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Air Leak Test in the Paediatric Intensive Care Unit (ALTIPICU): Rationale and Protocol for a Prospective Multicentre Observational Study

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ABSTRACT

Introduction: In children, respiratory distress (RD) due to upper airway obstruction (UAO) is a common complication of extubation that increases morbi-mortality. The quantitative cuff-leak test (qtCLT) is a simple, rapid, and non-invasive test that has not been extensively studied in children. The objective of the ongoing study whose protocol is reported here is to investigate how well the qtCLT predicts UAO-related post-extubation RD in paediatric intensive care unit (PICU) patients.

Methods and Analysis: ALTIPICU is a multicentre, prospective, observational study that will recruit 900 patients who are aged 2 days post-term to 17 years and ventilated through a cuffed endotracheal tube for at least 24 h in any of 19 French PICUs. Within an hour of planned extubation, the qtCLT is performed as a sequence of six measurements of the tidal volume with the cuff inflated then deflated. The patient is extubated according to local procedures. The primary outcome is the occurrence within 48 h after extubation of severe UAO defined as combining a requirement for intravenous corticosteroid therapy to decrease the laryngeal oedema and/or ventilator support by high-flow nasal cannula (HFNC) and/or by NIV or repeat iMV with a Westley score ≥ 4 with at least 1 point for stridor at each initiation. The study results are expected to definitively determine whether qtCLT deserves to be used routinely before the extubation of critically ill children as a reliable method for predicting severe UAO. Moreover, the study will identify risk factors for UAO-related post-extubation RD and extubation failure, thereby enabling the identification of the patient sub-groups most likely to require preventive interventions.

Ethics and dissemination: The study was approved by the Robert Debré University Hospital institutional review board on September 2021 (approval #2021-578). The results will be submitted for publication in a peer-reviewed journal.

Trial registration: ClinicalTrials.gov, NCT05328206

Strengths and limitations of this study

- This is the largest multicentre prospective observational study to date investigating the ability of the quantitative cuff-leak test to predict post-extubation upper-airway obstruction responsible for respiratory distress in critically ill children extubated after cuffed ventilation.
- The trial is being conducted in 19 paediatric intensive care units throughout France and is therefore expected to produce highly generalisable results.
- Using a primary outcome that combines a therapeutic measure with a clinical score reduces the risk of bias caused by inter-observer variability.
- The management of post-extubation respiratory distress is not standardised and follows usual protocols in each participating centre.
- The use of pre-extubation corticosteroid therapy, which may affect cuff-leak test results and the risk of post-extubation upper airway obstruction, is not standardised and follows usual protocols in each participating centre.

INTRODUCTION

Invasive mechanical ventilation (iMV) is very often required in patients admitted to the paediatric intensive care unit (PICU). Respiratory distress (RD), the main reason for PICU admission, requires iMV in 30%–40% of cases.[1,2] Moreover, iMV may be needed after surgery or for non-respiratory life-threatening conditions such as neurological, haemodynamic, or metabolic failure.[1–3] In a marked departure from historical practice, cuffed endotracheal tubes are now recommended in children.[4,5] Complications that may develop during iMV or after extubation include ventilator-associated pneumonia, airway injury, laryngeal ischemia, and post-extubation respiratory distress (PERD).[6–8]

The main cause of PERD in paediatric patients is upper airway obstruction (UAO) due to laryngeal oedema, which results in a characteristic high-pitched sound known as stridor. UAO-related PERD (UAO-PERD) occurs after 5% to 30% of extubations in children and requires re-intubation in 2% to 5% of cases.[9–11] Severe UAO-PERD is associated with a need for non-invasive ventilation (NIV) or re-intubation, a longer PICU stay, and tracheal stenosis.[9,12] Preventing tracheal inflammation in intubated patients is therefore crucial. Moreover, before extubation, each patient should be assessed for the risk of UAO-PERD. One risk marker is the result of the cuff-leak test (CLT). This simple, rapid, and non-invasive test consists in measuring the air leak after deflation of the endotracheal tube cuff. Leakage is expected to occur through the space left free around the tube. In the event of oedema, however, the tube is in contact with the airway after cuff deflation and leakage does not occur. Thus, the greater the leak, the lower the risk of UAO-PERD. The latest PALISI network guidelines recommend performing the CLT before extubation in children, despite underlying evidence of only very low certainty.[13]

The qualitative variants of the CLT consists in listening for expired air around the endotracheal tube when the cuff is deflated. Sensitivity for predicting PERD is low, probably due to the subjective nature of the assessment.[14–16] For the quantitative CLT (qtCLT), the expiratory tidal volume (exVT) is measured with the cuff inflated then deflated. The difference between the two values reflects the size of the leak.[17] In a meta-analysis of studies in adults, the qtCLT had 87% specificity (95% confidence interval [95%CI], 0.82%–0.90%) and 62% sensitivity (95%CI, 0.49%–0.73%) for UAO.[16] However, of the 28 included studies, five used only the qualitative CLT and one either the qualitative CLT or the qtCLT, possibly decreasing the estimated sensitivity. Moreover, no standardised definition of UAO was used. We are aware of a single paediatric study providing information on the performance of the qtCLT in predicting post-extubation stridor.[17] A leak of less than 11% was 61% sensitive, 53% specific, and 59% accurate. The corresponding values for an ultrasound-measured air column width between the vocal cords of less than 0.8 mm were 93%, 86%, and 91%. In this study, post-extubation stridor was defined as "a high-pitched inspiratory wheeze requiring medical intervention (corticosteroid therapy or reintubation) within 24 hours of extubation and associated with respiratory distress". Although clear and simple, this outcome is not fully satisfactory: RD is not defined objectively, the use of NIV after extubation is not considered among the medical interventions for RD, and the time interval for stridor to develop is only 24 h. Moreover, the study included 400 patients, all of whom were recruited at a single centre with more than half were admitted for surgical causes. Consequently, there is a need for a large study capable of providing definitive data on the performance of the qtCLT in predicting UAO-PERD after extubation of PICU patients.

We designed a multicentre observational study with a large sample size, obtained through the participation of 19 PICUs, to evaluate the performance of the qtCLT for predicting UAO-PERD. We used a strong definition of UAO-PERD combining a requirement for

intravenous corticosteroid therapy (IV CS) to decrease the laryngeal oedema and/or ventilator support by high-flow nasal cannula (HFNC) and/or by NIV or repeat iMV with a Westley score ≥4 with at least 1 point for stridor at each initiation.

METHODS

Study design

This is an observational, non-randomised, prospective, cohort study that is being conducted in 19 French PICUs (final version n°1). Enrolment began on 5 October 2022 and is expected to last 18 months, the planned sample size being 900. The occurrence of UAO-PERD is recorded during the first 48 h after extubation, and additional outcomes are recorded until day 28.

The study was approved by the appropriate ethics committee on September 2021 (approval #CEER-RD 2021-578) and was registered prior to initiation on ClinicalTrials.gov (NCT05328206).

A monthly newsletter about the progress of the study is sent to all investigators.

Participants

The inclusion criteria are full-term birth, age at least 2 days and less than 18 years, intubation with a cuffed endotracheal tube, iMV for at least 24 h, and oral informed consent to study participation. The exclusion criteria are tracheostomy before extubation, indication for long-term NIV, history of upper airway abnormalities, upper airway surgery within one month before the assessment of eligibility, decision to withdraw or withhold life-sustaining treatment, and previous inclusion in the study (Figure 1).

Involvement of the patients and public

Neither the patients nor their parents were involved in identifying the research question or designing the study. The study findings will be published in a peer-reviewed journal and reported at one or more scientific meetings.

Recruitment

Eligible children are identified by the study investigator at each participating PICU (Table 1), who explains the study and requests oral informed consent by the parents or legal guardian and, when able to understand, the patients (Figure 1).

Study intervention

When extubation is planned, qtCLT is performed according to the protocol developed by Miller and Cole[17] and used by El Amrousy et al.,[17,18]within 1 h before extubation (Table 2). The ventilator is set to assist-volume control mode with a tidal volume (VT) of 8 to 10 mL/kg of predicted body weight, up to 450 mL. Six consecutive expiratory tidal volume (exVT) measured by the ventilator is recorded with the cuff inflated then deflated. The mean exVT values (in mL) are computed for the values obtained with the cuff inflated and deflated. Leak volume is defined as the difference between exVT infalted and exVT deflated. Leak percentage (%) is calculated as follows: 100 x (exVT inflated- exVT deflated) / exVT inflated.[17,19]

Extubation was performed according to each centre's procedure. No specific instructions were given for the study. The intensivist records the Westley score immediately after extubation and then over the next 48 hours before the initiation of intravenous corticosteroid therapy (IV CS) and/or ventilatory support (HFNC, NIV or reintubation). The value serves to define UAO-PERD, as described below in the section on the primary outcome. Thus, if none of these treatments is given, the Westley score is recorded only once, immediately after extubation (Figure 1).

Surveys completed by the participating PICUs indicated that 80% used automatic leak compensation, regardless of the ventilator model. Automatic leak compensation relies chiefly on the minute volume and therefore starts only after more than 1 minute. In our study, the qtCLTs are performed within less than 1 minute. Consequently, automatic leak compensation cannot affect the measured values. We therefore require no changes to the ventilator setups that are part of standard practice in each participating PICU.

Study objectives

The primary study objective is to assess the performance of qtCLT in predicting severe UAO-PERD with onset within 48 h after extubation.

The secondary objectives are to determine the frequency of extubation failure; identify risk factors for severe UAO-PERD within 48 h after extubation; describe the frequency and effects of pre extubation IV CS within 12 h; and develop a score predicting severe UAO-PERD within 48 h after extubation, which would subsequently undergo an external validation study.

Primary endpoint

The primary endpoint is the cumulative incidence of UAO-PERD within 48 h after planned extubation. UAO-PERD is defined as the initiation of IV CS and/or ventilatory assistance (HFNC, NIV, or re-intubation) with a Westley score ≥4, including at least 1 point for stridor, (indicating laryngeal obstruction).

Each participating PICU is asked to ensure that, to the extent possible, the primary endpoint is assessed by a person different from the person who performs the qtCLT.

Secondary endpoints

The secondary endpoints are the cumulative incidence of extubation failure, defined as re-intubation for RD within 48 h after extubation combined with a pre-re-intubation Westley score ≥4 with at least 1 point for the stridor item; the frequency of intravenous

corticosteroid therapy given within 12 h before extubation; the frequency of UAO-PERD in patients with vs. without this treatment; the number of PICU-free days by day-28 after enrolment; in-PICU mortality; and, in patients who died in the PICU, the time to death. The predictive score for UAO-PERD will be assessed by computing the area under the receiver operating characteristic curve (AUROC).

Data collection

The study data are collected prospectively by the investigator at each participating PICU, using a secure online database (CleanWEB® 2022 Telemedicine Technologies, Boulogne-Billancourt, France). For each patient we recorded the age (months); weight (kg), sex; reason for PICU admission; Paediatric Index of Mortality 3 (PIM-3; %) and Paediatric Logistic Organ Dysfunction 2 (PELOD-2; %) scores; internal diameter of the cuffed endotracheal tube (mm); number of intubations during the index PICU stay; whether intravenous corticosteroid therapy was given within 12 hours before extubation; history of failed extubation during the same PICU stay before enrolment; and iMV duration (hours). The qtCLT results (mean of the six exVT values with the cuff inflated and mean of the six exVT values with the cuff deflated); date and time of extubation, and Westley score immediately after extubation are collected; as well as the use within 48 h after extubation of IV CS and/or ventilatory assistance (HFNC, NIV, or re-intubation), with the time to initiation. The PICU stay length, number of PICU-free days by day 28, and in-PICU mortality with the time to death are recorded.

Statistical analysis

Sample size estimation

Based on the literature, the expected proportion of patients with severe UAO-PERD is 15%.[14,17,20,21] Therefore, 900 patients (135 with vs. 765 without UAO-PERD) are needed to estimate the qtCLT AUROC with a two-sided 95.0% confidence interval (95%CI) of less than

0.10 for AUROC values greater than 0.75 (e.g., 95%CI of 0.071 if the AUROC equals 0.90). Recruiting 765 patients without PERD will allow the identification of a cut-off having 90% specificity, with an exact two-sided 95%CI of 0.044.

The analyses will be repeated in the following age sub-groups: [2 days to 2 years[, [2 years to 8 years[, and [8 years to 18 years[. The smallest expected ROC curve width for AUROC values greater than 0.75 is 0.199 (0.141 for an AUROC of 0.90) within each age sub-group. The cut-off having 90% specificity will have an exact two-sided 95%CI of 0.09 within the same age sub-group.

Based on data recorded in each of the 19 participating PICUs during the year preceding study initiation, 18 months will be required to recruit 900 patients meeting all the study inclusion criteria and none of the study exclusion criteria.

Statistical analysis principles

All enrolled patients will be included in the analysis. Descriptive statistics will be computed for the included patients, as median [interquartile range] for quantitative variables and as number (percentage) for qualitative data.

Primary endpoint

The AUROCs for the leak as a percentage and as a volume associated with the occurrence of UAO-PERD will be estimated with their 95%CIs as described by Delong and Delong, in the overall population and in each of the above-defined age sub-groups.[22] Bootstrapping will be used to check 95%CI boundaries. Age-adjusted AUROC values will be estimated according to the age sub-groups defined above.

The analyses will consider death within 48 h after extubation and re-intubation due to non UAO-PERD, as defined in the protocol, as competing risks. Missing data will be handled by multiple imputation, and an analysis of cases with no missing data will also be performed.

Secondary endpoints

The cumulative incidence of extubation failure, defined as re-intubation performed within 48 hours after extubation after documenting a Westley score ≥4, including at least 1 point for stridor, will be estimated with its 95%CI, using Gray's estimator and considering two competing risks, namely, death and re-intubation due to causes other than UAO-PERD. This cumulative incidence will be estimated in the overall population and in each age sub-group.

The frequency of intravenous corticosteroid therapy within 12 h before extubation will be determined. Potential associations between this treatment and the occurrence of UAO-PERD will be assessed using a weighted propensity score approach. Risk factors for UAO-PERD within 48 h after extubation will be sought by building a logistic model for predicting UAO-PERD. Only baseline variables, i.e., variables recorded at the admission and the extubation, will be considered. Continuous variables may be transformed to ensure log-linearity of their effect. If the effect is non-linear, spline modelling will be considered. The characteristics and possible over-optimism of the predictive score thus developed will be evaluated using bootstrapping and cross-validation.

The PICU stay length, number of PICU-free days by day 28, and in-PICU mortality with the time to death will be reported as descriptive statistics.

ETHICS AND DISSEMINATION

The study was approved by the institutional review board of the Robert Debré University Hospital in Paris, France, on September 2021 (approval #2021-578). The study carries no risk to the participants. The results will be submitted for publication in a peer-reviewed journal and reported at one or more scientific meetings.

DISCUSSION

The paucity of available evidence has not allowed the development of strong recommendations about performing a qtCLT before the extubation of paediatric patients.[13] To our knowledge, this is the first multicentre study evaluating the performance of the qtCLT in predicting UAO-PERD after extubation in the PICU. The age range is broad, from 2 days to 18 years. The main research question is whether the qtCLT reliably predicts the risk of UAO-PERD, thereby providing information likely to improve patient management. In addition, the study will identify risk factors for UAO-PERD and prospectively collect information on current ventilator weaning and post-extubation practices in French PICUs. Finally, we will develop a score for predicting UAO-PERD that should be suitable for use in daily practice. This score will require external validation in a separate study.

No validated method for assessing UAO-PERD in paediatric patients has been reported to date. UAO-PERD is often defined as the onset of stridor or the need for re-intubation within 48 h after planned extubation.[11,23] Although re-intubation is a strong objective marker, it is required in less than 10% of paediatric patients with UAO-PERD, and this proportion is declining, notably due to the increasing use of NIV for managing ventilator weaning.[10,11,24] Consequently, using only re-intubation to define UAO-PERD would require a very large sample size. Moreover, re-intubation may be needed for reasons other than UAO. On the other hand, isolated stridor is not associated with worse patient outcomes. Only stridor combined with evidence of RD, with or without a need for intervention (IV CS and/or HFNC, NIV, or re-intubation), is relevant. Our strong definition includes RD defined as requiring intervention (IV CS and/or ventilatory assistance) with a Westley score ≥4, with at least 1 point for stridor. To differentiate PERD due to UAO vs. other causes, the Westley score has to include at least 1 point for stridor. Thus, use of the interventions is linked to objective evidence of RD.[25–27] UAO-PERD shares pathophysiological similarities with croup. Based on the study of Yang et *al*, we chose 4 as the cut-off for defining severe UAO-PERD.[28] The

combined use of treatments in the definition decreases the risk of bias due to inter-observer variability in Westley score determination.

Several factors support the feasibility of conducting and completing our study. First, the project was presented several times at meetings of the French PICU research network on respiratory conditions (Groupe francophone de reanimation et urgences pédiatriques, GFRUP). This dissemination effort allowed us to obtain the participation of 19 PICUs, accounting for over 85% of all PICUs in France. Second, the study carries no risk to the participants. The qtCLT is a safe procedure that is part of standard care. All other investigations and treatments used in the study patients are also part of standard care. Third, all local investigators followed a training session on protocol procedures and Westley-score determination. Finally, given that the primary outcome is assessed after only 2 days, the number of missing data for the primary outcome is expected to be very small.

Our study design has limitations. First is that extubation management were left to the discretion of each centre. In order to limit the impact, we recorded pre-extubation measures such as use of intravenous corticosteroids. Second, the management of UAO-PERD will probably vary across participating PICUs, given the absence of guidelines for initiating IV CS , HFNC, NIV, or repeat iMV. However, our use of a definition that comprises not only these interventions but also the physical findings, as reflected by the Westley score and stridor sub-score, will limit this potential source of bias.

CONCLUSION

This protocol for a prospective multicentre observational study of qtCLT performance in predicting UAO-PERD has important strengths and is therefore expected to produce definitive results. Among these strengths is the composite definition of UAO-PERD combining clinical features, reflected by the Westley score and presence of stridor, with a

range of treatment requirements that includes post-extubation NIV. External validation of the predictive score designed based on the study results will be performed subsequently.

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Table 1: List of the 19 study sites

Réanimation pédiatrique - **CHU Robert Debré**
Réanimation et surveillance continue médicochirurgicale - **CHU Necker-Enfant Malades**
Anesthésie et Réanimation pédiatrique - **CHU Necker-Enfant Malades**
Réanimation néonatale et pédiatrique - **CHU Armand Trousseau**
Réanimation pédiatrique et Néonatale - **CHU Kremlin Bicêtre**
Réanimation pédiatrique - **CHU Raymond Poincaré**
Réanimation pédiatrique - **CH Marie Lannelongue**
Réanimation pédiatrique - **CHRU Jeanne de Flandre, Lille**
Réanimation médicale pédiatrique - **CHRU Nancy Brabois**
Réanimation pédiatrique - **CHU Hospices Civils de Lyon**
Réanimation et soins intensifs pédiatrique - **CHU Grenoble Alpes**
Anesthésie et Réanimation pédiatrique - **CHU de la Timone, Marseille**
Médecine néonatale et Réanimation pédiatrique - **CHU Clermont-Ferrand**
Réanimation néonatale et pédiatrique - **CHU Toulouse**
Réanimation pédiatrique – **CHU Pellegrin Bordeaux**
Maladie cardio-vasculaires congénitales – **CHU Haut-Lévêque Bordeaux**
Réanimation pédiatrique et unité de surveillance continue - **CHRU de Tours**
Réanimation et soins intensifs pédiatriques - **CHU de Caen**
Réanimation pédiatrique, surveillance continue pédiatriques et réanimation des cardiopathies congénitales - **CHU de la Réunion Pôle Nord**

Table 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrolment, Interventions and Assessments

	STUDY PERIOD					
Time point	**Enrolment**	**Immediately before extubation**	**Baseline (T0): Extubation**	**Immediately after T0**	**T0 to T48 h**	**D28**
ENROLMENT **Eligibility screen:** **-iMV≥24 h, cuffed tube** **-age ≥2 days to <18 years** **-informed consent**	 ✓ ✓ ✓					
INTERVENTION **-qtCLT**		✓				
ASSESSMENTS **-Westley score** **-use of PERD treatments;** **if yes, Westley score:** **IVCS** **HFNC** **NIV** **Re-intubation**				✓	 ✓ ✓ ✓ ✓	
PICU-free days						✓
In-PICU mortality Time to in-PICU death						✓ ✓

D: day; iMV: invasive mechanical ventilation; qtCLT: quantitative cuffed leak test; Westley score: Westley score; PERD: post-extubation respiratory distress; IVCS: intravenous corticosteroid therapy; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; PICU: paediatric intensive care unit

Authors' contributions

BL, AH, JN, AM, GG, GP, ML, and SD contributed to conceive and prepare the study.

BL, MRR, and SD contributed to design the study.

BL and AH wrote the first draft of the manuscript. JN, AM, GG, GP, ML, MRR, and SD contributed to draft the manuscript then to review it for important intellectual content.

BL, AH, MRR and SD are contributing to manage the study and to collect, analyse, and interpret the data.

All authors have read the final version of this manuscript and approved its submission to *BMJ Open.*

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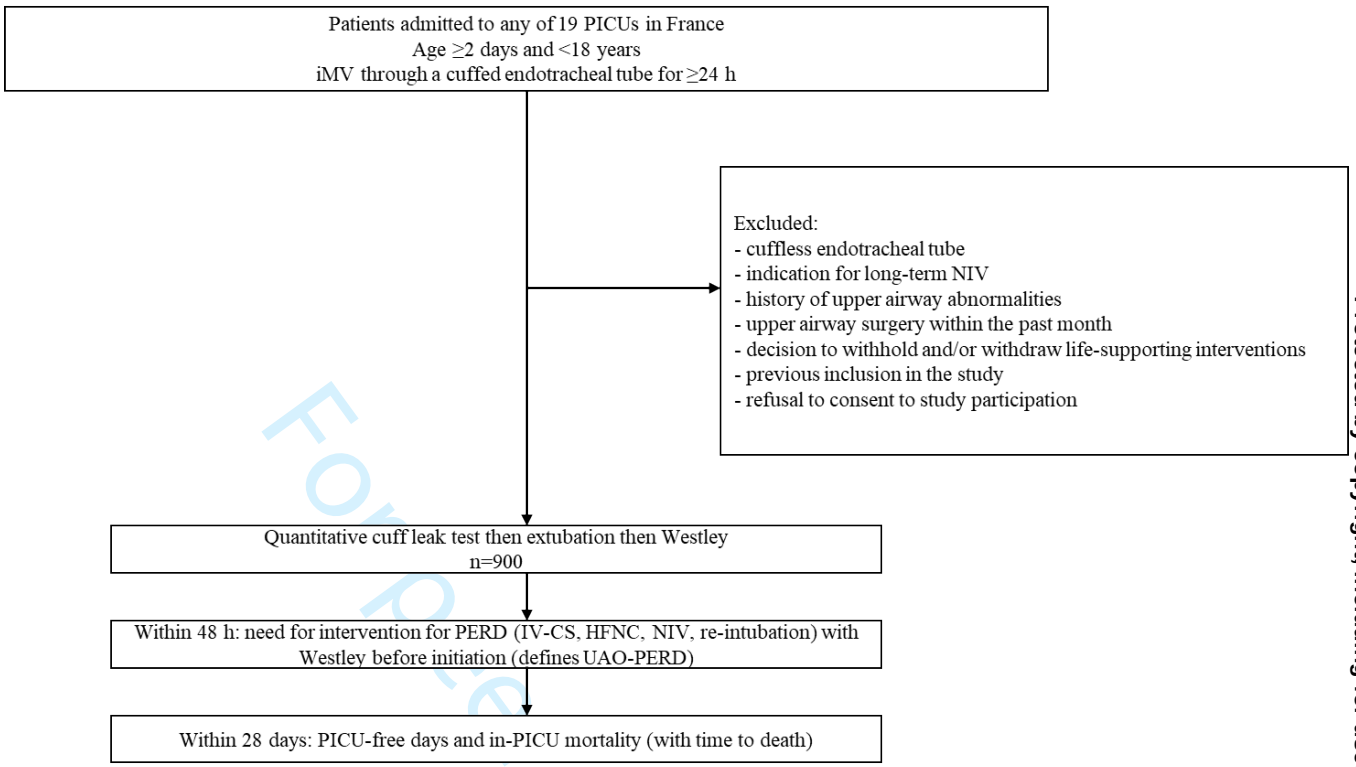
Competing interests statement

None of the authors has any conflicts of interest to declare.

Patients and Public Involvement

The patients, their parents, and the public had no role in designing this protocol or in writing the present manuscript. They have no role in conducting the study and will not be involved in analysing, interpreting, or disseminating its results. The study findings will be published in a peer-reviewed journal and reported at one or more scientific meetings.

Figure 1. Patient flow chart



PICU: paediatric intensive care unit; iMV: invasive mechanical ventilation; NIV: non-invasive ventilation; mWestley: modified Westley score; PERD: post-extubation respiratory distress; HFNC: high-flow nasal cannula; IV CS: intravenous corticosteroid therapy; UAO-PERD: PERD related to upper airway obstruction

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	_1_____
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	_3_____
	2b	All items from the World Health Organization Trial Registration Data Set	_ClinTrials.gov___
Protocol version	3	Date and version identifier	__6_____
Funding	4	Sources and types of financial, material, and other support	_21_____
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	_21_____
	5b	Name and contact information for the trial sponsor	_NA_____
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	_NA_____
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	_NA_____
Introduction			

Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	_4,5_____
	6b	Explanation for choice of comparators	_NA_____
Objectives	7	Specific objectives or hypotheses	_5_____
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	_6_____
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	_6, 17
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	_6_____
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	_7_____
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	_NA_____
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	_13_____
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	_NA_____
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	_8,9_____
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	_Figure 2_____

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	_10_____
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	_10,13_____
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	__NA_____
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	__NA_____
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	_NA_____
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	_NA_____
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	_NA_____
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	_9,10_____
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	_NA_____

Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	_9_____
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	_10,11,12_____
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	_10,11_____
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	_NA_____
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	__NA_____
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	_NA_____
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	_NA_____
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	_NA_____
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	_6,12_____
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	_NA_____

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	__6_____
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	__NA_____
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	__NA_____
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	_21_____
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	__19_____
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	__NA_____
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	_2,12_____
	31b	Authorship eligibility guidelines and any intended use of professional writers	_NA_____
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	__NA_____
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	_NA_____
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	_NA_____

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Air Leak Test in the Paediatric Intensive Care Unit (ALTIPICU): Rationale and Protocol for a Prospective Multicentre Observational Study

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Air Leak Test in the Paediatric Intensive Care Unit (ALTIPICU): Rationale and Protocol for a Prospective Multicentre Observational Study

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ABSTRACT

Introduction: In children, respiratory distress due to upper airway obstruction (UAO) is a common complication of extubation. The quantitative cuff-leak test (qtCLT) is a simple, rapid, and non-invasive test that has not been extensively studied in children. The objective of the ongoing study whose protocol is reported here is to investigate how well the qtCLT predicts UAO-related post-extubation respiratoy distress in paediatric intensive care unit (PICU) patients.

Methods and Analysis: ALTIPICU is a multicentre, prospective, observational study that will recruit 900 patients who are aged 2 days post-term to 17 years and ventilated through a cuffed endotracheal tube for at least 24 h in any of 19 French PICUs. Within an hour of planned extubation, the qtCLT will be performed as a sequence of six measurements of the tidal volume with the cuff inflated then deflated. The primary outcome is the occurrence within 48 h after extubation of severe UAO defined as combining a requirement for intravenous corticosteroid therapy and/or ventilator support by high-flow nasal cannula (HFNC) and/or by NIV or repeat IMV with a Westley score ≥ 4 with at least 1 point for stridor at each initiation. The results of the study are expected to identify risk factors for UAO-related post-extubation respiratory distress and extubation failure, thereby identifying patient subgroups most likely to require preventive interventions. It will also determine whether qtCLT appears to be a reliable method to predict an increased risk for postextubation adverse events as severe UAO.

Ethics and dissemination: The study was approved by the Robert Debré University Hospital institutional review board (IRB) on September 2021 (approval #2021-578). The report of Robert Debré University Hospital IRB is valid for all sites, given the nature of the study with

respect to the French law. The results will be submitted for publication in a peer-reviewed journal.

Trial registration: ClinicalTrials.gov, NCT05328206

Strengths and limitations of this study

- This is the largest multicentre prospective observational study to date investigating the ability of the quantitative cuff-leak test to predict the risk of post-extubation upper-airway obstruction responsible for respiratory distress in critically ill children extubated after cuffed ventilation.
- The trial is being conducted in 19 paediatric intensive care units throughout France and is therefore expected to produce highly generalisable results.
- Using a primary outcome that combines a therapeutic measure with a clinical score reduces the risk of bias caused by inter-observer variability.
- The management of post-extubation respiratory distress is not standardised and follows usual protocols in each participating centre.
- The use of pre-extubation corticosteroid therapy, which may affect cuff-leak test results and the risk of post-extubation upper airway obstruction, is not standardised and follows usual protocols in each participating centre.

INTRODUCTION

Invasive mechanical ventilation (IMV) is very often required in patients admitted to the paediatric intensive care unit (PICU). Respiratory distress, the main reason for PICU admission, requires IMV in 30%–40% of cases.(1,2) Moreover, IMV may be needed after surgery or for non-respiratory life-threatening conditions such as neurological, haemodynamic, or metabolic failure.(1–3) In a marked departure from historical practice, cuffed endotracheal tubes are now recommended in children.(4,5) Complications that may develop during IMV or after extubation include ventilator-associated pneumonia, airway injury, laryngeal ischemia, and post-extubation respiratory distress (PERD).(6–8)

The main cause of PERD in paediatric patients is upper airway obstruction (UAO) due to laryngeal oedema, which results in a characteristic high-pitched sound known as stridor. UAO-related PERD (UAO-PERD) occurs after 5% to 30% of extubations in children. The severe form may requires re-intubation in 2% to 5% of cases, and is also associated with the need for non-invasive ventilation (NIV), prolonged PICU stay, and tracheal stenosis.(9–12) Moreover, before extubation, each patient should be assessed for the risk of UAO-PERD. One risk marker is the result of the cuff-leak test (CLT). This simple, rapid, and non-invasive test consists in measuring the air leak after deflation of the endotracheal tube cuff. Leakage is expected to occur through the space left free around the tube. In the event of oedema, however, the tube is in contact with the airway after cuff deflation and leakage does not occur. Thus, the greater the leak, the lower the risk of UAO-PERD. The latest PALISI network guidelines recommend performing the CLT before extubation in children, despite underlying evidence of only very low certainty.(13)

The qualitative variants of the CLT consists in listening for expired air around the endotracheal tube when the cuff is deflated. Sensitivity for predicting PERD is low, probably due to the subjective nature of the assessment.(14–16) For the quantitative CLT (qtCLT), the

expiratory tidal volume (exVT) is measured with the cuff inflated then deflated. The difference between the two values reflects the size of the leak.(17) In a meta-analysis of studies in adults, the qtCLT had 87% specificity (95% confidence interval [95%CI], 0.82%–0.90%) and 62% sensitivity (95%CI, 0.49%–0.73%) for UAO.(16) However, of the 28 included studies, five used only the qualitative CLT and one either the qualitative CLT or the qtCLT, possibly decreasing the estimated sensitivity. Moreover, no standardised definition of UAO was used. We are aware of a single paediatric study providing information on the performance of the qtCLT in predicting post-extubation stridor.(17) A leak of less than 11% was 61% sensitive, 53% specific, and 59% accurate. The corresponding values for an ultrasound-measured air column width between the vocal cords of less than 0.8 mm were 93%, 86%, and 91%. In this study, post-extubation stridor was defined as "a high-pitched inspiratory wheeze requiring medical intervention (corticosteroid therapy or reintubation) within 24 hours of extubation and associated with respiratory distress". Although clear and simple, this outcome is not fully satisfactory: respiratory distress is not defined objectively, the use of NIV after extubation is not considered among the medical interventions for respiratory distress, and the time interval for stridor to develop is only 24 h. Moreover, the study included 400 patients, all of whom were recruited at a single centre with more than half were admitted for surgical causes. Consequently, there is a need for a large study capable of providing definitive data on the performance of the qtCLT in predicting UAO-PERD after extubation of PICU patients.

We designed a multicentre observational study with a large sample size, obtained through the participation of 19 PICUs, to evaluate the performance of the qtCLT for predicting UAO-PERD. We used a strong definition of UAO-PERD combining a requirement for intravenous corticosteroid therapy (IV CS) to decrease the laryngeal oedema and/or ventilator

support by high-flow nasal cannula (HFNC) and/or by NIV or repeat IMV with a Westley score ≥4 with at least 1 point for stridor at each initiation.

METHODS

Study design

This is an observational, non-randomised, prospective, cohort study that is being conducted in 19 French PICUs (final version n°1). Enrolment began on 5 October 2022 and is expected to last 18 months, the planned sample size being 900. The occurrence of UAO-PERD is recorded during the first 48 h after extubation, and additional outcomes are recorded until day 28.

The study was approved by the appropriate ethics committee on September 2021 (approval #CEER-RD 2021-578) and was registered prior to initiation on ClinicalTrials.gov (NCT05328206).

A monthly newsletter about the progress of the study is sent to all investigators.

Participants

The inclusion criteria are full-term birth, age at least 2 days up to including 17 years, intubation with a cuffed endotracheal tube, IMV for at least 24 h, and oral informed consent to study participation. The exclusion criteria are tracheostomy before extubation, indication for long-term NIV, history of upper airway abnormalities, upper airway surgery within one month before the assessment of eligibility, decision to withdraw or withhold life-sustaining treatment, and previous inclusion in the study (Figure 1). We also, recommended that investigator systematically check for the absence of supraglottic obstruction.

Patients and Public Involvement

The patients, their parents, and the public had no role in designing this protocol or in writing the present manuscript. They have no role in conducting the study and will not be involved

in analysing, interpreting, or disseminating its results. The study findings will be published in a peer-reviewed journal and reported at one or more scientific meetings.

Recruitment

Eligible children will be identified by the study investigator at each participating PICU (Table 1), who explains the study and requests oral informed consent by the parents or legal guardian and, when able to understand, the patients (Figure 1).

Study intervention

If extubation is planned, qtCLT will be performed according to the protocol developed by Miller and Cole and used by El Amrousy et al., within 1 h before extubation (Table 2) (17,18). The ventilator will be set to assist-volume control mode with a tidal volume (VT) of 8 to 10 mL/kg of predicted body weight, up to 450 mL. Six consecutive expiratory tidal volume (exVT) measured by the ventilator will be recorded with the cuff inflated then deflated. The mean exVT values (in mL) are computed for the values obtained with the cuff inflated and deflated. Leak volume is defined as the difference between exVT infalted and exVT deflated. Leak percentage (%) is calculated as follows: 100 x (exVT inflated- exVT deflated) / exVT inflated.(17,19)

Extubation will be performed according to each centre's procedure. No specific instructions were given for the study. The intensivist will record the Westley score immediately after extubation and then over the next 48 hours before the initiation of intravenous corticosteroid therapy (IV CS) and/or ventilatory support (HFNC, NIV or reintubation). The value serves to define UAO-PERD, as described below in the section on the primary outcome. Thus, if none of these treatments is given, the Westley score will be recorded only once, immediately after extubation (Figure 1).

Surveys completed by the participating PICUs indicated that 80% used automatic leak compensation, regardless of the ventilator model. Automatic leak compensation relies chiefly

on the minute volume and therefore starts only after more than 1 minute. In our study, the qtCLT will be performed within less than 1 minute. Consequently, automatic leak compensation cannot affect the measured values. We therefore require no changes to the ventilator setups that are part of standard practice in each participating PICU.

Study objectives

The primary study objective is to assess the performance of qtCLT in predicting severe UAO-PERD with onset within 48 h after extubation.

The secondary objectives are to determine the frequency of extubation failure; identify risk factors for severe UAO-PERD within 48 h after extubation; describe the frequency and effects of pre extubation IV CS within 12 h; and develop a score predicting severe UAO-PERD within 48 h after extubation, which would subsequently undergo an external validation study.

Primary endpoint

The primary endpoint is the cumulative incidence of UAO-PERD within 48 h after planned extubation. UAO-PERD is defined as the initiation of IV CS and/or ventilatory assistance (HFNC, NIV, or re-intubation) with a Westley score ≥4, including at least 1 point for stridor, (indicating laryngeal obstruction).

Each participating PICU is asked to ensure that, to the extent possible, the primary endpoint is assessed by a person different from the person who performs the qtCLT.

Secondary endpoints

The secondary endpoints are the cumulative incidence of extubation failure, defined as re-intubation for respiratory distress within 48 h after extubation combined with a pre-re-intubation Westley score ≥4 with at least 1 point for the stridor item; the frequency of intravenous corticosteroid therapy given within 12 h before extubation; the frequency of UAO-PERD in patients with vs. without this treatment; the number of PICU-free days by day-

28 after enrolment; in-PICU mortality; and, in patients who died in the PICU, the time to death. The predictive score for UAO-PERD will be assessed by computing the area under the receiver operating characteristic curve (AUROC).

Data collection

The study data will be collected prospectively by the investigator at each participating PICU, using a secure online database (CleanWEB® 2022 Telemedicine Technologies, Boulogne-Billancourt, France). For each patient we will record the age (months); weight (kg), sex; reason for PICU admission; Paediatric Index of Mortality 3 (PIM-3; %) and Paediatric Logistic Organ Dysfunction 2 (PELOD-2; %) scores; internal diameter of the cuffed endotracheal tube (mm); history of failed extubation during the same PICU stay prior to enrolment; if planned intubation (in the operating room); emergency intubation; out-of-hospital intubation; number of intubations during the index PICU stay; whether intravenous corticosteroid therapy was given within 12 hours before extubation; history of failed extubation during the same PICU stay before enrolment; and IMV duration (hours). The qtCLT results (mean of the six exVT values with the cuff inflated and mean of the six exVT values with the cuff deflated); date and time of extubation, and Westley score immediately after extubation will be collected; as well as the use within 48 h after extubation of IV CS and/or ventilatory assistance (HFNC, NIV, or re-intubation), with the time to initiation. All the Westley score items will be precisely reported for each evaluation. The PICU stay length, number of PICU-free days by day 28, and in-PICU mortality with the time to death are recorded.

Statistical analysis

Sample size estimation

Based on the literature, the expected proportion of patients with severe UAO-PERD is 15%.(14,17,20,21) Therefore, 900 patients (135 with vs. 765 without UAO-PERD) are

needed to estimate the qtCLT AUROC with a two-sided 95.0% confidence interval (95%CI) of less than 0.10 for AUROC values greater than 0.75 (e.g., 95%CI of 0.071 if the AUROC equals 0.90). Recruiting 765 patients without PERD will allow the identification of a cut-off having 90% specificity, with an exact two-sided 95%CI of 0.044.

The analyses will be repeated in the following age sub-groups: [2 days to 2 years], [2 years to 8 years], and [8 years to 17 years]. The smallest expected ROC curve width for AUROC values greater than 0.75 is 0.199 (0.141 for an AUROC of 0.90) within each age sub-group. The cut-off having 90% specificity will have an exact two-sided 95%CI of 0.09 within the same age sub-group.

Based on data recorded in each of the 19 participating PICUs during the year preceding study initiation, 18 months will be required to recruit 900 patients meeting all the study inclusion criteria and none of the study exclusion criteria.

Statistical analysis principles

All enrolled patients will be included in the analysis. Descriptive statistics will be computed for the included patients, as median [interquartile range] for quantitative variables and as number (percentage) for qualitative data.

Primary endpoint

The AUROCs for the leak as a percentage and as a volume associated with the occurrence of UAO-PERD will be estimated with their 95%CIs as described by Delong and Delong, in the overall population and in each of the above-defined age sub-groups.(22) Bootstrapping will be used to check 95%CI boundaries. Age-adjusted AUROC values will be estimated according to the age sub-groups defined above.

The analyses will consider death within 48 h after extubation and re-intubation due to non UAO-PERD, as defined in the protocol, as competing risks. Missing data will be handled by multiple imputation, and an analysis of cases with no missing data will also be performed.

Secondary endpoints

The cumulative incidence of extubation failure, defined as re-intubation performed within 48 hours after extubation after documenting a Westley score ≥4, including at least 1 point for stridor, will be estimated with its 95%CI, using Gray's estimator and considering two competing risks, namely, death and re-intubation due to causes other than UAO-PERD. This cumulative incidence will be estimated in the overall population and in each age sub-group.

The risk factors for UAO-PERD will be investigated using a logistic model predicting the presence or absence of respiratory distress. Only inclusion variables will be considered. Continuous variables may be transformed to ensure that the effect of the variable is log-linear. In the event of a non-linear effect, spline modelling will be considered. We will analyze the impact of inadapted internal diameter of the cuffed endotracheal using the Khine formula.

The frequency of intravenous corticosteroid therapy within 12 h before extubation will be determined. Potential associations between this treatment and the occurrence of UAO-PERD will be assessed using a weighted propensity score approach. Risk factors for UAO-PERD within 48 h after extubation will be sought by building a logistic model for predicting UAO-PERD. Only baseline variables, i.e., variables recorded at the admission and the extubation, will be considered. Continuous variables may be transformed to ensure log-linearity of their effect. If the effect is non-linear, spline modelling will be considered. The characteristics and possible over-optimism of the predictive score thus developed will be evaluated using bootstrapping and cross-validation.

The PICU stay length, number of PICU-free days by day 28, and in-PICU mortality with the time to death will be reported as descriptive statistics.

ETHICS AND DISSEMINATION

The study was approved by the institutional review board of the Robert Debré University Hospital in Paris, France, on September 2021 (approval #2021-578). Specific agreements have been made with all participating centers and the report of Robert Debre Committee is valid for all sites, given the nature of the study with respect to the French law. As soon as a new center is added, a new approval will be submitted to the Robert Debre Ethics Commitee. Only after approval can the center be added. Thus, the 19 participating centers had ethical approval to conduct the study. This study requires a signed "no objection" agreement to the use of the data, as it is considered by the ethics committee, in accordance with French law, to be a non-interventional study, as it is observational, devoid of risk, does not modify patient care and the procedures performed are the usual ones. Finally, prior enrollment, information and verbal consent will be obtained from the parents and from the minor if he/her age and condition allow him/her to understand. We have specific patient consent form for minor (one from 7- to 11-year-old and another 12- to 17-year-old) and parents. The results will be submitted for publication in a peer-reviewed journal and reported at one or more scientific meetings.

DISCUSSION

The paucity of available evidence has not allowed the development of strong recommendations about performing a qtCLT before the extubation of paediatric patients.(13) To our knowledge, this is the first multicentre study evaluating the performance of the qtCLT in predicting the risk of UAO-PERD after extubation in the PICU. The age range is broad, from 2 days up to including 17 years. As there does not seem to be a clear high-risk age group in the literature (varying between studies, either under two years or under five years), we

decide to include patients up to and including 17 years and perform subgroup analyses by age. The main research question is whether the qtCLT reliably predicts the risk of UAO-PERD, in children without upper airways abnormalities, thereby providing information likely to improve patient management. We excluded children with upper airway abnormalities or surgery, first because we focused on the effect of an endotracheal tube on healthy airway. Second, the Westley score is not adapted for children with such abnormalities. Finally, these cases are more likely to receive known preventive measures (corticosteroid…), which introduce bias into analysis. In addition, the study will identify risk factors for UAO-PERD and prospectively collect information on current ventilator weaning and post-extubation practices in French PICUs. Finally, we will develop a score for predicting UAO-PERD that should be suitable for use in daily practice. This score will require external validation in a separate study.

No validated method for assessing UAO-PERD in paediatric patients has been reported to date. UAO-PERD is often defined as the onset of stridor or the need for re-intubation within 48 h after planned extubation.(10,23) Although re-intubation is a strong objective marker, it is required in less than 10% of paediatric patients with UAO-PERD, and this proportion is declining, notably due to the increasing use of NIV for managing ventilator weaning.(10,11,24) Consequently, using only re-intubation to define UAO-PERD would require a very large sample size. Moreover, re-intubation may be needed for reasons other than UAO. On the other hand, isolated stridor is not associated with worse patient outcomes. Only stridor combined with evidence of respiratory distress, with or without a need for intervention (IV CS and/or HFNC, NIV, or re-intubation), is relevant. The Westley score, first described by Westley et al in 1978 assesses the severity of UAO in acute conditions such as croup, has since been validated on numerous occasions as a reliable tool for clinicians at the bedside.(25–28) It consists of 5 items, scored from 0 (absent) to 5 (maximum), and it is now

the most widely used score in the clinical and therapeutic evaluation of respiratory distress induced by UAO.(20,26) Because of the intrinsic qualities of the Westley test and the pathophysiological and semiological similarity between acute laryngitis and post-extubation UAO, this score has been used in a paediatric study of UAO.(29)

Our strong definition includes respiratory distress defined as requiring intervention (IV CS and/or ventilatory assistance) with a Westley score ≥4, with at least 1 point for stridor. The use of the Westley score at each initiation makes it possible to distinguish between the use of support for inspiratory and non-inspiratory reasons and to neglect the planned or systemic use of post-extubation support. However, to differentiate PERD due to UAO vs. other causes, the Westley score has to include at least 1 point for stridor. Thus, use of the interventions is linked to objective evidence of respiratory distress.(29–31) UAO-PERD shares pathophysiological similarities with croup. Based on the study of Yang et *al*, we chose 4 as the cut-off for defining severe UAO-PERD.(26) The combined use of treatments in the definition decreases the risk of bias due to inter-observer variability in Westley score determination.

Several factors support the feasibility of conducting and completing our study. First, the project was presented several times at meetings of the French PICU research network on respiratory conditions (Groupe francophone de reanimation et urgences pédiatriques, GFRUP). This dissemination effort allowed us to obtain the participation of 19 PICUs, accounting for over 85% of all PICUs in France. Second, the study carries no risk to the participants. The qtCLT is a safe procedure that is part of standard care. All other investigations and treatments used in the study patients are also part of standard care. Third, all local investigators followed a training session on protocol procedures and Westley-score determination. Finally, given that the primary outcome is assessed after only 2 days, the number of missing data for the primary outcome is expected to be very small.

Our study design has limitations. First the quantitative CLT is associated with incredible amount of variation, depending upon the respiratory effort or diaphragm weakness or the status of the patient during cuff deflation, or the ventilators used and accuracy of VT measurements. These limitations are a strong issue and explain why the American and European Society guidelines for weaning adult and peadiatric patients off mechanical ventilation are based on very low-quality evidence for performing the qtCLT.(13,32) In fact, we chose to give priority to carrying out a test that could be used on a daily basis, at the patient's bedside, without the need for additional equipment. This choice therefore does not allow us to study the validity of the qtCLT intrinsically. This is a conscious decision, and although it is a limitation of the study, it is also a strength, as it allows us to include many patients in many centers. Depending on results, a question to be discussed will concern the technical conditions for performing the leak test and the relevance of repeating the study with more precise and specifically dedicated equipment.

Second, extubation management were left to the discretion of each centre. In order to limit the impact, we recorded pre-extubation measures such as use of intravenous corticosteroids, and intubation procedure. Third, the management of UAO-PERD will probably vary across participating PICUs, given the absence of guidelines for initiating IV CS, HFNC, NIV, or repeat IMV. However, our use of a definition that comprises not only these interventions but also the physical findings, as reflected by the Westley score and stridor sub-score, will limit this potential source of bias. To limit interventions to those that increase patient morbidity, we decided not to include inhaled racemic epinephrine in the study protocol, which is almost systematically used by several PICU teams whatever the patients' respiratory status after extubation. Finally, we decided to focus only on the quantitative test to avoid repeating the many studies that have already been done in this area, with conflicting results, probably due to the many limitations associated with this test. If we carried out the two tests in parallel,

there would be a high risk of obtaining different results between the two, without knowing what to make of them, given that the limitations of each test are very different.

CONCLUSION

This protocol for a prospective multicentre observational study of qtCLT performance in predicting UAO-PERD has important strengths and is therefore expected to determine whether the result of qtCLT is a risk factor for the development of post-extubation respiratory distress due to upper airway obstruction. If this is the case, the qtCLT could be used in an RCT to guide the management of extubation in paediatric patients. Among these strengths is the composite definition of UAO-PERD combining clinical features, reflected by the Westley score and presence of stridor, with a range of treatment requirements that includes post-extubation NIV. External validation of the predictive score designed based on the study results will be performed subsequently.

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Figure 1: Patient flow chart

Legend: PICU: paediatric intensive care unit; IMV: invasive mechanical ventilation; NIV: non-invasive ventilation; PERD: post-extubation respiratory distress; HFNC: high-flow nasal cannula; IV CS: intravenous corticosteroid therapy; UAO-PERD: PERD related to upper airway obstruction

Table 1: List of the 19 study sites

Réanimation pédiatrique - **CHU Robert Debré**
Réanimation et surveillance continue médicochirurgicale - **CHU Necker-Enfant Malades**
Anesthésie et Réanimation pédiatrique - **CHU Necker-Enfant Malades**
Réanimation néonatale et pédiatrique - **CHU Armand Trousseau**
Réanimation pédiatrique et Néonatale - **CHU Kremlin Bicêtre**
Réanimation pédiatrique - **CHU Raymond Poincaré**
Réanimation pédiatrique - **CH Marie Lannelongue**
Réanimation pédiatrique - **CHRU Jeanne de Flandre, Lille**
Réanimation médicale pédiatrique - **CHRU Nancy Brabois**
Réanimation pédiatrique - **CHU Hospices Civils de Lyon**
Réanimation et soins intensifs pédiatrique - **CHU Grenoble Alpes**
Anesthésie et Réanimation pédiatrique - **CHU de la Timone, Marseille**
Médecine néonatale et Réanimation pédiatrique - **CHU Clermont-Ferrand**
Réanimation néonatale et pédiatrique - **CHU Toulouse**
Réanimation pédiatrique – **CHU Pellegrin Bordeaux**
Maladie cardio-vasculaires congénitales – **CHU Haut-Lévêque Bordeaux**
Réanimation pédiatrique et unité de surveillance continue - **CHRU de Tours**
Réanimation et soins intensifs pédiatriques - **CHU de Caen**
Réanimation pédiatrique, surveillance continue pédiatriques et réanimation des cardiopathies congénitales - **CHU de la Réunion Pôle Nord**

Table 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist. Enrolment, Interventions and Assessments

	STUDY PERIOD					
Time point	**Enrolment**	**Immediately before extubation**	**Baseline (T0): Extubation**	**Immediately after T0**	**T0 to T48 h**	**D28**
ENROLMENT **Eligibility screen:** **-iMV≥24 h, cuffed tube** **-age ≥2 days to <18 years** **-informed consent**	 ✓ ✓ ✓					
INTERVENTION **-qtCLT**		✓				
ASSESSMENTS **-Westley score** **-use of PERD treatments;** **if yes, Westley score:** **IVCS** **HFNC** **NIV** **Re-intubation**				✓	 ✓ ✓ ✓ ✓	
PICU-free days						✓
In-PICU mortality Time to in-PICU death						✓ ✓

D: day; iMV: invasive mechanical ventilation; qtCLT: quantitative cuffed leak test; Westley score: Westley score; PERD: post-extubation respiratory distress; IVCS: intravenous corticosteroid therapy; HFNC: high-flow nasal cannula; NIV: non-invasive ventilation; PICU: paediatric intensive care unit

Authors' contributions

BL, AH, JN, AM, GG, GP, ML, and SD contributed to conceive and prepare the study.

BL, MRR, and SD contributed to design the study.

BL and AH wrote the first draft of the manuscript. JN, AM, GG, GP, ML, MRR, and SD contributed to draft the manuscript then to review it for important intellectual content.

BL, AH, MRR and SD are contributing to manage the study and to collect, analyse, and interpret the data.

All authors have read the final version of this manuscript and approved its submission to *BMJ Open.*

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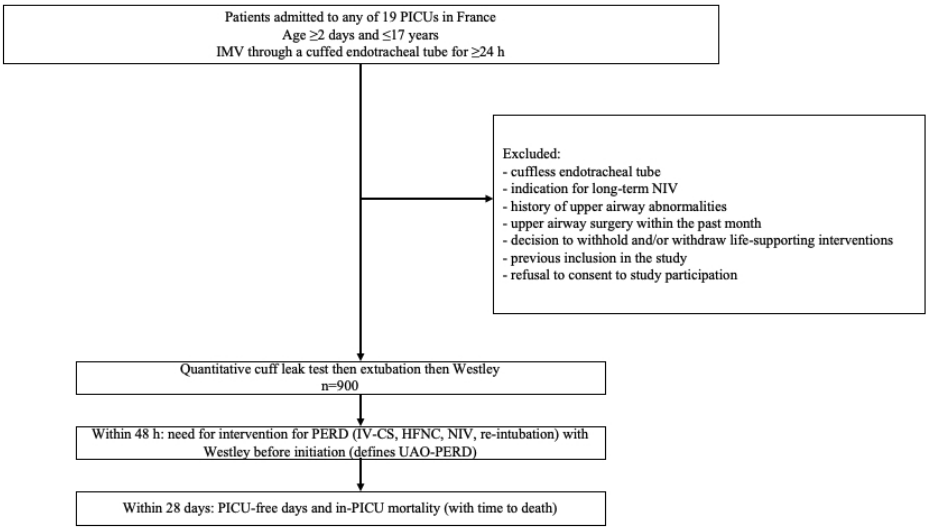
Competing interests statement

None of the authors has any conflicts of interest to declare.



Patient flow chart

314x186mm (72 x 72 DPI)