mortality*

Study or Subgroup	NRS Events	NRS Total	COT Events	COT Total	Weight	Odds Ratio M-H, Random, 95% CI
Wijakpraset 2018	4	76	3	76	100.0%	1.35 [0.29, 6.26]
Total (95% CI)		76		76	100.0%	1.35 [0.29, 6.26]
Total events	4		3			

Heterogeneity: Not applicable
Test for overall effect: Z = 0.39 (P = 0.70)

Odds Ratio M-H, Random, 95% CI — Favours [NRS] Favours [COT]

2. CPAP vs HFNC Pairwise Meta-analysis

A. Forest plot in pairwise analysis: Reintubation, ever

	CPAP		HFNC			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	
Ramnarayan 2018	9	41	14	43	18.4%	0.58 [0.22, 1.55]	
Ramnarayan 2022	42	269	57	279	81.6%	0.72 [0.46, 1.12]	
Total (95% CI)		310		322	100.0%	0.70 [0.47, 1.04]	
Total events	51		71				

Heterogeneity: Chi² = 0.15, df = 1 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.78 (P = 0.08)

B. Forest plot in pairwise analysis: Mortality, PICU

	CPAP		HFNC			Odds Ratio	
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	
Ramnarayan 2018	1	41	1	43	16.4%	1.05 [0.06, 17.36]	
Ramnarayan 2022	3	267	5	277	83.6%	0.62 [0.15, 2.61]	
Total (95% CI)		308		320	100.0%	0.69 [0.19, 2.47]	
Total events	4		6				

Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.57 (P = 0.57)

C. *Forest plot in pairwise analysis: Mortality, Hospital*

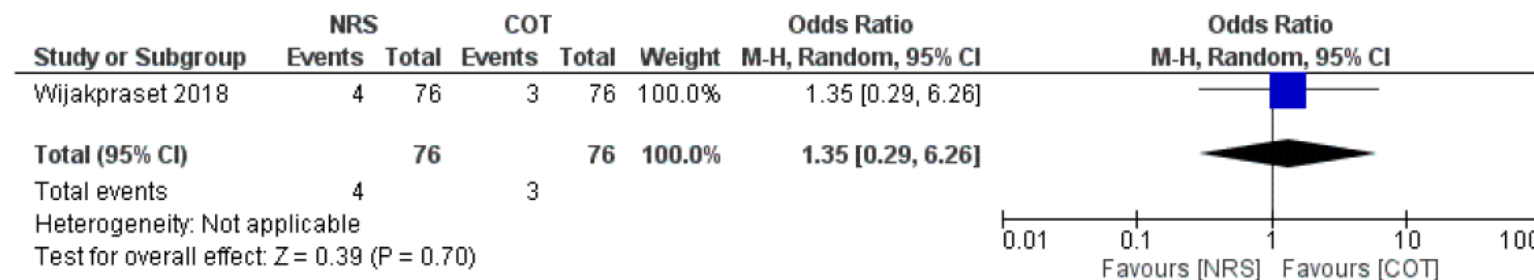D. *Forest plot in pairwise analysis: PICU LOS*

E. *Forest plot in pairwise analysis: Hospital LOS*
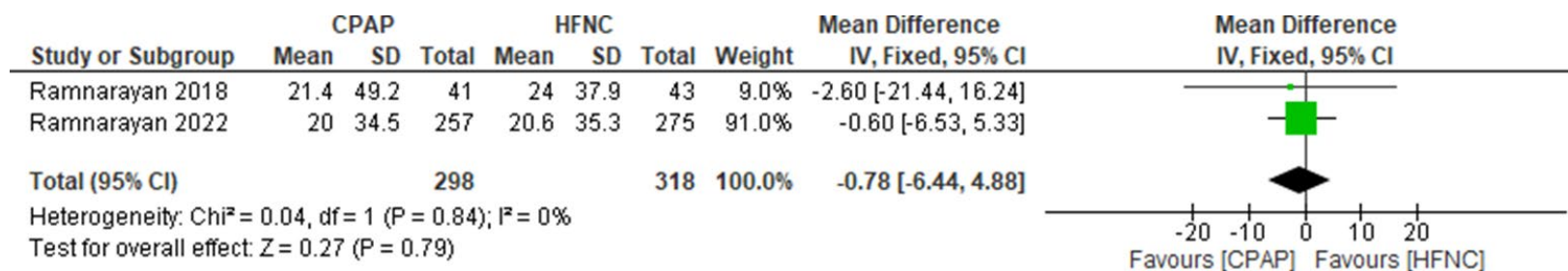
3. Network metanalysis (NMA): Conventional oxygen therapy (COT) is the reference treatment

A. Forest plot in NMA: Reintubation 48 to 72 hours

Odds Ratio (95% CrI)

Compared with COT

CPAP_NIV   0.489 (0.186, 1.20)
HFNC   0.531 (0.229, 1.15)

B. Forest plot in NMA: Reintubation, ever

Odds Ratio (95% CrI)

Compared with COT

CPAP_NIV   0.413 (0.158, 1.03)
HFNC   0.563 (0.244, 1.21)
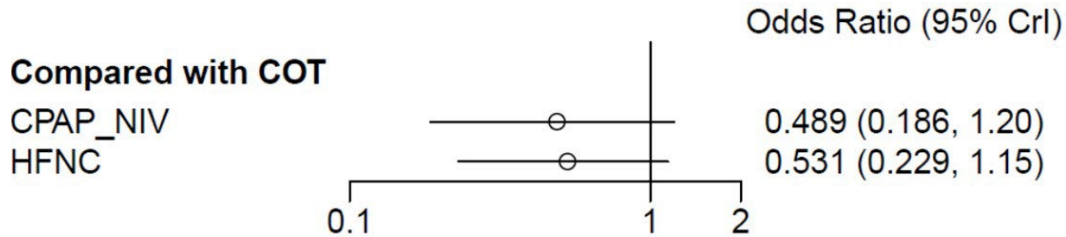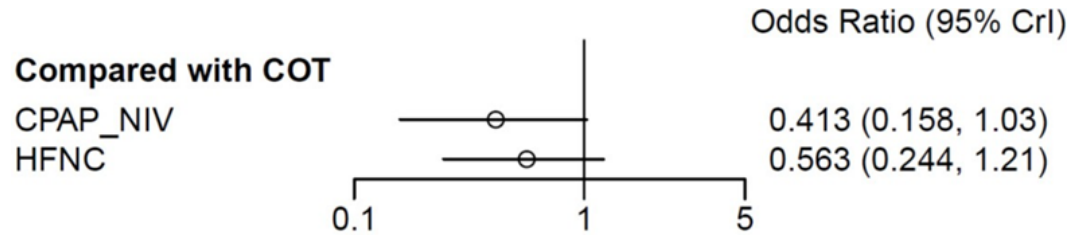
C. Forest plot in NMA: Treatment failure

Odds Ratio (95% CrI)

Compared with COT

CPAP_NIV   0.302 (0.112, 0.697)
HFNC   0.349 (0.143, 0.731)

     Page 110 | 150
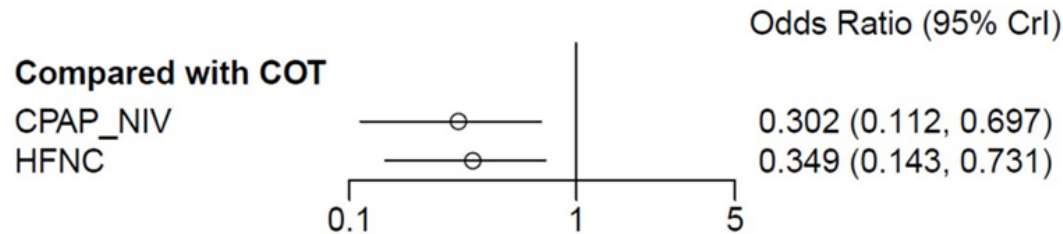
Rankogram: Probability (0-1= 0% to 100%) of being rank 1-3

A. RankogramReintubation 48 to 72 hours

Treatment	Rank 1	Rank 2	Rank 3	SUCRA
COT	0.019	0.066	**0.913**	5.32
NIV/CPAP	**0.598**	0.354	0.046	77.60
HFNC	0.381	**0.579**	0.039	67.06

B. Rankogram: Reintubation, ever

Treatment	Rank 1	Rank 2	Rank 3	SUCRA
COT	0.014	0.063	**0.921**	4.67
CPAP NIV	**0.827**	0.153	0.019	90.37
HFNC	0.158	**0.783**	0.058	54.95

C. Rankogram: Treatment failure

Treatment	Rank 1	Rank 2	Rank 3	SUCRA
COT	0.001	0.007	**0.991**	0.474
CPAP NIV	**0.686**	0.308	0.004	84.12
HFNC	0.312	**0.683**	0.004	65.4

GRADE format for network meta-analysis: COT is reference treatment

Classification	Intervention	Estimate (95% CrI)	Rank (highest probability)	Certainty of estimate
Reintubation (48 – 72 hours). Control rate 13%				
Large effect (5.6%)	HFNC	0.53 (0.22, 1.15)	2 (67%)	Low
Large effect (6.2%)	CPAP	0.48 (0.18, 1.20)	1 (78%)	Low
Reintubation, ever. Control rate 20%				
Large effect (7.7%)	HFNC	0.56 (0.24, 1.21)	2 (55%)	Low
Large effect (10.6%)	CPAP	0.41 (0.15, 1.03)	1 (90%)	Low
Treatment failure. Control rate 30%				
Large effect (17%)	HFNC	0.34 (0.14, 0.73)	2 (65%)	Low
Large effect (18.5%)	CPAP	0.30 (0.11, 0.69)	1 (84%)	Low

Supplemental Table E16: Evidence to decision table for non-invasive respiratory support

Should noninvasive respiratory support vs. conventional oxygen therapy be used for post-extubation support in critically ill children?	
POPULATION:	Pediatric patients receiving conventional mechanical ventilation more than 24 hours
INTERVENTION:	Non-invasive respiratory support (HFNC, CPAP, or NIV)
COMPARISON:	conventional oxygen therapy (COT)
MAIN OUTCOMES:	Reintubation; Extubation failure plus Treatment failure (Sensitivity); Extubation failure without NIV (sensitivity); PICU length of stay (Only HFNC versus COT); Mortality; Hospital length of stay;
SETTING:	PICU, PEDIATRIC CARDIAC ICU

Assessment

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	• Post-extubation support is associated with critical outcomes such as reintubation, effort of breathing, length of PICU and hospital stay, and possibly mortality and tracheostomy. • There is significant variation is post-extubation support within an institution, within a region, and around the world. • There is also variation in post-extubation support strategy: prophylactic vs rescue	
Desirable Effects How substantial are the desirable anticipated effects?		
○ Trivial ● **Small** ○ Moderate ○ Large ○ Varies ○ Don't know	**Reducing reintubation:** in the combined (NIV/CPAP and HFNC as one intervention versus conventional oxygen therapy) metanalysis the odds ratio is 0.60 (95% CI, 0.31-1.14) which, if the effect estimate were correct, result in 30 fewer reintubations per 1000 patients treated with non-invasive respiratory support post-extubation in a context where the control population have a reintubation rate of 8% (number needed to treat= 33). The effect size will be larger if the risk of reintubation is expected to be higher than 8%.	

The effect sizes for NIV/CPAP and HFNC versus COT, when analyzed in a network metanalysis, NIV/CPAP had odds ratio of 0.49 compared to 0.53 for HFNC, which if effect estimate were correct, results in 39 (NIV/CPAP) and 36 (HFNC) fewer reintubations per 1000 patients treated with NIV/CPAP or HFNC post-extubation in a context where the control population have a reintubation rate of 8% (number needed to treat= 26 (NIV/CPAP) and 27 (HFNC).

Reducing extuabtion failure/treatment failure- in the combined (NIV/CPAP and HFNC as one intervention versus conventional oxygen therapy) metanalysis the odds ratio is 0.33 (95%CI, 0.13-0.84) which, if the effect estimate are correct, result in 52 fewer escalations per 1000 patients treated with non-invasive respiratory support post-extubation in a context where the control population have a reintubation rate of 8% (number needed to treat= 19). The effect size will be larger if the risk of reintubation is expected to be higher than 8%.

The effect sizes for NIV/CPAP and HFNC versus COT, when analyzed in a network metanalysis, are not very different and have an odds ratio of 0.30 and 0.35 respectively, which if effect estimate is correct, results in 55 (NIV/CPAP) and 50 (HFNC) fewer reintubations per 1000 patients treated with NIV/CPAP or HFNC post-extubation in a context where the control population have a reintubation rate of 8% (number needed to treat= 18 (NIV/CPAP), 20 (HFNC).

The rank probabilities based on the studies included in the network metanalysis, NIV/CPAP had the highest probability of being ranked first (69%), followed by HFNC (31%) for reducing extubation failure/escalation to non-invasive support; NIV/CPAP had the highest probability of being ranked first (60%), followed by HFNC (38%) for the outcome reintubation (48-72 hours). Conventional oxygen therapy had 99% probability of being ranked 3rd for both outcomes.

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	**Total hospital LOS:** One study reported a clinically significant but statistically non-significant reduction of 9 days (95%CI -0.97 to 18.9) with conventional oxygen therapy compared to HFNC. **PICU LOS:** In two studies favored conventional oxygen therapy compared to HFNC, with a statistically and clinically non-significant reduction of 0.74 days (%CI -0.72 to 2.19). Tolerance of NIV has only been reported in one study (**Fioretto, 2015**) where 9/67 (13%) children could not tolerate it. Treatment with CPAP resulted in higher rates of patient discomfort over HFNC, a 6% increase in on RCT comparing HFNC and CPAP (**Ramnarayan 2022**)	

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	The network metanalysis comparisons for COT versus HFNC and COT versus NIV/CPAP both had very low certainty of evidence based on serious risk of bias and imprecision. The certainty of evidence for NIV/CPAP versus HFNC is low.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	A quick reintubation may not be much more superior than staying extubated on non-invasive support for several days and then getting reintubated. Length of hospital stay and PICU stay are important but probably less so than reintubation.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ● **Varies** ○ Don't know	Data on undesirable effects was not reported in all studies. We are unable to compare the competing outcomes with certainty. In children at high risk for reintubation (example, if the risk of reintubation is thought to be ~ >20%, children with respiratory muscle weakness, those that have equivocal SBT): Panel felt the balance of effects probably favors HFNC/CPAP/NIV, given that number needed to treat will be more favorable (10 with reintubation rate of 25%) Use of HFNC/CPAP/NIV as a 'rescue treatment': Panel felt the balance of effects probably favors HFNC/CPAP/NIV, given that the metanalysis for the outcome 'treatment failure/escalation' favored HFNC/CPAP/NIV.	

Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ● **Don't know**	Costs for COT, HFNC and NIV/CPAP vary around the world. There may not be much costs savings from preventing reintubation if the child remains on non-invasive support for prolonged period of time with increased length of PICU and hospital stay.	

Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ○ High ● **No included studies**	No evidence	

Cost effectiveness

Does the cost-effectiveness of the intervention favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**	No evidence	

Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ○ Probably increased ○ Increased ● **Varies** ○ Don't know	Access to therapy due to costs or availability of technology may limit the use of HFNC/CPAP/NIV in resource limited settings.	

Acceptability Is the intervention acceptable to key stakeholders?		
Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	Prophylactic use for all extubations may not be acceptable to clinicians or patients. Use in children at high risk of failure and for children who are having post-extubation respiratory distress may be acceptable to clinicians and parents.	

Feasibility Is the intervention feasible to implement?		

Judgement	Research evidence	Additional considerations
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	Access to therapy due to costs or availability of technology may limit the use of HFNC/CPAP/NIV in resource limited settings. Safe use of NIV/CPAP possibly requires high level of nursing supervision which may be an added limitation.	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	**Small**	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	**Varies**	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	**Don't know**
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	Probably no impact	Probably increased	Increased	**Varies**	Don't know

	JUDGEMENT					
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
○	○	○	○	○

CONCLUSIONS

Recommendation

- For children at high-risk for extubation failure, we suggest using non-invasive respiratory support (NRS which includes HFNC, CPAP or NIV) over conventional oxygen therapy immediately after extubation (Table 3) (Conditional recommendation, very low certainty of evidence).
- For children developing respiratory distress while on conventional oxygen therapy post-extubation, we suggest using NRS over continued use of conventional oxygen therapy (Conditional recommendation, very low certainty of evidence).

Justification

The overall benefit of HFNC/CPAP/NIV is possibly larger in children at high risk of reintubation and for those experiencing respiratory distress post-extubation. In this situation, the panel valued prevention of reintubation over the possible increased hospital and PICU length of stay.

Subgroup considerations

Implementation considerations

HFNC level: usual practice and acceptable ranges
CPAP and NIV: Settings, devices
Weaning issues
Tolerance issues: sedation may be needed
Ideal nursing ratio when HFNC/CPAP/NIV is used

Monitoring and evaluation

Abdominal distension,
Emesis/aspiration,
nasal ulcer
air leaks
Tolerance

Should CPAP vs. HFNC be used for post-extubation support in critically ill children?

POPULATION:	Pediatric patients receiving conventional mechanical ventilation more than 24 hours
INTERVENTION:	CPAP
COMPARISON:	HFNC
MAIN OUTCOMES:	Reintubation; Extubation failure plus Treatment failure (Sensitivity); Extubation failure without NIV (sensitivity); PICU length of stay (Only HFNC versus COT); Mortality; Hospital length of stay;

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know		
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ● **Moderate** ○ Large ○ Varies ○ Don't know	Reintubation, ever (22% baseline): • Pairwise estimate: 0.70 (0.47, 1.04) • Absolute risk reduction/NNT: 57 fewer per 1000 (105 fewer to 7 more)/ 17 • GRADE CoE: Low Mortality (5% baseline): • Pairwise estimate: 0.38 (0.15, 0.97) • Absolute risk reduction: 30 fewer per 1000 (100 fewer to 1 fewer)/ 33 • GRADE CoE: Moderate There is very serious imprecision for the estimates for treatment failure and reintubation (within 48-72 hours)	
Undesirable Effects		

How substantial are the undesirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ● **Small** ○ Trivial ○ Varies ○ Don't know	Patient discomfort requiring crossover: • HFNC: 7/272 (2.6%) • CPAP: 24/252 (9.5%) 6% difference noted in one study (**Ramnarayan 2022**).	

Certainty of evidence What is the overall certainty of the evidence of effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● **Low** ○ Moderate ○ High ○ No included studies	Downgraded for imprecision and serious risk of bias.	

Values Is there important uncertainty about or variability in how much people value the main outcomes?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ○ No important uncertainty or variability	A quick reintubation may not be much superior is you stay extubated on non-invasive support for several days.	

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ● **Probably favors the intervention** ○ Favors the intervention ○ Varies ○ Don't know	In pooled analysis of trials that predominantly included infants and young toddlers, • CPAP was ranked higher than HFNC for a. Reintubation, 48- 72 hours: 78% (CPAP) vs 67% (HFNC) b. Reintubation, ever: 90% (CPAP) vs 55% (HFNC) c. Treatment failure: 84% (CPAP) vs 65% (HFNC) • CPAP vs HFNC: a. CPAP has small to moderate (3.1%) clinical benefit for Reintubation (ever) b. Mortality benefit: 3% benefit with CPAP c. Intolerance/patient discomfort to CPAP: 6% more in CPAP	Physiologic differences between infants and older children may account for higher efficacy of CPAP compared to HFNC in infants
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large costs ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ● Varies ○ Don't know	HFNC costs: HFNC may be more difficult to deliver in contexts where oxygen availability is limited (some LMIC countries). HFNC may entail separate equipment in some contexts and add to costs. In US, HFNC may be cheaper by 'freeing' up a ventilator. CPAP costs: CPAP may tie up a ventilator or separate equipment • Net: If CPAP delivered using ventilators- cost higher. But PICU may be saving money overall if they use the same device to deliver NIV as they used for IMV.	
Certainty of evidence of required resources What is the certainty of the evidence of resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

JUDGEMENT		
o Very low o Low o Moderate o High ● **No included studies**		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison o Does not favor either the intervention or the comparison o Probably favors the intervention o Favors the intervention o Varies ● **No included studies**		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Reduced o Probably reduced ● **Probably no impact** o Probably increased o Increased o Varies o Don't know	Costs and access to therapy are important for equity	

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	• CPAP interface related issues • Feeding/ability to feed may be an issue to consider	

Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	• Both HFNC and CPAP are feasible in high resource setting • Appropriate (good fit) interface that is also comfortable may be hard to find	

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	**Moderate**	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	**Small**	Trivial		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	**Low**	Moderate	High			No included studies
VALUES	**Important uncertainty or variability**	Possibly important uncertainty or variability	Probably no important uncertainty or variability	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	**Probably favors the intervention**	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know

CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	**Conditional recommendation for the intervention**	Strong recommendation for the intervention
o	o	o	●	o

CONCLUSIONS

Recommendation

For children <1 year of age who are being started on NRS (either planned or rescue), we suggest the use of CPAP over HFNC. (Conditional recommendation, low certainty of evidence).

Justification

Subgroup considerations

● For children >1 year of age who are started on NRS; CPAP, HFNC, or NIV are appropriate first line therapies and the choice will depend on the clinical setting and patient circumstances.
● NIV can be considered if CPAP or HFNC does not relieve post-extubation respiratory distress, or for children who receive NIV for other chronic conditions.

Implementation considerations

Monitoring and evaluation

Abdominal distension
Emesis/aspiration,
nasal ulcer
air leaks

Research priorities

F. Sedation management

Supplemental Table E17: Search strategies for sedation management

Sedation management question

In acutely hospitalized children receiving conventional mechanical ventilation for more than 24 hours, should a goal-directed sedation protocol be used compared to non-protocolized sedation management to guide sedation management during mechanical ventilation and endotracheal extubation?

P Pediatric patients receiving conventional mechanical ventilation > 24 hours

I Goal-directed sedation protocol during mechanical ventilation and endotracheal extubation

C Non-protocolized sedation management

O Liberation from non-invasive respiratory support rate, liberation from invasive mechanical ventilation rate, total duration of invasive mechanical ventilation, duration of non-invasive respiratory support, failure rate to liberate from invasive mechanical ventilation (including re-intubation rates), VFDs, PICU length of stay, hospital length of stay, Incidence of delirium, incidence of withdrawal, mortality.

I. MEDLINE (Ovid)

Databases selected: Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R)

Line	Query
1	(Adaptive adj2 Support Ventilat*).mp.
2	Airway Extubation/
3	Airway extubat*.mp.
4	Artificial Respirati*.mp.
5	((intubation or extubation*) adj3 (airway or tracheal or intratracheal or endotracheal or early)).mp.
6	exp Intermittent Positive-Pressure Breathing/
7	Intermittent Positive-Pressure Breathing.mp.
8	exp Intermittent Positive-Pressure Ventilation/
9	Intermittent Positive-Pressure Ventilat*.mp.
10	Intubation, Intratracheal/
11	Mechanical* Ventilat*.mp.
12	Neurally Adjusted Ventilatory Assist*.mp.
13	open lung ventilat*.mp.
14	Peep.mp.
15	Positive End Expiratory Pressure*.mp.
16	exp Positive-Pressure Respiration/
17	Positive-Pressure Ventilat*.mp.
18	pressure controlled ventilat*.mp.
19	Proportional Assist Ventilat*.mp.
20	Reintubat*.mp.
21	Respiration, Artificial/
22	Respirator Weaning*.mp.
23	Ventilator*.mp.
24	(Ventilat* adj3 Liberation*).mp.

25	exp Ventilators, Mechanical/
26	exp Ventilator Weaning/
27	Ventilator* Weaning*.mp.
28	Ventilation Weaning*.mp.
29	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28
30	Adolescent/
31	Adolescen*.mp.
32	Teen*.mp.
33	Youth*.mp.
34	exp Child/
35	Child*.mp.
36	Infant/
37	Infant, Newborn/
38	Infant*.mp.
39	Infanc*.mp.
40	Newborn*.mp.
41	Neonat*.mp.
42	Pediatrics/
43	P?ediatric*.mp.
44	Hospitals, Pediatric/
45	Intensive Care Units, Pediatric/
46	PICU*.mp.
47	(Kid or kids).mp.
48	Toddler*.mp.
49	30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48
50	Agitation*.ti,ab.
51	Deep Sedation/
52	((pain or agitat* or arousal or withdrawal) adj2 (measurement* or assessment*)).ti,ab.
53	(pain adj2 (scale* or test* or score* or questionnaire* or evaluation*)).ti,ab.
54	Pain Measurement/
55	Numeric rating scale*.ti,ab.
56	Sedation*.ti,ab.
57	Wake-up test*.ti,ab.
58	Pain/
59	Breakthrough Pain/
60	Pain, Procedural/
61	(pain* adj (breakthrough or procedural)).mp.
62	Analgesics/
63	Analgesic*.ti,ab.
64	Clonidine/
65	Clonidine*.ti,ab.
66	Ketamine/
67	Ketamine*.ti,ab.
68	Narcotics/
69	Narcotic*.ti,ab.
70	Morphine/
71	Morphine*.ti,ab.

72	Hydromorphone/
73	Hydromorphone*.ti,ab.
74	Sufentanil/
75	Sufentanil*.ti,ab.
76	Analgesics, Opioid/
77	Opioid*.ti,ab.
78	Opiate*.ti,ab.
79	Fentanyl/
80	Fentanyl*.ti,ab.
81	Remifentanil/
82	Remifentanil*.ti,ab.
83	"Hypnotics and Sedatives"/
84	Hypnotic*.ti,ab.
85	Sedative*.ti,ab.
86	Chloral Hydrate/
87	Chloral Hydrate*.ti,ab.
88	Dexmedetomidine/
89	Dexmedetomidine*.ti,ab.
90	Diazepam/
91	Diazepam*.ti,ab.
92	Lorazepam/
93	Lorazepam*.ti,ab.
94	Medetomidine/
95	Medetomidine*.ti,ab.
96	Midazolam/
97	Midazolam*.ti,ab.
98	Pentobarbital/
99	Pentobarbital*.ti,ab.
100	Propofol/
101	Propofol*.ti,ab.
102	Benzodiazepines/
103	Benzodiazepine*.ti,ab.
104	50 or 51 or 52 or 53 or 54 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103
105	29 and 49 and 104

II.   Embase (Elsevier)

Line	Query
#1	adaptive NEAR/2 support NEXT/1 ventilat*
#2	'extubation'/de
#3	'airway extubat*'
#4	(intubation* OR extubation*) NEAR/3 (airway OR tracheal OR intratracheal OR endotracheal OR early)
#5	'intermittent mandatory ventilation'/exp
#6	'intermittent positive-pressure breathing'
#7	'intermittent positive pressure ventilation'/exp
#8	'intermittent positive-pressure ventilat*'
#9	'endotracheal intubation'/exp
#10	'invasive ventilation'/exp

P a g e 130 | 150

#11	'inverse ratio ventilation'/de
#12	'mechanical* ventilat*'
#13	'neurally adjusted ventilatory assist*'
#14	'noninvasive positive pressure ventilation'/exp
#15	'open lung ventilat*'
#16	peep
#17	'positive end expiratory pressure ventilation'/exp
#18	'positive end expiratory pressure*'
#19	'positive pressure ventilation'/de
#20	'positive-pressure ventilat*'
#21	'pressure controlled ventilation'/de
#22	'pressure controlled ventilat*'
#23	'pressure support ventilation'/de
#24	'proportional assist ventilat*'
#25	'protective ventilation'/exp
#26	reintubat*
#27	'artificial ventilation'/de
#28	'respirator weaning*'
#29	'tracheal extubation'/de
#30	'ventilator'/de
#31	ventilator*
#32	ventilat* NEAR/3 liberation*
#33	'mechanical ventilator'/de
#34	'ventilator weaning'/de
#35	'ventilator* weaning*'
#36	'ventilation weaning*'
#37	'volume controlled ventilation'/exp
#38	'artificial respirati*'
#39	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38
#40	'adolescent'/exp/mj
#41	'adolescence'/mj
#42	adolescen*:ti,ab
#43	teen*:ti,ab
#44	youth*:ti,ab
#45	'child'/exp/mj
#46	child*:ti,ab
#47	'infant'/exp/mj
#48	'infancy'/exp/mj
#49	'newborn'/exp/mj
#50	infant*:ti,ab
#51	infanc*:ti,ab
#52	newborn*:ti,ab
#53	neonat*:ti,ab
#54	'pediatrics'/mj
#55	p$ediatric*:ti,ab
#56	'pediatric intensive care unit'/mj
#57	picu*:ti,ab
#58	kid:ti,ab OR kids:ti,ab
#59	'toddler'/exp/mj

#60	toddler*:ti,ab
#61	#40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60
#62	'agitation'/mj
#63	'agitation assessment'/exp/mj
#64	agitation*:ti,ab
#65	'sedation'/mj
#66	'deep sedation'/mj
#67	((pain OR agitat* OR arousal OR withdrawal) NEAR/2 (measurement* OR assessment*)):ti,ab
#68	(pain NEAR/2 (scale* OR test* OR score* OR questionnaire* OR evaluation*)):ti,ab
#69	'pain measurement'/mj OR 'numeric rating scale'/mj
#70	sedation*:ti,ab
#71	'wake up test'/mj
#72	'wake-up test*':ti,ab
#73	'pain'/mj
#74	'breakthrough pain'/mj
#75	'procedural pain'/mj
#76	(pain* NEAR/1 (breakthrough OR procedural)):ti,ab
#77	'analgesic agent'/mj
#78	analgesic*:ti,ab
#79	'clonidine'/mj
#80	clonidine*:ti,ab
#81	'ketamine'/mj
#82	ketamine*:ti,ab
#83	'narcotic agent'/mj
#84	narcotic*:ti,ab
#85	'morphine'/mj
#86	morphine*:ti,ab
#87	'hydromorphone'/mj
#88	hydromorphone*:ti,ab
#89	'sufentanil'/mj
#90	sufentanil*:ti,ab
#91	'opiate'/mj
#92	opioid*:ti,ab
#93	opiate*:ti,ab
#94	'fentanyl'/mj
#95	fentanyl*:ti,ab
#96	'remifentanil'/mj
#97	remifentanil*:ti,ab
#98	'hypnotic sedative agent'/mj
#99	'hypnotic agent'/mj
#100	'sedative agent'/mj
#101	hypnotic*:ti,ab
#102	sedative*:ti,ab
#103	'chloral hydrate'/mj
#104	'chloral hydrate*':ti,ab
#105	'dexmedetomidine'/mj
#106	dexmedetomidine*:ti,ab
#107	'diazepam'/mj
#108	diazepam*:ti,ab

#109	'lorazepam'/mj
#110	lorazepam*:ti,ab
#111	'medetomidine'/mj
#112	medetomidine*:ti,ab
#113	'midazolam'/mj
#114	midazolam*:ti,ab
#115	'pentobarbital'/mj
#116	pentobarbital*:ti,ab
#117	'propofol'/mj
#118	propofol*:ti,ab
#119	'benzodiazepine'/mj
#120	benzodiazepine*:ti,ab
#121	#62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71 OR #72 OR #73 OR #74 OR #75 OR #76 OR #77 OR #78 OR #79 OR #80 OR #81 OR #82 OR #83 OR #84 OR #85 OR #86 OR #87 OR #88 OR #89 OR #90 OR #91 OR #92 OR #93 OR #94 OR #95 OR #96 OR #97 OR #98 OR #99 OR #100 OR #101 OR #102 OR #103 OR #104 OR #105 OR #106 OR #107 OR #108 OR #109 OR #110 OR #111 OR #112 OR #113 OR #114 OR #115 OR #116 OR #117 OR #118 OR #119 OR #120
#122	#39 AND #61 AND #121
#123	#122 AND [21-4-2021]/sd NOT [5-10-2021]/sd

III. CINAHL Complete (EBSCO)

Line	Query
S1	(MH "Agitation")
S2	Agitation*
S3	(MH "Sedation")
S4	((pain or agitat* or arousal or withdrawal) N2 (measurement* or assessment*))
S5	(pain N2 (scale* or test* or score* or questionnaire* or evaluation*))
S6	(MH "Pain Measurement") OR "numeric rating scale*"
S7	Sedation*
S8	"wake up test*"
S9	(MH "Pain")
S10	(MH "Breakthrough Pain")
S11	(MH "Pain, Procedural")
S12	Pain* N1 (breakthrough OR procedural)
S13	(MH "Analgesics")
S14	Analgesic*
S15	(MH "Clonidine")
S16	Clonidine*
S17	(MH "Ketamine")
S18	Ketamine*
S19	(MH "Analgesics, Nonnarcotic")
S20	Narcotic*
S21	(MH "Morphine")
S22	Morphine*
S23	Hydromorphone*
S24	(MH "Sufentanil")
S25	Sufentanil*
S26	(MH "Analgesics, Opioid")
S27	Opioid*
S28	Opiate*
S29	(MH "Fentanyl")

S30	Fentanyl*
S31	(MH "Remifentanil")
S32	Remifentanil*
S33	(MH "Hypnotics and Sedatives")
S34	(MH "Sedatives, Barbiturate")
S35	(MH "Sedatives, Nonbarbiturate")
S36	Hypnotic*
S37	Sedative*
S38	(MH "Chloral Hydrate")
S39	"chloral hydrate*"
S40	Dexmedetomidine*
S41	(MH "Diazepam")
S42	Diazepam*
S43	(MH "Lorazepam")
S44	Lorazepam*
S45	Medetomidine*
S46	(MH "Midazolam")
S47	Midazolam*
S48	(MH "Pentobarbital")
S49	Pentobarbital*
S50	(MH "Propofol")
S51	Propofol*
S52	(MH "Antianxiety Agents, Benzodiazepine")
S53	Benzodiazepine*
S54	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR S51 OR S52 OR S53
S55	Toddler*
S56	Kid OR kids
S57	PICU*
S58	(MH "Intensive Care Units, Pediatric")
S59	P#ediatric*
S60	(MH "Pediatrics")
S61	Neonat*
S62	Newborn*
S63	Infanc*
S64	Infant*
S65	(MH "Infant, Newborn")
S66	(MH "Infant") OR (MH "Infant, Hospitalized") OR (MH "Infant, High Risk")
S67	Child*
S68	(MH "Child") OR (MH "Child, Hospitalized") OR (MH "Child, Medically Fragile") OR (MH "Child, Preschool")
S69	Youth*
S70	Teen*
S71	Adolescen*
S72	(MH "Adolescence+")
S73	S72 OR S71 OR S70 OR S69 OR S68 OR S67 OR S66 OR S65 OR S64 OR S63 OR S62 OR S61 OR S60 OR S59 OR S58 OR S57 OR S56 OR S55
S74	Ventilation Weaning*
S75	ventilator* weaning*
S76	(MH "Ventilator Weaning")

S77	(MH "Ventilators, Mechanical")
S78	ventilat* N3 liberation*
S79	ventilator*
S80	'respirator weaning*'
S81	(MH "Respiration, Artificial")
S82	reintubat*
S83	proportional assist ventilat*
S84	(MH "Pressure Support Ventilation")
S85	pressure controlled ventilat*
S86	positive-pressure ventilat*
S87	(MH "Positive Pressure Ventilation")
S88	Positive End Expiratory Pressure*
S89	(MH "Positive End-Expiratory Pressure")
S90	peep
S91	open lung ventilat*
S92	neurally adjusted ventilatory assist*
S93	mechanical* ventilat*
S94	(MH "Mandatory Minute Volume Ventilation")
S95	(MH "Inverse Ratio Ventilation")
S96	(MH "Intubation, Intratracheal")
S97	Intermittent Positive-Pressure Ventilat*
S98	(MH "Intermittent Positive Pressure Ventilation")
S99	intermittent positive pressure breathing
S100	(MH "Intermittent Positive Pressure Breathing")
S101	(intubation* OR extubation*) N3 (airway OR tracheal OR intratracheal OR endotracheal OR early)
S102	artificial respirati*
S103	airway extubat*
S104	(MH "Extubation")
S105	adaptive N2 support ventilat*
S106	S105 OR S104 OR S103 OR S102 OR S101 OR S100 OR S99 OR S98 OR S97 OR S96 OR S95 OR S94 OR S93 OR S92 OR S91 OR S90 OR S89 OR S88 OR S87 OR S86 OR S85 OR S84 OR S83 OR S82 OR S81 OR S80 OR S79 OR S78 OR S77 OR S76 OR S75 OR S74
S107	S54 AND S73 AND S106

Supplemental Figure E8: PRSIMA chart for sedation management

Identification of new studies via databases and registers

Identification

| Records identified from:
Databases (n = 11,735)
Registers (n = 0) | → | Records removed before screening:
Duplicate records (n = 3,721) |

Screening

| Records screened
(n = 8,014) | → | Records excluded
(n = 7,926) |

| Reports sought for retrieval
(n = 88) | → | Reports not retrieved
(n = 0) |

| Reports assessed for eligibility
(n = 88) | → | Reports excluded:
Conference Abstract (n = 23)
Wrong intervention (n = 21)
Wrong outcomes (n = 10)
Wrong study design (n = 15)
Review Paper/Guideline/metaanalysis (n = 8)
Letter/comment (n = 5)
Adult population (n = 3)
NICU population (n = 1) |

Included

| New studies included in review
(n = 2)
Reports of new included studies
(n = 2) |

Supplemental Table E18: Evidence table for sedation management

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	goal directed sedation protocol	non-protocolized sedation management	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
			Certainty assessment				№ of patients		Effect			

In hospital mortality, 90 days (Acute Respiratory Failure, ARF)

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	goal directed sedation protocol	non-protocolized sedation management	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1[1]	randomised trials	not serious	not serious	not serious	serious[a]	none	67/1225 (5.5%)	88/1224 (7.2%)	**RR 0.76** (0.56 to 1.03)	**17 fewer per 1,000** (from 32 fewer to 2 more)	⊕⊕⊕◯ Moderate	CRITICAL

In hospital mortality (all Mechanical Ventilation, MV)

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	goal directed sedation protocol	non-protocolized sedation management	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1[2]	randomised trials	not serious	not serious	not serious	serious[a,b]	none	268/4278 (6.3%)	200/3785 (5.3%)	**RR 1.15** (0.82 to 1.63)	**8 more per 1,000** (from 10 fewer to 33 more)	⊕⊕⊕◯ Moderate	CRITICAL

PICU Mortality (all MV)

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	goal directed sedation protocol	non-protocolized sedation management	Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
1[2]	randomised trials	not serious	not serious	not serious	serious[b]	none	220/4682 (4.7%)	173/4154 (4.2%)	**RR 1.06** (0.73 to 1.54)	**2 more per 1,000** (from 11 fewer to 22 more)	⊕⊕⊕◯ Moderate	CRITICAL

	Certainty assessment						№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	goal directed sedation protocol	non-protocolized sedation management	Relative (95% CI)	Absolute (95% CI)		

Length of invasive mechanical ventilation (ARF)

1[1]	randomised trials	not serious	not serious	not serious	serious[a]	none	1225	1224	-	median **0 days**	⊕⊕⊕◯ Moderate	CRITICAL

Length of invasive mechanical ventilation (all MV)

1[2]	randomised trials	not serious	not serious	not serious	serious[c]	none	4684	4144	-	median **0.25 days lower** (0.34 lower to 0.22 lower)	⊕⊕⊕◯ Moderate	CRITICAL

Reintubation within 24 hours (ARF)

1[1]	randomised trials	not serious	not serious	not serious	serious[b]	none	97/1225 (7.9%)	104/1224 (8.5%)	**RR 0.93** (0.71 to 1.21)	**6 fewer per 1,000** (from 25 fewer to 18 more)	⊕⊕⊕◯ Moderate	CRITICAL

	Certainty assessment						Nº of patients		Effect		Certainty	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	goal directed sedation protocol	non-protocolized sedation management	Relative (95% CI)	Absolute (95% CI)		

Reintubation within 48 hours (all MV)

1[2]	randomised trials	not serious	not serious	not serious	serious[b]	none	544/4688 (11.6%)	507/4155 (12.2%)	HR 1.10 (0.89 to 1.36)	11 more per 1,000 (from 13 fewer to 40 more)	⊕⊕⊕◯ Moderate	CRITICAL

PICU length of stay (ARF)

1[1]	randomised trials	not serious	not serious	not serious	serious[a]	none	1225	1224	-	median **0 days**	⊕⊕⊕◯ Moderate	CRITICAL

PICU length of stay (all MV)

1[2]	randomised trials	not serious	not serious	not serious	serious[a]	none	4688	4155	-	median **0 days**	⊕⊕⊕◯ Moderate	CRITICAL

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations
a. 95% confidence intervals include possibility of benefit and harm with the use of the intervention.
b. 95% confidence intervals cross the threshold for clinical significance and statistical significance.
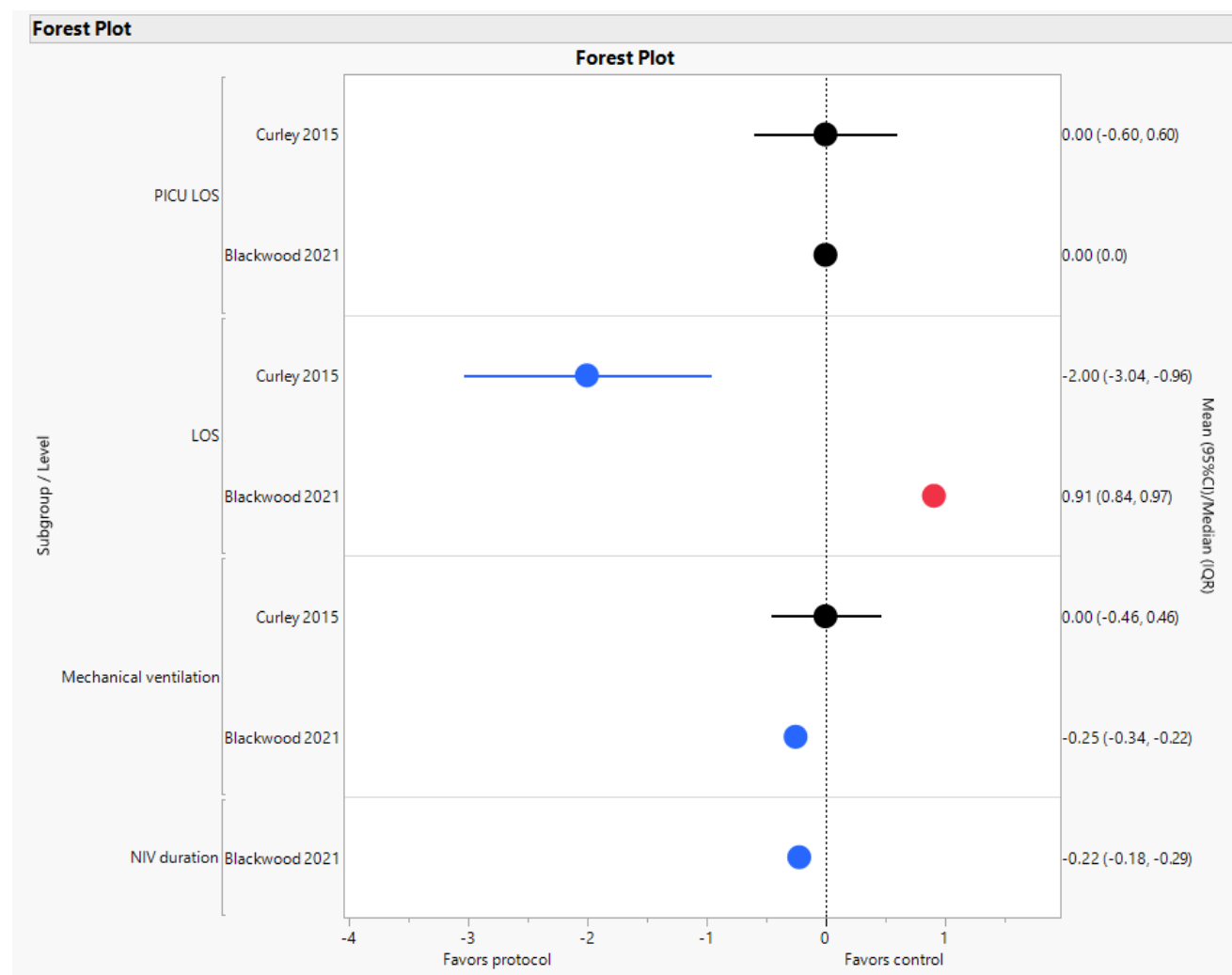c. 95% CI cross the threshold for clinical significance

References:
1. Curley MA, Wypij D, Watson RS, et al. Protocolized sedation vs usual care in pediatric patients mechanically ventilated for acute respiratory failure: a randomized clinical trial. JAMA 2015;313:379-89.
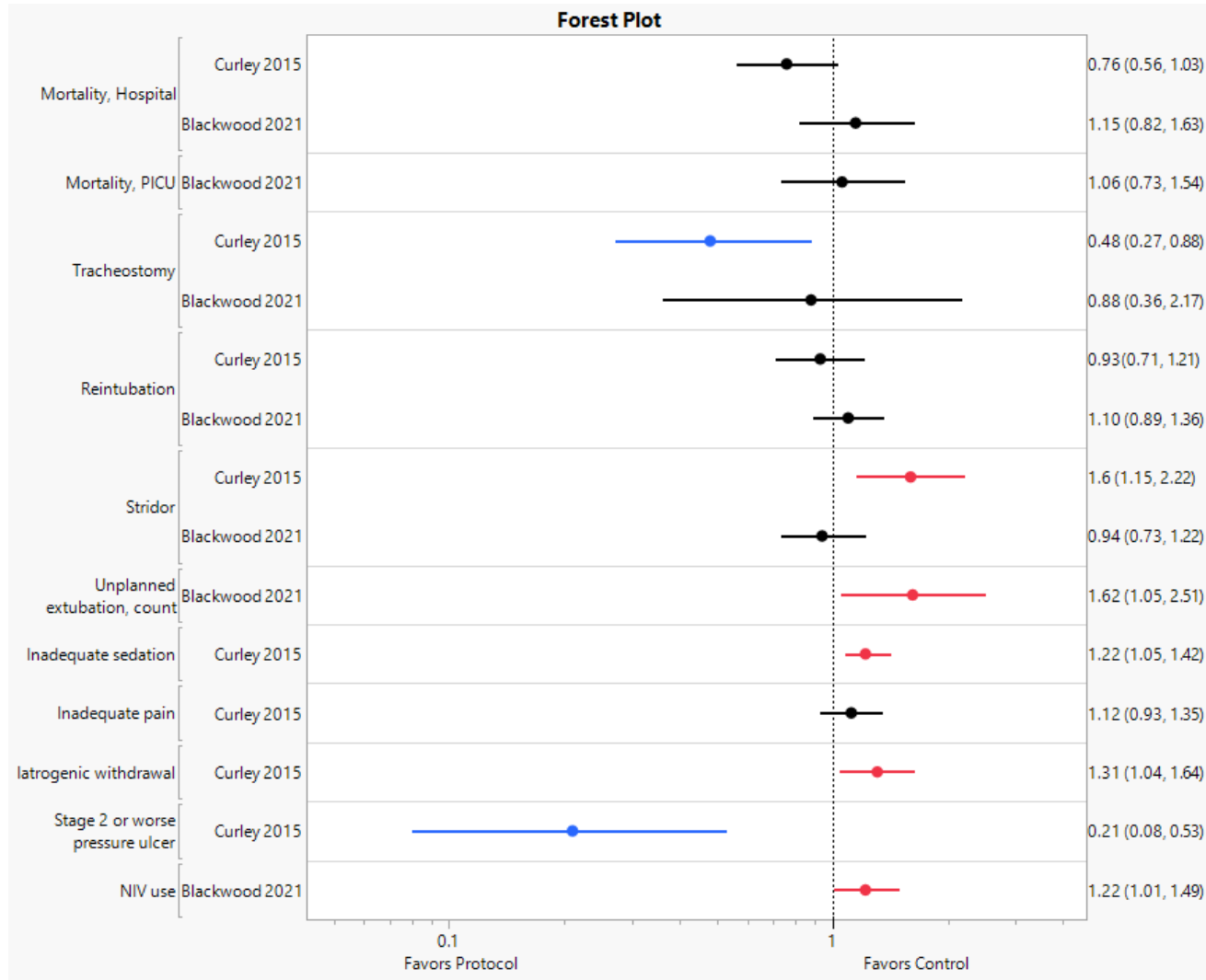
Page 139 | 150

2. Blackwood B, Tume LN, Morris KP, et al. Effect of a Sedation and Ventilator Liberation Protocol vs Usual Care on Duration of Invasive Mechanical Ventilation in Pediatric Intensive Care Units: A Randomized Clinical Trial. JAMA 2021;326:401-10

Forest Plot of different outcomes separated by the two Trials- Curley 2015 (unadjusted estimates) and Blackwood 2021 (adjusted estimates)

Continuous outcomes:

Dichotomous outcomes (Risk ratios):

Forest Plot

		RR (95% CI)
Mortality, Hospital	Curley 2015	0.76 (0.56, 1.03)
	Blackwood 2021	1.15 (0.82, 1.63)
Mortality, PICU	Blackwood 2021	1.06 (0.73, 1.54)
Tracheostomy	Curley 2015	0.48 (0.27, 0.88)
	Blackwood 2021	0.88 (0.36, 2.17)
Reintubation	Curley 2015	0.93 (0.71, 1.21)
	Blackwood 2021	1.10 (0.89, 1.36)
Stridor	Curley 2015	1.6 (1.15, 2.22)
	Blackwood 2021	0.94 (0.73, 1.22)
Unplanned extubation, count	Blackwood 2021	1.62 (1.05, 2.51)
Inadequate sedation	Curley 2015	1.22 (1.05, 1.42)
Inadequate pain	Curley 2015	1.12 (0.93, 1.35)
Iatrogenic withdrawal	Curley 2015	1.31 (1.04, 1.64)
Stage 2 or worse pressure ulcer	Curley 2015	0.21 (0.08, 0.53)
NIV use	Blackwood 2021	1.22 (1.01, 1.49)

0.1 — Favors Protocol   1 — Favors Control

Supplemental Table E19: Evidence table of evidence for sedation management

Should goal directed sedation protocol vs. non-protocolized sedation management be used for sedation management during mechanical ventilation and endotracheal extubation?	
POPULATION:	Pediatric patients receiving conventional mechanical ventilation > 24 hours
INTERVENTION:	Goal directed sedation protocol
COMPARISON:	Non-protocolized sedation management
MAIN OUTCOMES:	In hospital mortality, 90 days (ARF); In hospital mortality (all MV); PICU Mortality (all MV); Length of invasive mechanical ventilation (ARF); Length of invasive mechanical ventilation (all MV); Reintubation within 24 hours (ARF); Reintubation within 48 hours (all MV); PICU length of stay (ARF); PICU length of stay (all MV); Stridor (ARF); Stridor (all MV); Tracheostomy (ARF); Tracheostomy (all MV); NIV use; Hospital length of stay (ARF); Hospital length of stay (all MV);
SETTING:	PICU, pediatric cardiac ICU

ASSESSMENT

Problem Is the problem a priority?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
○ No ○ Probably no ○ Probably yes ● **Yes** ○ Varies ○ Don't know	Considerable variation in practice occurs internationally regarding formalized sedation assessment and management being a component of extubation readiness trials. This question therefore requires examination, to enable a recommendation to be made. Oversedation with opiates and or sedatives reduces the respiratory drive, thus inhibiting spontaneous breathing and preventing successful extubation. Minimizing extubation failure is important both for patients/parents and for healthcare professionals.	
Desirable Effects		

How substantial are the desirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
● **Trivial** ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	(see table below)	

Outcomes	Importance	Certainty of the evidence (GRADE)
Length of invasive mechanical ventilation (ARF)	CRITICAL	⊕⊕⊕◯ Moderate[a]
Length of invasive mechanical ventilation (all MV)	CRITICAL	⊕⊕⊕◯ Moderate[b]
Reintubation within 24 hours (ARF)	CRITICAL	⊕⊕⊕◯ Moderate[c]
Reintubation within 48 hours (all MV)	CRITICAL	⊕⊕⊕◯ Moderate[c]
Tracheostomy (ARF)	IMPORTANT	⊕⊕⊕⊕ High
NIV use	IMPORTANT	⊕⊕◯◯ Low[b,d]
Hospital length of stay (ARF)	IMPORTANT	⊕⊕⊕⊕ High

a. 95% confidence intervals include possibility of benefit and harm with the use of the intervention.
b. 95% CI cross the threshold for clinical significance
c. 95% confidence intervals cross the threshold for clinical significance and statistical significance.
d. Centers were allowed to use NIV as per their regular practice

Undesirable Effects How substantial are the undesirable anticipated effects?		
JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

		Large
		Moderate
		Small
		● Trivial
		Varies
		Don't know

Outcomes	With non-protocolized sedation management	With goal directed sedation protocol	Difference	Relative effect (95% CI)
Stridor (all MV)	86 per 1,000	**81 per 1,000** (63 to 105)	**5 fewer per 1,000** (23 fewer to 19 more)	**RR 0.94** (0.73 to 1.22)
Hospital length of stay (all MV)	The mean hospital length of stay (all MV) was **0 days**	The mean hospital length of stay (all MV) in the intervention group was 0.82 days higher (1.96 lower to 3.61 higher)	median **0.82 days higher** (1.96 lower to 3.61 higher)	-

Certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
Very low Low **● Moderate** High No included studies	•Decreased from 'High' by one level due to 'imprecision'- lack of clinical significance to estimates that are statistically significant.	

Values
Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

o Important uncertainty or variability o Possibly important uncertainty or variability ● **Probably no important uncertainty or variability** o No important uncertainty or variability	Critical outcomes: •Mortality is considered a critical outcome but is only indirectly related to sedation protocol •IMV duration, PICU length of stay are valued similarly Important outcomes that are valued similarly: • Pain control, sedation, iatrogenic withdrawal, stridor not requiring reintubation, hospital length of stay, NIV use and NIV duration	

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Favors the comparison o Probably favors the comparison ● **Does not favor either the intervention or the comparison** o Probably favors the intervention o Favors the intervention o Varies o Don't know	No 'critical' outcomes show any meaningful difference	

Resources required
How large are the resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
o Large costs o Moderate costs o Negligible costs and savings o Moderate savings o Large savings ● **Varies** o Don't know	No extra resources where 1:1 or 1:2 RN to patient ratio. With >1:2 RN:patient ratio may require increased resources. But even here the resources required for ongoing IMV or extubation failure will still be higher compared to resources needed for sedation assessment during ERT.	Nurses/doctors or other trained providers may be used to do the assessment. Educating providers to assess sedation and translating tools will all need resources.

Certainty of evidence of required resources
What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Very low ○ Low ○ Moderate ○ High ● **No included studies**		

Cost effectiveness
Does the cost-effectiveness of the intervention favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies ● **No included studies**		

Equity
What would be the impact on health equity?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ● **Probably no impact** ○ Probably increased ○ Increased ○ Varies ○ Don't know		

Acceptability
Is the intervention acceptable to key stakeholders?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	Acceptability concerns probably exist with implementation of a nurse-driven protocol: example lack of compliance in SANDWICH	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	Feasibility depends on developing translated tools, integrated tools, training, workflow.	Translated tools, integrated tools, training, workflow.

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	**Trivial**	Small	Moderate	Large		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	**Trivial**		Varies	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	**Moderate**	High			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	**Does not favor either the intervention or the comparison**	Probably favors the intervention	Favors the intervention	Varies	Don't know
RESOURCES REQUIRED	Large costs	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	**Varies**	Don't know

	JUDGEMENT						
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	Moderate	High			**No included studies**
COST EFFECTIVENESS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	**No included studies**
EQUITY	Reduced	Probably reduced	**Probably no impact**	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

Type of recommendation

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
○	○	●	○	○

Conclusions

Recommendation

- We recommend that the level of sedation, cough effectiveness, and capacity to manage oropharyngeal secretions be evaluated prior to extubation (Ungraded, good practice statement).
- We recommend a targeted sedation management strategy using a validated, reliable tool to set sedation targets (Ungraded, good practice statement).
- We suggest either the use of a standardized sedation titration protocol or no standardized protocol to guide targeted sedation management during IMV and ERT (Conditional recommendation, moderate certainty of evidence).

Justification

- As concepts, the benefits of assessing cough, secretions and sedation levels prior to extubation clearly outweigh any risks associated with such assessments. These assessments are standard practice.
- Using targeted sedation management using validated, reliable tool for sedation assessment has the obvious benefit of improving team communication and focusing therapy to specific goals.
- The balance of effects is not in favor or against the protocol.

Implementation considerations

- Use only validated and reliable tools