Evaluating Risk Factors for Pediatric Post-extubation Upper Airway Obstruction Using a Physiology-based Tool

Robinder G. Khemani^{1,2}, Justin Hotz¹, Rica Morzov¹, Rutger Flink³, Asavari Kamerkar¹, Patrick A. Ross^{1,2}, and Christopher J. L. Newth^{1,2}

¹Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, California; ²Department of Pediatrics, Keck School of Medicine, University of Southern California, Los Angeles, California; and ³Med-E Link, Amsterdam, the Netherlands

Abstract

Rationale: Subglottic edema is the most common cause of pediatric extubation failure, but few studies have confirmed risk factors or prevention strategies. This may be due to subjective assessment of stridor or inability to differentiate supraglottic from subglottic disease.

Objectives: Objective 1 was to assess the utility of calibrated respiratory inductance plethysmography (RIP) and esophageal manometry to identify clinically significant post-extubation upper airway obstruction (UAO) and differentiate subglottic from supraglottic UAO. Objective 2 was to identify risk factors for subglottic UAO, stratified by cuffed versus uncuffed endotracheal tubes (ETTs).

Methods: We conducted a single-center prospective study of children receiving mechanical ventilation. UAO was defined by inspiratory flow limitation (measured by RIP and esophageal manometry) and classified as subglottic or supraglottic based on airway maneuver response. Clinicians performed simultaneous blinded clinical UAO assessment at the bedside.

Measurements and Main Results: A total of 409 children were included, 98 of whom had post-extubation UAO and 49 (12%) of whom were subglottic. The reintubation rate was 34 (8.3%) of 409, with 14 (41%) of these 34 attributable to subglottic UAO. Five minutes after extubation, RIP and esophageal manometry better identified patients who subsequently received UAO treatment than clinical UAO assessment ($P < 0.006$). Risk factors independently associated with subglottic UAO included low cuff leak volume or high preextubation leak pressure, poor sedation, and preexisting UAO ($P < 0.04$) for cuffed ETTs; and age (range, 1 mo to 5 yr) for uncuffed ETTs ($P < 0.04$). For uncuffed ETTs, the presence or absence of preextubation leak was not associated with subglottic UAO.

Conclusions: RIP and esophageal manometry can objectively identify subglottic UAO after extubation. Using this technique, preextubation leak pressures or cuff leak volumes predict subglottic UAO in children, but only if the ETT is cuffed.

Keywords: intubation; endotracheal; airway obstruction; pediatrics; artificial respiration

Post-extubation upper airway obstruction (UAO) is a frequent complication of pediatric mechanical ventilation. It is estimated to explain one-third of all extubation failures (1). Reintubation because of UAO or increased length of stay for additional monitoring and treatment

likely contributes to hundreds of millions of dollars in healthcare costs each year (2, 3).

Although obstruction can occur throughout the upper airway (supraglottic, glottic, subglottic), children are at particularly high risk of developing subglottic edema from the endotracheal tube (ETT).

However, prevention strategies targeting subglottic edema (such as systemic corticosteroids) have not been successful when applied universally to children receiving mechanical ventilation (4). In adults, prophylactic corticosteroids benefit patients deemed to be at high risk

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Correspondence and requests for reprints should be addressed to Robinder G. Khemani, M.D., Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, 4650 Sunset Boulevard, Mailstop 12, Los Angeles, CA 90027. E-mail: rkhemani@chla.usc.edu

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At a Glance Commentary

Scientific Knowledge on the

Subject: Subglottic edema is the most common cause of pediatric extubation failure, but few studies have confirmed risk factors or prevention strategies. This lack of identification of risk factors may be due to the subjective nature of stridor assessment or the inability to differentiate supraglottic from subglottic disease.

What This Study Adds to the

Field: Using an objective tool to measure inspiratory flow limitation and increased breathing effort, which is strongly associated with both treatment for upper airway obstruction (UAO) and reintubation, we identified risk factors for subglottic UAO that differed based on whether the endotracheal tube was cuffed or uncuffed. For cuffed tubes, low cuff leak volume or high preextubation leak pressure, poor sedation, and preexisting UAO were associated with subglottic UAO, whereas age (1 mo to 5 yr) was associated with subglottic UAO when the endotracheal tube was uncuffed. The presence or absence of a leak preextubation (regardless of pressure) was not associated with subglottic UAO for uncuffed endotracheal tubes.

for subglottic edema by virtue of low ETT cuff leak volume before extubation (4–6).

Unfortunately, pediatric data identifying risk factors (7–13) for subglottic post-extubation UAO are limited. Causes of this paucity of data in previous studies include use of imprecise or impractical outcomes or not having differentiated subglottic from supraglottic obstruction. Reintubation is an impractical outcome for UAO studies because reintubation rates are near 10%, with less than half of reintubations attributable to UAO (1). Stridor plus retractions with or without treatment for subglottic UAO (such as racemic epinephrine) is sometimes used in UAO studies, but stridor and retractions are subjective, and we have previously demonstrated significant interobserver variability among bedside providers (14). Patients frequently receive UAO treatments

even when there is disagreement among providers on the presence of UAO (14). Finally, risk factors and prevention strategies for subglottic UAO are likely different from those for supraglottic UAO, and previous studies have not systematically addressed this difference.

We have validated a minimally invasive objective tool to measure extrathoracic UAO in an animal model of pediatric UAO (15), used previously in adults (16). This tool uses calibrated respiratory inductance plethysmography (RIP) and esophageal manometry to identify inspiratory flow limitation. Our study had two main objectives. Objective 1 was to determine whether this UAO tool, when used almost immediately after extubation, has potential clinical utility as an early detection tool by being equal or superior to clinicians' judgment in identifying patients who will progress to a UAO-specific treatment or be reintubated. Objective 2 was to identify preextubation risk factors for post-extubation subglottic UAO for which treatment was initiated. Given adult data supporting cuff leak volume as a risk factor for post-extubation UAO, we stratified by cuffed and uncuffed ETTs. Some of the reported results have been published previously in abstract form (17).

Methods

We screened intubated children admitted to the pediatric and cardiothoracic intensive care units at Children's Hospital Los Angeles (CHLA) between July 2012 and April 2015. The inclusion criteria were more than 37 weeks gestational age to age 18 years, intubated for at least 12 hours with planned extubation from 7:00 A.M. to 5:00 P.M. between Monday and Friday. The exclusion criterion was contraindication to esophageal catheter or RIP bands. Informed consent was obtained from the child's parent or guardian. The study was approved by the CHLA Institutional Review Board.

Study Protocol

Details of the study protocol are summarized in Figure 1, with additional methods described in the online supplement. An age-appropriate esophageal balloon catheter, RIP bands, and a self-calibrating pneumotachometer were placed before extubation. Catheter position was

verified by pressure deflections during ETT occlusions or by chest radiography (18). RIP flow was calibrated before extubation (*see online supplement*) (15, 16, 19). Mallinckrodt cuffless and Hi/Lo Intermediate cuffed Murphy eye endotracheal tubes (Medtronic, Minneapolis, MN) were predominantly used during the study period.

Data regarding potential risk factors for post-extubation UAO were gathered preextubation, including ETT size, subject demographics, length of ventilation, fluid balance, intubation and preextubation leak data, cuff leak volume, intubation details, diagnostic information, and nurse-assessed standardized pain scores for the previous 24 hours (a surrogate for adequacy of sedation) (*see online supplement*). Preextubation ETT leak pressure (leak test) was assessed after suctioning with the subject's head in midline position and the leak audible to the ear (without a stethoscope) to a maximal pressure of 40 cm H₂O. Cuff leak volume and leak percentage were calculated on the basis of standard ventilator settings (pressure control rate 10–20 bpm, peak inspiratory pressure 20 cm H₂O, positive end-expiratory pressure 5 cm H₂O). For uncuffed ETTs, leak percentage was calculated as (inspiratory tidal volume – expiratory tidal volume)/(inspiratory tidal volume). For cuffed ETTs, cuff leak volume was calculated as (expiratory tidal volume with cuff inflated – expiratory tidal volume with cuff deflated)/(expiratory tidal volume with cuff inflated) (5, 20).

Standardized UAO measurements using RIP and esophageal manometry (UAO tool) and simultaneous clinical UAO assessment were performed 5 and 60 minutes post-extubation. Clinical UAO assessment was performed by a minimum of three bedside clinicians of different disciplines (registered nurse, respiratory therapist, and physician [MD]) using a previously validated scoring system (14). Clinicians were blinded to each other and to the UAO tool. At least one clinician had received common training through a consensus-based training course on UAO assessment (core trained). The data provided by the clinician with the most years of experience in each specialty (registered nurse, respiratory therapist, MD) were used for analysis. Research personnel were present for all extubations. When UAO was suspected based on use of the tool, an airway maneuver (jaw thrust) was performed to identify if the obstruction was likely supraglottic (*see below*) (21).

Figure 1. Details of the study protocol from the time of consent until study completion. Measurements required for the upper airway obstruction (UAO) tool are presented in *light gray* along the left side of the study protocol section. CPAP = continuous positive end-expiratory pressure; NIF = negative inspiratory force; RIP = respiratory inductance plethysmography.

UAO Determination and Classification

Diagnoses of UAO were made using the tool by examining the plot of calibrated RIP flow and esophageal pressure for inspiratory flow limitation. Inspiratory flow limitation is characterized by disproportionately high inspiratory effort (negative esophageal pressure) relative to the increase in flow (16, 22, 23). The pressure · rate product (PRP) is a measure of breathing effort and is the product of the respiratory rate and the change in esophageal pressure during the respiratory cycle. Patients were labeled as having tool-assessed post-extubation UAO (supraglottic or subglottic) when inspiratory flow limitation was new post-extubation and associated with an increase in PRP of at least 50% over

preextubation values on continuous positive end-expiratory pressure of 5 cm H₂O. Tool-assessed UAO was further classified as supraglottic or glottic (labeled supraglottic for analysis) if an airway maneuver reduced PRP by at least 50% (Figure 2). The remainder of tool-assessed UAO cases were labeled subglottic (Figure 3). Labeling patients as having tool-assessed UAO was blinded to clinical UAO assessments. Clinical allocation of UAO was based on the presence of stridor plus a minimum of mild retractions.

Analysis and Outcome Measures

Our first research question (objective 1) was whether this UAO tool, when used almost immediately post-extubation, was equal or

superior to clinicians' judgment in identifying patients who subsequently receive a UAO treatment or are reintubated (i.e., potential clinical utility for early detection). To address this question, we compared the number of patients with tool-versus clinician-assessed UAO 5 minutes post-extubation who subsequently (1) received UAO treatment (including racemic epinephrine, heliox, post-extubation corticosteroids, or reintubation within 60 min) or (2) were reintubated for any reason within 48 hours. The decision to treat UAO or reintubate was made by the clinical team. We compared test statistics (sensitivity, specificity, likelihood ratios) and areas under the curve (AUCs) of receiver operating characteristic (ROC)

Figure 2. An example of supraglottic upper airway obstruction data of a 10-year-old patient after tonsillectomy and adenoidectomy. Data show improvement of flow limitation, less change in esophageal pressure, and increased flow during an airway maneuver. Esophageal pressure is measured in centimeters of water. RIP = respiratory inductance plethysmography.

plots for clinicians and the UAO tool 5 minutes post-extubation. AUCs were compared using the method suggested by DeLong and colleagues with the *roccomp* command in Stata 10 software (StataCorp, College Station, TX) (24, 25).

With our second research question (objective 2), we sought to determine preextubation risk factors for the outcome of subglottic UAO in patients who received treatment post-extubation and if these risk factors differed based on whether the ETT was cuffed or uncuffed. Patients with subglottic UAO receiving treatment were defined as those with tool-assessed subglottic UAO within 60 minutes of extubation plus a UAO treatment (as defined above). This metric was chosen because it decreases the subjectivity in the clinical assessment of stridor and retractions but retains clinical importance, as these patients all received post-extubation UAO treatment. We provide descriptive statistics for three groups: (1) no UAO, which includes patients with tool-assessed UAO who did not receive UAO treatment; (2) supraglottic UAO; and (3)

subglottic UAO receiving treatment. Analysis was stratified by cuffed versus uncuffed ETTs. Continuous variables were analyzed using Kruskal-Wallis analysis of variance. Categorical variables were analyzed with Pearson's χ^2 tests, along with pairwise multiple comparisons using Yates-corrected Pearson's χ^2 or Fisher's exact tests. $P < 0.025$ was considered significant. Distance-weighted least squares regression was used to explore the relationship between rates of supraglottic and subglottic UAO by age (as a continuous variable). Test statistics (sensitivity, specificity, likelihood ratios) were computed for preextubation leak percentage variables, and nonparametric tests were performed for linear trend as an extension of the Wilcoxon rank-sum test (26). A multivariable logistic regression model was built, taking into consideration risk factors with a univariate association with subglottic UAO receiving treatment ($P < 0.2$) and retaining variables that remained statistically significant ($P < 0.05$) when all variables were included. Finally, we

present our sensitivity analysis (see details in the online supplement) in which we examined risk factors for UAO treatment independent of the diagnosis of UAO based on use of the tool or differentiation of subglottic from supraglottic UAO. Statistical analysis was performed using Statistica 10 (StatSoft, Tulsa, OK) and Stata 10 software.

Results

A total of 1,159 patients were eligible for the study, and 409 were included. Common reasons why patients were not included were extubation on nights and weekends (study team not available), parents unavailable to provide consent, or parents' refusal of consent (Figure 4). The subjects' median age was 5 months (interquartile range, 1–16 mo), and approximately half were postoperative cardiac surgery patients. More patients had uncuffed ($n = 240$, 59%) than cuffed ETTs. Using data available from the UAO tool for the first 60 minutes post-extubation to classify patients, we

Figure 3. An example of subglottic upper airway obstruction data of a 4 month old after extubation. The data indicate severe inspiratory flow limitation (*left*) and no rise in flow despite continual decrease in esophageal pressure. There was no improvement with an airway maneuver (not shown), but significant improvement occurred 20 minutes after racemic epinephrine administration (*right*). Esophageal pressure is measured in centimeters of water. RIP = respiratory inductance plethysmography.

found that 49 (12%) had supraglottic UAO, 49 (12%) had subglottic UAO and received a UAO treatment, and 311 (76%) had no UAO (including 9 patients with tool-assessed subglottic UAO who did not receive UAO treatment). Thirty-four patients were reintubated (8.3%) within 48 hours. The reintubation rates were 4.8% without UAO, 10.2% with supraglottic UAO, and 28.6% with subglottic UAO. Nineteen (56%) of the 34 patients who were reintubated had post-extubation UAO (supraglottic or subglottic), and 14 (41%) were subglottic. One hundred patients received at least one UAO treatment (Figure 4). Two patients were reintubated almost immediately post-extubation (5-minute assessments done immediately after extubation).

Objective 1: Tool versus Clinician UAO Assessment 5 Minutes Post-extubation and UAO Treatment

To determine whether the UAO tool provided earlier identification of patients who subsequently received UAO treatment, we compared independent blinded diagnosis of UAO based on use of the tool and by clinicians 5 minutes post-extubation. The UAO tool identified patients who subsequently received UAO treatment better than any of the clinicians did (Table 1), with higher sensitivity, specificity, and AUC of the ROC plots ($P < 0.01$). The UAO tool and most providers had similar sensitivity,

specificity, and AUC of ROC plots for identifying patients who subsequently were reintubated within 48 hours, although the tool appeared to be superior to the opinion of the MDs ($P = 0.004$).

When we compared the most experienced clinician's assessment of UAO 5 minutes post-extubation with the UAO tool (Table 2), when both tool and clinician agreed on UAO, we found high rates of UAO treatment (87%) and reintubation within 48 hours (28%). However, 44 patients were judged to have UAO based on the tool 5 minutes post-extubation, but the clinicians did not reach this diagnosis. Of these 44 patients, 23 (52%) subsequently received UAO treatment and 6 (13.6%) were reintubated within 48 hours. The 34 patients identified as having UAO by the most experienced clinician 5 minutes post-extubation, but not identified by the UAO tool, had low rates of UAO treatment (17%) and reintubation (3%). Similar patterns were seen among all clinicians (Table 2). There was significant interobserver variability in the assessment of UAO between the UAO tool and the clinicians, as well as among clinicians (Table E1 in the online supplement).

Objective 2: Risk Factors for Subglottic UAO Receiving Treatment

In pursuing objective 2, we sought to identify specific risk factors for the outcome

of subglottic UAO receiving treatment ($n = 49$), stratified by cuffed versus uncuffed ETT. We present data categorized into no UAO, supraglottic UAO, and subglottic UAO receiving treatment to illustrate how risk factors may differ based on UAO type.

The rate of supraglottic versus subglottic UAO differed substantially by age (Figure 5). For further analysis, age was broken down into five categories (Table E2). Subglottic UAO receiving treatment was extremely uncommon for children younger than 1 month of age (1.5%) or children older than 5 years of age. The highest rates occurred in children 6–18 months of age (24%), followed by children ages 1–6 months (15%). Although uncuffed ETTs are more common in younger children, there were similar rates of subglottic UAO receiving treatment between cuffed and uncuffed ETTs overall ($P = 0.3$) and when stratified by age (all $P > 0.08$) (Table E2).

Risk factors for subglottic UAO receiving treatment with cuffed ETT. Among children with cuffed ETTs ($n = 169$) (Table 3, Table E3), 20 (12%) had supraglottic UAO and 17 (10%) had subglottic UAO receiving treatment. Univariate risk factors for subglottic UAO receiving treatment, after adjusting for multiple comparisons, included intubation for UAO, smaller absolute ETT size, absence of a preextubation leak and higher preextubation leak pressure, cuff kept

Figure 4. Consolidated Standards of Reporting Trials diagram showing eligible, consented, and included patients. The overall consent rate was 77%. The most common reason for refusal of consent was related to parental discomfort regarding placement of the esophageal catheter. A total of 409 patients were included, with more patients having uncuffed than cuffed endotracheal tubes (ETTs). Available data derived from the upper airway obstruction (UAO) tool within the first 60 minutes after extubation were used to classify patients as having supraglottic UAO, subglottic UAO with UAO treatment, and no UAO (including nine patients with tool-gauged subglottic UAO who did not receive UAO treatment). There was an equal number of patients with subglottic UAO versus supraglottic UAO. Patients with subglottic UAO had the highest rates of reintubation and UAO treatment, although close to 50% of patients with supraglottic UAO received a UAO treatment.

deflated on the day of extubation, and lower cuff leak volume. Nonsignificant differences were noted for younger age (as a continuous variable) ($P = 0.052$), higher pain scores ($P = 0.055$), absence of leak at the time of intubation ($P = 0.07$), and higher rates of subglottic UAO in those who received steroids before extubation ($P = 0.055$). Risk factors for supraglottic UAO included lower Glasgow Coma Scale score at extubation. Rates of subglottic UAO receiving

treatment increased as cuff leak volume fell ($P = 0.002$) or preextubation leak pressure climbed ($P < 0.001$) (Table 4). A cuff leak volume less than 10% or leak pressure (with cuff deflated) greater than 25 cm H₂O yielded positive likelihood ratios near 2 with negative likelihood ratios of 0.2 (Table 4). Therefore, if the estimated prevalence of subglottic UAO receiving treatment is 10% (as it is in our cohort), the presence of a preextubation leak at 25 cm H₂O assures against

subglottic UAO (posttest probability 2%), whereas the absence of leak at 25 cm H₂O predicts that 18–19% of patients will have subglottic UAO needing treatment. In a multivariable model, cuff leak volume or preextubation leak pressure (not put in the same model, owing to collinearity), average pain score, and intubation for UAO remained associated with subglottic UAO receiving treatment (all $P < 0.03$) with good discrimination (AUCs, 0.834 [cuff leak

Table 1. Sensitivity, Specificity, and AUC of UAO Tool versus Clinical Assessments 5 Minutes after Extubation in Predicting Reintubation and Clinical Treatment of UAO

	UAO Tool		Most Experienced MD		Most Experienced RN		Most Experienced RT		Core-Trained Provider		Most Experienced Provider	
	Reintubation	Treatment	Reintubation	Treatment	Reintubation	Treatment	Reintubation	Treatment	Reintubation	Treatment	Reintubation	Treatment
UAO absent	15/319	37/319	23/334	62/334	17/327	59/327	17/331	52/331	16/320	49/320	20/329	54/329
UAO present	19/90	63/90	10/69	38/69	17/82	41/82	17/78	48/78	13/57	35/57	14/80	46/80
Sensitivity	21.1%	70%	14.5%	55.1%	20.7%	50%	21.8%	61.5%	22.8%	61.4%	17.5%	57.5%
Specificity	95.3%	88.4%	92.8%	81.4%	94.8%	82%	94.8%	84.7%	95.0%	84.7%	93.9%	83.6%
AUC	0.6847	0.7713	0.5671	0.6388	0.6633	0.6687	0.661	0.6708	0.661	0.6708	0.6179	0.675
AUC <i>P</i> value compared with UAO tool	Ref.	Ref.	0.004	<0.001	0.685	<0.001	0.716	0.006	0.46	0.01	0.09	<0.001

Definition of abbreviations: AUC = area under the curve; MD = physician; Ref. = reference; RN = registered nurse; RT = respiratory therapist; UAO = upper airway obstruction. For the UAO tool, UAO was deemed present with inspiratory flow limitation and increase in pressure · rate product more than 1.5 times the preextubation value on continuous positive end-expiratory pressure. For clinical assessment, UAO was deemed present with stridor plus minimum mild retractions. When multiple providers of the same job description provided assessments, the assessment by the most experienced MD, RN, or RT was used. Core-trained providers could be from any of the three disciplines and received common training on UAO assessment. The most experienced provider was the clinical provider with the most years of experience in critical care from any of the three disciplines. The presence of UAO as gauged by the tool 5 min after extubation was better able to predict eventual treatment for UAO than any of the clinical provider groupings (all $P < 0.01$) and predicted reintubation better than physicians did ($P = 0.004$). Significant P values are shown in bold type.

Table 2. Rates of Clinical Treatment of UAO and Reintubation within 48 Hours Classified by Agreement versus Disagreement between UAO Tool and Clinicians 5 Minutes after Extubation

	MD vs. Tool		RN vs. Tool		RT vs. Tool		Core Trained vs. Tool		Most Experienced vs. Tool	
	Reintubation	Treatment	Reintubation	Treatment	Reintubation	Treatment	Reintubation	Treatment	Reintubation	Treatment
Both agree no UAO	15/285 (5%)	31/285 (11%)	10/277 (4%)	30/277 (11%)	12/287 (4%)	29/287 (10%)	11/280 (4%)	28/280 (10%)	14/285 (5%)	31/285 (11%)
Both agree yes UAO	10/41 (24%)	32/41 (78%)	12/40 (30%)	34/40 (85%)	14/46 (30%)	40/46 (87%)	11/32 (34%)	28/32 (87%)	13/46 (28%)	40/46 (87%)
Clinician no UAO, tool yes UAO	9/49 (18%)	31/49 (63%)	7/50 (14%)	29/50 (58%)	5/44 (11%)	23/44 (52%)	5/40 (13%)	21/40 (53%)	6/44 (14%)	23/44 (52%)
Clinician yes UAO, tool no UAO	0/28 (0%)	6/28 (21%)	5/42 (12%)	7/42 (17%)	3/32 (9%)	8/32 (25%)	2/25 (8%)	7/25 (28%)	1/34 (3%)	6/34 (17%)

Definition of abbreviations: MD = physician; RN = registered nurse; RT = respiratory therapist; UAO = upper airway obstruction. High rates of reintubation and UAO treatment were found when both provider and tool agreed that UAO was present. Low rates of reintubation and UAO treatment were seen when the bedside provider labeled the patient with UAO but the UAO tool did not. High rates of reintubation and UAO treatment occurred when the UAO tool detected UAO but the clinician did not.

Figure 5. Post-extubation upper airway obstruction (UAO) rate (in distance-weighted least-squares analysis) as a function of age, stratified by subglottic and supraglottic UAO. Age was modeled as a continuous variable for this analysis, with 49 of 409 patients having subglottic UAO and 49 of 409 patients having supraglottic UAO. Subglottic UAO appears to peak near 18 months of age and is very uncommon after 8 years of age. Supraglottic UAO appears relatively constant throughout the pediatric age spectrum.

volume model] and 0.854 [preextubation leak pressure model]).

Risk factors for subglottic UAO receiving treatment with uncuffed ETT. Among children with uncuffed ETTs ($n = 240$) (Table 5, Table E4), 29 (12%) had supraglottic UAO and 32 (13%) had subglottic UAO receiving treatment. Univariate risk factors for subglottic UAO receiving treatment after adjusting for multiple comparisons included older age (nonneonate) and intubation for UAO. Nonsignificant differences were noted for greater weight ($P = 0.05$), higher fluid balance ($P = 0.08$), and a protective effect of being intubated primarily for shock ($P = 0.052$). Children who had undergone cardiac surgery were less likely to have supraglottic UAO. There was no association between preextubation leak pressure values or percentages and subglottic UAO receiving treatment ($P = 0.8$ and $P = 0.85$, respectively, in test of trend). The positive and negative likelihood ratios of having subglottic UAO receiving treatment based on a preextubation leak were all very close to 1 with AUCs near 0.5 (Table E5). In a multivariable model, only age 1 month to 5 years remained associated with subglottic UAO receiving treatment, with fair discrimination ability (AUC, 0.66).

Sensitivity Analysis: Risk Factors for UAO Treatment

For cuffed ETT, multivariable risk factors for patients receiving UAO treatment (irrespective of tool-based diagnosis of UAO without classifying into supraglottic vs. subglottic) included lower cuff leak volume (or higher extubation leak pressure), higher 24-hour pain scores, age 6–18 months, receiving steroids before extubation, or having a genetic syndrome. For uncuffed ETT, multivariable risk factors for patients receiving UAO treatment included older age (nonneonate) and receiving steroids before extubation (see online supplement).

Discussion

We have demonstrated that an objective UAO tool combining RIP and esophageal manometry used 5 minutes post-extubation is equal to or better than even the most experienced clinicians at identifying patients who subsequently receive UAO treatment. Furthermore, combining data derived from using this tool with clinical therapies to treat UAO allowed us to identify risk factors for subglottic UAO, which differ based on whether the ETT is cuffed or uncuffed.

For objective 1, our data suggest that this UAO tool provides an early warning sign for patients not already identified as having UAO by the bedside clinician. This study was not designed to identify whether early identification of UAO could lead to early intervention to improve patient outcome, because clinicians were blinded to tool assessments. This hypothesis needs to be tested in a randomized controlled trial where identification and treatment of UAO are guided by the tool and compared with usual care, looking at outcomes such as reintubation or post-extubation length of stay. On average, patients who are reintubated have 5 additional days of mechanical ventilation (1) at a cost of thousands of dollars per day (2, 3). If the tool could prevent 25% of the cases of reintubation secondary to subglottic UAO, it would be cost-effective. Most importantly, preventing reintubation is an important patient-centered outcome.

Objective 2 was to identify risk factors for subglottic post-extubation UAO to inform clinical decision making and for consideration of future trials on prevention. Our analyses suggest major differences in the characteristics and outcomes of patients who have subglottic versus supraglottic post-extubation UAO, making it crucial to correctly identify subglottic UAO for future studies. Overall, the rates of subglottic UAO are comparable between children with cuffed ETTs (10%) and those with uncuffed ETTs (13.3%) as previously described (12). However, to our knowledge, we are the first to identify that preextubation leak pressures and percentages are relevant only for cuffed ETTs in children. Therefore, the common practice of delaying extubation to administer corticosteroids to a patient who has an uncuffed ETT and does not have a preextubation leak (regardless of pressure) cannot be justified by our data (27). It is unclear whether this practice would be warranted in children who have a cuffed ETT, because 20% of patients with extubation leak pressure greater than 25 cm H₂O (or cuff leak volume <10%) will have subglottic UAO. However, this should be the focus of future research. Furthermore, for uncuffed ETTs, the presence of a leak (regardless of pressure) does not assure against subglottic UAO, whereas it does if the patient has a cuffed ETT with a preextubation leak of 25 cm H₂O or less (posttest probability, 2%).

Table 3. Selected Univariate Risk Factors for Post-extubation UAO among Patients with Cuffed Endotracheal Tubes

	No UAO [n = 132 (78%)]	Supraglottic UAO [n = 20 (12%)]	Subglottic UAO [n = 17 (10%)]	Total [n = 169 (100%)]	P Value
Demographics					
Weight, kg	11.3 (5.9 to 28.1)	12.3 (8.7 to 20.9)	7.1 (5.4 to 11.1)	11.1 (5.7 to 25.5)	0.04
Age, mo	24 (4 to 117)	33 (13.5 to 97.5)	7 (5 to 15)	18 (5 to 108)	0.052
Reason for intubation					
UAO	6 (4.5%)*	5 (25%)	5 (29%)*	16 (9%)	0.0001
Cardiac surgery	33 (25%)	4 (20%)	2 (11.7%)	39 (23%)	0.45
Shock/cardiovascular	13 (10%)	3 (15%)	3 (17%)	19 (11%)	0.54
Intubation data					
ETT size, mmID	4 (3.5 to 5.5)*	4 (3.5 to 5.5)	3.5 (3.5 to 4)*	4 (3.5 to 5.5)	0.03
Actual ETT minus Cole [†]	−0.16 (−0.52 to 0.02)	−0.25 (−0.65 to −0.02)	−0.1 (−0.38 to 0.17)	−0.17 (−0.52 to −0.02)	0.53
Leak intubation (n = 96)	66 (89%)	9 (82%)	7 (63%)	81 (85%)	0.07
Traumatic intubation (n = 153)	10 (8.1%)	2 (11.7%)	3 (23%)	15 (10%)	0.2
Day of extubation data					
Cuff inflated (yes)	96 (73%)*	13 (65%)	6 (35%)*	115 (69%)	0.005
Leak at extubation (yes)	95 (72%)*	16 (80%) [‡]	7 (41%)* [‡]	118 (70%)	0.02
Leak pressure extubation, cm H ₂ O	20 (15 to 32)*	20 (15 to 26) [‡]	40 (30 to 40)* [‡]	20 (18 to 35)	0.0006
Cuff leak volume, %	16.1 (0 to 34)*	18.4 (3 to 40) [‡]	0 (0 to 2.7)* [‡]	14.2 (0 to 33)	0.001
GCS score	11 (9 to 11) [§]	9 (9 to 11) [§]	11 (11 to 11)	11 (9 to 11)	0.007
Fluid balance at midnight, ml/kg	11.5 (−7.0 to 28.7)	6.8 (−7.8 to 30.5)	8.2 (−5.0 to 22.1)	9.3 (−6.8 to 28.3)	0.85
Pain score	1.4 (0.54 to 1.9)	1.3 (0.7 to 2.6)	2.1 (0.9 to 2.6)	1.39 (0.67 to 2.1)	0.055
Length of intubation, h	122 (38.5 to 222)	75 (27 to 177)	134 (60 to 192)	122 (40 to 214)	0.49
Steroids preextubation	15 (12.6%)	5 (31.2%)	4 (30.7%)	24 (16%)	0.055
Outcomes					
Reintubated within 48 h	5 (3.8%)*	2 (10%)	4 (23.5%)*	11 (6.5%)	0.006
Racemic epinephrine after extubation	6 (5%)* [§]	7 (35%)* [§]	16 (94%)* [‡]	29 (17%)	0.0001
Steroids after extubation	7 (5.3%)*	4 (20%) [‡]	10 (58%)* [‡]	21 (12%)	0.0001

Definition of abbreviations: ETT = endotracheal tube; GCS = Glasgow Coma Scale; mmID = millimeters internal diameter; UAO = upper airway obstruction. A complete set of risk factors considered can be found in Table E3. Patients are grouped based upon tool-gauged UAO within the first 60 min post-extubation (all available data) into subglottic UAO requiring treatment (subglottic UAO), supraglottic UAO, or no UAO. Data are presented as number (%) or median (interquartile range). Significant *P* values are shown in bold type.

*Multiple comparisons statistically significantly different between subglottic and no UAO.

[†]Cole formula calculated as [age (yr) × 0.25] + 3.5.

[‡]Multiple comparisons statistically significantly different between subglottic and supraglottic UAO.

[§]Multiple comparisons statistically significantly different between supraglottic and no UAO.

The importance of leak for cuffed ETTs may be related to the fact that smaller cuffed tubes are often used because the cuff can be inflated to maintain tidal volume and pressure. Because the cuff sits in the subglottic space, the cuff leak volume appears to measure subglottic edema. Our unit's practice is to keep the cuff inflated to provide minimal leak at peak inspiratory pressure. Hence, our finding that patients in whom the cuff was kept deflated on the day of extubation had higher rates of subglottic UAO is likely explained by minimal cuff leak volume. There was a strong suggestion that children with cuffed ETTs without a leak at intubation were more likely to have subglottic UAO (Table 3). Hence, careful attention should be given to leak at the time of intubation with a cuffed tube. If a leak is large and

compromising ventilation with an uncuffed ETT, the ETT is often changed. This may explain why leak pressures are not predictive with uncuffed ETTs, because minimal leak is clinically desired.

The most common argument against the use of cuffed ETTs in young children is a perceived higher risk of subglottic edema. We found similar age-stratified rates of subglottic UAO between cuffed and uncuffed ETTs. Furthermore, age was no longer an independent risk factor for subglottic UAO with cuffed ETTs when we controlled for preextubation leak; 88% of cases of subglottic UAO had preextubation leak pressures >25 cm H₂O. Given that cuffed ETTs provide better ability to predict who is at high risk for subglottic UAO post-extubation and provide a way to maintain tidal volume, perhaps we

should rethink our practice of using uncuffed ETTs in young children. However, using cuffed ETTs (regardless of the age of the child) requires careful attention to cuff position, appropriate sizing and intubation leak, and using the minimal volume of air in the cuff to maintain ventilation.

Other independent risk factors for subglottic UAO include age (for uncuffed tubes), higher pain scores, and a history of preexisting clinical UAO (for cuffed tubes). This history of preexisting clinical UAO is not surprising and is consistent with previous reports in the literature (28, 29). The age group of 1 month to 5 years identified in this study as being at highest risk for subglottic UAO is consistent with previous reports (12). This higher risk may be related to size of the ETT

Table 4. Extubation Leak Pressure and Cuff Leak Volume for Cuffed Endotracheal Tubes on Outcome of Subglottic UAO Requiring Treatment

Statistic	Leak Pressure (cm H ₂ O)					Leak Percentage				
Leak	>20	>25	>30	>35	>40	0	<5	<10	<15	<20
Fraction with UAO	0.130	0.183	0.200	0.227	0.243	0.208	0.203	0.195	0.170	0.152
Sensitivity	0.944	0.882	0.764	0.588	0.529	0.647	0.765	0.882	0.882	0.941
Specificity	0.296	0.559	0.657	0.776	0.816	0.724	0.664	0.592	0.519	0.415
Positive LR	1.341	2.000	2.227	2.625	2.875	2.341	2.277	2.162	1.834	1.609
Negative LR	0.189	0.211	0.359	0.531	0.577	0.488	0.354	0.199	0.227	0.142
Pretest probability	10%	10%	10%	10%	10%	10%	10%	10%	10%	10%
Posttest probability (with leak)	2%	2%	4%	6%	6%	5%	4%	2%	3%	2%
Posttest probability (no leak)	13%	18%	20%	23%	24%	21%	20%	19%	17%	15%
AUC ROC	0.619	0.721	0.711	0.682	0.673	0.688	0.715	0.737	0.701	0.678

Definition of abbreviations: AUC ROC = area under the receiver operating characteristic curve; LR = likelihood ratio; UAO = upper airway obstruction. A leak pressure of 25 cm H₂O with the cuff deflated or a cuff leak volume of 10% yielded good test statistics to identify low- and high-risk patients for subglottic post-extubation UAO requiring treatment.

Table 5. Selected Univariate Risk Factors for Post-extubation UAO for Patients with Uncuffed Endotracheal Tubes

	No UAO [n = 179 (75%)]	Supraglottic UAO [n = 29 (12%)]	Subglottic UAO [n = 32 (13%)]	Total [n = 240 (100%)]	P Value*
Demographics					
Weight, kg	3.8 (3.2 to 6.0)	5.1 (3.5 to 7.2)	4.8 (3.4 to 7.0)	4 (3.2 to 6.2)	0.048
Age, mo	2 (0 to 5) [†]	3 (1 to 7)	4 (1.5 to 7) [†]	2 (0 to 6)	0.002
Reason for intubation					
UAO	14 (7.8%) ^{†‡}	10 (34.5%) [‡]	7 (21.8%) [†]	31 (13%)	0.0001
Cardiac surgery	127 (71%) [‡]	13 (45%) [‡]	22 (68%)	162 (68%)	0.02
Shock/cardiovascular	15 (8%)	5 (17%)	0 (0%)	20 (8%)	0.052
Intubation data					
ETT size, mmID	3.5 (3.5 to 4)	3.5 (3.5 to 4)	3.5 (3.5 to 4)	3.5 (3.5 to 4)	0.8
Actual ETT minus Cole [§]	-0.5 (-0.52 to -0.1)	-0.5 (-0.63 to -0.12)	-0.14 (-0.54 to -0.06)	-0.5 (-0.54 to -0.1)	0.28
Leak intubation (n = 166)	94 (79%)	20 (90%)	17 (68%)	131 (78%)	0.15
Traumatic intubation (n = 219)	6 (4%)	3 (11%)	3 (9%)	12 (5%)	0.17
Day of extubation data					
Leak at extubation (yes)	73 (41%)	15 (51%)	17 (53%)	105 (44%)	0.28
Leak pressure extubation, cm H ₂ O	35 (25 to 40)	30 (15 to 40)	35 (20 to 40)	30 (20 to 40)	0.28
Leak percentage	0 (0 to 7.7)	0 (0 to 14.6)	0 (0 to 4.5)	0 (0 to 8.3)	0.8
GCS score	11 (9 to 11)	11 (9 to 11)	11 (11 to 11)	11 (9 to 11)	0.34
Fluid balance at midnight, ml/kg	5.7 (-17.8 to 26.7)	13.6 (-1.6 to 28.3)	15 (-5 to 31.3)	11.6 (-14 to 27.7)	0.08
Pain score	1.1 (0.61 to 1.9)	1.3 (0.46 to 1.8)	1.4 (0.95 to 1.9)	1.4 (0.75 to 2.1)	0.25
Length of intubation, h	94 (33 to 176)	44 (25 to 185)	96 (50 to 182)	94 (31 to 179)	0.21
Steroids preextubation (n = 193)	16 (11%)	6 (27%)	3 (12%)	25 (13%)	0.1
Outcomes					
Reintubated within 48 h	10 (5.6%) [†]	3 (10.3%)	10 (31.3%) [†]	23 (9.6%)	0.0001
Racemic epinephrine after extubation	11 (6%) ^{†‡}	11 (38%) [‡]	31 (97%) [†]	53 (22%)	0.0001
Steroids after extubation	8 (4.5%) ^{†‡}	7 (24%) [‡]	16 (50%) [†]	31 (13%)	0.0001

Definition of abbreviations: ETT = endotracheal tube; GCS = Glasgow Coma Scale; mmID = millimeters internal diameter; UAO = upper airway obstruction. A complete set of risk factors considered can be found in Table E4. Patients are grouped based upon tool-gauged UAO within the first 60 min post-extubation (all available data) into subglottic UAO requiring treatment (subglottic UAO), supraglottic UAO, or no UAO. Data are presented as number (%) or median (interquartile range). Significant P values are shown in bold type.

*UAO versus none.

[†]Multiple comparisons statistically significantly different between subglottic and no UAO.

[‡]Multiple comparisons statistically significantly different between supraglottic and no UAO.

[§]Cole formula calculated as [age (yr) × 0.25] + 4.

^{||}Multiple comparisons statistically significantly different between subglottic and supraglottic UAO.

(many potential choices from 3.5–5.5 mm internal diameter based on interpretation of formulae), developmental issues related to the trachea, or sedation. In our multivariable modeling, pain scores (as a surrogate for sedation) were associated with subglottic UAO for children with cuffed ETTs. Children in this age range are typically difficult to keep calm during weaning. This is consistent with the results of the Randomized Evaluation of Sedation Titration for Respiratory Failure clinical trial, in which researchers found a higher incidence of clinically judged post-extubation stridor in a group of patients who were less sedated (30). Pain scores are an imprecise surrogate for sedation, but they reinforce that level of sedation or agitation may be relevant (13). We did not use actual doses of sedatives and analgesics, because level of sedation, not dose, reflects patient activity and risk for subglottic UAO. Neonates have a very low risk of subglottic UAO, perhaps related to the relative elasticity of the neonatal trachea, making it less subject to trauma or inflammation. This lower risk in neonates may also be from less movement while intubated or less variability in ETT size. Our analysis does not support ETT size as the explanation (Tables 3 and 5), although the ETTs used in this study were smaller than would be predicted by the Cole formula, which reflects institutional practice.

Our study has limitations. First, it is a single-institution study, albeit in two intensive care units with different practices. Second, we obtained a convenience sample, given that we did not study patients on nights or weekends or patients whose parents did not provide consent. Third, we based our risk factor analysis on a combination outcome of subglottic UAO identified based on use of the tool with the

need for clinical treatment. Although we did this in attempting to be objective, there was some variability in the interpretation of flow limitation and the decision to treat UAO. Hence, flow limitation was used to screen for UAO, but UAO presence required a significant increase in PRP, which is objective. Fourth, there is no gold standard for post-extubation UAO. We believe our tool is more objective than clinical assessment because it better predicts reintubation and subsequent UAO treatment immediately post-extubation, but it is unclear if this is an appropriate gold standard. Moreover, looking at our sensitivity analysis (*see online supplement*), it appears as if a suspicion that the patient would have UAO after extubation (i.e., decision to treat with corticosteroids before extubation, or a genetic syndrome) made the patient more likely to receive UAO treatment after extubation. Many of these patients were not classified as having UAO after extubation based on the tool. These potential biases, coupled with the perceived benign nature of UAO treatment, mandates that we not base the diagnosis of post-extubation UAO solely on receiving UAO treatment. Fifth, our classification of supraglottic versus subglottic may have flaws, but our analysis highlights that not all post-extubation UAO is a consequence of edema caused by the ETT. On the basis of our risk factor analysis, patients with supraglottic UAO resembled patients with no UAO more closely than those with subglottic UAO. However, patients with supraglottic UAO often were treated for subglottic UAO, with higher rates of racemic epinephrine and post-extubation corticosteroids than those without UAO (Tables 3 and 5). Differentiating these patients is crucial when considering prevention strategies for subglottic UAO

because, for example, supraglottic UAO is unlikely to be prevented by corticosteroids. Finally, despite the large sample size, we could not examine the risk factors for reintubation due to UAO, because the reintubation rate was less than 10%, with only 19 cases of reintubation due to UAO. As shown in Table 1, the UAO tool is a surrogate for reintubation risk and may make a prevention study of post-extubation subglottic UAO feasible.

In conclusion, we have demonstrated that a physiology-based objective tool may have clinical utility as an early marker of post-extubation UAO because it is predictive of subsequent UAO treatment and reintubation when used 5 minutes after extubation and is better than clinical assessment. Data derived from this tool, combined with clinical treatment, allowed us to identify risk factors for subglottic post-extubation UAO, which include low cuff leak volume or high preextubation leak pressure, poor sedation, and preexisting UAO if the ETT was cuffed and age (1 mo to 5 yr) if the ETT was uncuffed. The presence or absence of a leak preextubation (regardless of pressure) is not associated with subglottic UAO for uncuffed ETTs. ■

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